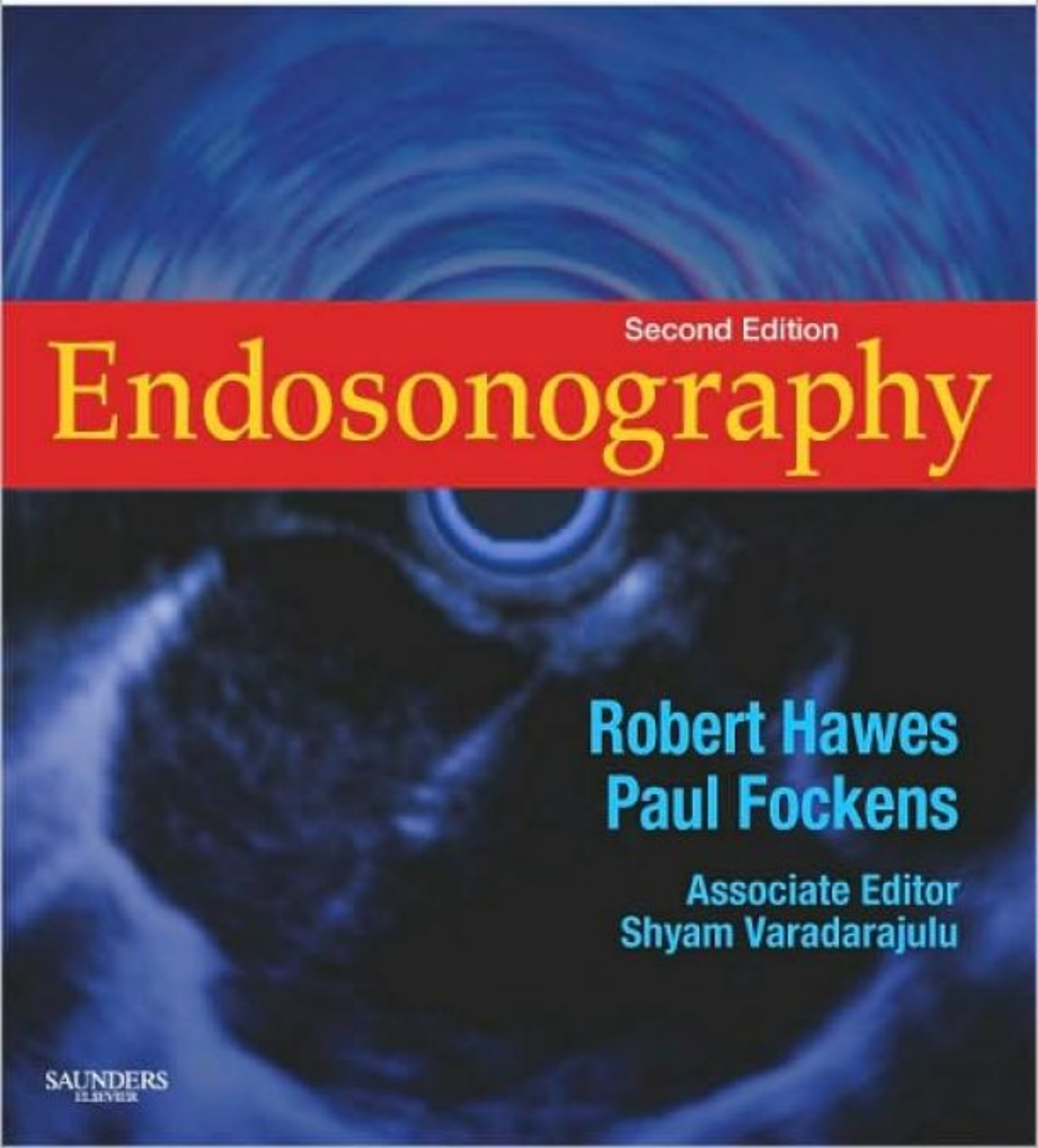
Expert CONSULT
Activate at expertconsult.com
Searchable Full Text Online



Second Edition

Endosonography

Robert Hawes
Paul Fockens

Associate Editor
Shyam Varadarajulu

SAUNDERS
ELSEVIER

Endosonography

Endosonography

SECOND EDITION

EDITORS **Robert H. Hawes, MD**
Professor of Medicine
Peter Cotton Chair for Endoscopic Innovation
Division of Gastroenterology and Hepatology
Digestive Disease Center
Medical University of South Carolina
Charleston, South Carolina

Paul Fockens, MD, PhD
Professor of Gastrointestinal Endoscopy
Department of Gastroenterology and Hepatology
Academic Medical Center
University of Amsterdam
Amsterdam, Netherlands

ASSOCIATE EDITOR **Shyam Varadarajulu, MD**
Associate Professor of Medicine
Director of Endoscopy
School of Medicine
University of Alabama at Birmingham
Birmingham, Alabama

ELSEVIER
SAUNDERS

ELSEVIER
SAUNDERS

1600 John F. Kennedy Blvd.
Ste 1800
Philadelphia, PA 19103-2899

ENDOSONOGRAPHY ISBN: 978-1-4377-0805-9

Copyright © 2011, 2006 by Saunders, an imprint of Elsevier Inc. All rights reserved.

No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, recording, or any information storage and retrieval system, without permission in writing from the publisher. Details on how to seek permission, further information about the Publisher's permissions policies and our arrangements with organizations such as the Copyright Clearance Center and the Copyright Licensing Agency, can be found at our website: www.elsevier.com/permissions.

This book and the individual contributions contained in it are protected under copyright by the Publisher (other than as may be noted herein).

Notices

Knowledge and best practice in this field are constantly changing. As new research and experience broaden our understanding, changes in research methods, professional practices, or medical treatment may become necessary.

Practitioners and researchers must always rely on their own experience and knowledge in evaluating and using any information, methods, compounds, or experiments described herein. In using such information or methods they should be mindful of their own safety and the safety of others, including parties for whom they have a professional responsibility.

With respect to any drug or pharmaceutical products identified, readers are advised to check the most current information provided (i) on procedures featured or (ii) by the manufacturer of each product to be administered, to verify the recommended dose or formula, the method and duration of administration, and contraindications. It is the responsibility of practitioners, relying on their own experience and knowledge of their patients, to make diagnoses, to determine dosages and the best treatment for each individual patient, and to take all appropriate safety precautions.

To the fullest extent of the law, neither the Publisher nor the authors, contributors, or editors assume any liability for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products, instructions, or ideas contained in the material herein.

Library of Congress Cataloging-in-Publication Data
Endosonography / editors, Robert H. Hawes, Paul Fockens ; associate editor, Shyam Varadarajulu. – 2nd ed.
p. ; cm.
Includes bibliographical references and index.
ISBN 978-1-4377-0805-9 (hardcover : alk. paper)
1. Endoscopic ultrasonography. I. Hawes, Robert H. II. Fockens, Paul. III. Varadarajulu, Shyam.
[DNLM: 1. Endosonography–methods. 2. Gastrointestinal Neoplasms–ultrasonography. WN 208]
RC78.7.E48E53 2011
616.07′543–dc22

2010038723

Senior Acquisitions Editor: Kate Dimock
Developmental Editor: Kate Crowley
Publishing Services Manager: Anne Altepeter
Team Manager: Radhika Pallamparthy
Senior Project Manager: Doug Turner
Project Manager: Preethi Varma
Designer: Ellen Zanolle

Printed in Canada

Last digit is the print number: 9 8 7 6 5 4 3 2 1

Working together to grow
libraries in developing countries
www.elsevier.com | www.bookaid.org | www.sabre.org
ELSEVIER BOOK AID International Sabre Foundation

For Chris, Grant, and Taylor

RH

For Marischka, Matthijs, and Kiki

PF

For Deepa, Archith, and Raksha

SV

CONTRIBUTORS

M. Victoria Alvarez-Sánchez, MD
Consultant Gastroenterologist
Department of Gastroenterology
Complejo Hospitalario de Pontevedra
Pontevedra, Spain

Mohammad Al-Haddad, MD
Assistant Professor of Clinical Medicine
Division of Gastroenterology and Hepatology
Director, Endoscopic Ultrasound Fellowship Program
Indiana University Medical Center
Indianapolis, Indiana

Jouke T. Annema, MD, PhD
Chest Physician
Department of Pulmonology
Leiden University Medical Center
Leiden, Netherlands

William R. Brugge
Professor of Medicine
Harvard Medical School
Massachusetts General Hospital
Boston, Massachusetts

John DeWitt, MD
Associate Professor of Medicine
Division of Gastroenterology
Indiana University Medical Center
Indianapolis, Indiana

Mohamad A. Eloubeidi, MD, MHS, FACP, FACG
Associate Professor of Medicine
American University of Beirut Medical Center
Beirut, Lebanon

Douglas O. Faigel, MD
Associate Professor of Medicine
Director of Endoscopy
Department of Gastroenterology
Oregon Health & Science University
Portland, Oregon

Steve Halligan, MD, FRCP, FRCR
Professor of Gastrointestinal Radiology
Department of Specialist Radiology
University College Hospital
London, United Kingdom

Gavin C. Harewood, MD, MSc
Consultant in Gastroenterology
Bon Secours Hospital
Dublin, Ireland

Joo Ha Hwang, MD, PhD
Acting Assistant Professor of Medicine
Division of Gastroenterology
University of Washington
Seattle, Washington

Darshana Jhala, MD, BMus
Associate Professor of Pathology
Department of Pathology and Laboratory Medicine
University of Pennsylvania
Philadelphia, Pennsylvania

Nirag Jhala, MD, MIAC
Professor of Pathology
Director of Cytopathology
Perelman Center for Advanced Medicine
University of Pennsylvania
Philadelphia, Pennsylvania

Eun Young (Ann) Kim, MD, PhD
Assistant Professor of Internal Medicine
Gastroenterology Department
Deagu Catholic University Medical Center
Deagu, South Korea

Michael B. Kimmey, MD
Consultant in Gastroenterology
Tacoma Digestive Disease Center
Tacoma, Washington

Christine Lefort
Consultant in Gastroenterology
Hôspital Privé Jean Mermoz
Lyons, France

Anne Marie Lennon, MD, PhD, MRCPI
Director
Pancreatic Cyst Clinic
Department of Gastroenterology and Hepatology
Johns Hopkins Medical Institutions
Baltimore, Maryland

Michael J. Levy, MD
Professor of Medicine
Division of Gastroenterology and Hepatology
Mayo Clinic
Rochester, Minnesota

Costas Markoglou, MD
Consultant Gastroenterologist
Second Department of Gastroenterology
Evangelismos Hospital
Athens, Greece

John Meenan, MD, PhD, FRCPI, FRCP
Consultant Gastroenterologist
Department of Gastroenterology
Guy's and St Thomas' Hospital
London, United Kingdom

Faris Murad, MD
Assistant Professor of Medicine
Division of Gastroenterology and Hepatology
Department of Internal Medicine
Washington University
St. Louis, Missouri

Bertrand Napoléon, MD
Consultant in Gastroenterology
Department of Gastroenterology
Clinique Sainte Anne Lumière
Lyons, France

Sarto C. Paquin, MD, FRCP(C)
Assistant Professor of Medicine
Department of Medicine
Division of Gastroenterology
Centre Hospitalier de l'Université de Montréal
Montréal, Canada

Ian D. Penman, MD, FRCP, (ED)
Consultant Gastroenterologist
Gastrointestinal Unit
Western General Hospital
Edinburgh, United Kingdom

Shajan Peter, MD
Assistant Professor of Medicine
University of Alabama at Birmingham
Birmingham, Alabama

Klaus F. Rabe, MD, PhD
Professor of Medicine
Chairman and Head of Department of Pulmonology
Leiden University Medical Centre
Leiden, Netherlands

Joseph Romagnuolo, MD, FRCPC, MScEpid
Associate Professor of Medicine
Division of Gastroenterology and Hepatology
Medical University of South Carolina
Charleston, South Carolina

Thomas Rösch, MD
Professor of Medicine
Department of Interdisciplinary Endoscopy
Hamburg Eppendorf University Hospital
Hamburg, Germany

Anand V. Sahai, MD, MScEpid, FRCPC
Associate Professor of Medicine
Department of Gastroenterology
Centre Hospitalier de l'Université de Montréal
Hôpital St Luc
Montreal, Canada

Michael K. Sanders, MD
Assistant Professor of Medicine
Division of Gastroenterolgy
School of Medicine
University of Pittsburg
Pittsburg, Pennsylvania

Thomas J. Savides, MD
Professor of Clinical Medicine
University of California, San Diego
UCSD Thornton Medical Center
Division of Gastroenterology
La Jolla, California

Hans Seifert, MD
Professor of Medicine
Department of Internal Medicine
Oldenburg Municipal Hospital
Oldenburg, Germany

Mark Topazian, MD
Associate Professor of Medicine
Division of Gastroenterology and Hepatology
Mayo Clinic
Rochester, Minnesota

Charles Vu, MB, FRACP, FAMS
Consultant Gastroenterologist
Department of Gastroenterology
Tan Tock Seng Hospital
Singapore

PREFACE

It is with great pleasure that we present the second edition of *Endosonography*. The first edition was a project that we embraced enthusiastically (albeit somewhat naively, not realizing how much work goes into a first edition textbook) because we believed there was a need for a comprehensive resource that could serve as a reference for those wishing to learn about EUS. At that time, EUS had matured in Japan, Europe, and the United States and was routinely taught in gastroenterology fellowships. To address the learning needs of the time, we selected expert endosonographers to write chapters that comprehensively covered all clinically relevant topics within the discipline of EUS while at the same time developing "how to" sections and a DVD that provided text and videos to teach the actual technique of EUS. The first edition was extremely well received, and we are grateful that the hard work by the authors and Elsevier has resulted in moving EUS forward.

Time marches on, and medicine is a constantly evolving discipline. Gastrointestinal endoscopy has undergone significant advances, and so has EUS. As we observed the progress in EUS and particularly the explosion of interest in Asia (especially in China and India), Eastern Europe, and the Middle East, it became apparent that it was time to develop a second edition. We are wiser now, and we decided that if we were to invest the effort in a second edition, we wanted to make sure that we could make substantial improvements and not just do a simple "makeover." The publishing landscape has changed, more and more people (young and old) have "gone digital," and we needed to analyze the needs of the current generation of EUS trainees. We also wanted this edition to maintain its relevance for a longer time. Discussing our ideas with Elsevier, we were pleasantly surprised that their thinking was in concert with ours. The improvements to the second edition include:

1. **Online version:** The field of endosonography is constantly evolving, and the EUS landscape had undergone a great transformation with time. Consequently, published information sometimes becomes outdated and irrelevant. To overcome this, the second edition of *Endosonography* has an online component. All chapters in the second edition will be updated on a quarterly basis. This will ensure that current information is available online to the readers at all times.
2. **Frequent e-mail updates from editors:** When one registers online for the electronic version of the textbook, frequent emails will be sent by the editorial team, which will provide updates on new contributions to the EUS literature. The editors will regularly review the most recent literature and will keep readers informed on how these articles influence the practice of endosonography. Thus we strongly encourage all readers to register online for the second edition of this textbook.
3. **Interventional EUS:** More comprehensive coverage of EUS includes significant modifications to existing chapters and the introduction of new chapters, especially in the area of interventional EUS. All procedural techniques have been carefully detailed in a stepwise fashion with accompanying videos (narratives included).
4. **"How to" sections**: Learning EUS remains a challenge for the beginner. Hence, the "how to" sections were revised, and combined with clearer correlations among the text, illustrations, and videos (with narration), these sections provide a better teaching system for those learning how to perform EUS.
5. **Video component:** The videos for the second edition will now be exclusively on the *Endosonography* Expert Consult website. This will allow frequent updating of the videos and will avoid the problems of losing or damaging the DVD.
6. **More focus on pulmonary medicine and cytopathology:** We recognized the rapid advance of EUS in pulmonary medicine and asked Jouke Annema, one of the world's experts in the role of EUS in pulmonary disease, to expand his chapter to include endobronchial ultrasound (EBUS) and to pay particular attention to issues facing pulmonologists and thoracic surgeons in constructing his chapter. He accomplished this task perfectly, and we believe that *Endosonography* can now serve as a valuable resource to pulmonary physicians as they learn and apply EUS to their practice. Likewise, the chapter on cytopathology has been suitably revised to be useful to pathologists who are interested in EUS. We hope that this will serve as a guide to both endosonographers and cytopathologists to collaborate and work closely, which is pivotal for establishing a successful EUS practice.

Perhaps the most significant improvement to the second edition is the addition of Shyam Varadarajulu as our associate editor. Shyam brought his increasingly legendary energy and enthusiasm, along with wisdom and vision, to this project. His ideas shaped the organization of the second edition, and he spearheaded the editing of all the chapters. He will also play a pivotal role in

organizing the regular updates to readers. It would have been difficult, if not impossible, to provide the same quality in the second edition without Shyam, and we are most grateful for his commitment to our vision for *Endosonography*.

We remain steadfastly committed to advancing EUS through education and training. We feel that the second edition of *Endosonography* can play an important role in enabling one to achieve excellence in EUS and that a more widespread practice of quality endoscopic ultrasound will ultimately improve patient care around the world. It is our sincere hope that *Endosonography* will play a key role in allowing you to master the discipline of EUS.

Robert H. Hawes

Paul Fockens

ACKNOWLEDGMENTS

I am extremely grateful for the support and encouragement I have received from my colleagues and friends at the Medical University of South Carolina (MUSC) in creating the second edition of *Endosonography*. Increasingly, academic endeavors such as editing textbooks must take place at night and on weekends so as not to interfere with patient care. As a result, one has to rely heavily on co-workers to get all of the work done. I am heavily indebted to Linda McDaniel and James Webb, who once again took on the task of editing our videos. They assumed this assignment with the same great proficiency and constant good cheer exhibited during the creation of the first edition.

I also owe a debt of gratitude to our endoscopic ultrasound fellows. We are blessed with tremendously talented individuals who come to MUSC to train in EUS, and they enthusiastically embraced the assignments of capturing images for the "how to" sections, as well as videos for the video library. Our recent fellows include Noah DeVicente, Christian Clark, Meghan Malone, and Caroline Loeser

I am also immensely grateful to our outstanding EUS nurses who routinely take the extra time and pay attention to detail, which allows us to perform clinical research and develop educational materials. Chris Abbey, Faye Connor, Linda Dean, Traci McClellan, and Kalundia Snipe have all contributed in their unique and special ways to enable the development of the second edition of *Endosonography*.

I am similarly indebted to my EUS partners, Brenda Hoffman and Joe Romagnuolo, whose hard work has created the video library and the large EUS service from which patient images were selected. Their wisdom and knowledge are a constant encouragement to me.

Robert H. Hawes

I want to thank my EUS partners at the Academic Medical Center of the University of Amsterdam: Jacques Bergman, Sheila Krishnadath, and Jeanin van Hooft. Together we see approximately 1000 patients for EUS per year and conduct EUS-related research such as studies on incidental pancreatic cysts, treatment of pancreatic fluid collections, and surveillance of familial pancreatic cancer families. The four of us train our advanced endoscopy fellows, who increasingly enjoy EUS because it offers the unique combination of high-resolution imaging combined with onsite cytologic diagnostics. Each year we receive many visitors from all over the world who spend anywhere from 2 hours to 2 months in the Academic Medical Center to observe EUS. And finally, over the past 12 years we have organized the annual EUS conference in Amsterdam in June, which now attracts between 150 and 200 participants.

I am grateful to our nursing staff, who provide expert support for all our procedures. More and more we are also supported by anesthesiology nurses or anesthesiologists who sedate our patients while we perform EUS examinations, especially when these examinations are interventional. I am also very grateful to Agaath Hanrath, Ann Duflou, and Marion de Pater, our senior nurses, who spend much time in the EUS room, and to Joy Goedkoop, who chairs our postgraduate school. I want to thank my secretary, Marion van Haaster, who succeeds in keeping me organized and takes care of the arrangements for all our visitors. Finally I am very grateful to my three pillars in life: Marischka, Matthijs, and Kiki.

Paul Fockens

I wish to thank my endoscopy partners Mel Wilcox, Shajan Peter, and Jessica Trevino at the University of Alabama at Birmingham (UAB) for their unstinting support and enthusiasm toward this project. I am indebted to my secretary Carol Lewis and nurse manager Jeanetta Blakely for their patience, as infinite as the vast ocean, a requisite imperative to work with me. These are the core members of my team and a vital part of my academic career at UAB, without whom it would have been hard to successfully complete this project. I am very thankful to my nursing staff, who support the 2500 EUS procedures that are performed annually and who helped me pioneer several new techniques in interventional EUS.

Many visitors from around the world, and particularly from my home country of India, have visited UAB over the years to learn EUS. Their presence at our center was a great source of inspiration for me. I hope to have the pleasure of seeing some of the *Endosonography* readers at UAB in the near future.

I wish to thank Rob and Paul for a once-in-a-lifetime opportunity to edit the second edition of this textbook. They gave me a free hand and offered all the support I needed to make this venture a success. I really wish and hope that in my second birth they would remain my mentors!

My parents and my family are my motivation to whom I owe my existence and every success in life. Thanks to Mom, Dad, Deepa, Archith, and Raksha.

Shyam Varadarajulu

CHAPTER 1 PRINCIPLES OF ULTRASOUND

Joo Ha Hwang | Michael B. Kimmey

Key Points

Ultrasound is mechanical energy in the form of vibrations that propagate through a medium such as tissue.

Ultrasound interacts with tissue by undergoing absorption, reflection, refraction, and scattering and produces an image representative of tissue structure.

Imaging artifacts can be recognized and understood based on a knowledge of the principles of ultrasound.

INTRODUCTION

A basic understanding of the principles of ultrasound is requisite for an endosonographer's understanding of how to obtain and accurately interpret ultrasound images. In this chapter, the basic principles of ultrasound physics and instrumentation are presented, followed by illustrations of how these principles are applied to ultrasound imaging and Doppler ultrasound and explanations of some common artifacts seen on endosonography. Knowledge of the basic principles of ultrasound will help the endosonographer to understand the capabilities of ultrasound imaging, as well as its limitations.

BASIC ULTRASOUND PHYSICS

Sound is mechanical energy in the form of vibrations that propagate through a medium such as air, water, or tissue.[1] The frequency of audible sound ranges from 20 to 20,000 Hz (cycles per second). Ultrasound involves a frequency spectrum that is greater than 20,000 Hz. Medical applications use frequencies in the range of 1,000,000 to 50,000,000 Hz (1 to 50 MHz). The propagation of ultrasound results from the displacement and oscillation of molecules from their average position and the subsequent displacement and oscillations of molecules along the direction of propagation of the ultrasound wave.

Ultrasound waves can be described using the common properties of waves. Figure 1.1 is an illustration of a sinusoidal wave with the pressure amplitude along the *y*-axis and the time or distance along the *x*-axis. Figure 1.1 is referred to in the following sections to introduce the basic properties of waves.

Wavelength, Frequency, and Velocity

The *wavelength* is the distance in the propagating medium that includes one complete cycle (see Fig. 1.1). The wavelength (λ) is dependent on the frequency (f) of the oscillations and the velocity (c) of propagation in the medium. The relationship of wavelength, frequency, and velocity is given in Equation 1.1.

$$c = f\lambda \tag{1.1}$$

The *frequency* of a wave is the number of oscillations per unit of time. Typically in ultrasound, this is stated in terms of cycles per second or Hertz (Hz) (1 cycle/sec = 1 Hz). The *period* of a wave (τ) is the inverse of the frequency and represents the time required to complete one cycle. The relationship between frequency and period is given in Equation 1.2.

$$f = \frac{1}{\tau} \tag{1.2}$$

The *velocity* of propagation depends on the physical properties of the medium in which the wave is propagating. The primary physical properties governing the velocity of propagation are the density and compressibility of the medium.

Density, Compressibility, and Bulk Modulus

The *density* (ρ) of a medium is the mass per unit volume of that medium (kg/m^3 in SI units). The *compressibility* (K) of a medium is a property that reflects the relationship between the fractional decrease in volume and the pressure applied to a medium. For example, air has high compressibility (a small amount of pressure applied to a volume of air will result in a large fractional decrease in volume), whereas bone has relatively low compressibility (a large amount of pressure applied to a volume of bone will result in a small fractional decrease in volume). Finally, the *bulk modulus* (β), which is the inverse of the compressibility, is the negative ratio of pressure applied to a medium and the fractional change in volume of the medium and reflects the stiffness of the medium.

The acoustic velocity (c) of a medium can be determined once the density (ρ) and the compressibility (K), or bulk modulus (β), are known. Equation 1.3 demonstrates the relationship of the three physical properties.

$$c = \frac{1}{\sqrt{K\rho}} = \frac{\sqrt{\beta}}{\sqrt{\rho}} \tag{1.3}$$

Density, compressibility, and bulk modulus are not independent of one another. Typically, as density increases, compressibility decreases and bulk modulus increases. However, compressibility and bulk modulus typically vary more rapidly than does density, and they dominate in Equation 1.3.

The acoustic velocity in different media can be determined by applying the equations to practice. For example, water at 30° C has a density of 996 kg/m^3 and a bulk modulus of 2.27×10^9 newtons/m^2.[2] Inserting these values into Equation 1.3 yields an acoustic velocity of 1509 m/sec in water. Values for density and bulk modulus have been characterized extensively and can be found in the literature.[2] A summary of relevant tissue properties

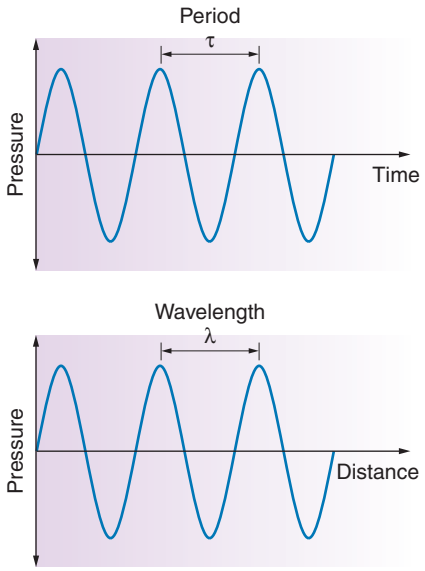


FIGURE 1.1 Sinusoidal wave depicted on the time axis and distance axis. The time to complete one cycle is the period (τ). The distance to complete one cycle is the wavelength (λ).

TABLE 1.1
Physical Properties of Tissue

Tissue or Fluid	Density (kg/m^3)	Bulk Modulus ($\times 10^9$ N/m^2)	Acoustic Velocity (m/s)
Water (30° C)	996	2.27	1,509
Blood	1,050-1,075	2.65	1,590
Pancreas (pig)	1,040-1,050	2.63	1,591
Liver	1,050-1,070	2.62	1,578
Bone, cortical	1,063-2,017	28.13	3,760

Adapted from Duck FA. *Physical Properties of Tissue.* London: Academic Press; 1990.

is given in Table 1.1. The acoustic velocity is not dependent on the frequency of the propagating wave (i.e., acoustic waves of different frequencies all propagate with the same acoustic velocity within the same medium).[3]

Ultrasound Interactions in Tissue

Ultrasound imaging of tissue is achieved by transmitting short pulses of ultrasound energy into tissue and receiving reflected signals. The reflected signals that return to the transducer represent the interactions of a propagating ultrasound wave with tissue. A propagating ultrasound wave can interact with tissue, and the results are *reflection*, *refraction*, *scattering*, and *absorption*.

Reflection

Specular reflections of ultrasound occur at relative large interfaces (greater than one wavelength) between two media of differing acoustical impedances. At this point, it is important to introduce the concept of *acoustic impedance*. The acoustic impedance (Z) of a medium represents the resistance to sound propagating through the medium and is the product of the *density* (ρ) and the *velocity* (c):

$$Z = \rho c \tag{1.4}$$

Sound will continue to propagate through a medium until an interface is reached where the acoustic impedance of the medium in which the sound is propagating differs from the medium that it encounters. At an interface where an acoustic impedance difference is encountered, a proportion of the ultrasound wave will be reflected back toward the transducer, and the rest will be transmitted into the second medium. The simplest case of reflection and transmission occurs when the propagating ultrasound wave is perpendicular (90 degrees) to the interface (Fig. 1.2). In this case, the percentage of the incident beam that is reflected is as follows:

$$\%reflected = \left(\frac{Z_2 - Z_1}{Z_2 + Z_1}\right)^2 \times 100 \tag{1.5}$$

The percentage of the incident beam that is transmitted is as follows:

$$\%transmitted = 100 - \%reflected \tag{1.6}$$

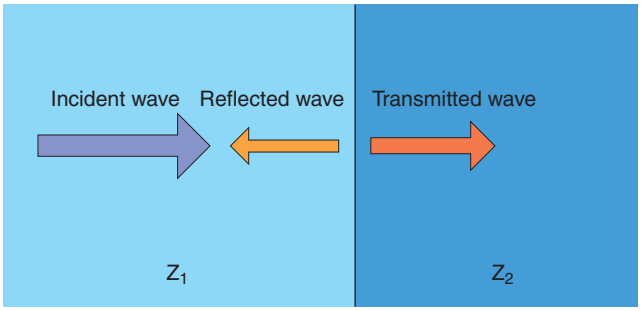


FIGURE 1.2 Reflection of an ultrasound wave at normal incidence to an interface between two media with different acoustic impedances (Z).

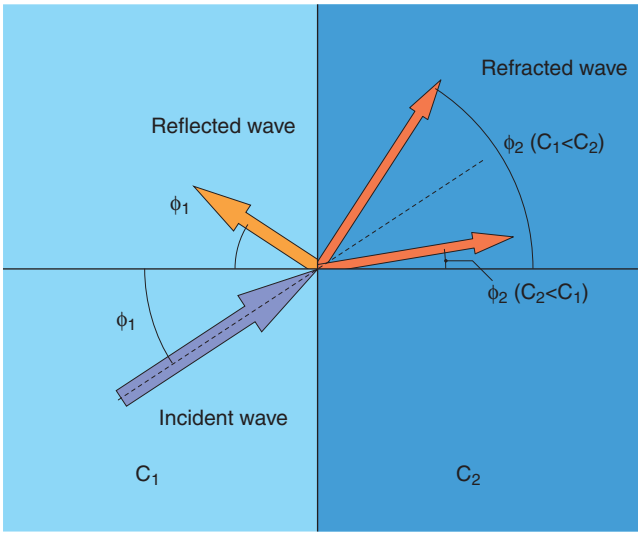


FIGURE 1.3 Refraction and reflection of an incident wave that is not normal to the interface between media with different acoustic velocities (c). The angle of reflection is identical to the angle of incidence. The angle of the refracted wave is dependent on the acoustic velocities of the two media and can be determined by applying Snell's law (see text).

Refraction

When the incident beam arrives at the interface at an angle other than 90 degrees, the transmitted beam path diverges from the incident beam path because of refraction (Fig. 1.3). The angle at which the transmitted beam propagates is determined by Snell's law:

$$\frac{\sin\phi_1}{\sin\phi_2} = \frac{c_1}{c_2} \tag{1.7}$$

The angle of *refraction* is determined by the *acoustic velocities* in the incident (c_1) and transmitted (c_2) media. There are three possible scenarios for a refracted beam, depending on the relative speeds of sound between the two media: (1) if $c_1 > c_2$, the angle of refraction will be bent toward normal ($\phi_1 > \phi_2$); (2) if $c_1 = c_2$, the angle of refraction will be identical to the angle of incidence, and the beam will continue to propagate without diverging from its path; (3) if $c_1 < c_2$, the angle of refraction will be bent away from normal ($\phi_1 < \phi_2$). Refraction of the ultrasound beam can lead to imaging artifacts that are discussed later in the chapter.

Scattering

Scattering, also termed *nonspecular reflection*, occurs when a propagating ultrasound wave interacts with different components in tissue that are smaller than the wavelength and have different impedance values than the propagating medium.[4] Examples of scatterers in tissue include individual cells, fat globules, and collagen. When an ultrasound wave interacts with a scatterer, only a small portion of the acoustic intensity that reflects off of the scatterer is reflected back to the transducer (Fig. 1.4). In addition, a signal that has undergone scattering by a single scatterer will usually undergo multiple scattering events before returning to the transducer. Scattering occurs in heterogeneous media, such as tissue, and is responsible for the different echotextures of organs such as the liver, pancreas, and spleen. Tissue containing fat or collagen scatters ultrasound to a greater degree than do other tissues, and this is why lipomas and the submucosal layer of the gastrointestinal tract appear hyperechoic (bright) on ultrasound imaging.[4]

Multiple reflections from nonspecular reflectors within the tissue returning to the transducer result in a characteristic acoustic speckle pattern, or echotexture, for that tissue.[4] Because speckle originates from multiple reflections and does not represent the actual location of a structure, moving the transducer will change the location of the speckle echoes while maintaining a similar speckle pattern. In addition, the noise resulting from acoustic speckle increases with increasing depth as a result of the greater number of signals that have undergone multiple reflections from nonspecular reflectors returning to the transducer.

Absorption

Ultrasound energy that propagates through a medium can be absorbed, resulting in the generation of heat. The *absorption* of ultrasound energy depends on tissue properties and is highly frequency dependent. Higher frequencies cause more tissue vibration and result in greater absorption of the ultrasound energy and more heat generation.

Ultrasound Intensity

The *intensity* of the ultrasound signal is a parameter that describes the power of the ultrasound signal over a cross-sectional area. As ultrasound waves propagate through tissue, the intensity of the wave becomes attenuated. Attenuation is the result of effects of both scattering and absorption of the ultrasound wave.[1] The *attenuation coefficient* (a) is a function of frequency that can be determined experimentally, and it increases with increasing frequency. The frequency of the ultrasound pulse affects both the depth of penetration of the pulse and the obtainable resolution. In general, as the frequency is increased, the depth of penetration decreases, owing to attenuation of the ultrasound intensity, and axial resolution improves, as discussed later in this chapter.

The intensity of the propagating ultrasound energy decreases exponentially as a function of depth and is given by the following equation:

$$I_x = I_0 e^{-2ax} \tag{1.8}$$

where I_0 is the initial intensity of the ultrasound pulse and I_x is the intensity of the ultrasound pulse after it has passed a distance x through tissue with an attenuation coefficient a in Neper/cm (Np/cm). As the attenuation coefficient increases with frequency, intensity also decreases exponentially as frequency increases. This equation partially explains the limitation on the depth of imaging because the returning ultrasound pulse from the tissue must be of sufficient intensity to be detected by the ultrasound transducer.

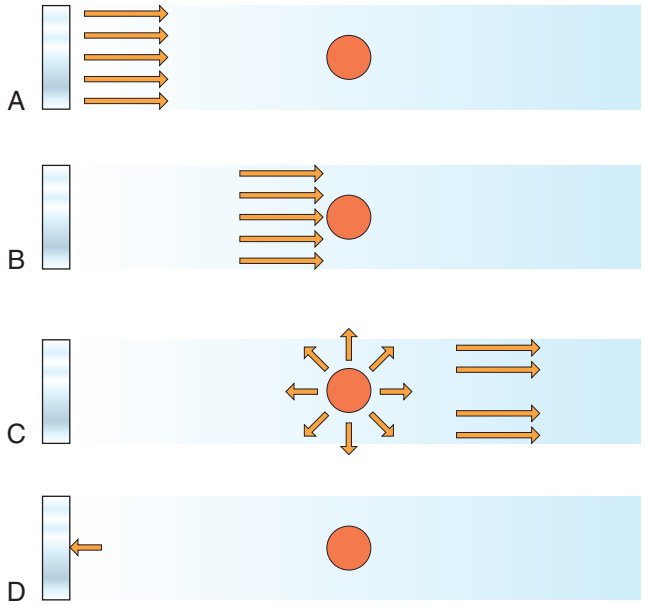


FIGURE 1.4 Schematic representation of single scattering. Scattering occurs from an interface that is smaller than the wavelength of the propagating ultrasound signal. The transducer is responsible for sending and receiving the signal. I_b is the back-scattered intensity that will propagate back to the transducer. **A,** The ultrasound signal is transmitted by the transducer and propagates toward the scatterer. **B,** The pulse reaches the scatterer. **C,** The incident acoustic intensity is scattered in different directions. **D,** The back-scattered energy received by the transducer is only a small fraction of the incident acoustic intensity that is scattered.

BASICS OF ULTRASOUND INSTRUMENTATION

The key component of an ultrasound system is the transducer. A *transducer* is a device that converts one form of energy to another. In the case of ultrasound transducers, electrical energy is converted to mechanical energy, resulting in the transmission of an ultrasound pulse. When an ultrasound signal is then received by the ultrasound transducer, the received mechanical signal is converted back to an electrical signal that is then processed and digitized by the ultrasound processor to yield a real-time image of the tissue being interrogated by the ultrasound transducer (Fig. 1.5).

Transducers

The active element of an ultrasound transducer, responsible for generating and receiving acoustic signals, is made typically from a piezoelectric ceramic. Piezoelectric ceramics are composed of polar crystals that are aligned in a particular orientation such that when an electric field is applied, the material changes shape.[3] Therefore, if an alternating electrical field is applied to the material at a particular frequency, the material will vibrate mechanically at that frequency, similar to an audio speaker. In addition, if the piezoelectric material is deformed by sufficient mechanical pressure (e.g., a reflected ultrasound wave), a detectable voltage will be measured across the material with a magnitude proportional to the applied pressure. The magnitude of the voltage then

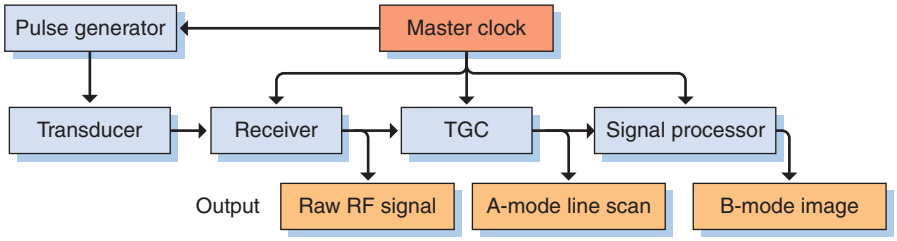


FIGURE 1.5 Ultrasound instrumentation schematic. The overall system is synchronized by a master clock. A pulse generator sends an electrical signal to the transducer, and the result is a transmitted ultrasound pulse. The transducer then receives the back-reflected signal resulting from the transmitted pulse. This signal is then passed on to the receiver, which amplifies the entire signal. The output from the receiver is the raw radiofrequency (*RF*) signal. The signal can then undergo time gain compensation (TGC), and the subsequent output will be the A-mode line scan. After TGC, the signal is further processed, including demodulation and registration, to yield a B-mode image.

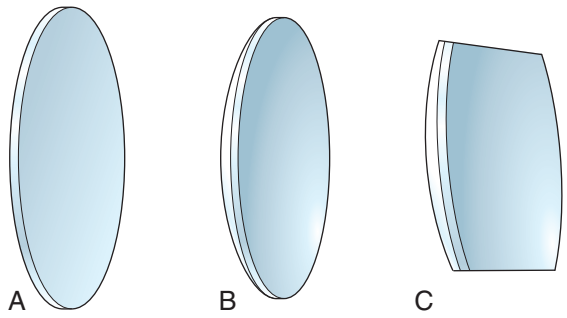


FIGURE 1.6 Potential configurations of single-element transducers. A, Flat circular disk. **B,** Spherically curved disk. **C,** Truncated, spherically curved disk.

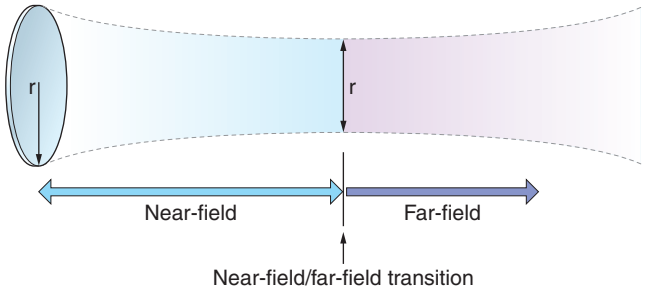


FIGURE 1.7 Single-element unfocused disk transducer. In a nonattenuating medium, an unfocused transducer has a self-focusing effect with the diameter of the ultrasound beam at the focus equal to the radius of the transducer (*r*). The location of the beam waist occurs at the near-field/far-field transition.

determines how brightly that signal is represented in B-mode imaging (this is explained in the later section on B-mode imaging).

Single-Element Transducers

The single-element transducer represents the most basic form of ultrasound transducer and the easiest to understand, owing to its geometric symmetry. Therefore, single-element disk transducers are explained in some detail, to illustrate the basic principles of ultrasound transducers. Single-element transducers can be of any shape or size, and they can be focused or unfocused. Figure 1.6 illustrates variations of a single-element disk transducer.

The beam width originating from a flat circular disk transducer in a nonattenuating medium is shown in Figure 1.7. Beam width is an important concept to understand because this parameter determines the lateral resolution (further discussed in the later section on imaging principles). The two distinct regions of the ultrasound field are termed the *near-field* and the *far-field*. The near-field/far-field transition is the location where the flat circular disk transducer has a natural focus, with the focal diameter equal to one-half of the diameter (or equal to the radius) of the transducer. The distance from the transducer at which this occurs is given by the following equation:

$$D = \frac{r^2}{\lambda} \tag{1.9}$$

where D is the near-field/far-field transition distance or focal length, r is the radius of the transducer, and λ is the wavelength of ultrasound in the propagating medium. Equation 1.9 demonstrates that, as the radius of the transducer decreases, the focal length is reduced if the frequency remains constant. In addition, for a constant radius, increasing the wavelength (i.e., decreasing the frequency) also reduces the focal length. However, in attenuating media such as tissue, this self-focusing effect is not seen, and

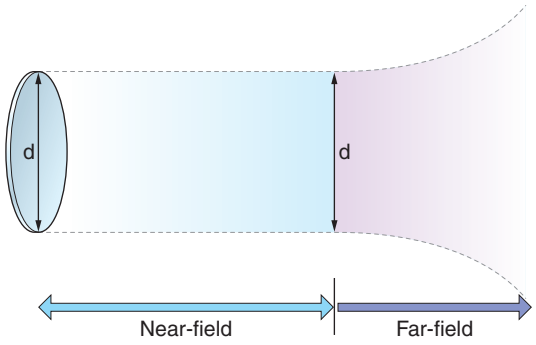


FIGURE 1.8 Single-element unfocused disk transducer. In an attenuating medium, the beam width of an unfocused transducer is approximately equal to the diameter of the transducer (*d*) until the near-field/far-field transition. The beam then rapidly diverges in the far-field.

the beam width in the near-field is approximately equal to the diameter of the transducer (Fig. 1.8). The beam width then rapidly diverges in the far-field.

Focusing. A single-element transducer can be focused by fabricating the transducer with a concave curvature (spherically curved) or by placing a lens over a flat disk transducer. Focusing is used to improve the lateral resolution and results in a narrow beam width at the focal length (distance from the transducer to the location of the beam width that is most narrow). However, the degree of focusing affects the depth of focus (the range where the image is in focus) and the focal length. For weak focusing, the focal length is long, as is the depth of focus. Conversely, for a beam that is highly focused, the focal length is short, as is the depth of focus (Fig. 1.9).

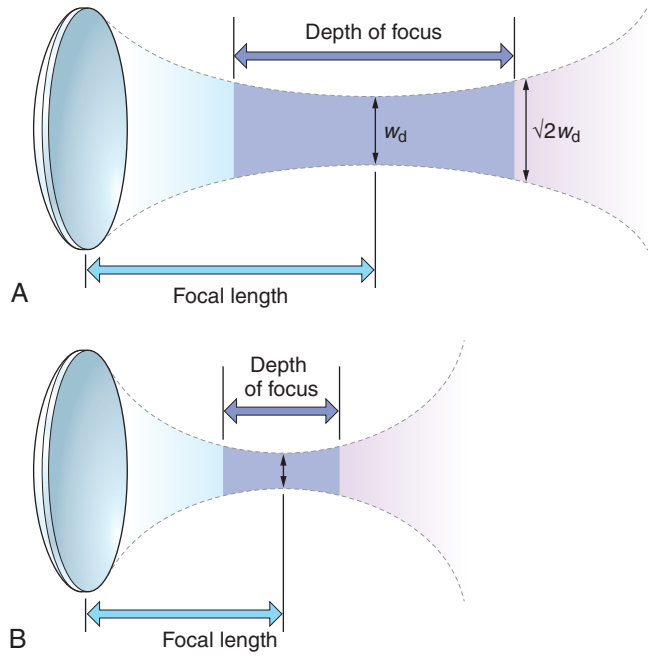


FIGURE 1.9 Effect of focusing. Focusing increases lateral resolution by decreasing the beam waist in the focal region *(highlighted in blue)*. The depth of focus is the distance between where the diameter of the beam is equal to $\sqrt{2}w_d$, where w_d is the diameter of the beam at the waist or focus. The degree of focusing influences the focal length, as well as the depth of focus. This figure compares two transducers of equal diameters with different degrees of focusing. The transducer in **A** exhibits weak focusing, whereas that in **B** exhibits strong focusing. The diameter of the waist at the focus is narrower with strong focusing, and this leads to improved lateral resolution in the focal region. However, the trade-off is a decrease in the depth of focus with rapid divergence of the beam beyond the focus. In addition, the focal length is much shorter (i.e., the focus is closer to the transducer) for the highly focused transducer.

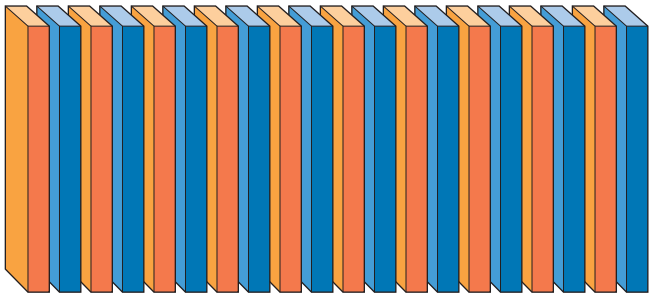


FIGURE 1.10 Configuration of a linear array transducer. This configuration consists of several rectangular elements, which are controlled individually. The sequence and timing of excitation of each individual element dictate the beam pattern that is transmitted from the array.

Arrays. Multiple single-element transducers can be combined in several different configurations. The linear array configuration is the most widely employed clinically. The array is composed of multiple identical crystals that are controlled electronically (Fig. 1.10). They can be fired individually in sequence or in groups, depending on the imaging algorithm. This configuration allows for electronic focusing at different depths based on the timing of the excitation of the individual transducer crystals.

Processors

Figure 1.5 is a block diagram of the components of an ultrasound imaging system. The main components are the ultrasound transducer, processor, and display. Within the processor are electronic components that are responsible for controlling the excitation of the transducer, amplification of the received signal, time gain compensation (TGC), and signal processing resulting in an output signal to the display.

Transmit/Receive

As described earlier, the ultrasound transducer is responsible for transmitting the ultrasound pulse and receiving reflected pulses. The time interval between the transmission of a pulse and the detection of the reflected pulse gives information about the distance from the interface or nonspecular reflector where the reflection occurred. The distance, or depth, of the interface from the transducer is given by the following equation:

$$D = \frac{v \times t}{2} \qquad (1.10)$$

where D is the distance from the transducer, v is the velocity of ultrasound in tissue (assumed to be uniform [1540 m/sec] by most ultrasound processors), and t is the time between the transmitted and received pulses. The product of v and t is divided by 2 because the pulse travels twice the distance (to the reflector and back). In addition, the strength of the received signal gives information regarding the impedance mismatch at the interface where the reflection occurred.

System Gain and Time Gain Compensation

The amplification of the output can be adjusted by the operator in two ways. One is to increase the overall gain of the system, an approach that uniformly increases the amplitude of all echoes received by the transducer. This can improve the detection of weak echoes; however, it generally comes at the expense of overall resolution.

TGC is used to compensate for the decreased intensity of echoes that originate from structures further from the transducer. As described earlier, the intensity of the ultrasound signal diminishes exponentially with distance (see Equation 1.8); therefore, reflections from interfaces further from the transducer have significantly decreased intensities. The TGC function of ultrasound processors allows selective amplification of echoes from deeper structures. Current EUS processors allow the operator to vary the gain by depth.

Signal Processor

After TGC of the signal has occurred, additional signal processing is performed. The algorithms for signal processing performed differ among ultrasound processors and are closely held proprietary information. In general, some form of demodulation of the radiofrequency (RF) signal is performed to obtain an envelope of the RF signal, which is used to produce a B-mode image. In addition, processing can include threshold suppression to eliminate signals that are below an operator-specified threshold. Leading edge detection, peak detection, and differentiation are additional methods that can be employed by processors to improve image quality.[1]

IMAGING PRINCIPLES

Now that the basic principles of ultrasound physics and instrumentation have been introduced, an overview of imaging principles can be described.

Resolution

In ultrasound imaging, three different aspects of resolution must be considered: axial, lateral, and elevation or azimuthal resolution.

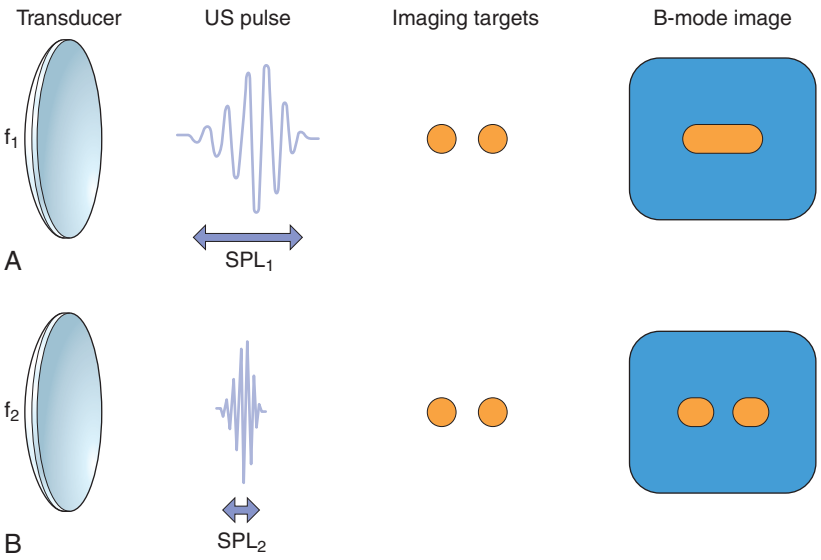


FIGURE 1.11 Concept of axial resolution. Axial resolution is limited by the spatial pulse length (SPL). This figure compares the axial resolution of two different ultrasound pulses with different frequencies ($f_1 < f_2$) and identical pulse lengths; therefore, $SPL_1 > SPL_2$. In **A**, the distance between the imaging targets is less than $SPL_1/2$, thus resulting in a B-mode image that is not able resolve the two discrete targets. In **B**, the distance between the imaging targets is greater than $SPL_2/2$, thus resulting in the ability to resolve the two discrete targets.

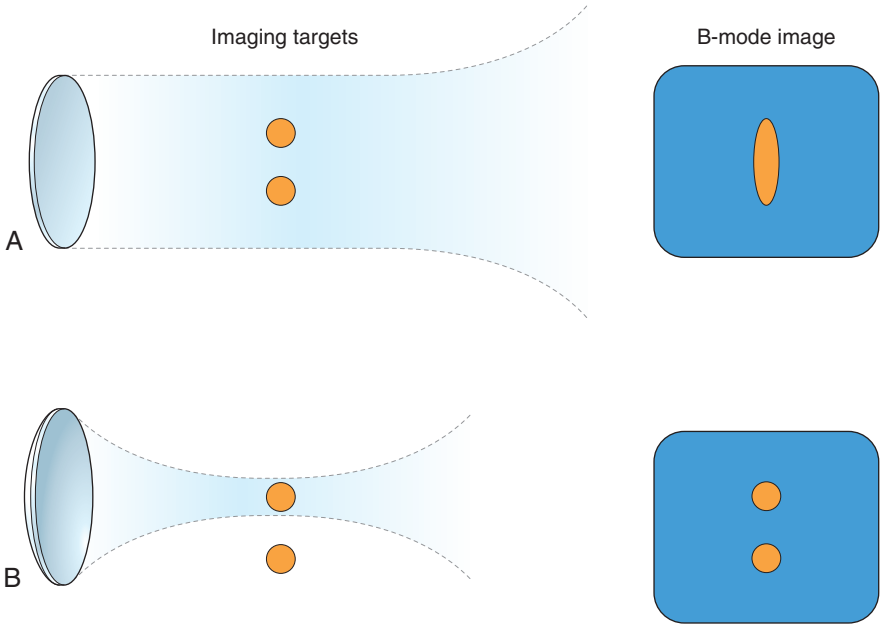


FIGURE 1.12 Concept of lateral resolution. Lateral resolution is determined by the ultrasound beam width. This figure compares the lateral resolution of an unfocused transducer (**A**) and a focused transducer (**B**) with apertures of the same diameter. The beam width of the unfocused transducer in **A** cannot resolve the two imaging targets; therefore, the two targets are displayed as one target on B-mode imaging. The beam width of the focused transducer in **B** is sufficiently narrow to resolve the two imaging targets. If the imaging targets were beyond the focus of the transducer in **B**, the broadened beam width would not be able to resolve the two objects, and the B-mode image would be similar to that in **A**.

Axial Resolution

Axial resolution refers to the smallest separation distance between two objects along the beam path that can be detected by the imaging system. Axial resolution is determined by the ultrasound frequency and the spatial pulse length (SPL) of the transmitted ultrasound pulse.[5] The SPL can be determined by the following equation:

$$SPL = \frac{c}{f} \times n \qquad (1.11)$$

where c is the speed of sound in tissue, f is the center frequency of the transmitted ultrasound pulse, and n is the number of cycles per pulse (typically four to seven cycles). The limit of axial resolution is equal to SPL/2. This equation demonstrates why using higher frequencies results in greater axial resolution (assuming that pulses have the same number of cycles per pulse). To illustrate this concept, two different ultrasound pulses with qualitatively different center frequencies and SPL are shown in Figure 1.11. Axial resolution is the most important property in imaging the layered structures of the gastrointestinal tract wall.

Lateral Resolution

The *lateral resolution* of an imaging system represents the ability to discriminate between two points that are in a plane perpendicular to the ultrasound beam. The beam width of the transducer determines the achievable lateral resolution and is a function of transducer size, shape, frequency, and focusing. Figure 1.12 illustrates the concept of lateral resolution.

Elevation Resolution

Elevation, or *azimuthal, resolution* relates to the fact that, although the image displayed is two dimensional, the actual interrogated

plane has a thickness associated with it. The factors governing elevation resolution are similar to those for lateral resolution. In fact, the elevation resolution for a focused, circular disk transducer (as used in the Olympus GF-UM series) is the same as for lateral resolution because of its circular symmetry. For the linear array transducers, the elevation resolution is determined by the beam width characteristics along the plane of imaging.

A-Mode Scanning

A-mode, or amplitude mode, scanning is obtained by the transmit/receive process described previously with an output yielding an RF line scan of the echoes detected along the axis of a stationary transducer after a pulse of ultrasound has been transmitted. The received signal by the transducer is amplified, yielding the A-mode signal (Fig. 1.13). This form of scanning, rarely used by the clinician, is the basis for all other modes of scanning including B-mode scanning. In addition, RF signal analysis is an important aspect of research in the area of advanced imaging techniques.

B-Mode Imaging

B-mode, or brightness mode, scanning results in additional signal processing and movement of the transducer either mechanically or electronically. A B-mode image is created by processing a series of A-mode signals (see Fig. 1.13). For each line in the B-mode image (corresponding to a single A-mode line scan), the digitized RF signal is demodulated, yielding an envelope of the RF signal.

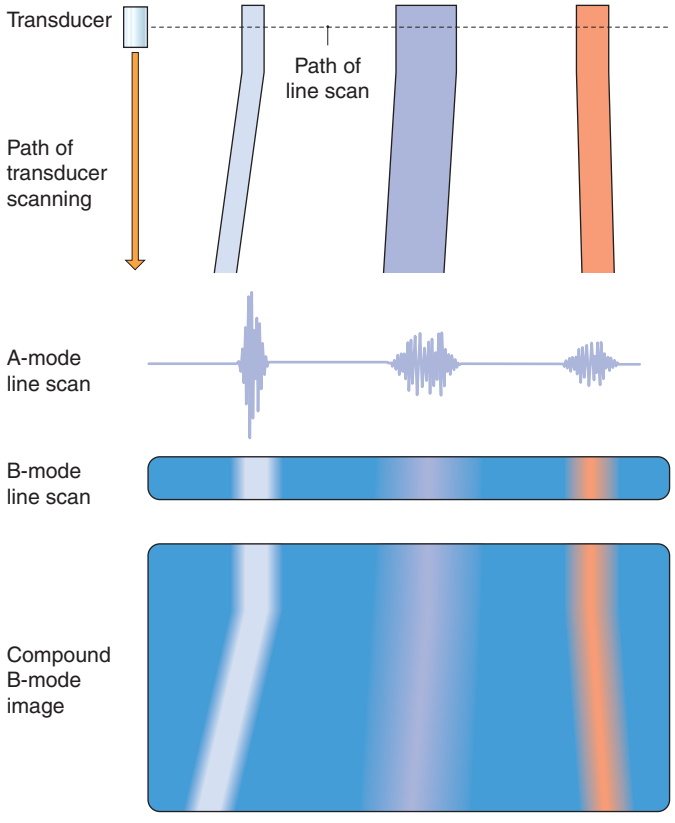


FIGURE 1.13 Conceptual representation of how A-mode line scans, B-mode line scans, and compound B-mode images are obtained. The transducer output is directed into the tissue determining the path of the line scan. An A-mode line scan is obtained after amplification of the received signals by the transducer. The B-mode line scan is obtained after demodulation and additional signal processing of the A-mode signal. The compound B-mode image is produced by obtaining multiple line scans by translating the path of the line scan. This can be accomplished either by mechanically scanning the transducer or by electronically steering a linear array transducer.

The amplitude of the demodulated signal is then used to determine the brightness of the dot corresponding to its location in the B-mode image. As the axis of the transducer output is translated (either mechanically or electronically), additional A-mode signals are obtained and processed, eventually yielding a compound B-mode image (see Fig. 1.13). EUS imaging systems generate a compound B-mode image.

DOPPLER

The Doppler effect is used in ultrasound applications to identify objects that are in motion relative to the transducer. In biologic applications, the reflective objects in motion are red blood cells. Doppler ultrasound is used in endoscopic ultrasonography (EUS) examinations to identify blood flow in vessels. The fundamental basis for the Doppler effect in ultrasound is that an object in motion relative to the source transducer will reflect an ultrasound wave at a different frequency relative to the frequency transmitted by the source transducer; this is termed the *Doppler shift*. The difference between the transmitted frequency and the shifted frequency is dictated by the velocity (v) of the object in motion relative to the transducer. The Doppler shift can be determined by the following equation:

$$f_D = \frac{2vf_t \cos\theta}{c} \qquad (1.12)$$

where f_D is the Doppler shift frequency, which is the difference between the transmitted and reflected frequencies; v is the velocity of the object in motion (red blood cells); f_t is the transmitted frequency; θ is the angle at which the object in motion is traveling relative to the direction of the source beam (Fig. 1.14); and c is the speed of sound in tissue (1540 m/sec). This equation illustrates why a Doppler shift is not detected if the transmitter is aimed perpendicular (90 degrees) to a blood vessel. At an angle of 90 degrees, Equation 1.12 demonstrates that $f_D = 0$, as cos 90 degrees = 0. Therefore, interrogation of a blood vessel should be at an angle other than 90 degrees, with the greatest Doppler shift detected when the object in motion is moving along the axis of the transmitted ultrasound wave (cos 0 degrees = 1 and cos 180 degrees = −1).

The different implementations of Doppler ultrasound include continuous-wave, pulsed-wave, color, and power Doppler.

Continuous-Wave Doppler

Continuous-wave Doppler represents the simplest configuration of Doppler ultrasound and requires two different transducers: a transmitting and a receiving transducer. The transmitting transducer produces a continuous output of ultrasound at a fixed

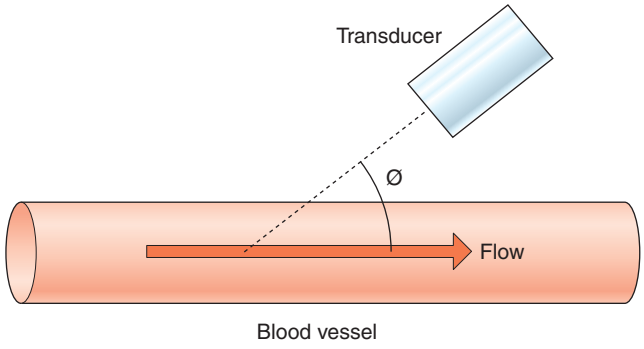


FIGURE 1.14 Conceptual image of Doppler measurements. The angle θ determines the strength of the Doppler signal. If θ is 90 degrees, then no Doppler signal can be detected.

frequency. The receiving transducer then receives the continuous signal. The transmitted and received signals are added, resulting in a waveform that contains a beat frequency that is equivalent to the Doppler shift frequency. Continuous-wave Doppler does not give any information regarding the depth at which the motion causing the Doppler shift is occurring.

Pulsed-Wave Doppler

Pulsed-wave Doppler was developed to obtain depth information regarding the location of the motion causing the Doppler shift. In addition, a pulsed-wave Doppler system required only a single transducer to transmit and receive ultrasound signals. The pulse length used for pulsed-wave Doppler is substantially longer than pulses used for imaging. Using electronic gating to time the interval between transmitting and receiving a pulse, this method allows the operator to interrogate a specific location along the axis of the transmitted ultrasound beam for motion. The output from pulsed-wave Doppler is usually in the form of an audible signal. The combination of pulsed-wave Doppler with B-mode imaging, termed *duplex scanning*, allows the operator to interrogate a specific location within a B-mode image.

Color Doppler

Color Doppler is a method of visually detecting motion or blood flow using a color map that is incorporated into a standard B-mode image. The principles of color Doppler are similar to those of pulsed-wave Doppler. However, a larger region can be interrogated, and detected blood flow is assigned a color, typically blue or red, depending on whether the flow is moving toward or away from the transducer. Frequency shifts are estimated at each point at which motion is detected within an interrogated region, thus yielding information on direction of motion and velocity. Shades of blue or red are used to reflect the relative velocities of the blood flow. All stationary objects are represented on a gray scale, as in B-mode imaging. The benefit of color Doppler is that information on the direction and relative velocity of blood flow can be obtained. Color Doppler is limited by its dependence on the relative angle of the transducer to the blood flow.

Power Doppler

Power Doppler is the most sensitive Doppler method for detecting blood flow. Again, the basis for power Doppler is similar to that for pulsed-wave and color Doppler. However, in processing the Doppler signal, instead of estimating the frequency shift as in color Doppler, the integral of the power spectrum of the Doppler signal is estimated. This method essentially determines the strength of the Doppler signal and discards any information on velocity or direction of motion. This method is the most sensitive for detecting blood flow and should be used to identify blood vessels when information on direction of flow and velocity is not needed.

IMAGING ARTIFACTS

Image artifacts are findings on ultrasound imaging that do not accurately represent the tissue being interrogated. An understanding of the principles of ultrasound can be used to explain image artifacts. It is important to identify and to understand the basis for image artifacts, to interpret ultrasound images correctly. Some common ultrasound imaging artifacts are discussed.

Reverberation

Reverberations occur when a single transmitted pulse undergoes multiple reflections from a strong reflector over the time of a single line scan. The transmitted pulse first is reflected by the reflector back to the transducer. The reflected pulse then is reflected off the transducer back toward the reflector. This sequence is repeated, and each time a reflection returns to the transducer a signal is generated, until the signal has been attenuated to the point where it is not detected by the transducer or the line scan has been completed (Fig. 1.15). The duration of the line scan depends on the depth of imaging. A reverberation artifact can be identified by the equal spacing between hyperechoic (bright) bands, with decreasing intensity as the distance from the transducer increases. Reverberation artifact from a mechanical radial scanning ultrasound probe is demonstrated in Figure 1.16. This particular reverberation artifact is also called the *ring artifact*.[6] The reflections are from the housing of the ultrasound transducer. Reverberation artifacts are also seen with air-water interfaces, such as bubbles (Fig. 1.17).

Reflection (Mirror Image)

The *reflection*, or *mirror image, artifact* occurs when imaging near an air-water interface such as a lumen filled partially with water.[7]

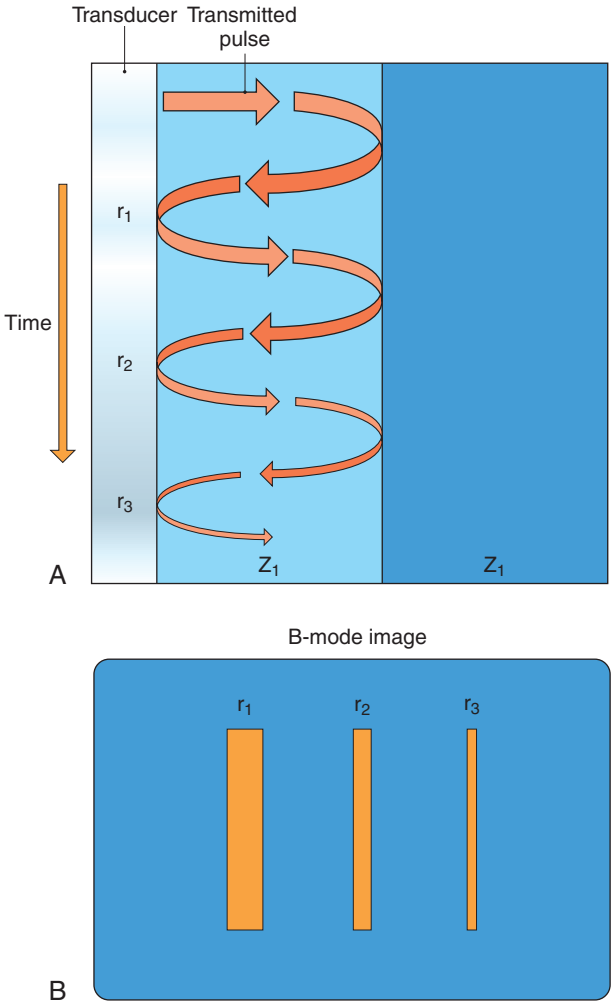


FIGURE 1.15 Reverberation artifacts result from strong reflections of a transmitted pulse from an interface with a large impedance mismatch (e.g., air-water interface). A, Depiction of how a transmitted signal is reflected by an interface with a large impedance mismatch. The reflected signal is detected by the transducer and is redirected back into the medium. This sequence can be repeated multiple times, depending on the depth of imaging. The reflected signal is progressively attenuated. **B,** The corresponding B-mode image from the reverberation depicted in **A**. The reflected signals (r_1, r_2, and r_3) are spaced equally.

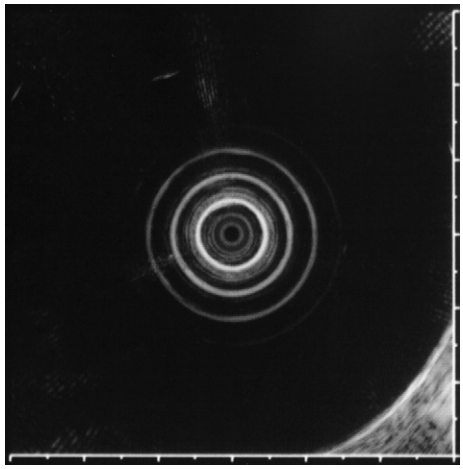


FIGURE 1.16 EUS image of reverberation artifact resulting from multiple reflections from the transducer housing. The concentric rings are equally spaced, with the intensity of the rings decreasing as the distance from the transducer increases.

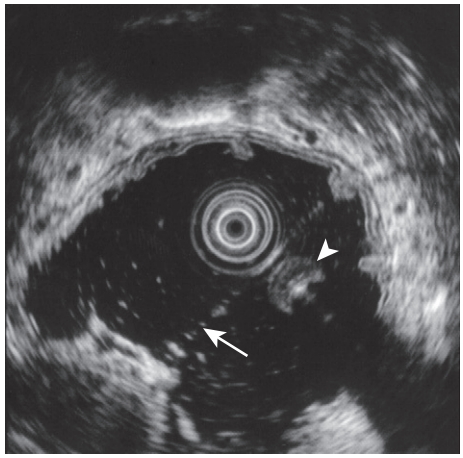


FIGURE 1.18 Reflection or mirror image artifact. A mirror image of the transducer *(arrowhead)* and gastric wall is produced by the reflection of the ultrasound signal from the interface between water and air *(arrow)* within the gastric lumen.

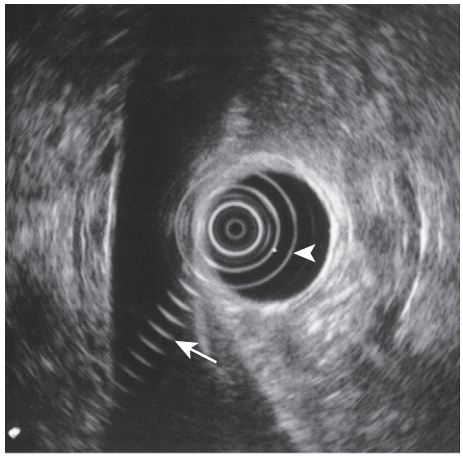


FIGURE 1.17 EUS image of reverberation artifact *(arrow)* resulting from multiple reflections from an air bubble in the water-filled balloon. The intensity of the artifact does not decrease as rapidly as the reverberation artifact *(arrowhead)* from the transducer housing. This is because the impedance mismatch of the air-water interface is much greater than the transducer housing interface, with resulting reflected signals of greater intensity.

In this situation, transmitted ultrasound pulses reflect off the air-water interface (because of the significant impedance mismatch). The result is the creation of multiple reflections that are eventually received by the transducer and lead to production of a mirror image opposite the air-water interface (Figs. 1.18 and 1.19). This artifact is easily identified and can be avoided by removing air and adding more water into the lumen.

Acoustic Shadowing

Acoustic shadowing is a form of a reflection artifact that occurs when a large impedance mismatch is encountered. When such a mismatch is encountered, a majority of the transmitted pulse is reflected with minimal transmission. This results in a hyperechoic signal at the interface with no echo signal detected beyond the interface, thus producing a shadow effect. This finding is useful in diagnosing calcifications in the pancreas (Fig. 1.20) and gallstones in the gallbladder (Fig. 1.21).

Acoustic shadowing can also result from refraction occurring at a boundary between tissues with different acoustic velocities, especially if the boundary is curved (e.g., tumor or cyst). As discussed earlier, refraction of an ultrasound beam occurs when the angle of incidence is not normal to the boundary between tissues with different acoustic velocities, with resulting bending of the ultrasound beam. Because the ultrasound beam is redirected at this boundary, some regions of the tissue are not interrogated by the ultrasound beam, and the result is an acoustic shadow (Fig. 1.22).[8]

Through Transmission

Through transmission is the enhancement of a structure beyond a fluid-filled structure such as a cyst. The structure beyond a fluid-filled structure demonstrates increased enhancement because the intensity of transmitted ultrasound undergoes less attenuation as it propagates through the cyst and as the reflected signal returns to the transducer. This finding is useful in diagnosing fluid-filled structures such as a cyst or blood vessel (Fig. 1.23).

Tangential Scanning

If the thickness of a structure is being measured, it is important that the ultrasound beam is perpendicular to the structure. If the transducer is at an angle other than 90 degrees to the structure, the thickness will be overestimated.[9] This is particularly important when assessing the thickness of the layers of the gastrointestinal (GI) tract wall and in staging tumors of the GI tract. On radial scanning examination of the GI tract, this artifact can be identified because the thicknesses of the wall layers will not be uniform throughout the image (Fig. 1.24). When staging tumors involving the GI tract wall, tangential imaging can result in overstaging of the tumor. To avoid this artifact, the endoscope tip should be maneuvered to maintain the proper orientation such that the plane of imaging is normal (at 90 degrees) to the structure being imaged.

Side Lobe Artifacts

Side lobes are off-axis secondary projections of the ultrasound beam (Fig. 1.25).[3] The side lobes have reduced intensities compared with the main on-axis projection; however, they can produce image artifacts. Usually, on-axis reflections are greater in intensity than side lobe reflections and thereby obscure any

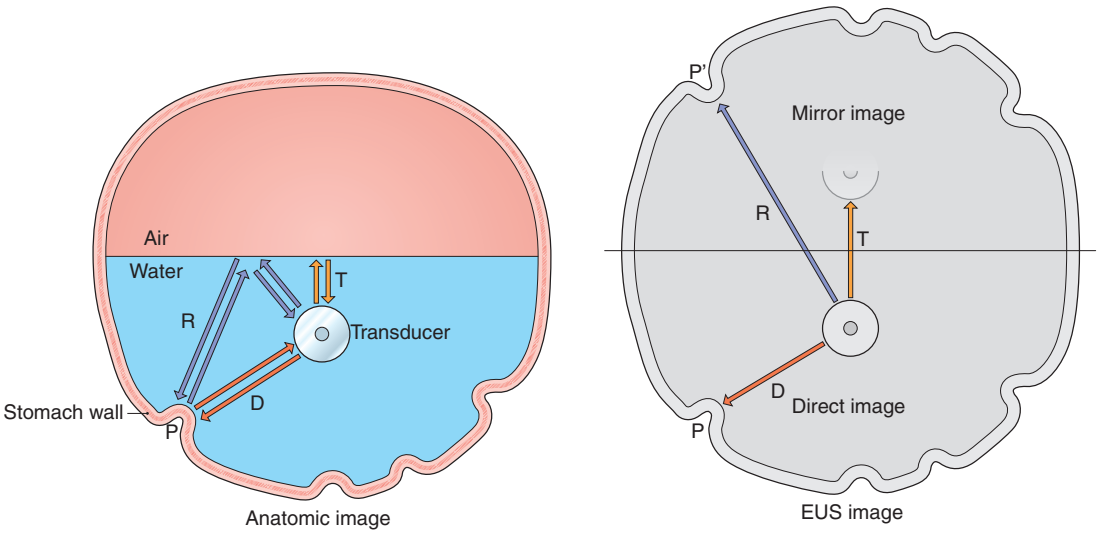


FIGURE 1.19 Reflection from an air-water interface produces a mirror image artifact. Because of the large impedance mismatch between water and air, an ultrasound signal that interacts with an air-water interface is reflected almost completely. The figure on the *left* is an illustration of an ultrasound probe imaging the gastric wall with an air-water interface. The path denoted by D directly images location P along the gastric wall. The path denoted by R images location P because of a reflection from the air-water interface. The path T images the transducer because of a reflection from the air-water interface. The figure on the *right* is an illustration of the resulting ultrasound image. The ultrasound processor registers the location of the image by the direction of the transmitted pulse and the time it receives the reflected signal. The processor accurately registers point P, resulting from the reflected signal from path D; however, the signal from path R is incorrectly registered as point P', with a resulting mirror image appearance. In addition, the reflected signal from path *T* results in shadowing artifact in the mirror image.

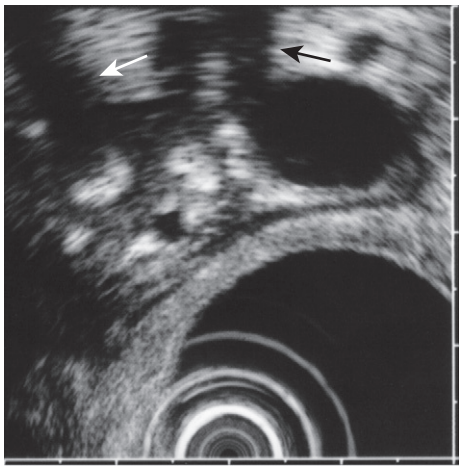


FIGURE 1.20 Shadowing artifact *(arrows)* resulting from calcifications in the pancreas.

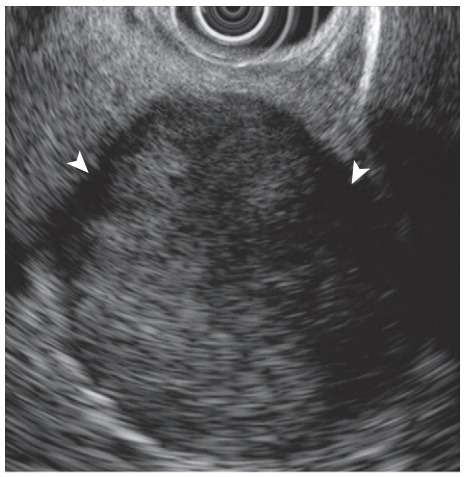


FIGURE 1.22 Acoustic shadowing *(arrowheads)* resulting from refraction from an interface between normal tissue and tumor.

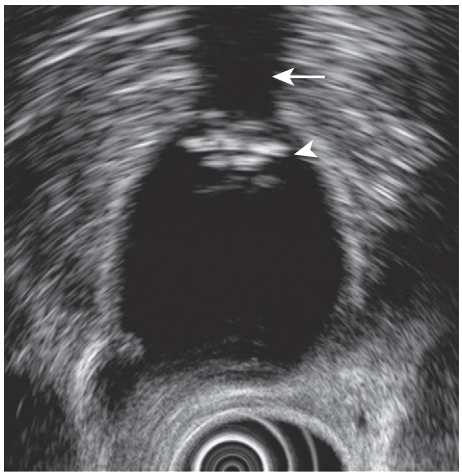


FIGURE 1.21 Shadowing artifact *(arrow)* resulting from gallstones *(arrowhead)*.

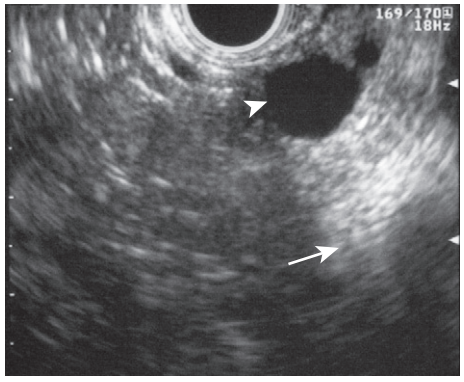


FIGURE 1.23 Anechoic cystic lesion *(arrowhead)* demonstrating enhancement beyond the cyst relative to other structures that are of similar distance from the transducer. This artifact is also called *through transmission*.

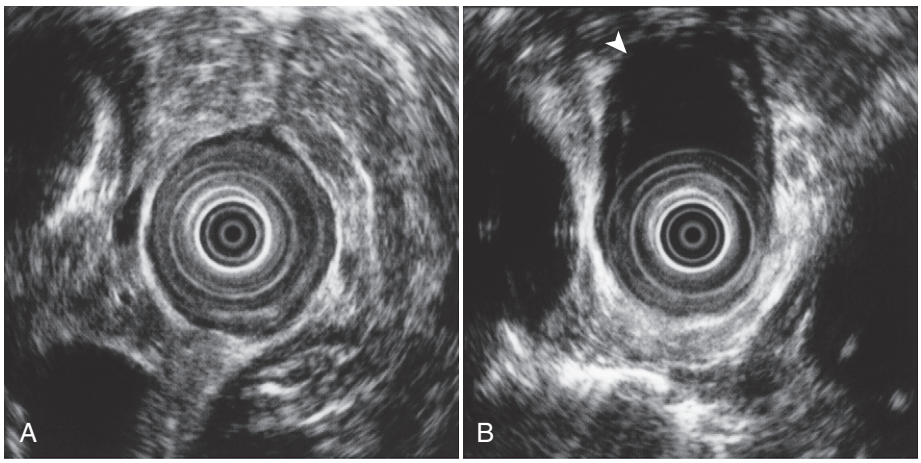


FIGURE 1.24 Tangential imaging artifact. A, Normal imaging of a hypertrophic lower esophageal sphincter in a patient with achalasia. **B,** Tangential imaging of the same lower esophageal sphincter (note that the balloon was not inflated during acquisition of this image). The gastrointestinal (GI) tract wall layers are distorted and are not uniformly thick circumferentially, a finding suggesting that the transducer is not imaging a normal GI tract wall. As a result, areas of abnormal thickening are noted on imaging and can give the incorrect appearance of a tumor in the GI tract wall *(arrowhead)*.

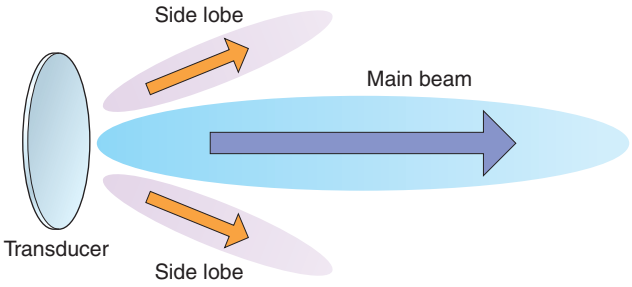


FIGURE 1.25 Side lobes represent secondary projections off-axis from the main beam. Side lobes have lower intensities than the main beam, but they can still produce back-reflected signals from the tissue of sufficient intensity to be detected by the transducer. However, the transducer assumes that all back-reflections originate from the main lobe. Therefore, image artifacts can result from side lobe projections.

side lobe reflections. However, during imaging of an anechoic structure, the reflected ultrasound energy from a side lobe can be of sufficient intensity to yield a detected signal that is then interpreted by the processor as an on-axis reflection.[10] A side lobe artifact is recognized when the hyperechoic signal does not maintain its position within an anechoic structure such as a cyst or the gallbladder. It may be misinterpreted as sludge in the gallbladder or a mass within a cyst.[6] Figure 1.26 is an image of a side lobe artifact within the gallbladder. Repositioning of the transducer causes the artifact to disappear.

SUMMARY

The basic principles of ultrasound physics and instrumentation are reviewed in this chapter. In addition, common imaging artifacts are presented and explained by applying the basic principles of ultrasound. These principles should provide an understanding of the capabilities and limitations of ultrasound and how ultrasound images are formed. Understanding these principles will aid the endosonographer in obtaining accurate, high-quality images.

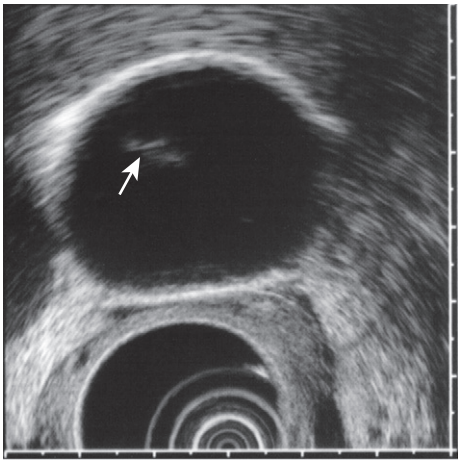


FIGURE 1.26 Side lobe artifact identified in the gallbladder *(arrow)*. Repositioning of the transducer results in disappearance of this signal.

REFERENCES

1. Hedrick WR, Hykes DL, Starchman DE. *Ultrasound Physics and Instrumentation*. 3rd ed. St. Louis: Mosby; 1995.
2. Duck FA. *Physical Properties of Tissue*. London: Academic Press; 1990.
3. Christensen DA. *Ultrasonic Bioinstrumentation*. New York: John Wiley; 1988.
4. Shung KK, Thieme GA. *Ultrasonic Scattering in Biological Tissues*. Boca Raton, FL: CRC Press; 2000.
5. Harris RA, Follett DH, Halliwell M, et al. Ultimate limits in ultrasonic imaging resolution. *Ultrasound Med Biol*. 1991;17:547–558.
6. Kimmey MB. Basic principles and fundamentals of endoscopic ultrasound imaging. In: Gress F, Bhattacharya I, eds. *Endoscopic Ultrasonography*. Malden: Blackwell Science; 2001:4–14.
7. Grech P. Mirror-image artifact with endoscopic ultrasonography and reappraisal of the fluid-air interface. *Gastrointest Endosc*. 1993;39:700–703.
8. Steel R, Poepping TL, Thompson RS, et al. Origins of the edge shadowing artifact in medical ultrasound imaging. *Ultrasound Med Biol*. 2004; 30:1153–1162.
9. Kimmey MB, Martin RW. Fundamentals of endosonography. *Gastrointest Endosc Clin N Am*. 1992;2:557–573.
10. Laing FC, Kurtz AB. The importance of ultrasonic side-lobe artifacts. *Radiology*. 1982;145:763–768.

CHAPTER 2 EQUIPMENT

John Meenan | Charles Vu

Key Points

Compatibility between scope and processor does not exist across every format of radial and linear EUS.

The choice of equipment should be based on the type of service that is to be provided, not the type of service that one would like or hope to provide.

The operating characteristics of needles for interventional EUS vary. It is important to try out several makes to determine which one is the most compatible with the way in which the center performs EUS.

Archiving and video editing are important features of practicing EUS.

INTRODUCTION

Providing an endoscopic ultrasonagraphy (EUS) service is demanding with respect to meeting the needs of those drawing on it and ensuring quality. Furthermore, endoscopic ultrasound equipment is expensive both to purchase and to maintain. For these reasons, focused and objective thought must go into developing such a service. It is not just an adjunct to endoscopic retrograde cholangiopancreatography (ERCP).

Before establishing an EUS service, the endosonographer must know why he or she wants to do it and where the true demand lies. Although the products available from the main manufacturers of EUS equipment are largely equivalent, subtle differences in specification can have a major impact on utility in certain disorders.

ESTABLISHING AN EUS SERVICE

Many of the practitioners who are setting up an EUS service are, one hopes, coming from an established facility where they have trained. Such services do not appear out of the blue or exist because of good luck or the presence in that institution of other successful units. It takes thought and attention to detail to found and sustain a new EUS service.

Several premises hold true across the globe for the founding of an EUS service. The single most important question to be answered is this: "What is the true demand for EUS?" One must not confuse a personal wish with a local imperative.

The range of standard indications for EUS is broad, from staging esophageal cancer to defining pancreaticobiliary disease. Therefore, some questions will need to be answered: If one works with upper esophageal and gastric surgeons, what will they want from EUS: a simple description of T stage and putative N stage or a lymph node biopsy? How many patients undergo magnetic resonance imaging (MRI) for possible choledocholithiasis? How many mature pancreatic pseudocysts does one really see in a year? Is backup available to permit one to attempt and fail at complex biliary or pancreatic duct drainage? Endosonographers should discuss these issues with colleagues, search whatever data bases are available, and talk with potential referring physicians, rather than guessing. It is also important to talk with thoracic practitioners because plans to introduce endobronchial ultrasound will potentially lower costs through a shared ultrasound platform. Equally, there may be some shared ground with endoanal services or, more broadly, with the imaging unit.

The numbers can reveal certain things, such as the key disorders likely to be encountered by EUS practitioners and the related financial implications. Many articles on the cost effectiveness of EUS in certain settings have been published, but the results of such work may not translate to other units or regions. Practitioners should do their own math. They should also talk with colleagues and local professional organizations about how they approach coding to maximize returns. Certain coding techniques can change the landscape of the possible. The numbers can also help one to decide what type of equipment to consider purchasing.

Who is to perform EUS? In most countries, the responsibility for EUS falls to gastroenterologists, but surgeons and radiologists also perform this procedure. No particular professional background has been shown to confer any advantage in proficiency. Indeed, in the United Kingdom, some centers have developed nurse-led EUS services. The presence of an ultrasound machine in the room does not automatically require involvement of a radiologist.

Dissemination of knowledge is the life blood of any service. It is possible, of course, to praise the benefits of any new service and garner test referrals, but one must be wary and be sensible. In talking about the strengths of EUS, it is important to give equal weight to the weaknesses. Using case studies can be a good way to get this message across and to preempt procedural failures when they are sure to happen. Whereas the weaknesses of computed tomography (CT) are largely ignored, those of a new EUS service are not. Even at the best of times, pancreatic cancer is improperly staged with EUS in one case out of five. That CT may have an equally prominent Achilles heel provides no protection against an unfavorable reputation.

Establishing an EUS service is not just about numbers of cases, revenues generated, or personal wishes. The available facilities, endoscopy staff, local cytopathology skills, and interactions with referring physicians all have a dramatic impact on the success or failure of the endeavor.

The training of endoscopy room staff is central to reducing running costs. For example, returns for repairs are expensive and are likely to interrupt services. Staff training also ensures that

procedures are optimized. It is easy to render a simple FNA procedure useless through poor teamwork. Some of the responsibility for this training falls on the practitioner, and some must be requested of the scope manufacturer at the time of equipment purchase. It is important to talk with both nursing and technical staff members about their EUS training needs.

The space required and the physical layout of the endoscopy room should be familiar to all EUS practitioners. However, when using equipment from different manufacturers on a trial basis, one must make sure that there is still room to allow for FNA specimens to be prepared comfortably. Equipment is discussed later in this chapter, but space-saving ultrasound processors are usually inferior to free-standing units.

An EUS service attracts cases from surgical departments at other institutions. What is the endosonographer's role? Is it to just perform a procedure and forward results, or will the endosonographer proffer an opinion on management? These questions are important to answer because giving opinions can confuse and upset patients and irritate their referring physicians. If the endosonographer is to provide an opinion, then it will be necessary to see the patient in consultation first and allow time to review investigation results. Usually, a recommendation for management of less common lesions such as subepithelial lesions is not contentious, but opinions may differ for pancreatic cysts or epithelial high-grade dysplasia, for example. One must tread carefully.

The difficult issue of cytopathology support must be grasped from the start, particularly because all EUS services should offer fine-needle aspiration (FNA). The days of "look but not touch" are numbered. One can obtain good cytopathologic results by preparing samples for later evaluation, but the literature indicates that results are better if a cytologic technician (not necessarily a cytologic pathologist) is present. The cytologic technician's role is to prepare high-quality specimens and comment on cellularity (i.e., adequacy), so the endosonographer knows when to stop the procedure. These technicians are not there to facilitate an immediate diagnosis. A rushed diagnosis does no one any favors and eventually backfires.

The endosonographer should talk to the local pathology service and see what experience they have, what can they provide, and whether use of their service is feasible or cost effective. Transenteric FNA is not the same as other forms of cytologic examination because of the presence of mucus. As a result, there is a learning curve (probably ≈60 cases) before pathologists stop diagnosing everyone as having a well-differentiated mucus-secreting tumor. If the technician cannot come to the procedures, the endosonographer should go to the technician and learn the optimal way of spreading slides and the laboratory's preferred method of preserving samples (e.g., in fixative, in buffered saline).

No matter how competent and well intentioned the endosonographer and staff are, poor administration, with respect to ease of booking, reliability of contact, and flexibility, will have a negative impact on the EUS service. The responsibility of the endosonographer is not confined solely to performance of the EUS procedure.

Poor communication can kill a service. The referring physician must understand what the endosonographer needs to know: degree of dysphagia, exact site and size of the lesion, unexpected findings on CT and other imaging methods, use of anticoagulants and antiplatelet agents, and, most important, whether FNA is to be done. When talking to the referring physician, the endosonographer should emphasize such points, along with the risks of seeding, for example. In addition, one must be precise when writing reports, and give exact sizes, numbers, and positions. Unfortunately, no good reporting systems are widely available for EUS, so most likely a module within a generic reporting system will have to be adapted. The endosonographer must e-mail or fax reports to the referring physician and ensure that all pathology results are forwarded in a timely fashion. If a result is particularly time sensitive, the endosonographer should phone or text (SMS) the referring physician. Again, one must be very careful in discussing results and their implications with the patient at the time of discharge if the patient is coming from another service.

The scheduling of EUS procedures is affected by factors such as number of scopes available, level of skill, likely presence of a trainee, and type of sedation administered. In general terms, an EUS procedure with FNA can be scheduled every 30 minutes, with 60 to 90 minutes allowed for recovery to discharge with the use of midazolam and an opiate. If the endosonographer is training fellows in EUS, fewer procedures are better than too many. The time and quality of teaching trump the quantity of cases. When scheduling procedures, one should give an indication of which endoscope is likely to be used, to allow proper list planning. Scheduling patients for EUS followed by ERCP at the same sitting can be ideal for patients with cancer, but this approach is wasteful of time slots when common bile duct stones are suspected.

EQUIPMENT

EUS equipment may be impressive in terms of electronic sophistication, but it is not kind to endoscopists. It is expensive, lacks versatility, and, when not bulky and fragile, it is small and exquisitely fragile.

Purchasing of equipment usually follows a long process of justifying a local need to obtain one-time access to limited funds. It is ironic that, more often than not, this project is led either by someone who has not found his or her endosonographic feet or by someone who sees a need and can make things happen but will not be involved in the service itself.

There is no right or wrong EUS equipment. The products of the main manufacturers are equivalent. There is, however, right and wrong equipment to meet a specific clinical requirement. It is perfectly feasible to run EUS equipment from one manufacturer in a room where the standard endoscopes are provided by another, but mixing EUS equipment from two different manufacturers does not work.

General

Echoendoscopes fall broadly into two categories: radial (or "sector") and linear (or "convex array"). Both electronic and mechanical (now largely superseded) formats are available in each category. Specialty probes designed for specific clinical needs provide bespoke tools to investigate subepithelial masses and pancreatobiliary ductal disease (mini-probes), esophageal and proximal gastric cancer (Olympus slim-probe and Hitachi backloaded probe), the colon proximal to the rectum (Olympus colonic echoendoscope), and the anal canal.

The coupling of electronic echoendoscopes to middle-range and upper-range standard ultrasound processors has brought to EUS the added dimensions of Doppler and power flow imaging, three-dimensional rendering, tissue elastography, the ability to use contrast agents, and indeed any future development in mainstream ultrasonography. It also brings many more illuminated buttons, most of which are ignored. The key features to look for remain high image quality and the feel of the scope in one's hands.

Radial echoendoscopes provide circumferential views at right angles to the shaft of the scope, similar to those provided by CT scans. This similarity to generally appreciated views of the gastrointestinal tract makes this format attractive to most trainees and endosonographers.

The linear format of EUS yields views more analogous to those obtained with transabdominal ultrasound. Because the view is in the same line or plane as the scope shaft, images are blinkered, and orientation is more difficult. It is very easy to feel lost when

landmarks are not visible. This perception of difficulty, fueled by a general lack of exposure to transabdominal ultrasound among most clinicians, has relegated linear EUS for many practitioners to being an interventional tool only. These practitioners are uncomfortable with the use of EUS beyond an unduly narrow range of indications. Consequently, linear EUS as a stand-alone, comprehensive modality is underappreciated. EUS, however, has moved resolutely in the direction of linear endoscopes. No one has shown that it is more difficult to learn linear than radial EUS, so do not be held back by the prejudices and weaknesses of others.

Radial Echoendoscopes

The three major manufacturers (Olympus, Hitachi-Pentax, and Fujinon) all offer electronic radial endoscopes with 360-degree fields of view that operate from an ultrasound platform common to that manufacturer's linear endoscopes. The scopes handle differently. Some are more flexible than others. Therefore, in equipment trials, the endosonographer must pay attention to the way in which the scope meets the challenges of passing into the second part of the duodenum. Just because a scope is forward viewing does not mean it is necessarily easier to use.

The endosonographer should look carefully at the shape of the scope because measurements given for distal tip diameter may be misleading; some scopes have a large bulge immediately behind the tip that cannot pass through a stricture. In addition, each manufacturer has a different way of controlling the distal water-filled balloon. The Olympus scope has a two-step button, whereas the Fujinon scope has a separate syringe channel with a knob directing water flow from the bowel lumen to the balloon. In practice, such design variations make little difference in ease of use.

Olympus offers both an electronic radial scope (Olympus GF-UE160; Fig. 2.1A; scanning at 5, 6, 7.5, and 10 MHz) and two mechanical formats: an older GF-UM130 (scans at either 7.5, and 12 MHz or 7.5 and 20 MHz) and the newer GF-UM160 (scans at 5, 7.5, 12, and 20 MHz; lighter model because the motor is in the shaft, not on top of the scope; see Fig. 2.1). All these scopes are luminally oblique-viewing scopes, so they cannot be relied on to substitute for a standard gastroscope fully. Balloon filling and emptying are achieved through ergonomically helpful dual-step suck and blow buttons. Again, all these scopes have a small accessory channel capable of taking bronchoscopy-size mucosal biopsy samples; an elevator lifts the forceps into view.

The continuing sale of mechanical scopes in an electronic age requires some explanation. These scopes provide images as clear as those reported with their electronic successor, and generally they tend to be cheaper. However, mechanical scopes do not support Doppler imaging and until recently required a stand-alone ultrasound processor that cannot be used for linear scopes. This disadvantage was addressed by the introduction of the dual-format EU-ME1 processor (see later).

Although mechanical scopes are robust and capable of a long clinical life, their dual requirement for a drive shaft and an exposed oil bath housing may be perceived to be inherent weaknesses. In practice, the mechanical nature of these scopes does not carry any greater susceptibility to breakdown. Care must be exercised, however, not to crush or dislocate the oil bath during placement or removal of the balloon. This problem is potentially significant in units with many trainees. The development of a bubble and the resulting diffuse degradation in the quality of the ultrasound image are signs that the oil bath requires replenishment; this may occur once or twice in a year.

Olympus scopes have one of two identification numbers. The more common 100 series scopes, available in most countries, have color CCD chips, whereas the 200 series scopes (mainly available in Japan and the United Kingdom) have black and white chips that permit narrow band imaging.

Pentax was the first company to market an electronic radial instrument. The initial scope was limited by an incomplete field of ultrasound view (270 degrees; Pentax-Hitachi EG-3630UR). This scope was replaced by a full 360-degree viewer, which scans at 5, 7.5, and 10 MHz (Pentax-Hitachi EG-367OURK; see Fig. 2.1B). Endoscopically, it is a forward-viewing scope (140 degrees), but this advantage is offset by an inability to retroflex fully; again, this instrument does not reliably replace a standard gastroscope for complete luminal inspection. It has a biopsy channel that can take standard-size mucosal biopsy forceps.

Fujinon offers the slimmest (11.5-mm) and most endoscopically flexible electronic radial echoendoscope (EG-530UR; 5, 7.5, 10 and 12 MHz; see Fig. 2.1C) that has forward luminal views and also permits 360-degree ultrasound scanning.

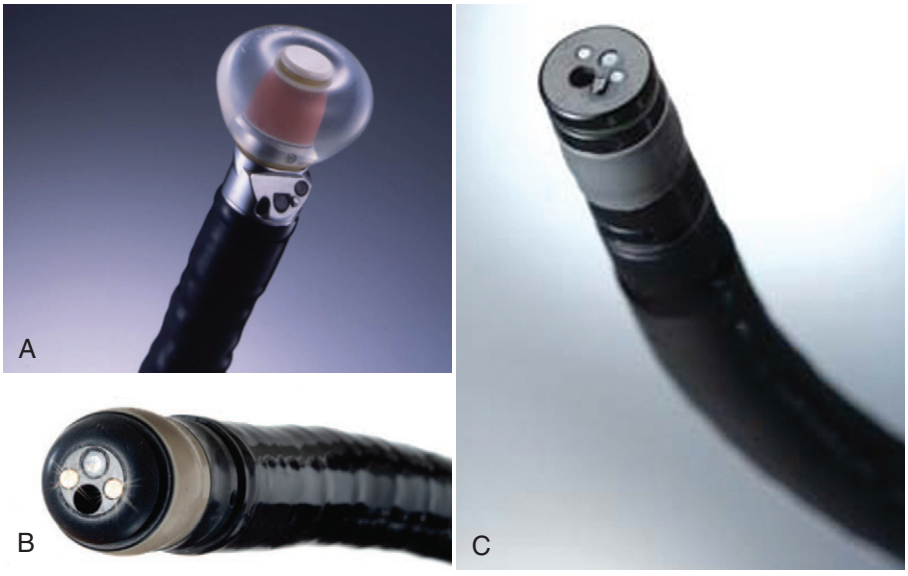


FIGURE 2.1 Radial echoendoscopes. A, Olympus GF-UE160. (Olympus America Inc., Center Valley, CA.) **B,** Pentax-Hitachi EG-367OURK. (Pentax Medical Company, Montvale, NJ.) **C,** Fujinon EG-53OUR. (Fujinon Inc., Wayne, NJ.)

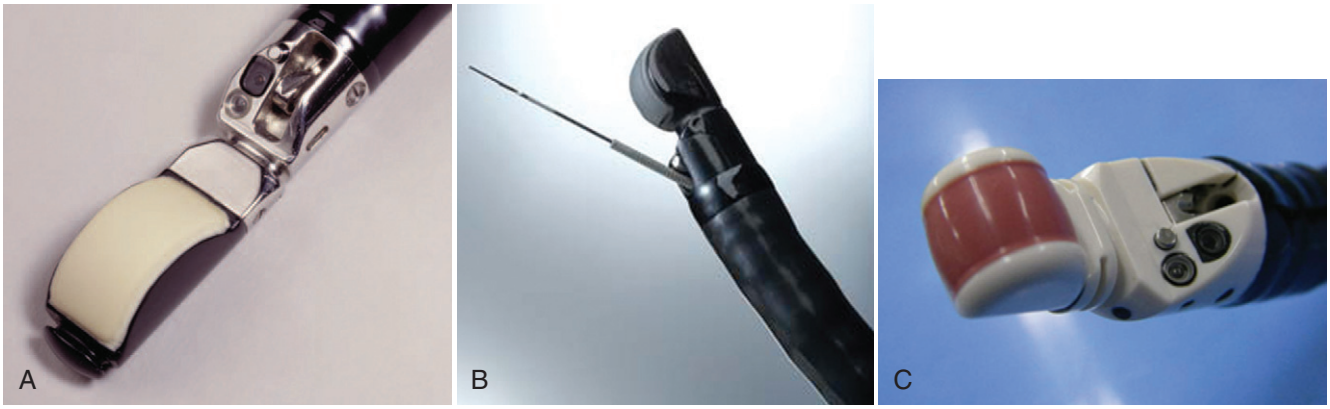


FIGURE 2.2 Linear echoendoscopes. A, Pentax EG-387OUTK. **B,** Fujinon EG-530UT. **C,** Olympus UCT180/UCT260.

Linear Scopes

The Pentax FG-32, launched in 1991, was the standard linear echoendoscope for many years. The EUS transducer sited distal to the viewing lens is gently curved, similar in shape to those used for transabdominal studies, to give a 120-degree field of ultrasonic view. The range has been expanded, by offering wider-bore channels and the presence of an elevator. Biopsy channels range in size from 2.0 to 3.8 mm (fiberoptic models: FG-34UX [2-mm channel] and FG-38UX [3.2-mm channel]; video models: EG-363OU [2.4-mm channel] and EG-383OUT [3.8-mm channel]). The smaller channel format is designed for the passage of FNA needles alone; the larger-bore scope permits placement of a 10-Fr stent (under ideal circumstances with a straight scope). The introduction of the Pentax color chip endoscope processor (EPK range) was matched by the introduction of a further linear echoendoscope (EG-387OUTK; Fig. 2.2A), which is now the standard model. It has an elevator for needle guidance and again has a 3.8-mm accessory channel. The older Pentax instruments have an extra control knob on the handle to redirect the suction and air and water controls to either lumen or balloon.

The Fujinon EG-530UT (see Fig. 2.2B) linear scope also has a 3.8-mm working channel and an elevator.

The Olympus linear echoendoscope has a pea-like tip transducer that allows for a 180-degree scanning plane. The two models are differentiated by accessory channel size: 2.8 mm (GF-UCT240P/140P-AL5) and 3.7 mm (GF-UCT240/140-AL5). Both scopes have elevators to assist needle guidance. The latter scope is said to be capable of deploying a 10-Fr stent; however, any angulation of the scope tip required to obtain appropriate views lessens the functional diameter of the accessory channel and makes passage of large-bore stents difficult. It could be conjectured that performing FNA with the larger-channel scope would be more problematic because of wobbling of the needle within the channel; in practice, however, this does not occur. As with the Pentax-scopes, there is no difference in actual scope size between the limited FNA versions and the larger-bore version of these Olympus scopes.

Olympus is scheduled to launch an updated linear scope (GF-UCT180/UCT260; see Fig. 2.2C) that will offer a new transducer tip as well as detachable cables. Much interest has been shown in another echoendoscope, the prototype, snub-nosed forward-viewing scope, designed especially for therapeutic procedures such as pseudocyst drainage. No information is available on the way in which the shape of this scope may cope with the demands of pancreatic tumor staging, which requires comprehensive views, including views of the uncinate process. This scope has no elevator, but its field of view makes it more "needle friendly" than standard scopes.

The Toshiba PEF-708FA linear echoendoscope handles well and allows views through a wide range of frequencies from 3 to 13 MHz. The lower frequency allows for greater depth of view in inspecting the liver. This scope is promoted for having the advantage of not requiring a balloon. Whether a balloon is required with any linear scope is a moot point, however, because of the constant pressure apposing the scope tip with the mucosa.

All the linear scopes mentioned earlier are electronic in format. The Olympus mechanical "linear" echoendoscope (GUMP) represents a very clever variation on the mechanical radial scope. If the problem with the radial scope is that the plane of view is perpendicular to the scope tip, then why not adjust the mirror so that it rotates in another plane and allows for a linear-type view? The resulting GUMP echoendoscope (GF-UMD240/140P) provides an impressive, although largely redundant, 270-degree linear view. It can be plugged into the same Olympus processor as the older mechanical models. However, the scope tip is bulbous, and concerns have been raised about depth of view. Moreover, this scope has no facility for Doppler imaging. This scope is certainly clever but essentially poor in performance.

EUS Processors

There is little to separate the various scope offerings available from the major companies. This can also be said, although perhaps less so, of the processors required to drive these instruments.

Compatibility between radial and linear systems is the standard. Both Olympus and Pentax run their scopes from freestanding standard ultrasound machines (Aloka and Hitachi, respectively), whereas Fujinon uses a proprietary machine (Fujinon SU-7000). This is not necessarily a problem, but it is important to pay attention to image quality during equipment trials.

If endobronchial EUS (EBUS) is to be performed (currently offered by Pentax and Olympus only), then the choice of platform is more limited. Furthermore, an additional processor may be required to allow the use of some specialty probes. This requirement differs depending on manufacturer; the devil is very much in the details. Olympus sees choice as a virtue, but for most practitioners it is problematic. Perhaps the best solution is to abandon radial EUS and dive resolutely into the world of linear ultrasound. Olympus has discontinued their collaboration with Philips to provide ultrasound platforms for echoendoscopes.

As mentioned earlier, Olympus has a broad range of radial scopes. If money is not a major issue, or if one does not have old mechanical scopes that must be kept in use, then it makes sense to purchase an electronic radial scope that will allow platform compatibility with a linear scope (Aloka Prosound Alpha 5 or 10). If the endosonographer needs to purchase a cheaper

FIGURE 2.3 Olympus EU-ME1 processor. This processor enables the use of mechanical and electronic radial echoendoscopes and the curvilinear array echoendoscope.

FIGURE 2.4 Olympus, wire-guided slim esophagoprobe (MH908), diameter 8.5 mm.

mechanical radial scope or must keep one in use, then the clever dual-format EU-ME1 will serve this purpose (Fig. 2.3). It is also possible to continue to use the old high-end Olympus radial processor (model EU-M2000 or EU-M60, depending on geographic area) in parallel with a new Aloka machine because the Olympus processor is not too bulky. This older processor allows for a broad range of available frequencies (5 to 20 MHz), fine focus (to a range of 1 cm), good image manipulation including instant video replay, and, with appropriate software, mini-probe three-dimensional rendering.

The Olympus EU-C60 is a very mobile, diminutive processor, measuring only 313 mm wide and 93 mm high. Its small size means that it can be attached to a radial processor trolley, thus allowing for some improvement in user convenience. Although this processor is cheaper, considerably smaller, and more mobile than standard ultrasound processors, compromise comes at a price. Screen images are the result of "averaging" factors such as frequency (7.5 MHz), depth of focus, and field of view (150 degrees as opposed to 180 degrees for the standard scope, an unimportant operating characteristic). In addition, the linear scopes run by the Olympus EU-C60 have a modified connecting box, so they cannot be switched between Aloka platforms and the mini-processor. To its credit, this processor is compatible not only with the Olympus gastrointestinal EUS linear scopes, but also with the first-generation EBUS scope. On the whole, however, this compromise is not entirely successful.

Hitachi processors run Pentax scopes. There is a broad range, but the top-end machines give the greatest clinical flexibility that includes EBUS (EUB-5500 HV, EUB-7000 HV, EUB-7500 HV, and the high-end HI VISION 900).

Specialty Probes

Numerous probes are available for specific clinical situations. Even though such instruments may be used relatively infrequently, the advantages of their use must be considered when planning for departmental needs.

Esophagus and Stomach

The Olympus MH908 slim esophagoprobe (Fig. 2.4) is perhaps the unsung hero of EUS. The value of this probe needs to be considered seriously when choosing equipment for units with a large volume of staging procedures for esophageal cancer.

The Olympus MH908 is a mechanical, radial probe (7.5 MHz) that is driven by the same range of processors as all other Olympus mechanical scopes. It is a "blind," cone-tipped scope that is passed over a standard ERCP wire, placed during endoscopy. The diameter of the scope is 8.5 mm, to allow passage through the majority of esophageal strictures without the need for dilatation. The short length of the insertion tube permits staging of proximal, but not distal, gastric tumors.

Concerns have been raised about the ability of the Olympus MH908 to inspect the celiac axis adequately, because the downward tip angulation is only 90 degrees, versus 130 degrees for standard Olympus echoendoscopes. This difficulty is probably overstated because good regional views can be obtained. Use of the Olympus MH908 does lead to fewer failed staging procedures as compared with use of a standard radial echoendoscope.[1]

The advantages of the Olympus MH908, which obviates the need for dilatation, are obviously lessened in units where nodal FNA is routine. Differences in practice can result from geographic variations (e.g., between the United States and Asia and Western Europe) in the nodal burden of "normal" lymph nodes. Could an EBUS scope be used as a slim-probe and thereby also permit FNA? Yes, but certainly not reliably, because these scopes do not handle well when they are passed through strictures.

The facility of adding an unplanned EUS examination to a gastroscopy procedure is an ever-present aspiration. The Fujinon PL2226B-7.5 is a torpedo-shaped mechanical radial probe (7.5 MHz; head diameter, 7.3 mm) that may be back loaded through a large-channel gastroscope in a fashion analogous to the loading of a variceal band cartridge. This cleverness in design is offset by a resultant loss in endoscopic luminal view, problematic with strictures. The probe is driven by the SP702 processor. This processor also permits easy switching between radial and linear formats (biplanar ultrasound) when Fujinon mini-probes are used.

Mini-Probes

Catheter probes range in size between 2 and 2.6 mm, are mostly mechanical radial, and require an additional, small motor-drive unit to intervene between the probe and the ultrasound processor. In length, all probes will reach the duodenum and terminal ileum (through a colonoscopy), but Fujinon offers a probe 2700 mm long that can be deployed through a balloon enteroscope. These probes are usually of high frequency (12 to 30 MHz, and most are $\geq$20 MHz) with a shallow depth of view and a resulting reduction in useful application. Although such probes are particularly good for inspecting small mucosal and subepithelial lesions and for intraductal use, they are not useful for regular staging of esophageal tumors or larger colonic polyps.

Another drawback of catheter probes is the difficulty of excluding air from the site of mucosal contact. Proprietary balloon sheaths are available, but these require the use of scopes with

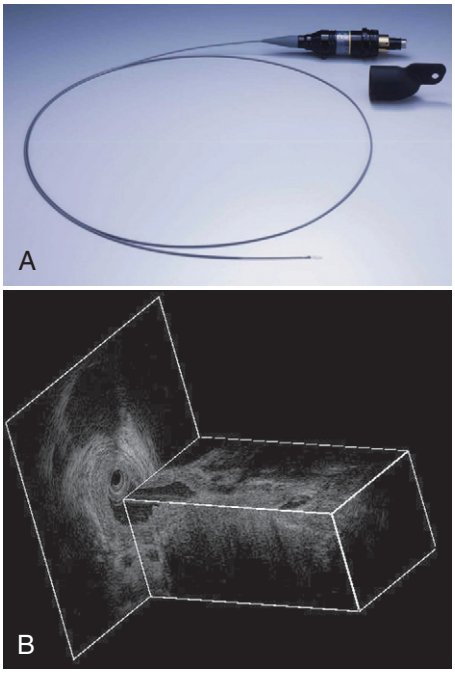


FIGURE 2.5 Olympus UM-DP range of mechanical probes. These probes "spiral" within the catheter (**A**) to yield dual-plane or three-dimensional images (**B**).

large-caliber accessory channels. There have been many reports of other methods to provide a water interface, including the use of (nonlubricated) condoms and water-flooding of the esophagus with prior cuffed intubation.

Mini-probes are said to have a useful life of 50 to 100 procedures. With care, the longevity of catheter probes can be extended considerably beyond this point. In particular, storing probes in a hanging position, rather than coiled flat, prolongs their life span. When using mini-probes, one should never have the transducer rotating when passing or withdrawing the probe through the scope and never be tempted to touch the elevator when a probe is in place.

Both Olympus and Fujinon offer a wide range of mini-probes. The probes manufactured by Olympus fall into two broad categories: those for general use (UM-2R [12 MHz], UM-3R [20 MHz], and UM-S30-25R [ultraslim, 30 MHz]) and those for intraductal studies (wire-guided UM-G20-29R [20 MHz]). The "spiraling" UM-DP12-25R, UM-DP-20-25R, and UM-DP-29R probes (Fig. 2.5) offer the added capacity to permit dual-plane (three-dimensional) rendering when they are used with the EU-M2000/EU-M60 processor, provided that the appropriate software has been loaded. The Olympus UM-BS20-26R is a 20-MHz probe, with a diameter of 2.6 mm and a built-in balloon. This balloon adds further potential for shortening the probe's life span. The MAJ-935 unit is required to drive these probes because they do not plug directly into the ultrasound console.

Fujinon provides a very broad range of catheter probes ranging in frequency from 12 to 20 MHz (PL-2220-12; PL-2220-15, and PL-2220-20, all 2 mm in diameter, and PL-2226-12, PL-2226-15, and PL-2226-20, all 2.6 mm in diameter).

Colon and Anorectum

At first thought, the idea of a dedicated echocolonoscope seems attractive, given that standard scopes are difficult to maneuver safely beyond the rectosigmoid junction. The Olympus CF-UMQ230 answers this need, but availability is restricted to certain geographic regions (the United Kingdom, Japan, and parts of Asia). The combination of standard colonoscope and mini-probe suffices for most needs, however.

FIGURE 2.6 Olympus electronic, endobronchial echoendoscope (BF-UC180F). This probe allows cables to be detached for easier handling during processing.

Endobronchial Probes

Olympus was the first company to offer a diminutive bronchial linear probe (outer diameter, 6.9 mm; operating length, 600 mm) with an FNA capability (BF-UC160). The 2-mm accessory channel allows passage of a dedicated transbronchial needle (NA-201SX-4022). The second-generation scope (BF-UC180F; Fig. 2.6) permits the cable (and bulky box) connecting the scope to the ultrasound processor to be detached and thus makes it easier to place the devices into washing machines. Probes can be run using either the EU-C60 processor or the better Aloka Prosound Alpha 5 and 10 processors.

The Pentax EBUS scope (EB-1970UK) is run with the Hitachi HI VISION platform, again common to their radial and linear scopes.

ACCESSORIES

Needles for Fine-Needle Aspiration

Needles for FNA remain expensive and less than ideal, but they have come a long way from being simple modifications of needles used for variceal injection. Needle sizes range from 19 to 25 G. Additionally, specialized needles for specific tasks, such as pancreatic sampling, celiac axis neurolysis, core biopsy, and pancreatic cyst drainage are available (availability subject to national licensing). Refinements of the attached suction syringes permit variable degrees of negative pressure to suit a specific clinical situation. The tips of all needles are specially treated to allow good EUS visualization.

Much tedious work has been performed in an attempt to define the best needle size and appropriate amount of negative pressure for a given task. These factors are covered elsewhere in this book, but the basic principle is that the larger the needle is, the more bloody the sample and the less happy the cytopathologist will be.

The 22-G needle has been the standard size for many years, but equivalent results can be obtained using the 25-G format, which is as useful for pancreatic sampling as it is for lymph nodes.[2] The use of negative pressure should be avoided for soft lesions (lymph nodes, neuroendocrine tumors, and gastrointestinal stromal tumors [GISTs]) and may be of questionable value for sampling other solid pancreatic lesions. A 22-G needle is the standard size to puncture small or medium-sized cystic lesions. If the needle tip is in a proper position (i.e., away from the wall or

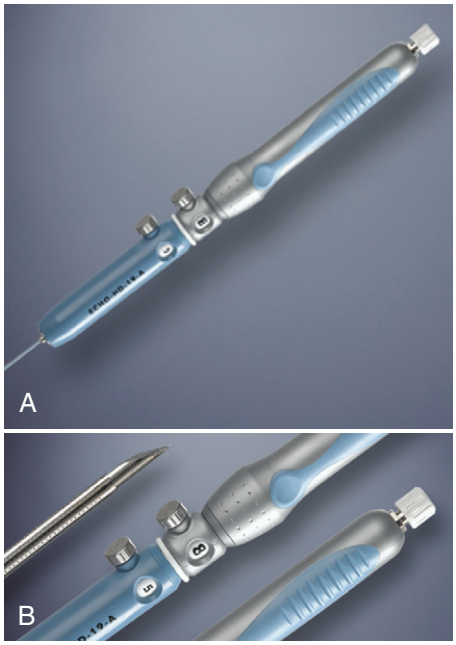


FIGURE 2.7 Cook 19-G needle (A) with a protruding stylet (B).

septation) and the tap is seemingly dry, it is worthwhile changing to a 19-G needle because the lesion may be mucoid. A capacity to fix the syringe plunger in different positions and thus vary the degree of negative pressure is an advantage for any needle format.

The larger, stiffer, and more awkward 19-G needle is often required for larger cyst drainage because it allows for a quicker procedure, the aspiration of viscous contents, and, when needed, the passage of an 0.035-inch guidewire. Core samples of lymph nodes and lesions such as GISTs may be obtained using this large needle without resorting to the Tru-Cut model.

Cook

Cook produces a broad, multiple-purpose range of fully disposable EUS-FNA needles (Echotip; 19, 22, and 25 G). These needles have a one-piece, sturdy, comfortable ergonomic handle, easily adaptable to the length of scope. Furthermore, the green-sheathed, slippery-coated Cook EUSN-3 22-G needle can be passed with great ease, even under conditions of marked scope torque. Both the 25-G and the 19-G needles retain the older, less slippery EUSN-1 blue sheath. The 19-G (Fig. 2.7) needle is difficult to advance when the scope is beyond the pylorus. The three needle sizes come with a two-step, double-trigger (5/10 mL) suction syringe.

The Cook EUSN-1 range comes with a stylet with a tip beveled to the needle tip, whereas a protruding ball-tip stylet accompanies the EUSN-3 needles. The ball-tip version may protect the scope channel should the needle be deployed accidentally. In general use, the ball-tip stylet must be withdrawn a centimeter or so before puncture, to "sharpen" the needle. Immediately following puncture and before sampling, the stylet is pushed in to extrude any plugs of extraneous tissue. The 19-G needle cannot be used with Pentax echoendoscope models FG-32UA or FG-34UA because of accessory channel size.

A 19-G Tru-Cut needle (Fig. 2.8) yields core samples. The Cook "Quick-Core" needle, however, is often not quick to use, nor does it always produce a core. The stiffness inherent to 19-G needles lessens the effectiveness of this instrument. Although it can be deployed successfully in the mediastinum and stomach, transduodenal sampling is often impossible. The range of sites that can be sampled using the Tru-Cut needle is subject to local licensing.

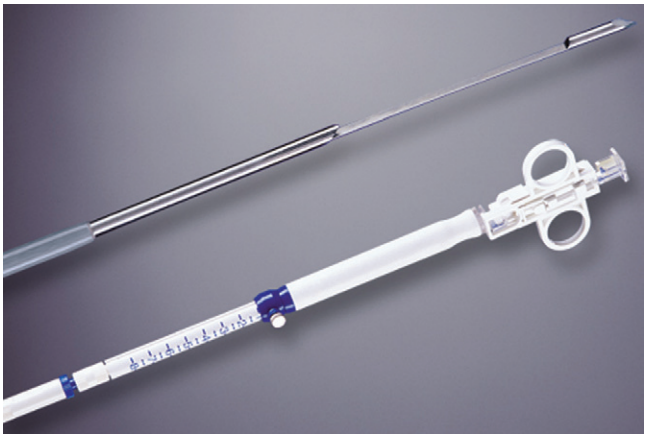


FIGURE 2.8 Cook 19-G Tru-Cut needle ("Quick-Core").

FIGURE 2.9 **This Cook needle is designed for celiac axis neurolysis.** The needle tip is solid, with proximal side-holes permitting a bilateral "spray" effect (Cook Echotip EUSN-20-CPN; not available in all geographic regions).

Both 19-G and 22-G needles can be used for celiac axis neurolysis. A specially styled 20-G "spray" needle is available for this task from Cook (EUSN-20-CPN; certain geographic regions only; Fig. 2.9). The needle has a solid, sharp, cone-tip with proximal side-holes, to allow for a bilateral spray effect.

Pancreatic pseudocyst drainage with placement of a transgastric or duodenal stent is achieved using a combination of 19-G needle, guidewire, biliary dilatation balloon, and biliary endoprosthesis. Cook, however, produces a single-step, 8.5-Fr, stent-loaded needle wire for this purpose (Giovannini needle wire; NWOA-8.5; certain geographic regions only). A 10-Fr cystotome delivering a 5-Fr catheter with 0.038-inch needle knife is also available (Cook CST-10; certain geographic regions only).

Cystic, potentially neoplastic lesions of the pancreas present specific problems for obtaining representative epithelial cell samples because standard aspirates are generally acellular. To address this difficulty, a dedicated EUS cytologic brush (Echobrush) is available, but results are mixed. There are different ways to use this brush. One method is to aspirate half the volume of the cyst (send for biochemical analysis; sample 1), pass the brush and sweep vigorously with the cytology brush (sample 2), and then aspirate the rest of the, one hopes, now cell-enriched fluid (sample 3). The occurrence of significant bleeding and a death have been reported in association with this tool.[3]

Olympus

Olympus produces both disposable and partially disposable FNA needles, as well as a spring-loaded device designed for hard lesions. The single-sized (22-G), fully disposable FNA needle (EZ-Shot; NA-200H-8022) comes with a 20-mL suction syringe that allows for variable degrees of negative pressure by twisting and locking the plunger in place. The brown needle sheath is not as slippery as that of the Cook 22-G needle. As a result, the Olympus EZ-Shot needle is slightly more difficult to deploy in the duodenum. Olympus also produces a reusable handle and sheath apparatus with a disposable needle piece (NA-10J-1).

The Olympus "Power-Shot" apparatus is a reusable, spring-loaded device that fires a disposable (22-G) needle into a lesion, to a defined depth (NA-11J-1). This instrument has been designed for pancreatic tumors. However, most pancreatic tumors are, in fact, soft, and that the sensation of hardness comes from poor scope positioning or gripping of the needle by the scope's elevator.

The Olympus NA-201SX-4022 needle is for use specifically with Olympus EUS bronchoscopes.

Mediglobe

The Mediglobe needles were perhaps the first dedicated EUS FNA needles to be developed. The disposable Sonotip II range (19-G, 22-G, and 25-G) needles have a double handle structure, somewhat akin to those made by Cook, that allows the sheath to be simply tailored to the make of scope in use. The shape of the handle has been altered so that it is larger and easier to grip than in its previous form. The stylet is of nitinol (a nickel-titanium alloy) and comes with both rounded (19-G, 22-G, and 25-G) and beveled (22-G) tips. Mediglobe offers two thicknesses of needle sheath, on the basis that needles may wobble in large-channel scopes. As mentioned before, this is not a problem in clinical practice. The aspiration syringe allows for a fixed negative-pressure volume.

Mediglobe provides 22-G needles that may be used with both Pentax and Olympus EBUS scopes (GUS-21-18-022 and GUS-25-18-022, respectively).

Three needles in the sizes of 19, 22, and 25 gauge are expected to be commercially available soon (Fig. 2.10).

FIGURE 2.10 The fine-needle aspiration system to be released by Boston Scientific (Boston Scientific Corporation, Natick, MA.)

Balloons

Proprietary balloons are offered by the major echoendoscope manufacturers, but usually at exorbitant prices. International Medical Products (Zutphen, The Netherlands) offer cheaper and reliable balloons for the Olympus radial EUS scopes. Where regulatory bodies allow such generic substitution, it is always worthwhile asking colleagues from other centers whether such products can be sourced in that region.

Because all EUS balloons contain latex, standard echoendoscopes must not be used in patients with latex sensitivity. Linear scopes can be used perfectly well without balloons. It may also be possible, depending on the disorder in question, to use a mini-probe; those made by Olympus are latex free.

Water Pump

The UWS-1 water instilling pump is available from Olympus in certain geographic regions. This pump permits the rapid instillation of water into the bowel lumen to allow for improved imaging of small, epithelial lesions. Care must be exercised when water is used in the esophagus without prior intubation. Furthermore, it is important to change a sterile connecting tube between each patient. It is always worth considering that sterile 50-mL syringes are universally available and cheap.

Reporting Systems

There is no good, universally available reporting system. Modules are offered by several sources, including Endosoft, Unisoft, Fujinon (ADAM), and Olympus (EndoWorks in the United States and EndoBase in continental Europe). The major drawback of these and other programs is that they require a tremendous amount of work to adapt them in for local use.

Archiving

Modern, full-size processors from all the major manufacturers have built-in image and video capture units including local hard disks, DVD burners, USB ports, and magneto-optical drives. The potential to store images in a Digital Imaging and Communications in Medicine (DICOM) format to digital archives (as in a radiology department picture archiving and communication [PACS] system) is common to current middle-range and upper-range ultrasound processors. However, such software options may not be included in the package offered for EUS users and so must be discussed at the time of purchase. If linking to a PACS system is possible, one must consider whether it will be for still images only or for video images as well, because storage capacity issues will likely arise for anything other than short runs of video footage.

Lengthy paper streamers of photographs from a simple "hot" black and white printer are always satisfying to see after an examination. Such images are a good option in most cases and will not fade even after many years, although folded paper may stick together. Making hard transparent copies with a laser printer is another, albeit more expensive, option.

Hard copy photographs can be scanned easily. If there is ever a chance that they may be used for publication, it is worthwhile scanning them as gray-scale images at a resolution of at least 300 dpi, but preferably 500 dpi (most scanners have a default setting of 200 dpi).

Video image capture is a mainstay of EUS teaching. Although high-specification digital recorders are available, they are expensive. A standard digital, tape, or disk video camera may be hooked up to an EUS processor through an internally fixed video-out cable or from the monitor or attached to the line-out connector of the printer. There seems to be little degradation in the quality of image using this solution. However, one should take care when checking the specifications of the camera because many cameras have only video-out sockets (e.g., for attaching to a television) but not video-in sockets. If a suitable camera is not available, the images can be streamed to a laptop computer instead.

Editing of captured video is simple using generally available programs such as those from Pinnacle. High-specification, very expensive video-editing software (e.g., Adobe) is not necessary. The type of connection between the video camera and the computer is important; the system relies on rapid data transfer. For this reason, one should use a video camera with either a USB-2 or "Fire-wire" socket. If other types of video cameras are used, including old VHS devices, special connection adaptors, such as those from Dazzle, are available relatively cheaply.

Downloaded videos may be in a format called .avi. The images from this file type are of very high quality but consequently are extremely large. Video-editing programs offer to convert the snippets of movie into a range of formats including MPEG1, MPEG2, and avi. Choosing MPEG1-type movies is a compromise in terms of quality, but these videos are widely playable on most computers, a feature that is important if these videos will be used for talks in many different places. Furthermore, most projectors used to show such videos cannot handle higher-quality file types. The MPEG2 format is superior to MPEG1 but will not play on many computers unless the appropriate piece of software (a "codec") has been installed. One minute of an MPEG1 movie takes approximately 11 MB of memory. Single, still frames can be captured from downloaded videos using Pinnacle, but the quality does not compare with that from true single-shot images taken at the time of the procedure.

When the EUS examination has been recorded, downloaded, edited, and put into a movie format, the next problem is how to show it. The easiest way is to double-click on the icon and allow a universal program such as Windows Media Player (WMP) to show it. This approach gives the advantage of control. The buttons of WMP allow freezing, fast forwarding, and other features. Another approach is to "insert" the movie into PowerPoint. This permits annotation and the incorporation of stills. PowerPoint is not good at handling video, however, and MPEG2 files are particularly problematic. Current smart-phones and iPods, among other devices, are capable of storing large amounts of video and displaying them with good fidelity, even when they are simply placed on the platform of a video-type radiographic viewing box or projector.

Patient confidentiality is a problem with videos because masking names with a black box does not work in PowerPoint; this program automatically puts any video in front of anything else on that page. Video-editing programs allow one to place a mask, but the process can be tedious. In general, it is much easier not to put the patient's name or details on the EUS screen at all.

CHOOSING EQUIPMENT

The equipment for endoscopic ultrasound is expensive. Consequently, compromise is an ever present reality. It is worth restating several points that must be addressed in drafting a call for tenders.

The single most important question to be answered is this: What is the equipment for? It is too easy to find a need for every type of equipment, but such loose thinking makes for an unfocused business plan.

Small lesions, celiac neurolysis, and pancreatic pseudocyst drainage are niche areas. The cornerstone of most EUS practice is cancer staging, supported possibly by examination of benign lesions to extend equipment use further. One example is the substitution of EUS for MRI in the investigation of possible choledocholithiasis. Another consideration is that not all centers manage all types of cancer.

When the staging of non–small cell lung cancer will be a significant source of referrals, a linear system capable of FNA is an absolute requirement. The information yielded by radial EUS is of little value in this disease. The situation is less clear for staging of esophageal and pancreatic cancer and is heavily influenced by local practice.

In the United Kingdom, all patients with operable esophageal cancers undergo neoadjuvant chemotherapy. Consequently, linear EUS is not an absolute requirement for initial staging. Given that the clinical significance of involved local lymph nodes after chemotherapy (operate? administer further chemotherapy?) is unknown, does a positive non–celiac node FNA result redirect management?

Pancreatic cancer can present an equally opaque decision dilemma. If the lesion is operable, what is the role of FNA? Does it add any useful information? If the lesion is inoperable, can percutaneous biopsy not be performed? Perhaps a radial scan is all that is required.

The point of these preceding few paragraphs is to highlight the importance of detailing exactly how EUS is to be used and where it will fit in a local care pathway algorithm. This approach helps to prioritize the equipment need.

Once the decision has been made about what the equipment is for, the next issue to tackle is which system to buy. Taking linear systems, is there a difference in performance characteristics among the linear echoendoscopes? Could the shape of the different transducers translate into better or worse endosonographic views? In essence, the answers are no and no.

Outside regions where nonradiologists routinely perform transabdominal ultrasound scanning, discussions with radiologic colleagues often yield preferences for one manufacturer over another, whether it be Hitachi, Toshiba, Aloka, or Philips, but a significant amount of the capability of these processors is redundant to EUS. There is little advantage in buying a top-end processor over a more modest one, provided that the quality of screen image is adequate. Most processors are ergonomically similar to use.

The case for a high-specification processor may come from sharing the unit between radiology and endoscopy departments. If this is the case, moving a complex electronic machine around an institution will expose it to risk, not to mention the inevitable aggravation of both parties who may need it at the same time.

Like beauty, cost is very much in the eye of the beholder. There are regional differences in how companies compete. In some areas, cost is the paramount issue, whereas in others, a perception of quality carries a premium. The final price is a balance between how much the unit is willing to pay and how much the company needs the business or the badge of a recognized, "trophy" name.

When choosing EUS equipment, the costs go well beyond those of the initial setup. This equipment is delicate, and pressure to train fellows exposes it to significant wear and tear. Support packages that include the availability of replacement echoendoscopes are of great importance. Cheaper scopes may come with very expensive or weak service support. A survey among 56 institutions that perform EUS demonstrated that mechanical radial scanning echoendoscopes tended to break, on average, after 68 procedures, whereas curved linear array echoendoscopes failed after an average of 107 procedures.[4] Institutions paid an average of $10,534 over 12 months for echoendoscope repairs. The average repair cost per procedure was $41. These data may serve as a guide in setting up a service. When obtaining bids for new scopes, one should ask for full, "no question" running costs over 5 years to be included in the price offered.

REFERENCES

1. Vu C, Tsang S, Doig L, et al. The preferred choice for radial endosonographic staging of esophageal cancer: standard echoendoscope or non-optic esophagoprobe? *Surg Endosc*. 2007;21:1617–1622.
2. Siddiqui UD, Rossi F, Rosenthal LS, et al. EUS–FNA of solid pancreatic masses: a prospective, randomized trial comparing 22-gauge and 25-gauge needles. *Gastrointest Endosc*. 2009;69:AB235.
3. Al-Haddad M, Raimondo R, Woodward T, et al. Safety and efficacy of cytology brushings versus standard FNA in evaluating cystic lesions of the pancreas: a pilot study. *Gastrointest Endosc*. 2007;65:894–898.
4. Schembre D, Lin O. Frequency and costs of echo endoscope repairs: results of a survey of endosonographers. *Endoscopy*. 2004;36:982–986.

CHAPTER 3 TRAINING AND SIMULATORS

Michael K. Sanders | Douglas O. Faigel

Key Points

EUS is an advanced endoscopic procedure that requires a level of training exceeding that of general endoscopy. Acquisition of the skills necessary to perform EUS competently often requires training beyond the scope of a traditional gastroenterology fellowship program.

Competence in routine endoscopic procedures should be documented because it provides a vital foundation for EUS training.

Competence in EUS requires both cognitive and technical skills, including an understanding of the appropriate indications for EUS, performance of appropriate preprocedure and postprocedure evaluations, and management of procedure-related complications.

On successful completion of EUS training, the trainee must be able to integrate EUS into the overall clinical evaluation of the patient.

A general consensus of expert endosonographers suggests that luminal endosonography requires at least 3 to 6 months of intensive training to establish competency and that pancreatobiliary EUS and fine-needle aspiration (FNA) may require up to 1 year.

Each program that teaches EUS should be able to provide sufficient numbers of procedures that will substantially surpass those required for minimal competence.

The threshold number of EUS FNA cases needed to achieve competence has not been studied. However, it is generally agreed that FNA of pancreatic lesions is more complex and carries a higher risk than EUS FNA at other anatomic sites.

INTRODUCTION

Since the 1990s, endoscopic ultrasonography (EUS) has emerged as a valuable endoscopic resource for the diagnosis and treatment of a variety of gastrointestinal (GI) disorders including, but not limited to, pancreatic cysts, mucosal and submucosal tumors, chronic pancreatitis, and various GI malignancies. The diagnosis, staging, and treatment of GI cancers have evolved into a multidisciplinary approach often using endosonography as the initial tool for both diagnosis and staging. Multiple studies have demonstrated the superiority of EUS compared with conventional abdominal computed tomography (CT) in the staging of esophageal, gastric, and pancreatic cancers.[1–4] Furthermore, the advent of EUS-guided fine-needle aspiration (EUS-guided FNA) provided an alternative approach to traditional percutaneous biopsies obtained under CT or ultrasound guidance. Compared with other modalities, EUS-guided FNA results from pancreatic masses are superior, with sensitivities ranging between 85% and 90% and a specificity of 100%.[5,6] EUS has been employed in the treatment of pancreatic adenocarcinoma with ultrasound-guided fine-needle injection of tumor-suppressing agents,[7] a finding that further expands the future potential for therapeutic endosonography. Clearly, the introduction of EUS into clinical practice has revolutionized the field of gastroenterology, in particular GI oncology, and potential applications continue to evolve.

As the applications for EUS have become increasingly recognized by other clinical practitioners, the demand for well-trained endosonographers has escalated.[8] The limited availability of EUS is largely the result of a lack of skilled endosonographers. Additional barriers include equipment cost, ease of use, and reimbursement costs. A relative lack of training centers combined with the extensive commitment required by the trainee has limited the growth of EUS and its availability in community practices. Ensuring adequate training of practicing endosonographers has become a priority for the American Society for Gastrointestinal Endoscopy (ASGE), as evidenced by guidelines set forth on advanced training in EUS.[9] EUS is an advanced endoscopic procedure that requires a level of training exceeding that of general endoscopy. Acquisition of the skills necessary for conducting and understanding EUS often requires training beyond the scope of a traditional gastroenterology fellowship program. Additional training often involves a 1-year fellowship following completion of an accredited gastroenterology training program. Although a few gastroenterology training programs provide adequate exposure to EUS during a traditional 3-year fellowship, it is unacceptable to give only brief exposure to EUS and then allow independent practice by inadequately trained fellows. Clinical workshops with hands-on training may provide an understanding of the indications and complications of EUS, but these workshops are not a substitute for formal fellowship training. This chapter covers the guidelines for individual trainees, training programs, and credentialing in EUS. Although computer-based training simulators are in their infancy in the field of endosonography, they represent an exciting adjunct to formal training and are also discussed.

GUIDELINES FOR TRAINING

Guidelines for training in advanced endoscopy have been published by the ASGE.[10] Although many gastroenterology training programs have incorporated advanced endoscopy training into the second and third year curriculum, most programs are now requiring an additional fourth year of training for advanced procedures (i.e., endoscopic retrograde cholangiopancreatography [ERCP], EUS). EUS training is available at relatively few academic centers in the United States. Currently, according to the ASGE, approximately 50 recognized programs in the United States offer a fourth year fellowship in EUS (www.asge.org). Many of these programs provide dual training in both ERCP and EUS, whereas others separate the training into either EUS or ERCP. Although these programs may vary in the design of their training experience, two critical components are necessary for a qualified training program: large patient volume and recognized faculty expertise.

In certain unusual circumstances, a trainee may acquire the necessary skills for EUS in a standard 3-year fellowship, provided that an adequate patient volume is available, and the trainee can demonstrate the necessary aptitude and skills required for advanced endoscopy. However, given the complexity of these procedures and the necessary volume of cases required to achieve competency, it seems less likely that an individual would be adequately trained in a traditional 3-year program. A survey by Azad et al[11] found that most gastroenterology fellowship programs in the United States have established the necessary EUS volume to train at least one EUS fellow annually. However, most 3-year and many advanced fellows receive insufficient EUS training, according to ASGE guidelines.[11] For 3-year GI fellows, 55% received less than 3 months of training; 43% received no actual hands-on experience, and 61% did not learn EUS-guided FNA. Programs offering advanced training in EUS had a median advanced-trainee EUS volume of 200 procedures (range, 50 to 1100). Of the advanced fellows, 20% failed to receive hands-on training, whereas 52% performed fewer than 200 procedures. Although this study has limitations, the findings highlight some of the inadequacies in training for EUS and demonstrate areas for improvement.

Competency is defined as the minimum level of skill, knowledge, or expertise acquired through training and experience that is required to perform a task or procedure safely and proficiently.[12] Unfortunately, there have been few published reports regarding training of individuals in EUS or numbers of procedures required to attain competence.[13–15] A common goal for all gastroenterology training programs is the production of knowledgeable, experienced, and competent endoscopists. Recognizing this goal and understanding the limitations of a 3-year curriculum have provided the major impetus for establishing fourth-year fellowships in EUS.

Although the demand for qualified endosonographers is increasing, not all trainees should pursue such advanced training, both because of variations in individual skill level and because of regional manpower needs. Similarly, not all training programs should offer EUS training, owing to restraints on patient volume and faculty interests. Individuals wishing to pursue further training in EUS must have completed at least 24 months of a standard GI fellowship or must demonstrate equivalent training. Moreover, competence in routine endoscopic procedures should be documented because it provides a vital foundation for advanced endoscopic training. Obviously, trainees in endoscopy develop skills at widely varying rates that can be evaluated objectively by experienced endoscopists. However, the use of an absolute or threshold number of procedures may be misleading and should therefore be employed with caution in the evaluation of individual trainees. The minimum number of procedures required to achieve competency in EUS will vary based on the individual's skill level, understanding of ultrasound principles, and quality of the training experience. Performing an arbitrary number of procedures does not necessarily guarantee competency.

TABLE 3.1

Minimum Number of EUS Procedures Required before Competency Can Be Assessed

Site/Lesion	Number of Cases Required
Mucosal tumors (cancers of the esophagus, stomach, and rectum)	75
Submucosal abnormalities	40
Pancreaticobiliary	75
EUS-guided FNA	
Nonpancreatic	25
Pancreatic	25
Comprehensive competence	150*

*Including at least 75 pancreaticobiliary and 50 FNAs.

FNA, fine-needle aspiration.

From American Society for Gastrointestinal Endoscopy. Guidelines for credentialing and granting privileges for endoscopic ultrasound. *Gastrointest Endosc.* 2001;54:811-814.

Although the Standards of Practice Committee of the ASGE published a minimum number of procedures necessary to assess competency (Table 3.1), these numbers simply represent a minimum requirement and should serve only as a guide for evaluating individual trainees. These numbers are derived from studies on training in EUS, published expert opinion, and consensus of the Ad Hoc EUS and Standards of Practice committees of the ASGE. Ideally, competency should be gauged on objective criteria and direct observation by an experienced endosonographer.

Competence in EUS requires both cognitive and technical skills,[16] including an understanding of the appropriate indications for EUS, conducting of appropriate preprocedure and postprocedure evaluations, and managing of procedure-related complications. Trainees must be able to perform the procedure in a safe and efficient manner while also recognizing and understanding the ultrasound images. Furthermore, understanding the implications for EUS in staging GI malignancies must be appreciated for integration of the endosonographic findings into the treatment plan for each patient (i.e., surgical versus medical or radiation oncology referrals). Formal supervised EUS training should also include reviews of cross-sectional anatomy, atlases of endoscopic or abdominal ultrasonography, videotaped teaching cases, and didactic courses in EUS. A combination of well-supervised EUS procedures and didactic teaching will aid in ensuring an adequate training experience, as well as an overall understanding of EUS.

A crucial component to any EUS training program is GI tumor staging. When available, EUS has become the standard of care in staging several GI malignancies, including esophageal, gastric, rectal, and pancreatic cancers. Determining the accuracy of tumor staging by a trainee is an important aspect of training by allowing the differentiation between potentially curable early-stage tumors and unresectable late-stage tumors. Studies in endosonographic staging of esophageal cancer suggested that at least 75 to 100 procedures were required before an acceptable level of accuracy was achieved.[14,15] Ideally, the accuracy of EUS staging should be compared to a gold standard such as surgical histopathologic examination. However, surgical specimens are not always readily available, and patients may have received preoperative radiation and chemotherapy that can affect staging. In these circumstances, staging by a trainee should be compared with staging performed by a skilled and competent endosonographer. Appropriate documentation of all EUS procedures in a training log, along with review of surgical pathology results, will further assist in determining both the quantity and the accuracy of tumor staging cases.

On successful completion of EUS training, the trainee must be able to integrate EUS into the overall clinical evaluation of the patient. A thorough understanding of the indications, contraindications, individual risk factors, and benefit-to-risk considerations for individual patients must be demonstrated. The ability to describe the procedure clearly and accurately and to obtain informed consent are necessary requirements. A knowledge of GI anatomy and surrounding anatomic structures as imaged by EUS and of the technical features of the equipment, workstation, and accessories is vital for future independent practice. The trainee must be able to intubate the esophagus, pylorus, and duodenum safely, to acquire the necessary images. Moreover, accurately identifying and interpreting the EUS images and recognizing normal and abnormal findings must be demonstrated and assessed by the mentor. The trainee should be able to achieve accuracy in tumor staging comparable to that reported in the medical literature (Table 3.2).[9] Finally, the trainee must be able to document and communicate the EUS findings with referring physicians and must understand the implications of these findings in formulating treatment plans for patient care. Adhering to these training requirements for EUS will further assist in ensuring the production of skilled endosonographers.

TRAINING PROGRAM REQUIREMENTS

Although several institutions across the United States, Canada, and Europe offer brief training courses in EUS, these programs provide only limited exposure and arguably do not adequately train individuals as independent endosonographers. Even though formal, supervised training is the most accepted mode of training, experience may be gained in other settings, such as hands-on short courses, use of animal models, EUS teaching videotapes, and computer-based training simulators. However, these teaching methods simply represent useful adjuncts to formal training and should not be used in lieu of a more formal supervised training experience.

The general consensus of expert endosonographers is that luminal endosonography requires at least 3 to 6 months of intensive training to establish competency, whereas pancreaticobiliary EUS and FNA may require up to 1 year.[17] In fact, one study demonstrated a learning curve for EUS-guided FNA of solid pancreatic masses following third-tier EUS training and suggested that the learning curve continues to develop after fellowship training because more procedures are needed to gain proficiency and efficiency with EUS-guided FNA.[18] Although short courses and computer-based learning are useful, this form of training without direct supervision may result in an inadequate understanding and appreciation for the technical challenges and complexity of EUS.

When considering advanced training in EUS, a trainee should investigate all aspects of the training program. Arguably, the most important aspects of a training program are the reputation and expertise of the endosonographer. Programs should have a minimum of one skilled endosonographer who is acknowledged as an expert by his or her peers and is committed to teaching EUS. Unfortunately, most EUS programs across the United States have limited, if any, extramural funding and may require additional clinical responsibilities to help support the trainee's salary. With an understanding of the financial limitations of most institutions, training programs should strive to limit the clinical responsibilities unrelated to EUS when developing their core curriculum. Ideally, programs should provide protected research time and should encourage academic pursuits such as designing research protocols, preparing manuscripts, writing grant proposals, and attending EUS courses. Creating an environment that emphasizes endoscopic research and clinical investigation should be a fundamental goal for each training program. Trainees should be provided with the protected time and necessary funds to attend at least one scientific meeting during the course of their training, preferably one related to endosonography. A common goal for all committed trainees should be presenting their endoscopic research at a national or international meeting.

Exposure to endoscopy unit management including scheduling, staffing, equipment maintenance, and management skills is also a valuable asset to any training program. Many trainees in EUS may pursue future academic positions, and these are invaluable skills to acquire early in an academic career. Although a common goal for most training programs is the development of future academic endosonographers, some trainees may express different career interests that conflict with the goals of the training program. Understanding and recognizing the program's expectations and the trainee's career interests are crucial to an enjoyable and successful training experience.

Each program in EUS should have the ability to provide numbers of procedures that will substantially surpass those required for minimal competence (see Table 3.1). Although a large procedure volume does not necessarily guarantee competence, it is highly unlikely that a low volume of cases will provide sufficient exposure to these highly complicated and technically challenging procedures to allow adequate assessment of competency. Requiring a large volume of cases is not an elitist attempt by tertiary centers to exclude others from potential training opportunities, but rather an attempt at guaranteeing the delivery of skilled endosonographers into the workforce and answering the demand for EUS. For these reasons, training in EUS has largely been limited to academic tertiary centers with highly skilled endosonographers conducting a large volume of cases. This approach ensures retention of the necessary skills to train individuals interested in learning EUS.

Equally important to the technical training of endosonography is the cognitive training. This curriculum should focus on a thorough understanding of the relevant anatomic and clinical aspects of EUS (Box 3.1). These aspects include knowledge of the cross-sectional anatomy of the human body and an understanding of the principles of ultrasonography. EUS is used to stage malignancies, and the trainee must understand not only

TABLE 3.2

Reported Accuracy of EUS Compared with Histopathology for the Local Staging of Esophageal Carcinoma, Gastric Cancer, Ampullary Carcinoma, and Rectal Cancer

Indication	Number of Procedures	T Stage	N Stage
Esophageal cancer	739	85%	79%
Gastric cancer	1,163	78%	73%
Pancreatic cancer	155	90%	—
Ampullary carcinoma	94	86%	72%
Rectal cancer	19	84%	84%

From American Society for Gastrointestinal Endoscopy. Guidelines for Training in Endoscopic Ultrasound. *Gastrointest Endosc.* 1999;49:829-833.

BOX 3.1 EUS CURRICULUM

- Cross-sectional human anatomy
- Principles of ultrasonography
- Principles of oncology
- TNM staging systems
- Stage-directed therapy
- Indications and risks of EUS
- Alternatives to EUS
- EUS terminology

TNM staging, but also how these stages are used to guide therapy. The trainee must be able to describe the indications and risks of EUS. The trainee should also understand the alternatives to EUS and their strengths and limitations. In addition, the trainee must be able to understand and use EUS terminology, to report EUS findings effectively and accurately.

CREDENTIALING IN EUS

Credentialing is the process of assessing and validating the qualifications of a licensed independent practitioner to provide patient care. Determining qualifications for credentialing is based on an assessment of the individual's current medical license, knowledge base, training or experience, current competence, and ability to perform the procedure or patient care requested independently. The ASGE has provided guidelines for credentialing and granting hospital privileges to perform routine GI endoscopy.[19] Furthermore, the ASGE has also established guidelines for credentialing and granting privileges in advanced endoscopic procedures, including EUS.[20] Credentialing for EUS should be determined separately from other endoscopic procedures such as sigmoidoscopy, colonoscopy, esophagogastroduodenoscopy, ERCP, or any other endoscopic procedure.

Determining competency and qualifications for credentialing can be somewhat challenging because trained individuals possess varying degrees of skill in EUS, along with recognized limitations. Nevertheless, providing a minimum number of procedures necessary before assessing competency (see Table 3.1) creates objective criteria for assessment in the credentialing process. As with credentialing in general GI endoscopy, competency is ultimately assessed by the training director or other independent proctor.

EUS is performed in a variety of anatomic locations for various indications.[21] These locations and indications include evaluation and staging of mucosally based neoplasms (esophagus, stomach, colon, and rectum), evaluation of subepithelial abnormalities, assessment of the pancreaticobiliary ducts, and performance of EUS-guided FNA. An endoscopist may be competent in one or more of these areas, depending on his or her level of training and interest. Privileging in one or more of these areas may be considered separately, but training must be considered adequate in the areas for which privileging is requested.

MUCOSAL TUMORS

Safe intubation of the esophagus, pylorus, and duodenum is essential when evaluating mucosal tumors in the esophagus, stomach, and duodenum. Accurate imaging of the lesion and recognition of surrounding lymphadenopathy, in particular the celiac axis region for upper GI tract cancers, are critical to the diagnosis and correct staging of mucosally based tumors. Evaluation of rectal cancers should include intubation of the sigmoid colon and identification of the iliac vessels. A prospective study reported that competent intubation of the esophagus, stomach, and duodenum was achieved in 1 to 23 procedures (median, 1 to 2), with visualization of the gastric or esophageal wall in 1 to 47 procedures (median, 10 to 15).[13] Adequate evaluation of the celiac axis region required 8 to 36 procedures (median, 10 to 15).

Unfortunately, studies addressing the learning curve for evaluating mucosal tumors of the GI tract are limited. Only two studies addressed the learning curve in staging esophageal cancers. Fockens et al[14] reported that adequate staging accuracy was achieved only after 100 examinations, whereas Schlick et al[15] reported 89.5% T-stage accuracy after a minimum of 75 cases. A survey of the American Endosonography Club in 1995 suggested an average 43 cases for esophageal imaging, 44 for gastric, and 37 for the rectum.[22] Once competence is achieved in one anatomic location, the threshold number of procedures for other anatomic locations may be reduced, depending on the skill and training of the endosonographer. The ASGE currently recommends a minimum of 75 supervised cases, at least two thirds in the upper GI tract, before competency for evaluating mucosal tumors can be assessed.[20]

SUBEPITHELIAL ABNORMALITIES

Evaluation of subepithelial lesions has become a common indication for EUS. Discriminating among neoplasms, varices, enlarged gastric folds, and extrinsic compression from extramural masses can be performed with traditional echoendoscopes or catheter-based ultrasound probes. With the advent of the catheter-based probes, some practitioners have developed competency in subepithelial abnormalities without achieving competence in other indications for EUS. Although no studies are available for determining the threshold number of cases required to assess subepithelial abnormalities accurately, the ASGE Standards of Practice Committee currently recommends a minimum of 40 to 50 supervised cases.[23]

PANCREATICOBILIARY IMAGING

Most endosonographers agree that accurate imaging and interpretation of images of the pancreaticobiliary system, including the gallbladder, bile duct, pancreatic duct, and ampulla, are more technically challenging than evaluations of mucosal and submucosal lesions. For this reason, a larger volume of supervised pancreaticobiliary cases is required before competence can be adequately assessed. A multicenter, 3-year prospective study reported that adequate imaging of the pancreatic and bile ducts required 13 to 135 cases (median, 55), whereas imaging of the pancreatic parenchyma required 15 to 74 cases (median, 34).[13] Adequate assessment of the ampulla required 13 to 134 cases (median, 54). Although technical competence in pancreaticobiliary imaging may be achieved with fewer than 100 cases, a survey from the American Endosonography Club suggested that interpretive competence of pancreatic images may require additional procedures (120 cases).[22] Other expert opinion suggests a higher threshold of 150 cases before assessing interpretative competence.[16] Currently, the ASGE Standards of Practice Committee recommends a minimum of 75 pancreaticobiliary cases before competency can be assessed.[20]

EUS-GUIDED FINE-NEEDLE ASPIRATION

EUS-guided FNA has emerged as an important diagnostic tool for obtaining tissue from intramural lesions, peri-GI adenopathy, and pancreatic lesions.[24] Training in EUS-guided FNA requires knowledge of basic principles of EUS, along with mastery of the skills necessary for obtaining and interpreting EUS images. Understanding and appreciating the complexity and risk that EUS-guided FNA adds to the procedure are critical for successful training. Unfortunately, the threshold number of FNA cases needed to achieve competence has not been studied. However, it is generally agreed that EUS-guided FNA of pancreatic lesions carries a higher complexity and risk for potential complications than does EUS-guided FNA at other anatomic sites. Therefore, the number required for FNA of pancreatic lesions is considered separately from other anatomic locations. For nonpancreatic lesions (i.e., intramural lesions, lymph nodes, ascites), it is recommended that a trainee be competent in nonpancreatic EUS and conduct at least 25 supervised FNA cases before competency can be assessed.[20] Competence in EUS-guided FNA of pancreatic lesions requires demonstration of competence in pancreaticobiliary EUS ($\geq$75 cases), in addition to 25 supervised FNA procedures of pancreatic lesions.[20] Because of the absence of literature supporting a threshold number for EUS-guided FNA,

these threshold numbers were adopted from the guidelines set forth for therapeutic ERCP that require a minimum of 25 supervised cases in addition to 75 diagnostic cases.[23] The similarities between EUS and ERCP, such as side-viewing instruments and combined endoscopic and radiologic imaging, led to these recommendations. Clinical studies addressing this question for EUS-guided FNA of pancreatic and nonpancreatic lesions are needed to assess the validity of these recommendations further.

One of the problems facing EUS trainees is the absence of an appropriate model for teaching EUS-guided FNA. Practicing EUS-guided FNA on a model before performing the procedure on a patient may potentially avoid safety and credentialing issues that would ordinarily limit the training endosonographer. Parupudi et al[25] developed a porcine model for EUS-guided FNA. The authors injected autologous blood admixed with carbon particles into the mediastinal lymph nodes of female pigs. After 2 weeks, the pigs were re-examined with EUS, which demonstrated significant lymph node enlargement and thereby allowed EUS-guided FNA of lymph nodes in various locations within the mediastinum. This represents an interesting in vivo hands-on porcine model for future training in EUS-guided FNA.

COMPREHENSIVE EUS COMPETENCE

Some practitioners may be interested in acquiring competence in only one or two areas of EUS and can therefore focus their efforts on specific anatomic locations, as outlined earlier. However, for those practitioners interested in achieving competence in multiple areas of EUS, training must include exposure to a variety of procedures with differing clinical disorders. It is generally recognized that once competence in one area of EUS has been established, the number of cases required to achieve competence in other areas may be reduced. For trainees interested only in mucosal and submucosal lesions, it is generally recommended that a minimum of 100 supervised cases be performed. Consideration for comprehensive EUS competence, including pancreaticobiliary imaging and FNA, requires a minimum of 150 cases, including 50 EUS-guided FNAs and at least 75 pancreaticobiliary cases.[20]

RECREDENTIALING AND RENEWAL OF EUS PRIVILEGES

Over the course of time, physicians who have received appropriate privileges to perform EUS may change the scope of their clinical practice and subsequently reduce the frequency of performing one or more EUS procedures. Investigators have suggested that ongoing experience in advanced endoscopy is necessary to retain the technical skills required to perform these technically challenging procedures safely and adequately.[26,27] The goal of recredentialing is to ensure continued clinical competence while promoting continuous quality improvement and maintaining patient safety. If ongoing experience is not maintained at some objective level, the quality of care provided to the patient may diminish, potentially leading to adverse events.

The ASGE has provided useful guidelines for renewing endoscopic privileges and ensuring continued clinical competence in EUS.[28] However, it is the responsibility of each institution to develop and maintain individual guidelines for granting and renewing privileges. The threshold number of procedures necessary for recredentialing may vary among institutions; however, this threshold must be commensurate with the technical and cognitive skills required for advanced procedures such as EUS. Individual institutions must establish a frequency for the renewal process along with contingency plans when minimal competence cannot be assured. The Joint Commission mandated that renewal of clinical endoscopic privileges be made for a period of no more than 2 years.[29] Endosonographers seeking renewal of privileges must document an adequate case load over a set period of time to maintain the necessary skills required for EUS. This documentation may include procedure log books or patient records and should focus on objective measures such as number of cases, success rates, and complications. Continued cognitive training through participation in educational activities should also be a prerequisite for the recredentialing process. New EUS procedures and clinical applications continue to emerge and require a commitment to continued medical education within this specialized field.

SIMULATORS IN EUS

Endoscopic simulators have been developed for training in flexible sigmoidoscopy, esophagogastroduodenoscopy, colonoscopy, ERCP, and most recently EUS.[30] Since the development of the first endoscopic mannequin simulator in the late 1960s,[31] considerable technologic advances have been made in the development of endoscopic simulators. Various simulators are available today, ranging from animal-based simulators (Erlangen Endo-Trainer; Erlangen, Germany) to the computer-based simulators manufactured by Immersion Medical Corporation (Accutouch Endoscopy Simulator; Gaithersburg, Md) and Simbionix Corp. (GI Mentor II; Cleveland).[32] Validation studies and small, prospective, clinical trials assessing the utility of endoscopic simulators have been conducted for upper endoscopy, flexible sigmoidoscopy, and colonoscopy.[33–37] However, the benefits of simulator training have not been clearly demonstrated, and this finding emphasizes the need for further investigation with large, prospective trials. Nevertheless, this technology represents an exciting and potentially useful adjunct to formal endoscopic training.

Simbionix Corporation (www.simbionix.com) developed the first computer-based EUS simulator that provided a platform for hands-on training and practice of EUS procedures (Fig. 3.1).[32] The computer-based simulator generates ultrasound images in real-time from three-dimensional anatomic models constructed from CT and magnetic resonance imaging (MRI) images from real patients. The trainee inserts a customized echoendoscope

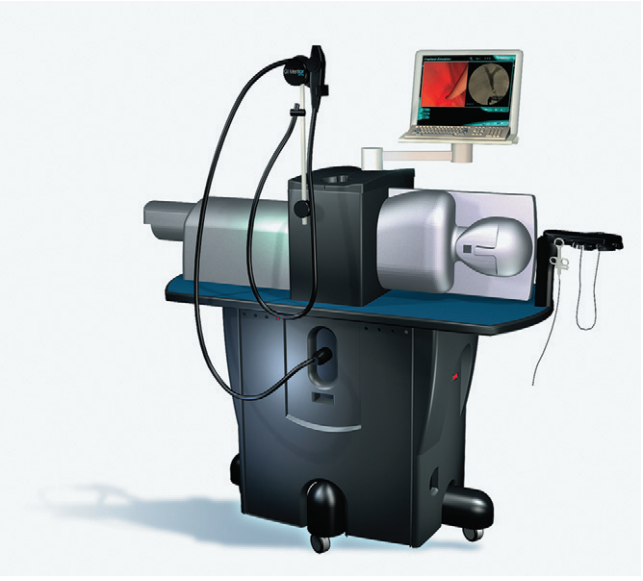


FIGURE 3.1 Simbionix GI-Mentor Simulator. *(Courtesy of Symbionix Corporation USA, Cleveland, OH.)*

into the specially designed GI-Mentor mannequin and simultaneously receives visual feedback from the monitor, along with tactile sensation from scope maneuvering during the procedure. A highly sensitive tracking system translates position and direction of the camera into realistic computer-generated images. The EUS module allows the trainee to switch from endoscopic to ultrasound images in real time and also provides training in both radial and linear ultrasound probes. Split-screen capability provides ultrasound images alongside three-dimensional anatomic maps that further assist in the interpretation and understanding of generated EUS images. The module also allows trainees to practice keyboard functions such as labeling of organs, magnifying images, changing frequencies, and measuring with calipers. Following completion of the examination, the computer software permits performance evaluation by reviewing all saved images ($\leq$50 frozen images per procedure) and indicating anatomy and landmarks that were improperly identified by the user.

Although the Simbionix GI-Mentor II EUS training module presents an exciting approach to training in EUS, there are currently no published validation studies or clinical trials assessing EUS simulators. A small study was published on learning EUS using the newer Erlangen Active Simulator for Interventional Endoscopy (EASIE-R) (ENDOSIM, LLC, Nahant, Mass.)[38] This simulator consists of a complete porcine GI tract explant with surrounding structures including the bile duct and pancreas, all embedded in an ultrasound gel. EASIE-R was used by 11 participants (5 beginners and 6 experts) during a 1-day EUS course. Overall, the simulator was thought to be easy to use and useful for teaching both basic and advanced EUS techniques. Although simulators represent useful educational tools, further studies are needed in a randomized controlled trial to determine their validity for EUS training. Unfortunately, these simulators are not readily available at most training institutions because of cost constraints and regional needs. However, at select institutions, there may be 1- to 2-week workshops in EUS that allow exposure to this technology.

SUMMARY

EUS has become an important imaging tool for the evaluation of a variety of GI disorders. It is a challenging endoscopic procedure requiring both cognitive and technical skills beyond the general scope of traditional gastroenterology fellowship training. As the demand for skilled endosonographers continues to increase, the guidelines for training must be critically analyzed to ensure the production of well-trained and competent future endosonographers. Although guidelines have been established for credentialing and granting privileges in EUS, additional studies of threshold numbers necessary to achieve competence are indicated to fill existing gaps in the current literature. Endoscopists interested in learning EUS must recognize and appreciate the complexity of these procedures and risks for potential complications. Clearly, a 1- to 2-week course in EUS is considered inadequate training and may potentially expose patients to unnecessary risks and poor quality of care. For clinicians truly interested in mastering the skills required for EUS, a formal supervised training program is far superior to hands-on workshops, teaching videotapes, simulators, and inadequate exposure during a standard GI fellowship.

Simulators for training in EUS represent an exciting and useful adjunct to supervised instruction. Although clinical trials investigating the efficacy of simulators in EUS training are lacking, the potential applications for this technology are promising. Unfortunately, these simulators are not readily available at most institutions because of cost constraints and regional needs. Further studies are necessary to determine the role of endoscopic simulators in EUS training.

REFERENCES

1. Botet JF, Lightdale CJ, Zauber AG, et al. Preoperative staging of esophageal cancer: comparison of endoscopic US and dynamic CT. *Radiology*. 1991;181:419–425.
2. Ziegler K, Sanft C, Friedrich M, et al. Evaluation of computed tomography, endosonography, and intraoperative assessment in TN staging of gastric carcinoma. *Gut*. 1993;34:604–610.
3. Palazzo L, Roseau G, Gayet B, et al. Endoscopic ultrasonography in the diagnosis and staging of pancreatic adenocarcinoma: results of a prospective study with comparison to ultrasonography and CT scan. *Endoscopy*. 1993;25:143–150.
4. Muller MF, Meyenberger C, Bertschinger P, et al. Pancreatic tumors: evaluation with endoscopic US, CT and MR Imaging. *Radiology*. 1994;190: 745–751.
5. Wiersema MJ, Vilmann P, Giovannini M, et al. Endosonography-guided fine needle aspiration biopsy: diagnostic accuracy and complication assessment. *Gastroenterology*. 1997;112:1087–1095.
6. Gress FG, Hawes RH, Savides TJ, et al. Endoscopic ultrasound-guided fine-needle aspiration biopsy using linear array and radial scanning endosonography. *Gastrointest Endosc*. 1997;45:243–250.
7. Senzer N, Hanna N, Chung T, et al. Completion of dose escalation component of phase II study of TNFerade combined with chemoradiation in the treatment of locally advanced pancreatic cancer [abstract]. In: *American Society of Clinical Oncology Gastrointestinal Cancers Symposium*. Hollywood, FL; 2005.
8. Parada KS, Peng R, Erickson RA, et al. A resource utilization projection study of EUS. *Gastrointest Endosc*. 2002;55:328–334.
9. American Society for Gastrointestinal Endoscopy. Guidelines for training in endoscopic ultrasound. *Gastrointest Endosc*. 1999;49:829–833.
10. American Society for Gastrointestinal Endoscopy. Guidelines for advanced endoscopic training. *Gastrointest Endosc*. 2001;53:846–848.
11. Azad JS, Verma D, Kapadia AS, et al. GI fellowship programs meet American Society for Gastrointestinal Endoscopy recommendations for training in EUS? A survey of U.S. GI fellowship program directors. *Gastrointest Endosc*. 2006;64:235–241.
12. American Society for Gastrointestinal Endoscopy. Methods of granting hospital privileges to perform gastrointestinal endoscopy. *Gastrointest Endosc*. 2002;55:780–783.
13. Hoffman B, Wallace MB, Eloubeidi MA, et al. How many supervised procedures does it take to become competent in EUS? Results of a multicenter three year study [abstract]. *Gastrointest Endosc*. 2000;51:139.
14. Fockens P, Van den Brande JHM, van Dullemen HM, et al. Endosonographic T-staging of esophageal carcinoma: a learning curve. *Gastrointest Endosc*. 1996;44:58–62.
15. Schlick T, Heintz A, Junginger T. The examiner's learning effect and its influence on the quality of endoscopic ultrasonography in carcinoma of the esophagus and gastric cardia. *Surg Endosc*. 1999;13:894–898.
16. Boyce HW. Training in endoscopic ultrasonography. *Gastrointest Endosc*. 1996;43(suppl):S12–S15.
17. American Society for Gastrointestinal Endoscopy. Role of endoscopic ultrasonography. *Gastrointest Endosc*. 2000;52:852–859.
18. Eloubeidi MA, Tamhane A. EUS-guided FNA of solid pancreatic masses: a learning curve with 300 consecutive procedures. *Gastrointest Endosc*. 2005;61:700–708.
19. American Society for Gastrointestinal Endoscopy. Guidelines for credentialing and granting privileges for gastrointestinal endoscopy. *Gastrointest Endosc*. 1998;48:679–682.
20. American Society for Gastrointestinal Endoscopy. Guidelines for credentialing and granting privileges for endoscopic ultrasound. *Gastrointest Endosc*. 2001;54:811–814.
21. Chak A, Cooper GS. Procedure-specific outcomes assessment for endoscopic ultrasonography. *Gastrointest Endosc Clin N Am*. 1999;9:649–656.
22. Hoffman BJ, Hawes RH. Endoscopic ultrasound and clinical competence. *Gastrointest Endosc Clin N Am*. 1995;5:879–884.
23. American Society for Gastrointestinal Endoscopy. Principles of training in gastrointestinal endoscopy. *Gastrointest Endosc*. 1999;49:845–850.
24. American Society for Gastrointestinal Endoscopy. Tissue sampling during endosonography. *Gastrointest Endosc*. 1998;47:576–578.
25. Parupudi A, Holland C, Milla P, et al. Development of porcine lymphadenopathy model for in vivo hands-on teaching and training of EUS-FNA [abstract]. *Endoscopy*. 2009;41(suppl 1):55.
26. Cass OW. Objective evaluation of competence: technical skills in gastrointestinal endoscopy. *Endoscopy*. 1995;27:86–89.
27. Jowell PS. Quantitative assessment of procedural competence: a prospective study of training in ERCP. *Ann Intern Med*. 1996;125:937–939.
28. American Society for Gastrointestinal Endoscopy. Renewal of endoscopic privileges. *Gastrointest Endosc*. 1999;49:823–825.
29. The Joint Commission. *Comprehensive Accreditation Manual for Hospitals 1997*. Oakbrook Terrace, IL: The Joint Commission; 1997.

30. American Society for Gastrointestinal Endoscopy. Endoscopy simulators. *Gastrointest Endosc*. 2000;51:790–792.
31. Markman HD. A new system for teaching proctosigmoidoscopic morphology. *Am J Gastroenterol*. 1969;52:65–69.
32. Gerson LB, Van Dam J. Technology review: the use of simulators for training in GI endoscopy. *Gastrointest Endosc*. 2004;60:992–1001.
33. Moorthy K, Munz Y, Jiwanji M, et al. Validity and reliability of a virtual reality upper gastrointestinal simulator and cross validation using structured assessment of individual performance with video playback. *Surg Endosc*. 2004;18:328–333.
34. Datta V, Mandalia M, Mackay S, Darzi A. The PreOp flexible sigmoidoscopy trainer: validation and early evaluation of a virtual reality based system. *Surg Endosc*. 2002;16:1459–1463.
35. MacDonald J, Ketchum J, Williams RG, Rogers LQ. A lay person versus a trained endoscopist: can the preop endoscopy simulator detect a difference? *Surg Endosc*. 2003;17:896–898.
36. Sedlack RE, Kolars JC, Alexander JA. Computer simulation training enhances patient discomfort during endoscopy. *Clin Gastroenterol Hepatol*. 2004;2:348–352.
37. Sedlack RE, Kolars JC. Colonoscopy curriculum development and performance-based criteria on a computer-based endoscopy simulator. *Acad Med*. 2002;77:750–751.
38. Yusuf TE, Matthes K, Lee Y, et al. Evaluation of the EASIE-R simulator for the training of basic and advanced EUS. *Gastrointest Endosc*. 2009;69 (suppl):S264.

CHAPTER 4

INDICATIONS, PREPARATION, RISKS, AND COMPLICATIONS

Faris Murad | Michael J. Levy | Mark Topazian

Key Points

The primary indications for EUS are cancer staging when there is potential additive value after computed tomography or magnetic resonance imaging has been performed, assessment (usually combined with EUS fine-needle aspiration [FNA]) of lymph node status, and evaluation of pancreatic disease and submucosal tumors.

Antibiotics are recommended for prophylactic use with EUS FNA of a cystic lesion.

No reliable data are available regarding EUS FNA in patients with increased risk of bleeding. In the absence of data, the following are reasonable rules:
- *International normalized ratio (INR) <1.5*
- *Platelet count >50,000*
- *Use of a 22- to 25-gauge needle*
- *Performance of as few passes as possible (cytopathologist in room)*

The risk of perforation associated with EUS is higher than for standard endoscopy. Caution should be exercised when intubating the patient, traversing stenotic tumors, and passing the instrument past the apex of the duodenal bulb; these are all situations in which the long, rigid tip increases the difficulty of passing the instrument.

INDICATIONS

Endoscopic ultrasonography (EUS) continues to evolve as a diagnostic and therapeutic modality. EUS should be performed when it has the potential to affect patient management,[1] such as when establishing a diagnosis, performing locoregional tumor staging, or providing therapeutic interventions. Since the introduction of EUS in 1980, its indications and role have continued to expand. This discussion of indications is limited to general comments, in recognition of the inevitable changes that future technologic advances will bring. A detailed discussion of specific indications can be found in relevant chapters throughout this book.

Diagnostic Imaging

The endosonographic appearance alone may provide a confident diagnosis for certain lesions including gut duplication cysts, lipomas, bile duct stones, and some branch duct intraductal papillary mucinous neoplasias. In none of these situations, however, does a "classic" EUS image provide 100% diagnostic accuracy. As a result, EUS-guided fine-needle aspiration (FNA) or Tru-Cut biopsy (TCB) is often indicated to allow for cytologic or histologic diagnosis. Follow-up imaging may be indicated when EUS demonstrates a benign-appearing lesion, to identify interval growth or other signs suggestive of malignancy.

Tumor Staging

Initial evaluation of patients with gastrointestinal (GI) cancers includes assessment of operative risk and determination of tumor stage. Accurate staging is necessary to determine prognosis, to guide administration of chemoradiation, and to select the ideal means and extent of resection when appropriate. Staging usually begins with noninvasive imaging such as computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography (PET), which are generally superior to EUS for excluding distant metastases. In the absence of metastases, EUS is often subsequently performed for T (tumor) and N (nodal) staging because it provides an accuracy of about 85% for GI luminal cancers.[2–5] Prior radiation therapy substantially decreases the T-staging accuracy of EUS.

EUS provides important nodal staging information in patients with lung, esophageal, and rectal cancer. Use of sonographic features of lymph nodes is at best 75% accurate for predicting malignancy. The typical EUS characteristics of malignant lymph nodes are echo-poor appearance, round shape, smooth border, and size greater than 1 cm in the short axis.[6–8] Overlap in appearance between benign and malignant lymph nodes makes nodal staging problematic, and the aforementioned criteria are less useful in lung cancer, rectal cancer, and cholangiocarcinoma.[9] Overstaging may result from enlarged reactive lymph nodes that are deemed malignant on the basis of their EUS appearance alone. The addition of FNA improves nodal staging accuracy, but it also introduces the possibility of false-positive results, particularly when luminal cancer is present.[10] When performing biopsy of lymph nodes, one should avoid traversing the primary tumor to minimize the risk of a false-positive cytologic findings and tumor seeding.

EUS has a limited role in establishing the presence or absence of distant metastasis (M stage). Occasionally, a suspicious lesion is best approached for aspiration through EUS, or a previously unsuspected metastasis is diagnosed during EUS performed for local staging (e.g., a liver lesion in a patient with pancreatic cancer). In these cases, EUS FNA appears reasonably safe, at least with regard to the liver and the adrenal glands.[11–14]

EUS has been compared with PET in staging of esophageal cancer. PET has the ability to identify distant non-nodal metastatic disease more accurately than EUS and CT.[15] Imaging with PET upstages patients who were previously considered to have local or locally advanced disease, and it excludes the possibility of curative R0 surgical resection. However, PET has limited accuracy in staging locoregional disease, and EUS remains superior to PET or CT for this indication.[16] It appears that PET and EUS are complementary for optimal staging. It is uncertain whether PET should be performed first, to allow patients with previously undetected metastases to avoid the cost and discomfort of EUS, or whether EUS should be performed first, with PET reserved for patients with locally advanced disease or incomplete EUS examinations resulting from esophageal obstruction.[17]

The role of EUS in pancreatic cancer staging has been debated. In patients whose tumor is visible on CT, EUS and CT provide comparable accuracy with regard to vascular involvement and nodal involvement. However, EUS retains a key role in the evaluation of pancreatic masses for two reasons: its ability to detect abnormalities missed by CT and the capability to obtain tissue specimens during the examination. Studies have shown that EUS can identify small metastatic lesions that were not identified on CT, including left lobe liver metastases, perivascular cuffing by tumor, and malignant involvement of celiac ganglia.[18–20] The ability to obtain tissue specimens from these sites or from the primary pancreatic mass is increasingly important. Pancreatic mass lesions may be adenocarcinoma, other neoplasms such as neuroendocrine tumors or metastases, or benign conditions such as autoimmune pancreatitis, and these lesions cannot always be differentiated by clinical findings, imaging, and laboratory tests. EUS FNA and TCB allow efficient diagnosis in many such cases. Finally, EUS remains superior to CT for detection of small pancreatic cancers that are most likely to be resectable. For this reason, EUS should be performed if clinical or CT findings raise the question of a small pancreatic cancer not visualized by CT.

EUS has an evolving role in lung cancer staging. Noninvasive methods for staging non–small cell lung cancer (NSCLC) include CT and PET. These modalities have low sensitivity and specificity for the detection of mediastinal lymph node metastasis. Patients with negative CT results for mediastinal adenopathy have up to a 35% prevalence of mediastinal adenopathy.[21] To limit false-positive and false-negative diagnoses of nodal stage, lymph node tissue sampling is advocated when it will change the management strategy (typically when a visualized lymph node is contralateral to the primary tumor). Sampling of all relevant nodal stations has traditionally required surgical mediastinoscopy. However, one study showed that a combination of EUS and endobronchial ultrasound (EBUS) for staging in NSCLC had a negative predictive value of 97% in the evaluation of mediastinal lymph nodes.[22] It appears that the combination of EUS and EBUS is comparable to mediastinoscopy for nodal staging. EUS and EBUS are complementary, given that neither test visualizes all relevant mediastinal lymph node stations.[23] EUS also allows evaluation of the left adrenal gland for previously undetected distant metastases.[24]

Tissue Acquisition

The development of linear EUS technology in the early 1990s allowed for EUS FNA and EUS TCB of lesions within and extrinsic to the GI tract wall.[25] Common indications for FNA include biopsy of pancreatic mass lesions and nodal staging of esophageal, pancreatic, and rectal cancers. EUS often provides the least invasive and most successful route to obtaining tissue specimens.

Less invasive approaches for establishing a tissue diagnosis include transabdominal ultrasound or CT-guided biopsy. The accuracy and safety of these methods are well established and support their use for initial attempts at diagnosis when these techniques are likely to provide the needed material (e.g., in patients with liver metastases). However, these methods may be limited by their poor sensitivity in the diagnosis of small lesions or by concern for potential tumor seeding of the biopsy needle tract. EUS may be favored in these situations, as well as when EUS is indicated for other reasons such as for locoregional staging or celiac plexus neurolysis. In such settings, FNA can be performed during the same examination, thereby offering a cost-effective approach and simplified patient care. This is in contrast to percutaneous approaches for biopsy that are routinely performed as a separate procedure. Although the diagnostic accuracy of EUS FNA for pancreatic cancer and nodal metastases is generally greater than 85%, this method is less accurate in other settings, including diagnosis of pancreatic cystic lesions, stromal tumors, and autoimmune pancreatitis, as a result of limitations associated with cytologic evaluation. An EUS-guided TCB device is available that provides a core biopsy for histologic assessment of tissue architecture.[26] EUS TCB safely improves the diagnostic accuracy of EUS in selected settings.[27,28]

Therapy

The ability to pass a hollow needle under ultrasound guidance has expanded the applications of EUS. The needle is essentially a conduit that allows for the passage or placement of materials with therapeutic intent. The first such therapy to be developed was EUS-guided celiac plexus neurolysis or block,[29,30] followed by EUS-guided pseudocyst drainage.[31] Both of these interventions are now commonly performed under EUS guidance. EUS fine-needle injection (EUS FNI) was introduced as a means to deliver novel, potentially therapeutic agents into solid pancreatic cancers,[32,33] as well as for treatment of pancreatic cystic neoplasms. However, limited data are available to judge the safety and efficacy of EUS FNI for these indications. Other EUS-guided therapeutic interventions have been described, including drainage of otherwise inaccessible biliary and pancreatic ducts,[34] coil embolization of bleeding varices, treatment of bleeding pancreatic pseudoaneurysm,[35,36] placement of fiducials to guide radiation therapy,[37] recovery of migrated stents, and transduodenal gallbladder drainage. Insufficient data are available to judge the safety, efficacy, and ultimate clinical role of most of these procedures, some of which are discussed in more detail in other chapters.

Contraindications

Absolute contraindications to EUS are few and include unacceptable sedation risks. EUS FNA is generally contraindicated in the presence of coagulopathy (international normalized ratio [INR] >1.5), thrombocytopenia (platelets <50,000), or intervening structures prohibiting biopsy. Relative contraindications to EUS include (1) newly diagnosed cancer in a patient who has not undergone appropriate initial evaluation, (2) altered anatomy prohibiting access, and (3) mild coagulopathy or thrombocytopenia. Mild coagulopathy is unlikely to cause clinically significant bleeding, but it may increase blood in the aspirates that can decrease diagnostic sensitivity. Limited data suggest that EUS FNA may be relatively safe in patients with portal hypertension.

PATIENT PREPARATION

General Measures

Although EUS is typically performed in an ambulatory setting, it is also performed in hospitalized patients, and practices are increasingly allowing open-access referrals. As a result, the setting of the preprocedure evaluation can vary, as may the extent of the evaluation. At a minimum, an initial evaluation including a history, physical examination, and review of the medical records must be conducted to identify factors that influence the need, risks, benefits, alternatives, and timing of EUS and to document acquisition of informed consent (Box 4.1).[38,39] Because emergency EUS is uncommon, involved parties should generally have

BOX 4.1 FACTORS THAT MAY AFFECT THE PERFORMANCE OF EUS

- Severity and urgency of EUS examination
- Prior endoscopic examinations (findings and complications)
- Other imaging studies (findings and results of tissue sampling)
- Administrations of chemoradiation (and timing relative to EUS)
- Comorbid illnesses
  - Cardiopulmonary disease
  - Hepatic disease
  - Hematologic disease
- Bleeding diathesis
- Altered anatomy
- Medications
  - Antihypertensives
  - Anticoagulants
  - Antiepileptics
  - Aspirin and other nonsteroidal anti-inflammatory agents
  - Cardiac
  - Hypoglycemic agents
  - Monoamine oxidase (MAO) inhibitors
  - Oral birth control pills
  - Pulmonary
  - Psychiatric
- Drug allergies
- Ability to give informed consent
- Available transportation

the necessary time for adequate evaluation, for discussion of patient and family concerns, and for answering questions. A professional and unhurried demeanor facilitates open communication and helps patients and their families develop trust and a bond with the physician.

Initial planning and preparation for EUS of the upper GI (UGI) and lower GI (LGI) tract are similar to those for routine endoscopy and colonoscopy.[40,41] Efforts are undertaken to help ensure a proficient and accurate EUS examination while maintaining the patient's comfort and safety. Before the procedure, patients are instructed on their preparation responsibilities, the use of other medications, and the need to avoid alcohol and other sedatives. Patients are advised of the use of conscious sedation and resulting restrictions on postprocedure activities and the need for transportation. The potential signs and symptoms of adverse outcomes, as well as contact persons and phone numbers, are given in the event of procedure-related complications. These instructions are reviewed after the procedure with the patient and accompanying adult.

Heavier sedation may be required for EUS than for routine endoscopic procedures because of the often longer examination time and the need to minimize movement of the patient. As for all patient-sedated endoscopic procedures, careful monitoring is required throughout the procedure and recovery period. Administration of supplemental oxygen to all patients receiving sedation is recommended. Although conscious sedation is routinely given for UGI EUS, it is optional for rectal EUS.

UGI EUS is ideally performed following an overnight fast. At a minimum, patients should avoid solid foods for 6 hours and liquids (except sips of water to ingest medications) for 4 hours before the procedure. When there is concern for incomplete gastric emptying as a result of dysmotility or obstruction, a 1- to 2-day diet of clear liquids may be advised. Retained gastric contents increase the risk of aspiration, may compromise acoustic coupling, produce image artifacts, and impair the overall examination quality.

Although some endosonographers perform rectal EUS after administering enemas alone, a full colon preparation is preferred, to optimize acoustic coupling, to minimize image artifacts, and potentially to reduce infectious complications associated with FNA by decreasing intraluminal contents. More intense or prolonged efforts at cleansing the colon may be required in patients with chronic constipation or a recent barium examination.

Laboratory Studies

The need for and benefits of routine laboratory evaluation have not been formally studied in patients undergoing endoscopic procedures. Current recommendations are based on extrapolation of surgical data. Surgical series have consistently demonstrated a lack of utility of routine preoperative studies such as hemoglobin level, blood crossmatching, routine chemistry studies, coagulation parameters, urinalysis, chest radiograph, and electrocardiogram for patients without evidence of relevant underlying disorders.[42–47] Routine preoperative testing in healthy patients rarely identifies abnormal findings and does not predict or correlate with patient outcomes.[47,48] Therefore, routine screening in asymptomatic patients is discouraged. Instead, endoscopists are advised to order preprocedure testing selectively, based on clinical suspicion arising from the initial evaluation, including a history of bleeding diathesis.[49–52] This more focused approach greatly enhances the yield of preoperative testing without compromising patient outcomes.[53]

An exception may be women of childbearing age in whom pregnancy is possible. Although pregnancy is not a contraindication to endoscopic procedures or conscious sedation, in some situations it is important to know whether a woman is pregnant, because of the impact on certain procedural aspects. Such circumstances include administration of general anesthesia (in patients who are difficult to sedate) or use of fluoroscopy (when performing EUS as part of a rendezvous procedure following failed endoscopic retrograde cholangiopancreatography [ERCP]).[54] When possible, it is advisable to avoid or delay EUS until after delivery. When EUS cannot be delayed, appropriate measures should be undertaken to lessen the risk to the unborn child.

Medications

Daily Medications

In the absence of controlled trials to guide management, patients are instructed to continue their cardiac, antihypertensive, pulmonary, antiepileptic, psychiatric, and contraceptive medications. These medications are ingested with sips of water early on the day of the procedure. Diabetic patients are advised to take half of their morning insulin dose at the usual time and the remaining dose with a postprocedure meal. Oral hypoglycemic agents are withheld the morning of the procedure and until resumption of a normal diet.

Prophylactic Antibiotics

There is minimal risk (0% to 6%) of developing bacteremia after "routine" procedures such as esophagogastroduodenoscopy (EGD), flexible sigmoidoscopy, and colonoscopy.[55] The risk of bacteremia is not increased as a result of mucosal biopsy, polypectomy, endoscopic mucosal resection, and sphincterotomy.[56] However, an increased rate of bacteremia or local infection is reported following other endoscopic procedures including esophageal sclerotherapy,[57] esophageal stricture dilation,[58,59] ERCP with biliary obstruction,[60] endoscopic drainage of a pancreatic pseudocyst,[61] and endoscopic placement of feeding tubes.[62] Although the risk of developing endocarditis or other infectious complication as a result of endoscopic procedures is low, the resulting morbidity and mortality are high. These findings led the American Heart Association,[63] American Society for Gastrointestinal Endoscopy (ASGE), and other societies and interest groups[64,65] to recommend antibiotic prophylaxis for high-risk patients undergoing procedures with a high risk of associated bacteremia.

TABLE 4.1

Cardiovascular Risk Factors for Endocarditis

Risk	Condition
High	Prosthetic heart valve (bioprosthetic and homograft)
	History of bacterial endocarditis
	Complex cyanotic congenital heart conditions
	Single ventricle states
	Transposition of the great arteries
	Tetralogy of Fallot
	Surgically constructed systemic-pulmonary shunt or conduits
	Synthetic vascular graft (<1 yr old)
Moderate	Most other congenital cardiac malformations (other than above and below)
	Acquired valve dysfunction (e.g., rheumatic heart disease)
	Hypertrophic cardiomyopathy (with latent or resting obstruction)
	Mitral valve prolapse
	With murmur and/or valve regurgitation and/or thickened leaflets and/or emergency need for procedure
Negligible*	Isolated secundum atrial septal defect
	Surgical repair of (without residua beyond 6 months)
	Atrial septal defect
	Ventricular septal defect
	Patent ductus arteriosus
	CABG (prior)
	Mitral valve prolapse (without valve regurgitation)
	Physiologic, functional, or innocent heart murmurs
	Prior Kawasaki's disease (without valve dysfunction)
	Prior rheumatic heart disease (without valve dysfunction)
	Pacemaker (intravascular and epicardial)
	Implanted defibrillators

*Same risk as the general population.

CABG, coronary artery bypass graft.

Adapted from Dajani AS, Taubert KA, Wilson W, et al. Prevention of bacterial endocarditis: recommendations by the American Heart Association. *Clin Infect Dis*. 1997;25:1448-1458; and Wilson W, Taubert KA, Gewitz M, et al. Prevention of infective endocarditis: guidelines from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. *Circulation*. 2007;116(15):1736-1754.

TABLE 4.2

American Society for Gastrointestinal Endoscopy Recommendations for Antibiotic Prophylaxis

Patient Condition	Procedure	Antibiotic Prophylaxis
High-risk cardiac lesion	High risk	Yes
	Low risk	±
Moderate-risk cardiac lesion	High risk	±
	Low risk	No
Low-risk cardiac lesion	High risk	No
	Low risk	No
Cirrhosis (with acute GI bleeding)	Any	Yes
Ascites, immunocompromised	High risk	±
Cirrhosis (without acute GI bleeding)	Low risk	No
Biliary obstruction	ERCP	Yes
Pancreatic cystic lesion	ERCP	Yes
	EUS FNA	Yes
All patients	PEG	Yes
Prosthetic joint	Any	No
Solid UGI lesions	EUS FNA	No
Solid LGI lesions	EUS FNA	No
Nonpancreatic cystic lesions	EUS FNA	Yes

ERCP, endoscopic retrograde cholangiopancreatography; FNA, fine-needle aspiration; GI, gastrointestinal; LGI, lower gastrointestinal; PEG, percutaneous endoscopic gastrostomy; UGI, upper gastrointestinal; ±, prophylaxis optional for patients with moderate-risk lesions (insufficient data to make a firm recommendation; physician should choose on case-by-case basis).

Adapted from ASGE Standards of Practice Committee, Banerjee S, Shen B, et al. Antibiotic prophylaxis for GI endoscopy. *Gastrointest Endosc*. 2008;67 (6):791-798.

Risk of Bacteremia and Antibiotic Recommendations for Other Endoscopic Procedures. Bacterial endocarditis usually develops in patients with high-risk congenital or acquired cardiac lesions who develop bacteremia with microorganisms commonly associated with endocarditis.[66] Cardiac abnormalities are stratified as high risk, moderate risk, and low or negligible risk on the basis of the relative risk of developing endocarditis and the potential outcome if endocarditis develops (Table 4.1).[63] In most patients, with or without underlying risk factors, the resulting transient bacteremia is limited in duration (<15 minutes) and of no clinical significance.[67] Rarely, bacteria may lodge on damaged or abnormal heart valves and result in bacterial endocarditis.

Most cases of bacterial endocarditis (60% to 75%) develop in the absence of a procedure or intervention typically associated with bacteremia.[68] However, certain endoscopic procedures are associated with a high frequency of bacteremia caused by microorganisms commonly associated with endocarditis. The reported rate of bacteremia following particular endoscopic procedures varied greatly among studies. These trials were mostly small and uncontrolled. The discrepancy in results can partly be explained by widely varying differences in methodology. Studies varied in regard to technical aspects of the procedures and in the timing, number, and volume of blood cultures. However, the general consensus is that several endoscopic procedures place patients at higher risk for developing bacteremia. High-risk procedures include esophageal stricture dilation and variceal sclerotherapy and are associated with bacteremia in approximately 30% of patients. Other high-risk procedures include endoscopic retrograde cholangiography with biliary obstruction and endoscopic drainage of a pancreatic pseudocyst. Although endocarditis rarely develops following these endoscopic procedures, antibiotic prophylaxis is recommended in properly selected patients because of the high morbidity and mortality associated with endocarditis (Table 4.2).[67]

EUS Studies. The data regarding the risk of infectious complications following EUS with or without FNA show a frequency of bacteremia in a range similar to that for diagnostic UGI endoscopy. Barawi et al[69] prospectively evaluated the risk of bacteremia and other infectious complications associated with EUS FNA. One hundred patients underwent EUS FNA of a total of 107 lesions. EUS FNA was performed for a variety of UGI indications. Contaminated blood cultures occurred in 6 patients, but none of the patients in this study developed bacteremia or any infectious complication. The absence of true bacteremia may be partly explained by the minimal quantity (10 mL) of blood collected and the delayed timing (30 minutes after EUS FNA) of the first blood culture, both of which are associated with lower rates of positive blood cultures.[57–59,70]

In a subsequent report of 52 patients who underwent EUS FNA of 74 sites from solid lesions of the UGI tract, with a mean of five needle passes, coagulase-negative *Staphylococcus* grew in three patients (5.8%; 95% confidence interval [CI], 1% to 15%) and was considered a contaminant. Three patients (5.8%; 95% CI, 1% to 15%) developed bacteremia as the result of viridans

group *Streptococcus* ($n = 2$) and an unidentified gram-negative bacillus ($n = 1$).[71] This rate is rate similar to that for routine endoscopy. None of the patients developed signs or symptoms of infection. Janssen et al[72] prospectively studied 100 patients undergoing diagnostic EUS (group A) along with 50 patients who underwent UGI EUS FNA (group B). Excluding contaminants, bacteremia developed in four patients overall, two from each group. These investigators concluded that the rate of bacteremia after EUS of UGI tract lesions with and without FNA is low and that routine administration of antibiotics is not warranted. It appears that EUS FNA of solid UGI tract lesions should be considered a low-risk procedure for infectious complications and does not warrant antibiotic prophylaxis for bacterial endocarditis.

Another prospective study evaluated the risk of bacteremia and other infectious complications in patients who underwent EUS FNA of LGI tract lesions. A total of 100 patients underwent a total of 471 FNA procedures to obtain cytologic samples from lymph nodes, the wall of the rectum, or the sigmoid colon. Blood cultures were positive in six patients, with four cultures deemed contaminants, and the remaining two patients had transient bacteremia. Hence it also appears that transrectal EUS FNA of solid lesions in or adjacent to the LGI tract should be considered a low-risk procedure for infectious complications and does not warrant prophylactic antibiotics.[73]

Although the aforementioned studies address the risks of infectious complications following EUS FNA for solid lesions, data support the use of antibiotic prophylaxis for EUS FNA of cystic lesions. In a large retrospective analysis of 603 patients who underwent EUS FNA of cystic lesions of the pancreas, a single infection was reported. Most patients in this study received antibiotic prophylaxis during the procedure and a 3-day course of postprocedure prophylaxis with a fluoroquinolone.[74] The ASGE recommends antibiotic prophylaxis for EUS FNA of pancreatic cystic lesions.[75]

Anticoagulants and Antiplatelet Agents

Anticoagulants are given to reduce the risk of stroke or systemic embolus in patients with atrial fibrillation, valvular heart disease, and mechanical heart valves.[76–78] In addition, these drugs help to prevent deep vein thrombosis, thrombosis resulting from a hypercoagulable state, and occlusion of coronary artery stents.[76–78] Warfarin must often be discontinued at the time of surgery or endoscopy to minimize the risk of procedure-induced bleeding. However, doing so puts the patient at risk of developing thromboembolic events. In addition, thromboembolism may result from the transient hypercoagulability that develops following discontinuation of anticoagulation and from a prothrombic effect associated with surgical intervention.[79] Therefore, "bridging therapy" with administration of unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) is often given to ameliorate the risk of thromboembolism.

ASGE Recommendations. The ASGE classified procedures as either high risk or low risk depending on the likelihood of inducing bleeding (Table 4.3).[77] EUS without FNA is regarded as a low-risk procedure. Although patients undergoing EUS FNA are not believed to be at increased risk of bleeding, EUS FNA is considered a high-risk procedure because resulting bleeding is inaccessible or uncontrollable by endoscopic means. In addition, patients' conditions are classified as high risk or low risk based on the likelihood of developing a thromboembolic event (Table 4.4).[80] Based on both procedural and condition-related risks, the ASGE made general guidelines for anticoagulation therapy in the periprocedure period in patients receiving long-term warfarin therapy (Table 4.5).[81] The ASGE recommended that for patients taking LMWH who are undergoing low-risk procedures (EUS without FNA), no change in anticoagulation therapy is necessary. For patients undergoing high-risk procedures (EUS FNA), the recommendations

TABLE 4.3

Risk of Bleeding Based on Endoscopic Procedure

High Risk	Low Risk
Increased risk of bleeding	Diagnostic (with or without biopsy)
Polypectomy	Esophagogastroduodenoscopy
Gastric (4%)	Flexible sigmoidoscopy
Colonic (1%-2.5%)	Colonoscopy
Laser ablation and coagulation (<6%)	Enteroscopy
Variceal therapy	Endoscopic ultrasound (without FNA)
Endoscopic sphincterotomy (2.5%-5%)	ERCP (without sphincterotomy)
	Biliary/pancreatic stent (without sphincterotomy)
Inaccessible or uncontrollable endoscopically	
Dilatation (pneumatic, bougie)	
PEG/PEJ	
EUS FNA	

ERCP, endoscopic retrograde cholangiopancreatography; FNA, fine-needle aspiration; PEG, percutaneous endoscopic gastrostomy; PEJ, percutaneous endoscopic jejunostomy.

Adapted from Zuckerman MJ, Hirota WK, Adler DG, et al. ASGE guideline: the management of low-molecular-weight heparin and nonaspirin antiplatelet agents for endoscopic procedures. *Gastrointest Endosc*. 2005;61(2):189-194.

TABLE 4.4

Risk of Thromboembolism Based on Underlying Medical Condition

High Risk	Low Risk
Atrial fibrillation (with valve disease)	Deep vein thrombosis
Mechanical valve (mitral)	Atrial fibrillation (no valve disease)
Mechanical valve (prior thromboembolic event)	Bioprosthetic valve
Mechanical valve (aortic)	

Adapted from Eisen GM, Baron TH, Dominitz JA, et al. Guideline on the management of anticoagulation and antiplatelet therapy for endoscopic procedures. *Gastrointest Endosc*. 2002;55:775-779.

TABLE 4.5

Recommendations for Anticoagulation Therapy in Patients Undergoing Endoscopic Procedures Based on the Relative Risks of the Procedure and Underlying Condition

	Condition Risk for Thromboembolism	
Procedure Risk	High	Low
High	Stop warfarin 3-5 days before procedure	Stop warfarin 3-5 days before procedure
	Consider heparin while INR below therapeutic range	Reinstitute warfarin after procedure
Low	No change in anticoagulation	
	Elective procedures should be delayed while INR is in supratherapeutic range	

INR, international normalized ratio.

Adapted from Zuckerman MJ, Hirota WK, Adler DG, et al. ASGE guideline: the management of low-molecular-weight heparin and nonaspirin antiplatelet agents for endoscopic procedures. *Gastrointest Endosc*. 2005;61(2):189-194.

TABLE 4.6

Recommendations for Management of Low-Molecular-Weight Heparin Patients Undergoing Endoscopic Procedures

Procedure Risk	High and/or Low Condition Risk for Thromboembolism
High	Consider stopping LMWH ≥8 hr before procedure Decision to restart should be individualized
Low	No change in anticoagulation

LMWH, low-molecular-weight heparin.

Adapted from Zuckerman MJ, Hirota WK, Adler DG, et al. ASGE guideline: the management of low-molecular-weight heparin and nonaspirin antiplatelet agents for endoscopic procedures. *Gastrointest Endosc*. 2005;61(2):189-194.

TABLE 4.7

Recommendations for Management of Nonaspirin Antiplatelet Agents (Clopidogrel or Ticlopidine) in Patients Undergoing Endoscopic Procedures*

Procedure Risk	Recommendation
High	Consider discontinuation 7-10 days before procedure
Low	No change in therapy

*Patients on combination therapy may be at increased risk of bleeding. Reinstitution of clopidogrel or ticlopidine should be individualized.

Adapted from Zuckerman MJ, Hirota WK, Adler DG, et al. ASGE guideline: the management of low-molecular-weight heparin and nonaspirin antiplatelet agents for endoscopic procedures. *Gastrointest Endosc*. 2005;61(2):189-194.

are to discontinue LMWH at least 8 hours before the anticipated diagnostic or therapeutic endoscopy.[80] Resumption of heparin or LMWH should be individualized; in many cases, it is appropriate to resume anticoagulation 2 to 6 hours after the endoscopic procedure (Table 4.6). Warfarin (Coumadin) can usually be resumed the night of the procedure, and overlapping therapy is recommended for 4 to 5 days or until the INR is therapeutic for 2 to 3 days.

Despite the recommendations of the ASGE, the ideal approach for managing anticoagulation in the perioperative period has not been established and is controversial.[76–80] Firm conclusions cannot be made concerning the efficacy and safety of different management strategies based on the current literature, owing to variations in patient populations, procedures, anticoagulation regimens, definitions of events, and duration of follow-up. The recommendations of the ASGE and most societies are based mostly on data from therapeutic regimens, treatment scenarios, and procedures that in many cases were quite dissimilar to those commonly faced by endoscopists. The need to stop warfarin and administer bridging therapy is controversial and varies among societies. In general, firm recommendations are not given, and many clinical situations are not addressed. This is understandable given the paucity of sound data. As for patient care in general, decisions regarding anticoagulation therapy must be made after careful consideration of the potential risks, benefits, and alternatives for an individual patient.

The use of anticoagulants may predispose patients to development of bloody aspirates and may thus impair cytologic analysis. This possibility should be considered when choosing the degree of negative pressure to apply during FNA, and it may even alter the timing of EUS.

Anticoagulant Administration (Timing and Technique)

Stopping Warfarin. When stopping warfarin (Coumadin), if the target INR is less than 1.5 and the initial INR is 2.0 to 3.0, then three to five doses of warfarin should be withheld.[77,79] If the initial INR is higher than 3.0, then four to six doses should be withheld, especially in elderly patients.[77,79] When the INR is not checked, the number of doses to withhold is based on the typical levels for a patient and the perceived risk of bleeding and thromboembolism.

Starting Bridging Therapy. If bridging therapy is used, it should be started when the INR is expected to be at the lower limit of normal. Because it is often impractical to check the INR daily, it is reasonable to start bridging therapy approximately 2 days after warfarin is discontinued.

Stopping Bridging Therapy. UFH should be stopped 4 to 8 hours before the procedure, and LMWH (when given as a single daily dose) should be discontinued the morning of the procedure. When LMWH is given twice daily, it should be stopped the evening before the procedure.

Resuming Anticoagulation. Anticoagulants should generally be restarted without a bolus.[77,79] The timing is greatly debated, however. Some investigators favor immediate administration with warfarin and either UFH or LMWH, whereas other investigators favor waiting 3 days after a procedure and administering warfarin alone (without UFH or LMWH). The approach is influenced by the occurrence of bleeding during the procedure, the risk of thromboembolism, and the patient's clinical course.

Antiplatelet therapy. For patients taking antiplatelet agents, few data are available to guide recommendations. In patients who take aspirin and other nonsteroidal anti-inflammatory drugs and who do not have a bleeding disorder, the ASGE reported that endoscopic procedures are safe. For patients taking clopidogrel (Plavix) and ticlopidine (Ticlid), low-risk procedures (regardless of the thromboembolic risk) require no change in anticoagulation (Table 4.7). In patients undergoing high-risk procedures (regardless of the thromboembolic risk), the need to discontinue therapy is uncertain. If antiplatelet therapy is discontinued, it should be done 7 to 10 days before the procedure. For dipyridamole, low-risk procedures (regardless of the thromboembolic risk) require no change in anticoagulation (unless there is an underlying bleeding disorder). For high-risk procedures (regardless of the thromboembolic risk), the need to discontinue therapy is uncertain, and no recommendation is given. Finally, glycoprotein IIb/IIIa inhibitors are given for acute coronary syndromes and therefore are not typically used in patients undergoing endoscopy. Although no guidelines are offered, the duration of action may help in guiding timing of the procedure; abciximab has a duration of action up to 24 hours, as compared with eptifibatide and tirofiban, which have a duration of action of approximately 4 hours.

RISKS AND COMPLICATIONS

EUS shares the risks and complications of other endoscopic procedures, including cardiovascular events, complications of conscious sedation, and allergic reactions to medications. This discussion focuses on adverse effects specifically associated with EUS. Some of these relate primarily to the unique features of echoendoscopes, whereas others are associated with the performance of FNA, TCB, or therapeutic interventions.

Perforation

The incidence of GI perforation during EUS ranged from 0%[81] to 0.4%[82] in prospective series enrolling more than 300 patients. Although available data are limited, perforation is probably more common with UGI EUS than with EGD.

The increased risk is partly accounted for by echoendoscope design, which combines oblique or side-viewing optics with a relatively long rigid tip that extends well beyond the optical lens.

The tip of the endoscope may cause luminal perforation during advancement, particularly in areas of angulation (oropharynx or apex of duodenal bulb), stenosis (esophageal cancer), or a blind lumen (pharyngeal or esophageal diverticula). Some evidence indicates that perforation is more common early in an endosonographer's experience.[82] The risk may also be increased when experienced endosonographers use new equipment with different tip design, length, and deflection characteristics.

Intubation of the esophagus with the echoendoscope remains a partially blind maneuver. A prospective study by Eloubeidi et al[83] reported the frequency of cervical perforations. A total of 4894 patients underwent UGI tract EUS, and only 3 patients experienced cervical esophageal perforations.[83] Understanding the possible risk factors (age >65 years, history of swallowing difficulties, known cervical osteophytes, kyphosis of the spine, or hyperextension of the neck) may help to identify high-risk patients.

Approximately 15% to 40% of patients with esophageal cancer have a nontraversable obstructing esophageal tumor.[73–76,84–87] Some investigators advocate dilation, given the greater accuracy of EUS for T and N staging for traversable versus nontraversable tumors (81% versus 28% and 86% versus 72%, respectively).[85,86] Other investigators discourage routine dilation given the risk and tendency for advanced disease (85% to 90% likelihood of T3 or T4 disease) in this setting.[86] However, distant lymphadenopathy (meriting M1a tumor staging) is diagnosed in 10% to 40% of patients requiring dilation.[85,86]

Although initial studies reported perforation rates as high as 24% with esophageal dilation followed by immediate EUS, more recent studies found this practice safe.[84–86] There are several likely explanations for the apparent improvement in safety over time. Radial echoendoscopes introduced in the mid-1990s were of smaller diameter than older devices, so dilation was usually performed to 14 or 15 mm rather than 16 to 18 mm, as in earlier studies. In addition, greater awareness of this potential complication has probably led to less aggressive dilation practices.

For patients with circumferential stenosis, judicious stepwise dilation is undertaken to a maximum of 15 mm. Two large studies reporting on the safety of dilation[87,88] followed the "rule of three" (three stepwise 1-mm increases in dilator diameter above the diameter at which resistance was first encountered) and did not use "unacceptable force" to dilate. Dilation allowed immediate passage of an echoendoscope beyond the tumor in 75% to 85% of cases. Extreme caution is necessary when semicircumferential infiltration is present because the normal (and hence thinner) esophageal wall may be at increased risk of tearing in this setting.

Mini-probes passed through a stenotic malignant esophageal tumor may improve the accuracy of T and N staging, but the limited depth of penetration does not allow a complete examination, particularly with regard to celiac axis nodes.[88] A small-caliber (7-mm) wire-guided echoendoscope without fiberoptic capability has been used for staging stenotic tumors (Olympus MH-908). Use of this instrument in 130 patients allowed complete endoscopic staging in 90% (27 of 30) cases, compared with 60% (60 of 100) in whom this device was not used.[89] Another alternative, if available, is the EBUS device. The EBUS scope is approximately 6.9 mm in diameter, can provide staging information, and has the ability to sample celiac nodes and liver lesions through FNA.

Bleeding

The risk of bleeding with EUS is mainly related to the performance of FNA. The incidence of bleeding was 0% to 0.4% in two prospective studies enrolling more than 300 patients, and it was 1.3% in a retrospective study.[90] FNA of pancreatic cystic lesions has been associated with a 6% rate of self-limited bleeding.[91]

A small amount of luminal bleeding is often seen endoscopically at FNA puncture sites, but it is generally without sequelae. Bleeding may also occur in the gut wall, adjacent tissue, or target structure undergoing aspiration. Such bleeding may be detected sonographically as a hypoechoic expansion of soft tissue or an enlargement of a lymph node or mass. Alternatively, echogenic material may be seen filling a previously anechoic cyst or duct lumen or collecting in ascites. As blood clots, it increases in echogenicity and may thus become less apparent. When the bleeding is into a large potential space (e.g., the peritoneal cavity), the extent of blood loss may be difficult to assess because of pooling of blood outside the range of EUS imaging.

EUS-induced extraluminal bleeding is seldom associated with clinically important sequelae such as need for transfusion, angiography, or surgical intervention. Because most endosonographers avoid sonographically visible vessels when selecting a needle path for FNA, bleeding usually occurs from small vessels. Because the bleeding site is often extraintestinal, methods of endoscopic hemostasis are usually not applicable. In some cases, it is possible to apply transmitted pressure to the bleeding site by deflecting the tip of the echoendoscope against the gut wall[91] or to inject epinephrine. The efficacy of these interventions is unknown.

Infection

Infectious complications have been reported in 0.3% of EUS FNA procedures and may include those associated with the endoscopy itself (aspiration pneumonia) or with FNA (abscess or cholangitis).

Infection may develop secondary to aspiration of cystic lesions in the pancreas, mediastinum, and elsewhere.[92] A 9% rate of infection has been reported after EUS FNA of cysts, the risk of which is markedly decreased by antibiotic administration before and after EUS FNA. The true incidence of cyst infection when antibiotics are given is unknown, but it is likely to be low. Iatrogenic *Candida* infection of a cystic lesion was reported after EUS FNA performed in a patient who received prophylactic antibiotics.[93] Technical issues may also affect the risk of cyst infection. Multiple needle passes into a cyst appear to increase the risk of infection, as does failure to aspirate all the cyst fluid completely.

As reviewed in detail previously, bacteremia after UGI EUS FNA is uncommon. Antibiotic prophylaxis for patients at increased risk of bacterial endocarditis is also discussed earlier.

Although little information is available regarding the risks of EUS-guided injection therapy, a retrospective study by O'Toole and Schmulewitz[94] found a complication rate of 1.8% after celiac plexus block or neurolysis, with a retroperitoneal abscess resulting after a block. Adrenal artery laceration has also been reported as a complication of EUS-guided celiac plexus block.

Pancreatitis

Pancreatitis may occur after EUS FNA of both solid and cystic pancreatic lesions. In a pooled analysis of data from 19 EUS centers in the United States, the incidence of pancreatitis after EUS FNA of solid pancreatic lesions masses was 0.3%.[95] The incidence was higher (0.6%) at two centers with prospectively collected data, and it was also 0.6% in another prospective study.[96] Aspiration of cystic lesions has been associated with pancreatitis in 1% to 2% of cases.[81] Pancreatitis occurring after EUS FNA is generally mild, but severe pancreatitis and fatal complications have been reported.[96]

The risk of pancreatitis may be ameliorated by limiting the number of needle passes, minimizing the amount of "normal" pancreatic parenchyma that must be traversed, and avoiding the pancreatic duct during EUS FNA procedures. In one small series, however, 12 patients with dilated pancreatic ducts underwent intentional EUS-guided aspiration of the duct without complications.[97] Cytologic yield on aspirated pancreatic duct fluid was 75%.

Other

There is a risk of tumor seeding along the needle tract when performing EUS FNA.[98] This risk is of minimal concern for pancreatic head lesions because of inclusion of the needle tract site within the field of resection during pancreaticoduodenectomy.

Bile peritonitis may result from traversal of the bile duct or gallbladder, especially in the presence of an obstructed biliary system.[99] If biliary puncture occurs, antibiotics should be administered to patients who do not have biliary obstruction. In the presence of biliary obstruction, biliary drainage is also recommended.

Left adrenal gland hemorrhage has been reported after EUS-FNA. Although EUS-FNA is a reportedly safe technique, sampling of the left adrenal gland should be limited to cases in which concern for neoplastic involvement exists.

A final adverse effect of EUS is missed or misstaged lesions. Although this error does no immediate, periprocedural harm to the patient, the long-term consequences have not been fully studied. Careful review of the patient's history and imaging studies, as well as formal training in EUS, may decrease the amount of missed lesions encountered in general practice.

REFERENCES

1. Hawes RH. Indications for EUS-directed FNA [abstract]. *Endoscopy*. 1998;30:A155–A157.
2. Tio TL, den Hartog Jager FC, Tytgat GN. The role of endoscopic ultrasonography in assessing local resectability of oesophagogastric malignancies: accuracy, pitfalls, and predictability. *Scand J Gastroenterol Suppl*. 1986;123:78–86.
3. Dittler HJ, Siewert JR. Role of endoscopic ultrasonography in esophageal carcinoma. *Endoscopy*. 1993;25:156–161.
4. Grimm H, Binmoeller KF, Hamper K, et al. Endosonography for preoperative locoregional staging of esophageal and gastric cancer. *Endoscopy*. 1993;25:224–230.
5. Rosch T. Endosonographic staging of esophageal cancer: a review of literature results. *Gastrointest Endosc Clin N Am*. 1995;5:537–547.
6. Bhutani MS, Hawes RH, Hoffman BJ. A comparison of the accuracy of echo features during endoscopic ultrasound (EUS) and EUS-guided fine needle aspiration for diagnosis of malignant lymph node invasion. *Gastrointest Endosc*. 1996;45:474–479.
7. Catalano MF, Sivak Jr MV, Rice T, et al. Endosonographic features predictive of lymph node metastasis. *Gastrointest Endosc*. 1994;40:442–446.
8. Grimm H, Hamper K, Binmoeller KF, et al. Enlarged lymph nodes: malignant or not? *Endoscopy*. 1992;24:320–323.
9. Gleeson FC, Rajan E, Levy MJ, et al. EUS-guided FNA of regional lymph nodes inpatients with unresectable hilar cholangiocarcinoma. *Gastrointest Endosc*. 2008;67(3):438–443.
10. Reddy RP, Levy MJ, Wiersema MJ. Endoscopic ultrasound for luminal malignancies. *Gastrointest Endosc Clin N Am*. 2005;15(3):399–429.
11. DeWitt J, LeBlanc J, McHenry L, et al. Endoscopic ultrasound-guided fine needle aspiration cytology of solid liver lesions: a large single-center experience. *Am J Gastroenterol*. 2003;98:1976–1981.
12. TenBerge J, Hoffman BJ, Hawes RH, et al. EUS-guided fine needle aspiration of the liver: indications, yield, and safety based on an international survey of 167 cases. *Gastrointest Endosc*. 2002;55:859–862.
13. Hollerbach S, Willert J, Topalidis T, et al. Endoscopic ultrasound-guided fine-needle aspiration biopsy of liver lesions: histological and cytological assessment. *Endoscopy*. 2003;35:743–749.
14. Jhala NC, Jhala D, Eloubeidi MA, et al. Endoscopic ultrasound-guided fine-needle aspiration biopsy of the adrenal glands: analysis of 24 patients. *Cancer*. 2004;102:308–314.
15. Rice TW. Clinical staging of esophageal carcinoma. CT, EUS, and PET. *Chest Surg Clin N Am*. 2000;10(3):471–485.
16. Lowe VJ, Booya F, Fletcher JG, et al. Comparison of positron emission tomography, computed tomography, and endoscopic ultrasound in the initial staging of patients with esophageal cancer. *Mol Imaging Biol*. 2005;7(6):422–430.
17. McDonough PB, Jones DR, Shen KR, et al. Does FDG-PET add information to EUS and CT in the initial management of esophageal cancer? A prospective single center study. *Am J Gastroenterol*. 2008;103(3):570–574.
18. Levy MJ, Gleeson FC, Zhang L. Endoscopic ultrasound fine-needle aspiration detection of extravascular migratory metastasis from a remotely located pancreatic cancer. *Clin Gastroenterol Hepatol*. 2009;7(2):246–248.
19. Singh P, Mukhopadhyay P, Bhatt B, et al. Endoscopic ultrasound versus CT scan for detection of the metastases to the liver: results of a prospective comparative study. *J Clin Gastroenterol*. 2009;43(4):367–373.
20. Levy MJ, Topazian M, Keeney G, et al. Preoperative diagnosis of extrapancreatic neural invasion in pancreatic cancer. *Clin Gastroenterol Hepatol*. 2006;4(12):1479–1482.
21. Micames CG, McCrory DC, Pavey DA, et al. Endoscopic ultrasound-guided fine-needle aspiration for non–small cell lung cancer staging: a systematic review and metaanalysis. *Chest*. 2007;131(2):539–548.
22. Wallace MB, Woodward TA, Raimondo M. Endoscopic ultrasound and staging of non–small cell lung cancer. *Gastrointest Endosc Clin N Am*. 2005;15(1):157–167.
23. Hasan MK, Gill KR, Wallace MB, et al. Lung cancer staging by combined endobronchial ultrasound (EBUS) and endoscopic ultrasound (EUS): the gastroenterologist's perspective. *Dig Liver Dis*. 2010;42(3):156–162.
24. Eloubeidi MA, Seewald S, Tamhane A, et al. EUS-guided FNA of the left adrenal gland in patients with thoracic or GI malignancies. *Gastrointest Endosc*. 2004;59(6):627–633.
25. Yusuf TE, Harewood GC, Clain JE, et al. International survey of knowledge of indications for EUS. *Gastrointest Endosc*. 2006;63(1):107–111.
26. Kipp BR, Pereira TC, Souza PC, et al. Comparison of EUS-guided FNA and Trucut biopsy for diagnosing and staging abdominal and mediastinal neoplasms. *Diagn Cytopathol*. 2009;37(8):549–556.
27. Levy MJ, Reddy RP, Wiersema MJ, et al. EUS-guided Trucut biopsy in establishing autoimmune pancreatitis as the cause of obstructive jaundice. *Gastrointest Endosc*. 2005;61:467–473.
28. Levy MJ, Wiersema MJ. EUS-guided Trucut biopsy. *Gastrointest Endosc*. 2005;62(3):417–426.
29. Gress F, Schmitt C, Sherman S, et al. Endoscopic ultrasound-guided celiac plexus block for managing abdominal pain associated with chronic pancreatitis: a prospective single center experience. *Am J Gastroenterol*. 2001;96:409–416.
30. Schmulewitz N, Hawes R. EUS-guided celiac plexus neurolysis: technique and indication. *Endoscopy*. 2003;35(suppl):S49–S53.
31. Seifert H, Dietrich C, Schmitt T, et al. Endoscopic ultrasound-guided one-step transmural drainage of cystic abdominal lesions with a large-channel echo endoscope. *Endoscopy*. 2000;32:255–259.
32. Chang KJ, Nguyen PT, Thompson JA, et al. Phase I clinical trial of allogeneic mixed lymphocyte culture (cytoimplant) delivered by endoscopic ultrasound-guided fine-needle injection in patients with advanced pancreatic carcinoma. *Cancer*. 2000;88:1325–1335.
33. Ashida R, Chang KJ. Interventional EUS for the treatment of pancreatic cancer. *J Hepatobiliary Pancreat Surg*. 2009;16(5):592–597.
34. Shami VM, Kahaleh M. Endoscopic ultrasound–guided cholangiopancreatography and rendezvous techniques. *Dig Liver Dis*. 2009; Nov 6 [Epub ahead of print].
35. Levy MJ, Wong Kee Song LM, Farnell MB, et al. Endoscopic ultrasound (EUS)-guided angiotherapy of refractory gastrointestinal bleeding. *Am J Gastroenterol*. 2008;103(2):352–359.
36. Levy MJ, Chak A. EUS 2008 Working Group. EUS 2008 Working Group document: evaluation of EUS-guided vascular therapy. *Gastrointest Endosc*. 2009;69(2 suppl):S37–S42.
37. Pishvaian AC, Collins B, Gagnon G, et al. EUS-guided fiducial placement for CyberKnife radiotherapy of mediastinal and abdominal malignancies. *Gastrointest Endosc*. 2006;64(3):412–417.
38. Informed consent for gastrointestinal endoscopy. *Gastrointest Endosc*. 1988;34(3 suppl):26S–27S.
39. Plumeri PA. Informed consent for gastrointestinal endoscopy in the '90s and beyond. *Gastrointest Endosc*. 1994;40:379.
40. Faigel DO, Eisen GM, Baron TH, et al. Preparation of patients for GI endoscopy. *Gastrointest Endosc*. 2003;57:446–450.
41. ASGE guidelines for clinical application. Position statement on laboratory testing before ambulatory elective endoscopic procedures: American Society for Gastrointestinal Endoscopy. *Gastrointest Endosc*. 1999;50:906–909.
42. Rucker L, Frye EB, Staten MA. Usefulness of screening chest roentgenograms in preoperative patients. *JAMA*. 1983;250:3209–3211.
43. Smallwood JA. Use of blood in elective general surgery: an area of wasted resources. *BMJ Clin Res Ed*. 1983;286:868–870.
44. Kaplan EB, Sheiner LB, Boeckmann AJ, et al. The usefulness of preoperative laboratory screening. *JAMA*. 1985;253:3576–3581.
45. Blery C, Charpak Y, Szatan M, et al. Evaluation of a protocol for selective ordering of preoperative tests. *Lancet*. 1986;1:139–141.
46. Rohrer MJ, Michelotti MC, Nahrwold DL. A prospective evaluation of the efficacy of preoperative coagulation testing. *Ann Surg*. 1988;208:554–557.
47. Kaplan EB, Sheiner LB, Boeckmann AJ, et al. The usefulness of preoperative laboratory screening. *JAMA*. 1985;253:3576–3581.
48. Eika C, Havig O, Godal HC. The value of preoperative haemostatic screening. *Scand J Haematol*. 1978;21:349–354.
49. Campbell IT, Gosling P. Preoperative biochemical screening. *BMJ*. 1988;297:803–804.
50. Suchman AL, Mushlin AI. How well does the activated partial thromboplastin time predict postoperative hemorrhage? *JAMA*. 1986;256:750–753.

51. Eisenberg JM, Goldfarb S. Clinical usefulness of measuring prothrombin time as a routine admission test. *Clin Chem*. 1976;22:1644–1647.
52. Robbins JA, Rose SD. Partial thromboplastin time as a screening test. *Ann Intern Med*. 1979;90:796–797.
53. ASGE Standards of Practice Committee, Levy MJ, Anderson MA, et al. Position statement on routine laboratory testing before endoscopic procedures. *Gastrointest Endosc*. 2008;68(5):827–832.
54. Jamidar PA, Beck GJ, Hoffman BJ, et al. Endoscopic retrograde cholangiopancreatography in pregnancy. *Am J Gastroenterol*. 1995;90:1263–1267.
55. Botoman VA, Surawicz CM. Bacteremia with gastrointestinal endoscopic procedures. *Gastrointest Endosc*. 1986;32:342–346.
56. Low DE, Shoenut JP, Kennedy JK, et al. Prospective assessment of risk of bacteremia with colonoscopy and polypectomy. *Dig Dis Sci*. 1987;32:1239–1243.
57. Lee TH, Hsueh PR, Yeh WC, et al. Low frequency of bacteremia after endoscopic mucosal resection. *Gastrointest Endosc*. 2000;52:223–225.
58. Antibiotic prophylaxis for gastrointestinal endoscopy: American Society for Gastrointestinal Endoscopy. *Gastrointest Endosc*. 1995;42:630–635.
59. Zuccaro Jr G, Richter JE, Rice TW, et al. Viridans streptococcal bacteremia after esophageal stricture dilation. *Gastrointest Endosc*. 1998;48:568–573.
60. Motte S, Deviere J, Dumonceau JM, et al. Risk factors for septicemia following endoscopic biliary stenting. *Gastroenterology*. 1991;101:1374–1381.
61. Kolars JC, Allen MO, Ansel H, et al. Pancreatic pseudocysts: clinical and endoscopic experience. *Am J Gastroenterol*. 1989;84:259–264.
62. Sharma VK, Howden CW. Meta-analysis of randomized, controlled trials of antibiotic prophylaxis before percutaneous endoscopic gastrostomy. *Am J Gastroenterol*. 2000;95:3133–3136.
63. Dajani AS, Taubert KA, Wilson W, et al. Prevention of bacterial endocarditis: recommendations by the American Heart Association. *Clin Infect Dis*. 1997;25:1448–1458.
64. Simmons NA. Recommendations for endocarditis prophylaxis: the Endocarditis Working Party for Antimicrobial Chemotherapy. *J Antimicrob Chemother*. 1993;31:437–438.
65. Leport C, Horstkotte D, Burckhardt D. Antibiotic prophylaxis for infective endocarditis from an international group of experts towards a European consensus: Group of Experts of the International Society for Chemotherapy. *Eur Heart J*. 1995;16:126–131.
66. el-Baba M, Tolia V, Lin CH, et al. Absence of bacteremia after gastrointestinal procedures in children. *Gastrointest Endosc*. 1996;44:378–381.
67. ASGE Standards of Practice Committee, Banerjee S, Shen B, et al. Antibiotic prophylaxis for GI endoscopy. *Gastrointest Endosc*. 2008;67(6):791–798.
68. Durack DT. Infective endocarditis. In: Alexander RW, Schlant RC, Fuster V, eds. *Hurst's the heart, arteries and veins*. New York: McGraw-Hill; 1998:2205–2239.
69. Barawi M, Gottlieb K, Cunha B, et al. A prospective evaluation of the incidence of bacteremia associated with EUS-guided fine-needle aspiration. *Gastrointest Endosc*. 2001;53:189–192.
70. Aronson MD, Bor DH. Blood cultures. *Ann Intern Med*. 1987;106:246–253.
71. Levy MJ, Norton ID, Wiersema MJ, et al. Prospective risk assessment of bacteremia and other infectious complications in patients undergoing EUS-guided FNA. *Gastrointest Endosc*. 2003;57:672–678.
72. Janssen J, Konig K, Knop-Hammad V, et al. Frequency of bacteremia after linear EUS of the upper GI tract with and without FNA. *Gastrointest Endosc*. 2004;59:339–344.
73. Levy MJ, Norton ID, Clain JE, et al. Prospective study of bacteremia and complications with EUS FNA of rectal and perirectal lesions. *Clin Gastroenterol Hepatol*. 2007;5(6):684–689.
74. Lee LS, Saltzman JR, Bounds BC, et al. EUS-guided fine needle aspiration of pancreatic cysts: a retrospective analysis of complications and their predictors. *Clin Gastroenterol Hepatol*. 2005;3(3):231–236.
75. Hirota WK, Petersen K, Baron TH, et al. Guidelines for antibiotic prophylaxis for GI endoscopy. *Gastrointest Endosc*. 2003;58:475–482.
76. Kearon C, Hirsh J. Management of anticoagulation before and after elective surgery. *N Engl J Med*. 1997;336:1506–1511.
77. Eisen GM, Baron TH, Dominitz JA, et al. Guideline on the management of anticoagulation and antiplatelet therapy for endoscopic procedures. *Gastrointest Endosc*. 2002;55:775–779.
78. Douketis JD, Johnson JA, Turpie AG. Low-molecular-weight heparin as bridging anticoagulation during interruption of warfarin: assessment of a standardized periprocedural anticoagulation regimen. *Arch Intern Med*. 2004;164:1319–1326.
79. Kearon C. Management of anticoagulation in patients who require invasive procedures. *Semin Vasc Med*. 2003;3:285–294.
80. Zuckerman MJ, Hirota WK, Adler DG, et al. ASGE guideline: the management of low-molecular-weight heparin and nonaspirin antiplatelet agents for endoscopic procedures. *Gastrointest Endosc*. 2005;61(2):189–194.
81. O'Toole D, Palazzo L, Arotcarena R, et al. Assessment of complications of EUS-guided fine-needle aspiration. *Gastrointest Endosc*. 2001;53:470–474.
82. Wiersema MJ, Vilmann P, Giovannini M, et al. Endosonography-guided fine-needle aspiration biopsy: diagnostic accuracy and complication assessment. *Gastroenterology*. 1997;112:1087–1095.
83. Eloubeidi MA, Tamhane A, Lopes TL, et al. Cervical esophageal perforations at the time of endoscopic ultrasound: a prospective evaluation of frequency, outcomes, and patient management. *Am J Gastroenterol*. 2009;104(1):53–56.
84. Kallimanis G, Gupta P, al-Kawas F, et al. Endoscopic ultrasound for staging esophageal cancer, with or without dilation, is clinically important and safe. *Gastrointest Endosc*. 1995;41:540–546.
85. Van Dam J, Rice T, Catalano M, et al. High-grade malignant stricture is predictive of esophageal tumor stage: risk of endosonographic evaluation. *Cancer*. 1993;71:2910–2917.
86. Wallace MB, Hawes RH, Sahai AV, et al. Dilation of malignant esophageal stenosis to allow EUS guided fine-needle aspiration: safety and effect on patient management. *Gastrointest Endosc*. 2000;51:309–313.
87. Pfau PR, Ginsberg GG, Lew RJ, et al. Esophageal dilation for endosonographic evaluation of malignant esophageal strictures is safe and effective. *Am J Gastroenterol*. 2000;95:2813–2815.
88. Menzel J, Hoepffner N, Nottberg H, et al. Preoperative staging of esophageal carcinoma: miniprobe sonography versus conventional endoscopic ultrasound in a prospective histopathologically verified study. *Endoscopy*. 1999;31:291–297.
89. Mallery S, Van Dam J. Increased rate of complete EUS staging of patients with esophageal cancer using the nonoptical, wire-guided echoendoscope. *Gastrointest Endosc*. 1999;50:53–57.
90. Affi A, Vazquez-Sequeiros E, Norton ID, et al. Acute extraluminal hemorrhage associated with EUS-guided fine needle aspiration: frequency and clinical significance. *Gastrointest Endosc*. 2001;53:221–225.
91. Varadarajulu S, Eloubeidi MA. Frequency and significance of acute intracystic hemorrhage during EUS-FNA of cystic lesions of the pancreas. *Gastrointest Endosc*. 2004;60:631–635.
92. Annema JT, Veselic M, Versteegh MIM, et al. Mediastinitis caused by EUS-FNA of a bronchogenic cyst. *Endoscopy*. 2003;35:791–793.
93. Ryan AG, Zamvar V, Roberts SA. Iatrogenic candidal infection of a mediastinal foregut cyst following endoscopic ultrasound-guided fine-needle aspiration. *Endoscopy*. 2002;34:838–839.
94. O'Toole TM, Schmulewitz N. Complication rates of EUS-guided celiac plexus blockade and neurolysis: results of a large case series. *Endoscopy*. 2009;41(7):593–597.
95. Eloubeidi MA, Gress FG, Savides TJ, et al. Acute pancreatitis after EUS-guided FNA of solid pancreatic masses: a pooled analysis from EUS centers in the United States. *Gastrointest Endosc*. 2004;60:385–389.
96. Eloubeidi MA, Chen VK, Eltoum IA, et al. Endoscopic ultrasound-guided fine needle aspiration biopsy of patients with suspected pancreatic cancer: diagnostic accuracy and acute and 30-day complications. *Am J Gastroenterol*. 2003;98:2663–2668.
97. Lai R, Stanley MW, Bardales R, et al. Endoscopic ultrasound-guided pancreatic duct aspiration: diagnostic yield and safety. *Endoscopy*. 2002;34:715–720.
98. Shah JN, Fraker D, Guerry D, et al. Melanoma seeding of an EUS-guided fine needle track. *Gastrointest Endosc*. 2004;59:923–924.
99. Chen HY, Lee CH, Hsieh CH. Bile peritonitis after EUS-guided fine-needle aspiration. *Gastrointest Endosc*. 2002;56:594–596.

CHAPTER 5

How to Perform EUS in the Esophagus and Mediastinum

Robert H. Hawes | Shyam Varadarajulu | Paul Fockens

ESOPHAGUS

Obtaining high-quality images of the esophageal wall is one of the more difficult tasks that an endosonographer will encounter. One has to deal with the "catch 22" that pits adequate coupling of the ultrasound signal to the esophageal wall against wall compression. This situation can lead to inaccurate assessment of invasion depth in patients with early esophageal cancer or to missing lesions completely in the case of varices. Numerous techniques can be employed to overcome these conflicting goals.

In the case of a relatively advanced mass in the esophagus, minimal or no balloon inflation is sufficient to couple the ultrasound signal to the esophageal wall without causing compression that adversely affects staging accuracy. In this circumstance, the electronic radial instrument has an advantage over the mechanical radial device because of the absence of ringdown artifact and the superior near-field resolution of electronic array technology. Periesophageal structures (e.g., lymph nodes) are not affected by the amount of balloon inflation.

When compression of the esophageal wall needs to be avoided, several different techniques can be employed. The simplest is to instill water into the gut lumen by pressing on the air/water button to its first position. This maneuver sprays water across the endoscopic image lens. Remarkably, this does a very good job of filling the lumen with water while reducing the risk of aspiration. This technique can be employed with the standard radial echoendoscope or when using a high-frequency catheter probe in conjunction with a single- or dual-channel forward-viewing endoscope. The images generated are often fleeting because of peristalsis and variability in water filling. As a result, the cine function on the console becomes important in that it allows one to freeze the image and then scroll through the stored images to save the best one. High-resolution esophageal images can be obtained only when the esophagus is in its relaxed state, and this occurs only periodically. Agents normally used to paralyze the stomach, duodenum, and colon have little to no effect on esophageal contractions.

A second method that can be used with a radial scanning echoendoscope is to instill water through the biopsy channel. If this technique is employed, it is recommended that water be slowly siphoned into the esophagus rather than actively pumped or vigorously instilled by syringe. There is a very real risk of aspiration if high volumes are instilled over a short time, especially when topical pharyngeal anesthesia has also been applied.

Until the advent of the electronic radial echoendoscope, the device of choice for high-quality images of the esophageal wall was a high-frequency ultrasound probe. However, the newer electronic radial echoendoscopes have excellent near-field resolution and provide superb images without the need for significant balloon inflation. Nonetheless, if one wishes to stage early (T1m, sm) esophageal cancer (to determine the presence or absence of penetration through the muscularis mucosa), high-frequency catheter probes (20 to 30 MHz) would still be considered the instruments of choice.

When catheter probes are used for esophageal imaging, several techniques can be employed. One method is to use a bare catheter and instill water through the air/water channel. A second method is to use an ultrasound catheter with an attachable balloon. This technique still risks compression of the esophageal wall layers with inflation of the balloon. However, because the focal length of the catheter is very short, only a small amount of balloon inflation is necessary, thereby minimizing this risk.

Another technique that has been described is to affix a transparent, low-compliance condom onto the end of a double-channel endoscope (Fig. 5.1). The condom is taped onto the end of the endoscope such that approximately 2 to 3 cm of the condom protrude beyond the tip of the endoscope. This redundant portion of the condom is folded across the imaging lens as the endoscope is passed into the esophagus. During the intubation process, it is extremely important to avoid instilling air (a common habit) because this will inflate the condom and could compromise the patient's airway. After entering the esophagus, the instrument is passed into the stomach lumen, and air is "bled" from the condom tip (instill water-aspirate; reinstill; reaspirate and repeat until all the air is gone). Once the condom has been bled, the endoscope is withdrawn to the level of the lesion, and the condom is filled with water. Because of the low compliance of the condom, it tends to elongate rather than compress the wall layers. The ultrasound catheter is then advanced into the lumen of the condom, and imaging proceeds (Video 5.1). With this technique, the coupling of the ultrasound waves to the esophageal wall is virtually perfect. With the transparent condom, the lesion can be viewed endoscopically in real time, thus assuring that the catheter probe is positioned correctly. Because the water is completely contained within the condom, there is no risk of aspiration.

Whichever technique is employed, the risk of aspiration should be minimized while good coupling of the ultrasound waves to the esophageal wall is achieved without inducing compression. These techniques are employed for patients with early

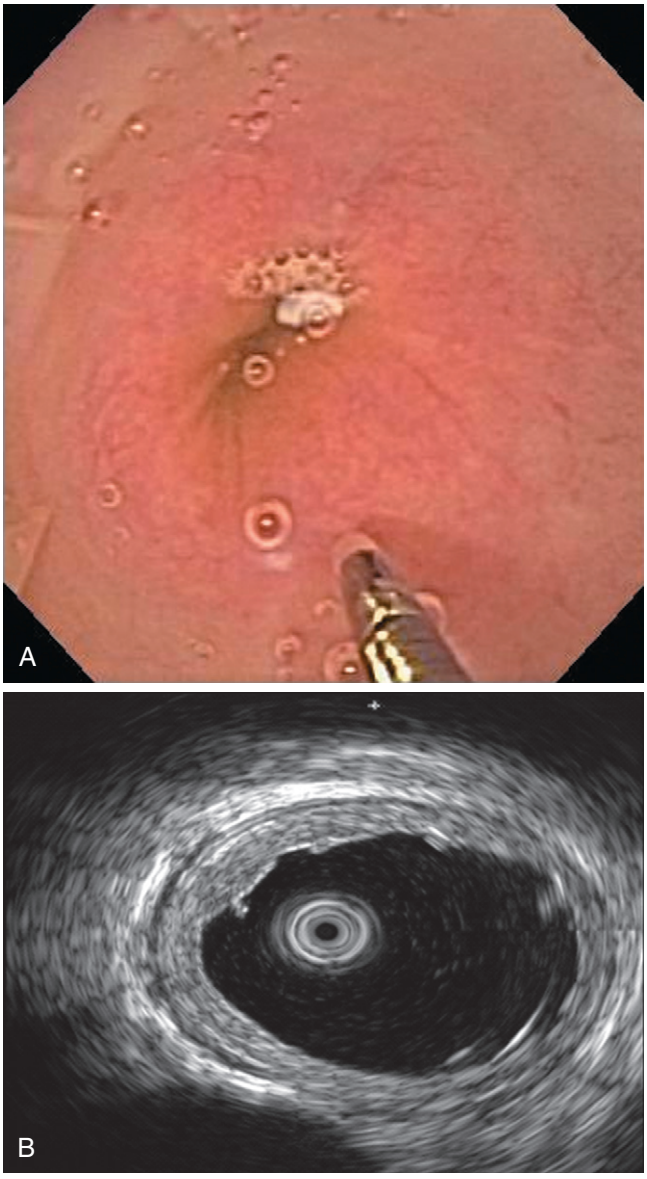


FIGURE 5.1 Endoscopic view of the esophageal lumen. View with a water-filled condom (**A**). The esophageal wall layers as visualized with a high-frequency catheter probe using the condom technique (**B**).

esophageal cancer, with Barrett's esophagus with or without nodules, and with small submucosal lesions.

The other major problem with esophageal EUS is tangential imaging. The esophagus is often perceived as a straight tube, but in most cases, it has some tortuosity. The imaging section of an echoendoscope, as well as a catheter probe, is straight and rigid. Imaging a tortuous tube with a straight instrument creates tangential imaging. The endosonographer must be trained to recognize tangential imaging and must be aware of the maneuvers that will correct it. The consequence of unrecognized tangential imaging is overstaging malignant lesions or missing the layer of origin of a submucosal lesion. Tangential imaging is characterized by focal thickening of the esophageal wall associated with blurring and triangulation of the deep border of the esophageal wall (Fig. 5.2) If one recognizes tangential imaging, the corrective action is usually to use all four directional dials *(do not torque the scope shaft)* to move the transducer in the direction where tangential imaging is seen. When the deep edge of the muscularis propria layer becomes smooth and the layer is seen sharply, tangential imaging has been corrected.

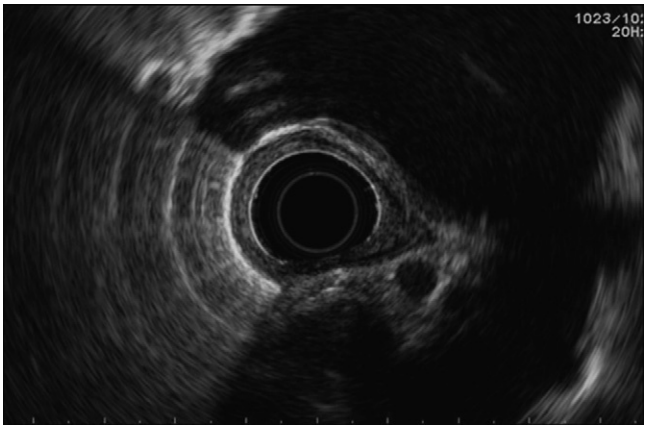


FIGURE 5.2 Muscularis layer of the esophageal wall. The muscularis layer of the esophageal wall appears blurred and focally thickened secondary to tangential imaging.

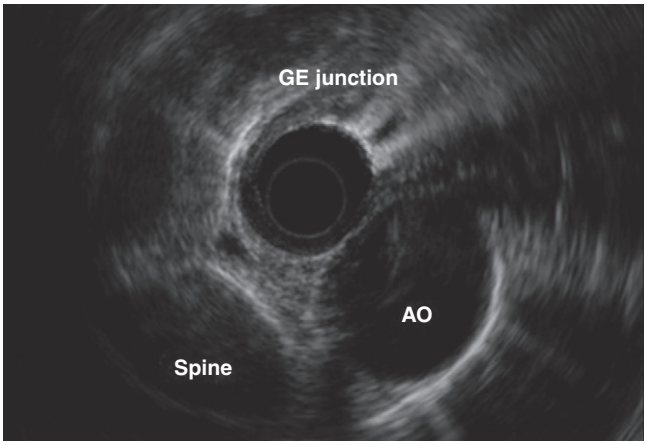


FIGURE 5.3 EUS image when the radial echoendoscope is positioned at the gastroesophageal junction. The aorta (AO) is located at the 5-o'clock position, and the spine is at 7 o'clock.

MEDIASTINUM

Radial Echoendoscope

Examination of the mediastinum with a radial echoendoscope is relatively straightforward. The learning curve should be short (compared with endoscopic ultrasonography [EUS] of the pancreas) because the EUS images correlate with a thoracic computed tomography (CT) scan. It is recommended that a systemic approach be applied to all EUS examinations and that images be presented with a standard orientation. This approach holds true for mediastinal imaging. To begin the mediastinal study, the echoendoscope tip is placed in the distal esophagus near the gastroesophageal junction. The aorta is a round, anechoic structure that is a constant anatomic finding throughout the examination until withdrawal proximal to the aortic arch. It is recommended that the endoscopic ultrasound image be presented on the monitor in an orientation that exactly matches a CT slice. To accomplish this, the aorta should be rotated (using the rotation function on the instrument panel, *not* by torquing the scope shaft) to the 5-o'clock position. This will present the spine at 7 o'clock (Fig. 5.3), and the heart and respiratory tree will emerge in the 12-o'clock position.

With the transducer placed in the distal esophagus and the aorta located in the 5 o'clock position, the examination begins (Video 5.2). The balloon should be inflated sufficiently to displace any intraluminal air, and the transducer itself should be placed roughly in the center of the balloon (again using right/left and up/down

dials and *not* by torquing the scope shaft). With this starting position, the echoendoscope is then slowly withdrawn.

The anatomy around the distal esophagus is not complex, and as the examination begins, the aorta, spine, and portions of the left and right lung are the only anatomic structures that can be identified. The lungs are seen only as a very bright white line. The area of the mediastinum surrounding the distal esophagus corresponds to area 8 of the American Thoracic Society (ATS) areas.[1]

As the instrument is slowly withdrawn, usually approximately 35 cm from the incisors, an anechoic structure begins to emerge at roughly the 12-o'clock position (it could emerge anywhere from 10- to 2-o'clock). This structure is the left atrium (Fig. 5.4).

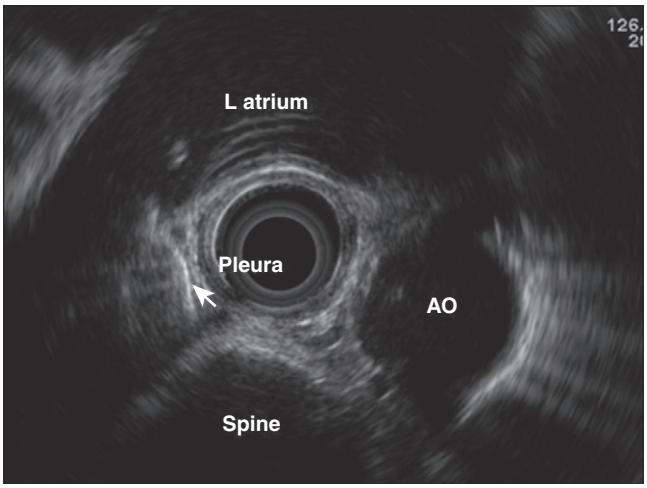


FIGURE 5.4 View of the left atrium. On gradual withdrawal of the radial echoendoscope from the gastroesophageal junction, the left atrium (L atrium) appears as a pulsating structure in the upper half of the EUS screen. AO, aorta; arrow, pleura.

As the echoendoscope is withdrawn further, the left atrium gradually disappears. The subcarinal space is located from 10 to 12 o'clock and extends from where the left atrium disappears to where the left and right main stem bronchi come together to form the trachea (Fig. 5.5).

The subcarinal space may be 3 to 4 cm in length and is designated area 7 by the ATS. The subcarina should be examined by withdrawing the echoendoscope in 1-cm increments while observing the 10- to 2-o'clock area for lymph nodes. Lymph nodes are typically well-circumscribed, relatively echo-poor structures that may be triangular, elongated, or round and located adjacent to the esophagus (see Fig. 5.5C). The inner echo architecture can vary from being almost anechoic to having a very bright central echo. On withdrawal of the endoscope, after the disappearance of the left atrium, eventually the right or left main stem bronchus emerges. Obviously, the left main stem bronchus is present on the same side of the screen as the aorta. Air-filled structures on EUS show up as very bright "ribs" on the monitor (see Fig. 5.5B).

On further withdrawal of the endoscope, three distinctive findings are seen over the span of 2 to 3 cm: the trachea, the elongated azygous vein, and the aortic arch (Fig. 5.6). First, the left and right main stem bronchi come together to form the trachea, which is represented as a typical air-filled structure (echogenic ribs) at the 12 o'clock position. The second anatomic landmark is the azygous vein, up to now seen as a round, anechoic structure near the spine, or occasionally between the spine and the aorta, that elongates and moves anteriorly to join the superior vena cava. The third anatomic landmark is the elongation of the aorta, representing the aortic arch.

The area at 3 o'clock, just distal to the arch of the aorta, is the aortopulmonary window (area 4L/5) (Fig. 5.7). After the aortic arch, further withdrawal of the endoscope demonstrates the great vessels coming off the aortic arch. Other than the trachea and the spine, however, this area is devoid of any significant anatomic landmarks. Nonetheless, this area is extremely important to

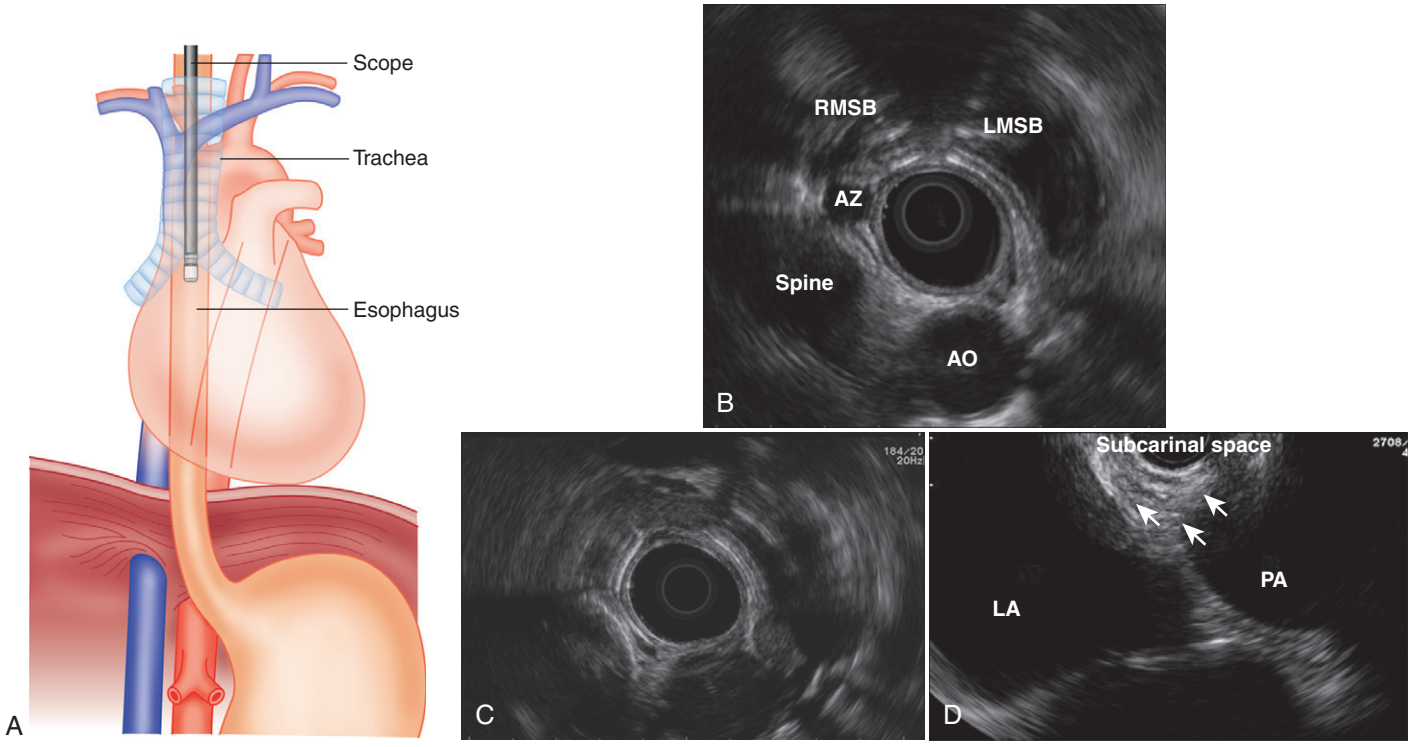


FIGURE 5.5 Subcarinal region. The position of the scope when visualizing the subcarinal region (**A**). At this site, on radial imaging, the right (RMSB) and the left main stem bronchi (LMSB) come together to form the trachea (**B**), and the characteristic draping lymph nodes are seen in this station (**C**). On linear imaging, two structures characterize the subcarinal space *(arrows)*: the one on the left is the left atrium, and the one on the right is the pulmonary artery (PA) (**D**). AO, aorta; AZ, azygous.

image in order to look for periesophageal and paratracheal lymph nodes (area 2). Any confirmed metastatic lymph node found above the aortic arch in association with upper gastrointestinal cancer essentially represents unresectable disease.

Linear Array Echoendoscope

Examination of the mediastinum with the linear array echoendoscope is more time consuming and tedious when compared with examination with the radial instrument. Because of the narrow field of view, it is critical to adopt a systematic approach to the examination. When examining the area around the distal esophagus (area 8), the starting point is the aorta, which appears as a linear, anechoic structure that essentially fills the field of view. From here, it is necessary to rotate the echoendoscope purposefully 180 degrees in a clockwise fashion, return to the neutral position (aorta), and then rotate 180 degrees in a counterclockwise direction. This needs to be done initially and then repeated after withdrawing 1 to 2 cm. Effective rotating (torquing) of the linear echoendoscope is a fundamental skill required to perform linear EUS competently. A simple method to determine whether the torquing technique is correct is to watch the distance numbers on the scope shaft. If they rotate around the axis of the scope 1 to 1 during torquing, then the maneuver is being performed correctly (Video 5.3).

The two most important areas in the mediastinum in which to look for lymph nodes are the subcarinal space (area 7) and the aortopulmonary window (area 4L/5). One should take a systematic approach to locate and image both areas with the linear echoendoscope. There are two ways to locate the subcarinal space. The first is to begin the examination in the distal esophagus (at 35 to 40 cm on the scope shaft). The instrument should be rotated in a clockwise or counterclockwise direction until the aorta is found. Once the aorta has been located, the instrument should be torqued 180 degrees (clockwise or counterclockwise, whichever is more comfortable) and then slowly withdrawn. The aorta is positioned posteriorly, and this maneuver orients the image anteriorly.

As the instrument is withdrawn, usually approximately 35 cm from the incisors, a large anechoic structure is seen, and this represents the left atrium. The instrument should then be subtly torqued either clockwise or counterclockwise until the left atrium is centered. The instrument is then further withdrawn until the left atrium is situated on the left side of the ultrasound image. When this has been achieved, a slight tip deflection upward will bring a round, anechoic structure into view on the right side of the screen; this represents the pulmonary artery. The area between the left atrium and the pulmonary artery represents the subcarinal space (see Fig. 5.5D). Full interrogation of the subcarinal space then requires careful clockwise and counterclockwise torquing.

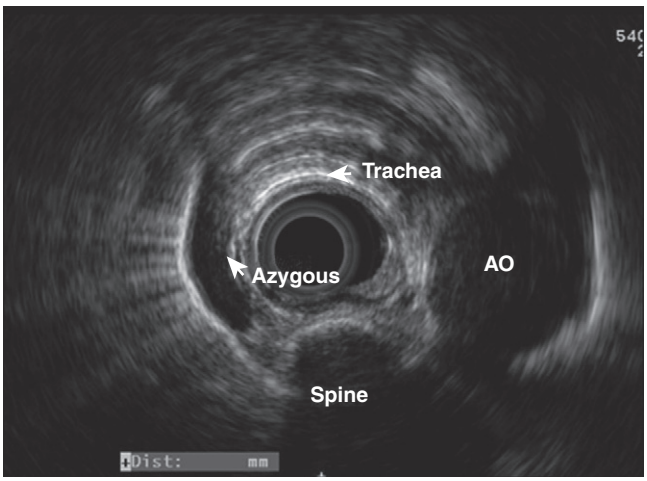


FIGURE 5.6 Trachea, azygous vein, and aortic arch (AO). On upward withdrawal of the radial echoendoscope 2 to 3 cm from the subcarina, the trachea, azygous vein, and the aortic arch are seen.

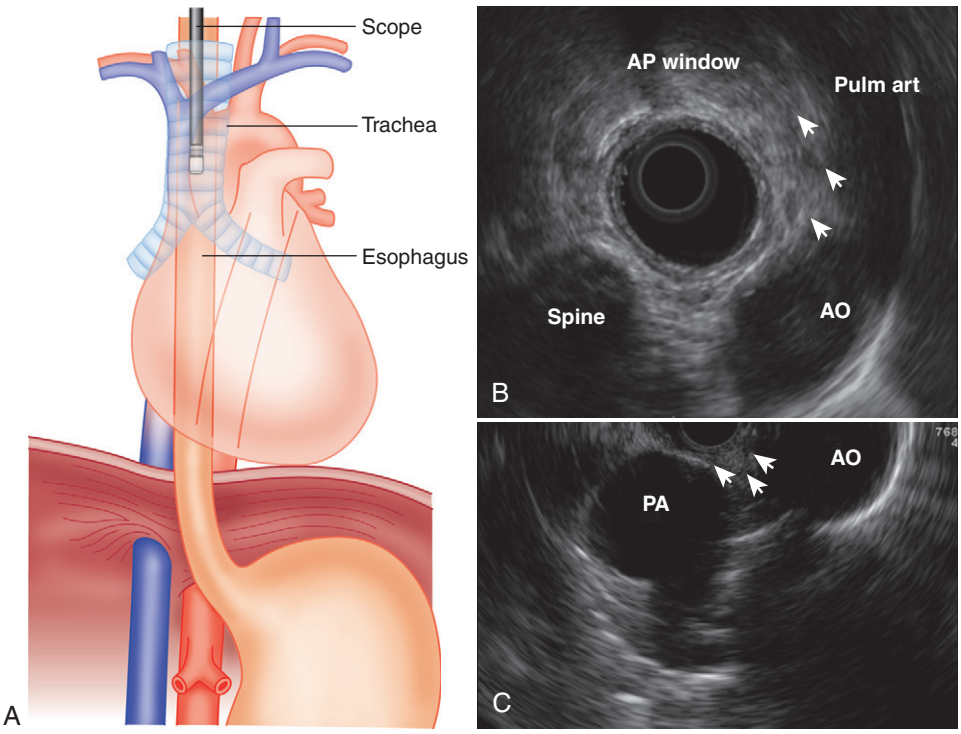


FIGURE 5.7 Aortopulmonary window. The position of the echoendoscope for visualizing the aortopulmonary (AP) window (**A**). On radial imaging, at 3 o'clock, the pulmonary artery is seen superior to the arch of the aorta (AO) (**B**). On linear imaging, the anechoic structure on the left of the screen is the pulmonary artery (PA), and the anechoic structure on the right is the aorta (AO) (**C**).

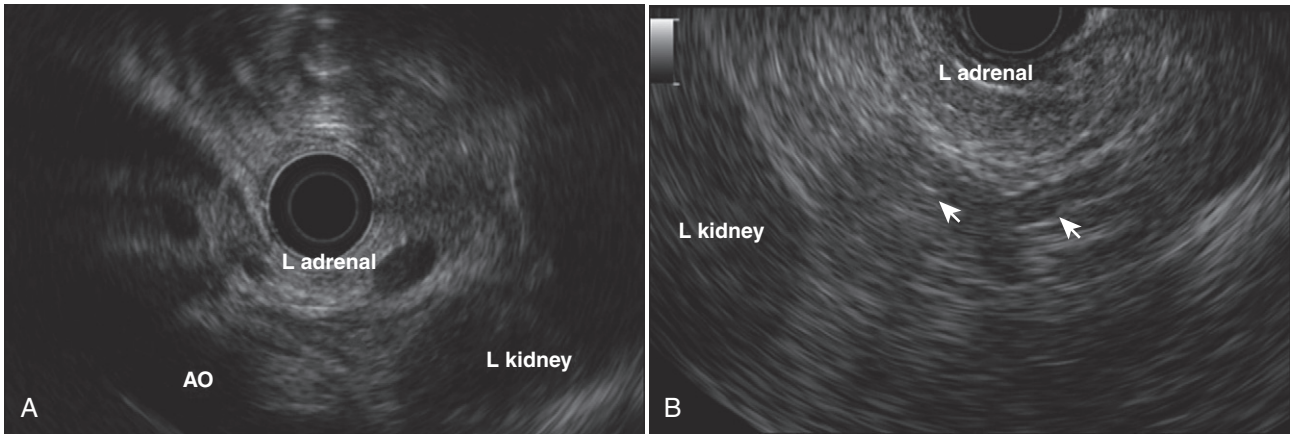


FIGURE 5.8 Left adrenal gland. The left adrenal gland *(arrows)* with the typical "seagull" appearance as seen using radial (**A**) and linear (**B**) echoendoscopes. AO, Aorta.

The second way to find the subcarinal space is to locate the aorta in the middle of the esophagus. With the aorta occupying the screen, the echoendoscope is slowly withdrawn until the aorta disappears; this represents the aortic arch. At this point, 180 degrees of clockwise torque are applied. This maneuver orients the image anteriorly, and one encounters the typical echogenic ribs, which represent the trachea. Once the trachea has been located, the scope is advanced 1 to 2 cm. When the trachea disappears, this represents the bifurcation into the left and right main stem bronchi. Thus, one is now viewing the subcarinal space. Just as with the first maneuver, the left atrium is seen on the left side of the screen, and the pulmonary artery is on the right.

The other important anatomic station in the mediastinum is the aortopulmonary window (area 4L/5). This is essentially the area underneath the arch of the aorta. This area can be found most easily by locating the aorta in the middle of the esophagus and then withdrawing the instrument until the aorta disappears. From this position, one advances the scope by 1 to 2 cm, at a level underneath the aortic arch. The scope is rotated 60 degrees in a clockwise direction and comes slightly "up" on the up/down dial. With the linear echoendoscope, the aortopulmonary window is seen as the space between the aorta (round, anechoic structure on the right side of the screen) and the pulmonary artery (round, anechoic structure on the left side of the screen; see Fig. 5.7C).

Above the area of the aortic arch, the left and right paratracheal area can be examined by torquing the scope clockwise and counterclockwise off the trachea every 2 cm (area 2). This is a critical area to examine in patients with distal esophageal cancer because malignant lymph nodes in this area represent metastatic disease.

How to Examine the Adrenal Glands

The left adrenal gland is an important landmark in lung cancer staging. This gland can be identified in more than 95% of EUS examinations by using either of the two techniques described here. It is easier to locate the adrenal gland with the linear scope as compared with the radial instrument. However, the technique for locating the adrenal gland is the same. The most straightforward approach involves locating the aorta at the gastroesophageal junction and then advancing the scope to the point where the celiac artery takes off. The scope is advanced along the celiac artery, and then slight clockwise torque is applied to the echoendoscope. The left adrenal gland is seen as a structure with a central "body" and two "wings" (Video 5.4). It is often described as resembling a seagull in flight. An echogenic line frequently runs in the middle of the wings (Fig. 5.8).

In the second technique, the echoendoscope is advanced into the proximal stomach, and the abdominal aorta is identified just below the gastroesophageal junction. The splenic vein is then identified by advancing the transducer forward with a clockwise rotation. The splenic hilum is found by following the splenic vein laterally. The left kidney is then imaged by advancing the scope from the splenic hilum. The left kidney is seen in cross section with a central echo-rich area representing the renal pelvis and caliceal system and a surrounding homogeneous echo-poor area representing the cortex. The left adrenal gland is found just below the splenic vein between the left kidney and the abdominal aorta.

The right adrenal gland generally cannot be well visualized by EUS because it is located farther away from the stomach and is superior to the duodenal sweep. In 20% of cases, it can be seen with the transducer deep into the duodenal lumen beyond the ampulla and with morphologic characteristics similar to those of the left adrenal gland. Even when detected by EUS, the right adrenal gland usually is located deep or adjacent to the inferior vena cava, thereby making EUS-guided fine-needle aspiration difficult, but not impossible.

SUMMARY

Evaluation of the mediastinum by EUS is relatively straightforward. Images obtained by the radial scanning instrument correlate very precisely with images of a CT scan. Linear images are more difficult to interpret, and successful examination of the mediastinum using a linear array echoendoscope requires a systematic approach.

REFERENCE

1. Mountain CF, Dresler CM. Regional lymph node classification for lung cancer staging. *Chest*. 1997;111:1718–1723.

CHAPTER 6

EUS AND EBUS IN NON–SMALL CELL LUNG CANCER

Jouke T. Annema | Klaus F. Rabe

Key Points

EUS-guided fine-needle aspiration (FNA) is an accurate technique for the analysis of mediastinal lymph nodes located in the aortopulmonary window and posterior mediastinum.

EUS FNA can diagnose intrapulmonary tumors adjacent to the esophagus directly and assess mediastinal tumor invasion (T4).

In patients with non–small cell lung cancer, EUS FNA can replace surgical staging to a large extent by demonstrating lymph node metastases or tumor invasion.

Incorporation of EUS FNA in staging logarithms for non–small cell lung cancer reduces the number of mediastinoscopies and unnecessary thoracotomies, as well as costs.

INTRODUCTION

Transesophageal endoscopic ultrasonography (EUS)-guided fine-needle aspiration (FNA) and endobronchial ultrasound (EBUS)–guided transbronchial needle aspiration (TBNA) are novel techniques for the diagnosis and staging of lung cancer. Worldwide, more than 1 million patients are diagnosed with lung cancer annually, and one third of these patients present with mediastinal metastases. Accurate diagnosis and staging are important for both prognostic and therapeutic reasons. Patients with non–small cell lung cancer (NSCLC) and mediastinal lymph node metastases or mediastinal tumor invasion (stage III) are preferably treated with chemoradiation therapy, whereas patients without locally advanced disease are treated primarily by surgical resection of the lung tumor.[1] Current mediastinal tissue staging of patients with NSCLC mainly depends on surgical interventions, predominantly mediastinoscopy. EUS FNA and EBUS TBNA are incorporated in current guidelines as minimally invasive alternatives to surgical staging to demonstrate nodal metastases.[2,3]

In this chapter, the role of EUS FNA and EBUS TBNA for the diagnosis and staging of lung cancer is evaluated. The indications for both methods are addressed (Table 6.1), as well as the concept of complete echoendoscopic staging of the mediastinum. The impact of EUS and EBUS on patient management is also discussed, in particular the role of these imaging techniques in preventing surgical staging procedures as well as the position of endosonography in staging algorithms for NSCLC.

EUS FINE-NEEDLE ASPIRATION FOR THE DIAGNOSIS AND STAGING OF LUNG CANCER

General Procedure

Evaluation of the mediastinum by EUS should be performed in a standardized fashion (see Chapter 5), to examine all mediastinal lymph node stations that can be detected from the esophagus (EUS FNA Examination Checklist). Lymph nodes should be described in relation to the anatomic (vascular) landmarks and given a number according to the tumor, node, metastasis (TNM) classification.[4,5] After an initial orientation, enlarged (short axis >10 mm) or sonographically suspicious nodes should be sampled for biopsy, starting with contralateral (N3) nodes before ipsilateral (N2) lymph nodes are analyzed.

EUS FNA EXAMINATION CHECKLIST*

Celiac axis
Left adrenal gland
Left liver lobe (optional)
Periesophageal space below carina (station 8L/R)
Subcarinal space (station 7)
Aortopulmonary window/pulmonary trunk (station 4L/5)
Paratracheal space (station 2R and 2L)
Intrapulmonary tumor visible?
Mediastinal tumor invasion (T4)

*See also reference 4 and Chapter 5.

Biopsy of Intrapulmonary Tumors

Intrapulmonary tumors that are located adjacent to or near the esophagus can be visualized by EUS.[6,7] Once the primary tumor has been identified, real-time EUS-guided biopsy of the intrapulmonary lesion is possible (Fig. 6.1). Left upper lobe tumors located adjacent to the aorta are often detected by EUS (Fig. 6.2). In a retrospective study of 18 patients with intrapulmonary tumors abutting the esophagus, EUS identified intrapulmonary tumors and obtained a tissue diagnosis in all patients.[7] In a prospective study of 32 patients with suspected lung cancer and a primary tumor located adjacent to the esophagus, intrapulmonary masses were detected in all patients, and the diagnosis of lung cancer was established in 97% of patients.[6]

Mediastinal Tumor Invasion (T4)

Once the primary tumor has been identified, in a subset of patients one can assess the presence or absence (see Fig. 6.2) of mediastinal tumor invasion (T4), defined as invasion in the mediastinum, centrally located large vessels, or vertebrae. Patients with T4 lung tumors (stage IIIB) are generally not considered eligible for surgical resection. Currently, mediastinal tumor invasion is frequently assessed during surgery because computed tomography (CT) has limited sensitivity and specificity (<75%) for mediastinal invasion,[8] and positron emission tomography (PET) has no value in detecting T4 tumors because of its limited anatomic resolution.[9] In a retrospective study that evaluated T4 staging in 308 patients, EUS had a sensitivity, specificity, and positive and negative predictive value of 88%, 98%, 70%, and 99%, respectively.[10] Most cases of tumor invasion were assessed based on EUS images alone. Tumor invasion in large vessels (Fig. 6.3B) or the heart is easier to assess than invasion in the mediastinum (see Fig. 6.3A), as a result of the increased ultrasound contrasts between tumor and blood as well as the possibility of using a Doppler signal (see Fig. 6.3C). In a few patients in the foregoing study, surgical verification of EUS T4 findings occurred, and therefore, the definitive value of EUS in T4 staging requires further investigation.

In conclusion, intrapulmonary tumors can be visualized and sampled for biopsy safely by EUS FNA provided the tumors are located adjacent to the esophagus. In addition to establishing a tissue diagnosis, EUS can detect mediastinal tumor invasion, especially of vascular structures.

TABLE 6.1

Indications for Endosonography for the Diagnosis and Staging of Lung Cancer

Mediastinal Lymph Nodes	EUS-FNA	EBUS-TBNA
Paratracheal to the left	++	++
Paratracheal to the right	−	++
Aortopulmonary window	+	−
Subcarinal	++	++
Lower mediastinum	++	−
Hilar	−	++
Mediastinal restaging	+	+
FDG PET uptake in lymph node within reach	++	++
Lung tumor located adjacent to the esophagus	++	−
Lung tumor located adjacent to the trachea or main bronchi	−	++
Suspected left adrenal metastasis	++	−

++, strong evidence; +, moderate evidence; −, no evidence; FDG, fluorodeoxyglucose; FNA, fine-needle aspiration; PET, positron emission tomography; TBNA, transbronchial needle aspiration.

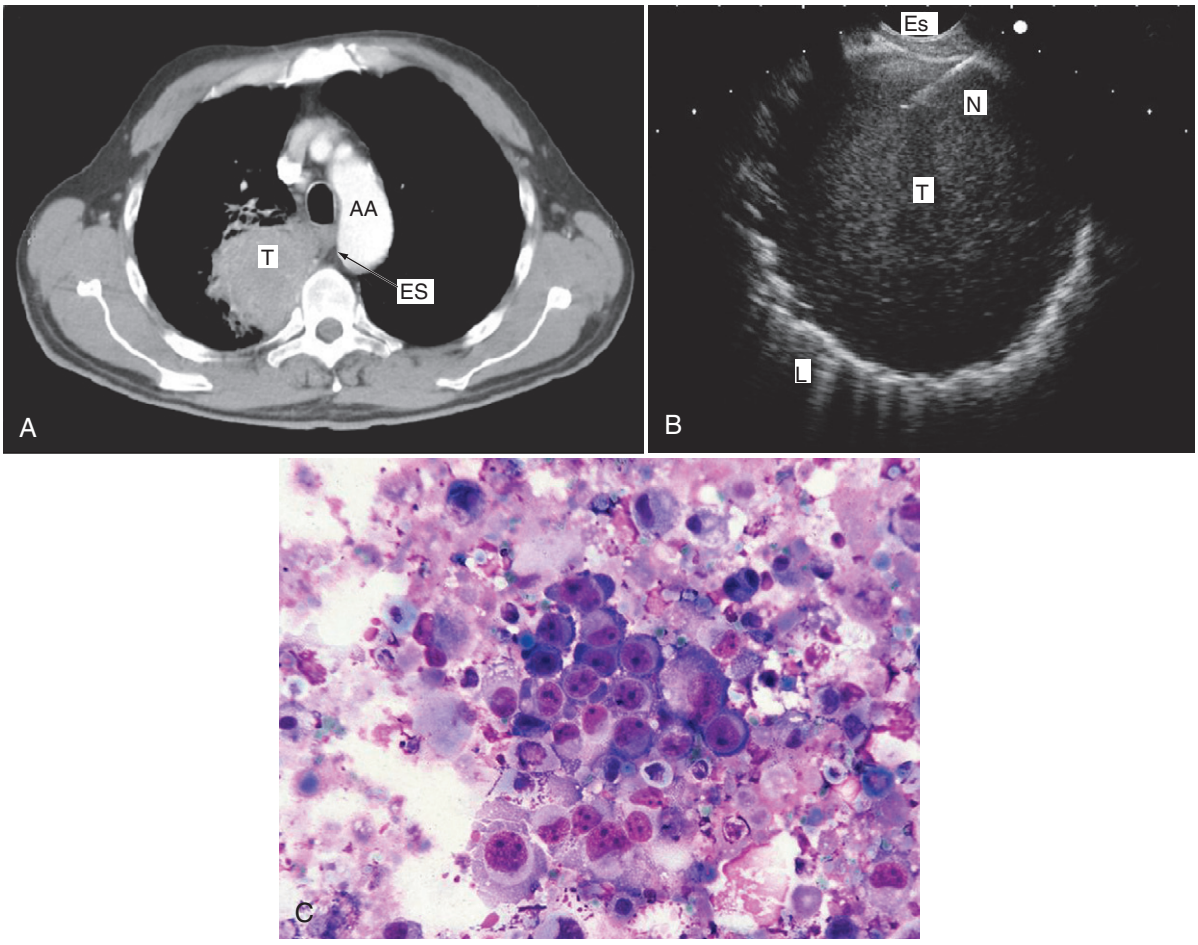


FIGURE 6.1 A 53-year-old smoker with suspected lung cancer in whom bronchoscopy did not establish a diagnosis. A, Computed tomography of the chest demonstrating an intrapulmonary tumor (T) in the right upper lobe located adjacent to the esophagus (ES). AA, aortic arch. **B,** Corresponding EUS fine-needle aspiration image. Notice the needle (N) located in the tumor (T). Es, esophagus; L, compromised lung tissue. **C,** Cytology of fine-needle aspirate demonstrating a squamous cell carcinoma.

Mediastinal Nodal Staging by EUS

Diagnostic Reach

Regional lymph nodes in NSCLC are classified using the TNM classification.[5] Only lymph nodes that lie adjacent to the esophagus or centrally located vessels can be visualized by EUS. These lymph nodes are located in the following regions: low paratracheal on the left (station 4L; Fig. 6.4), aortopulmonary window (station 5; Fig. 6.5), para-aortal (station 6; Fig. 6.6), subcarinal (station 7; Figs. 6.7 and 6.8), lower paraesophageal

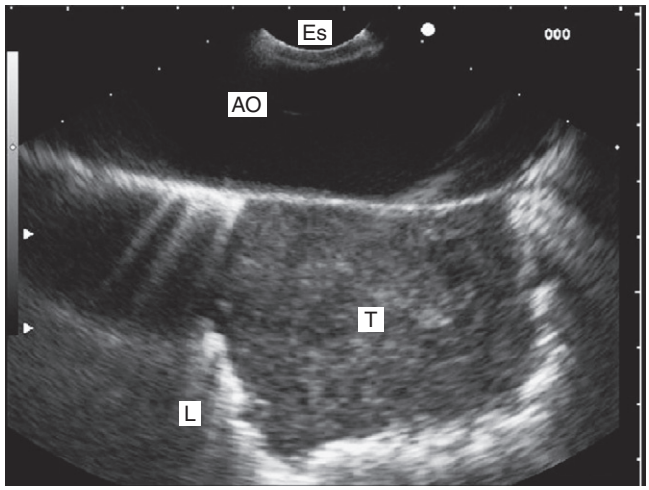


FIGURE 6.2 Left upper lobe tumor (T) located adjacent to the aorta (AO). There are no signs of tumor invasion in the aorta (T4). Es, esophagus; L, compromised lung tissue.

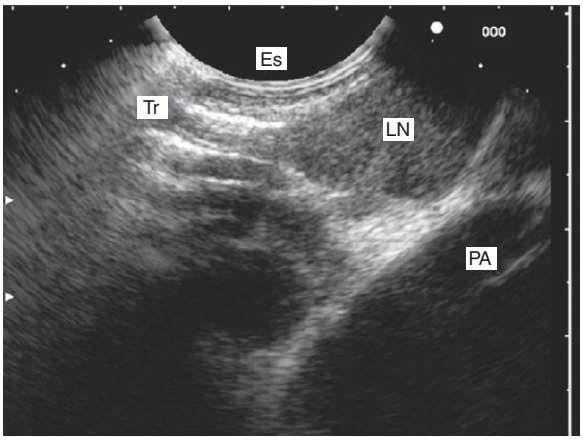


FIGURE 6.4 Lower paratracheal lymph node (LN) on the left (station 4L) located between the esophagus (Es), trachea (Tr), and pulmonary artery (PA).

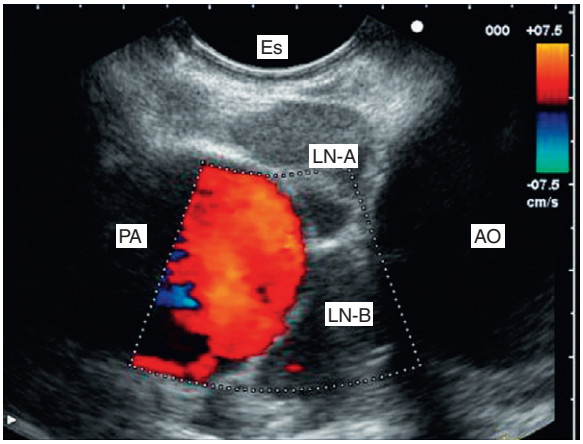
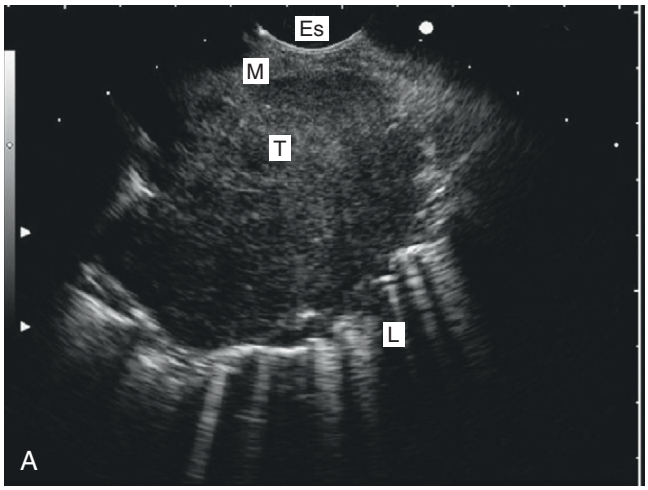
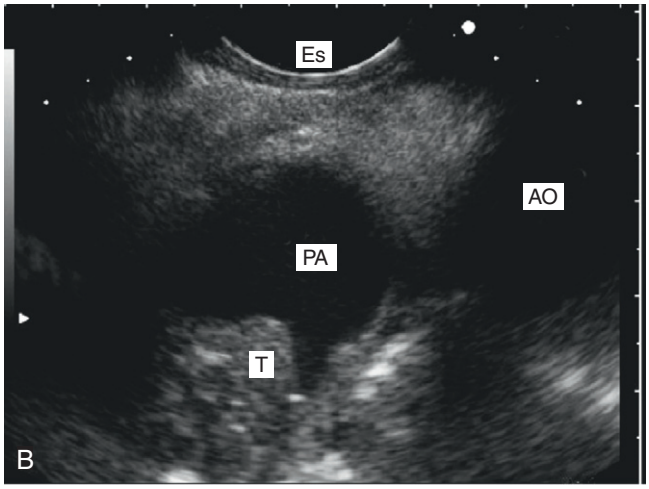


FIGURE 6.5 Left paratracheal lymph node (Station 4L, LN-A) located between the aorta (AO), pulmonary artery (PA), and esophagus (ES) and the aortopulmonary node (Station 5, LN-B).





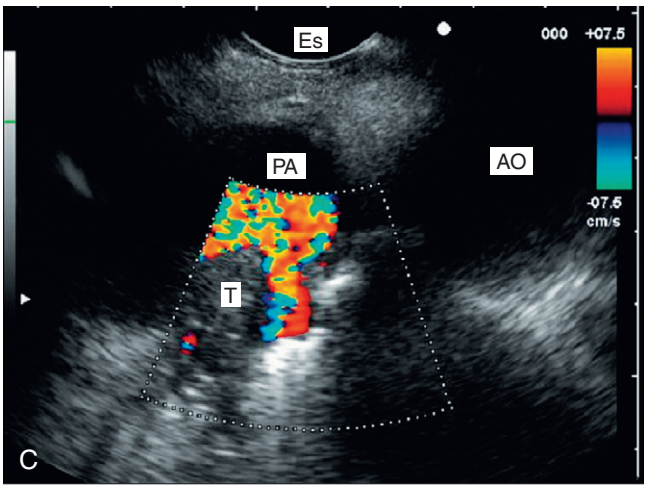


FIGURE 6.3 Large cell carcinoma. A, Centrally located large cell carcinoma (T) invading the mediastinum (M). Es, esophagus; L, compromised lung tissue. **B** and **C,** Centrally located left-sided tumor (T) invading the pulmonary artery (PA), with (**C**) and without (**B**) color Doppler. AO, aorta.

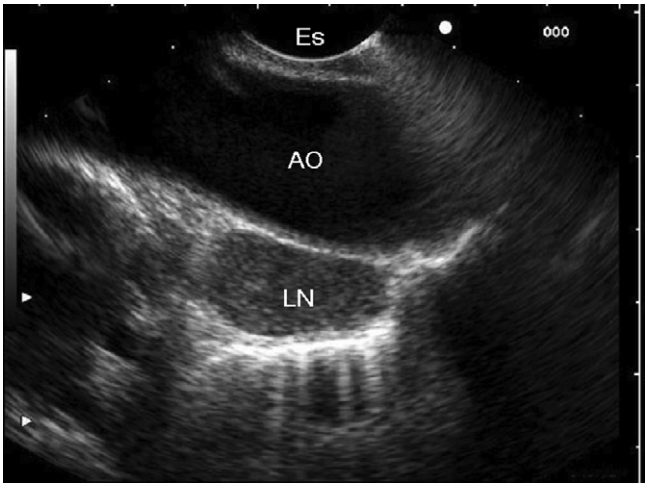


FIGURE 6.6 Lymph node (LN) located adjacent to the aortic arch (AO) (station 6). Es, esophagus.

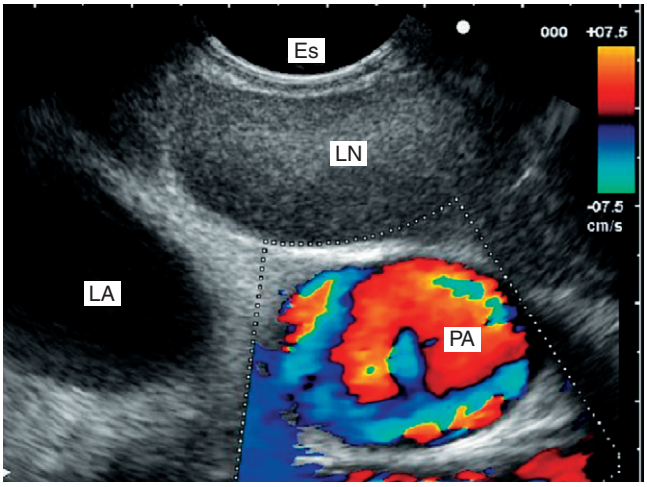


FIGURE 6.7 Subcarinal lymph node (LN) located between the esophagus (Es), pulmonary artery (PA), with color Doppler signal, and left atrium (LA).

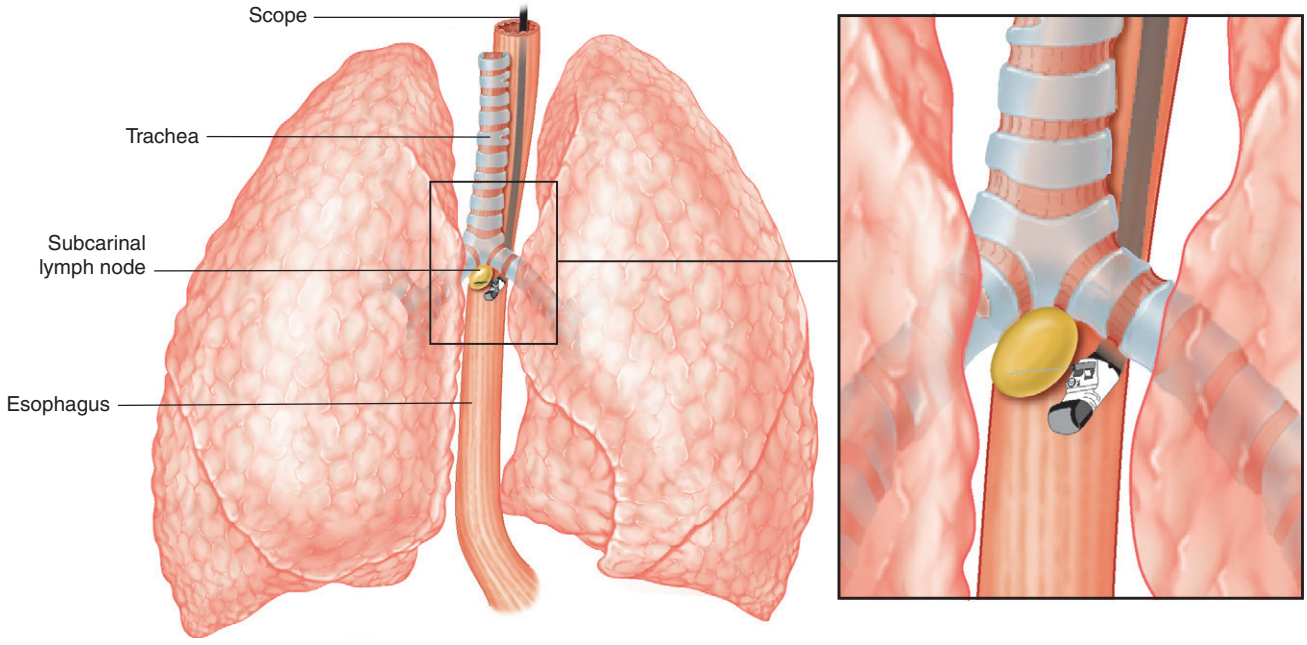


FIGURE 6.8 Diagram showing transesophageal ultrasound-guided fine-needle aspiration of a subcarinal lymph node.

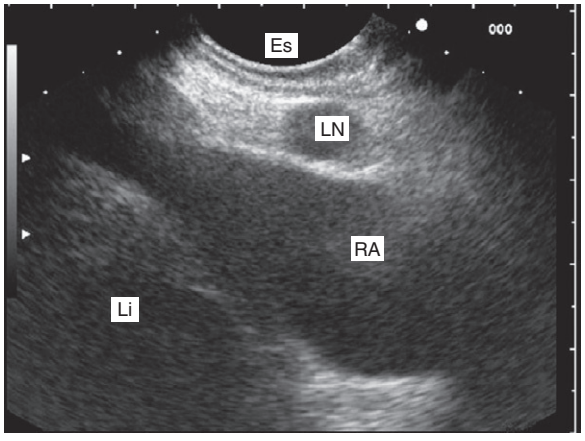


FIGURE 6.9 Lymph node (LN) located in the pulmonary ligamentum (station 9). Es, esophagus; Li, liver; RA, right atrium.

(station 8), and pulmonary ligamentum (station 9; Figs. 6.9 and 6.10). Lymph nodes located in the aortopulmonary window can be detected by EUS but not always sampled, given the interposition of the pulmonary artery. Para-aortal nodes are located on the other side of the aorta and can well be visualized by EUS (see Fig. 6.6). In selected cases, these lymph nodes can be aspirated transaortally to obtain a tissue diagnosis[11] from these nodes that can otherwise be reached only by mediastinotomy or video-assisted thoracoscopy (VATS). EUS has limitations in its diagnostic reach because air in the trachea and main bronchi inhibits visualization of the upper paratracheal lymph node (station 2) and the lower paratracheal station on the right (4R). EUS FNA can be used for the assessment of mediastinal nodes in patients with known (Fig. 6.11) or suspected lung cancer or in patients with mediastinal masses suspected of being lung cancer (Fig. 6.12). In addition to lymph node sampling, EUS FNA can be used for biopsy of the left adrenal gland and intrapulmonary tumors, provided these structures lie adjacent to the esophagus (Fig. 6.13).

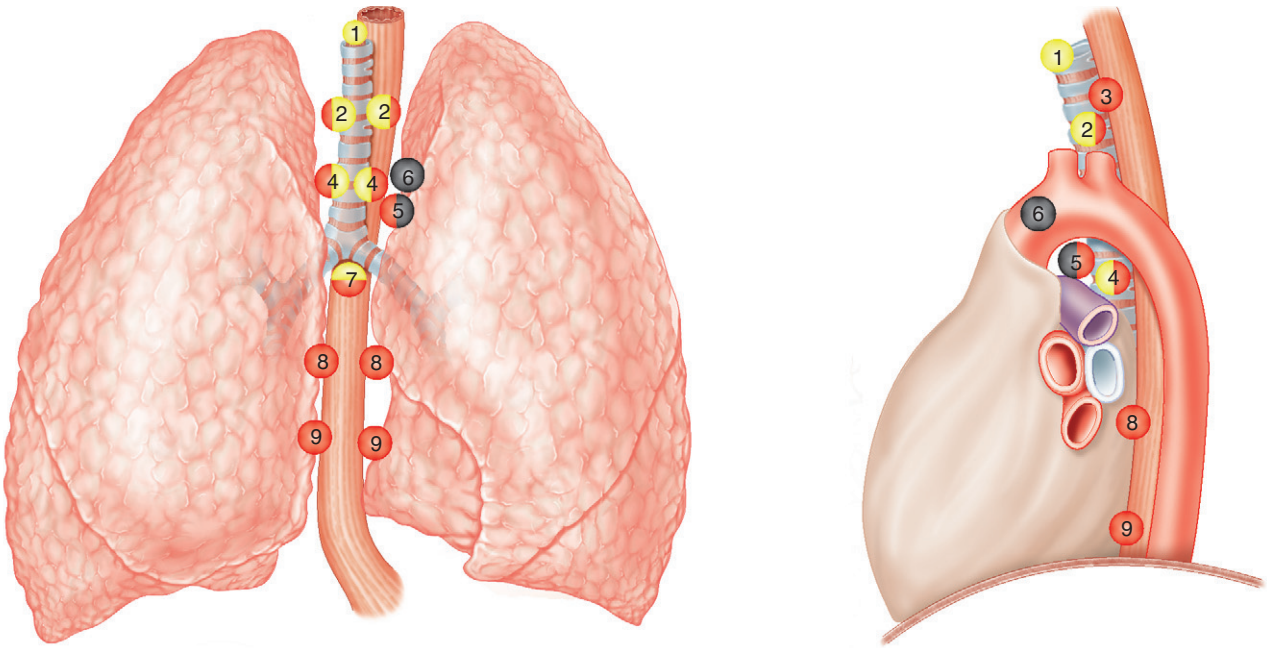


FIGURE 6.10 Mediastinal staging techniques and their diagnostic reach. *Yellow ball,* within reach of EBUS and mediastinoscopy; *red ball,* within reach of EUS; *black ball,* within reach of mediastinotomy or video-assisted thoracoscopy.

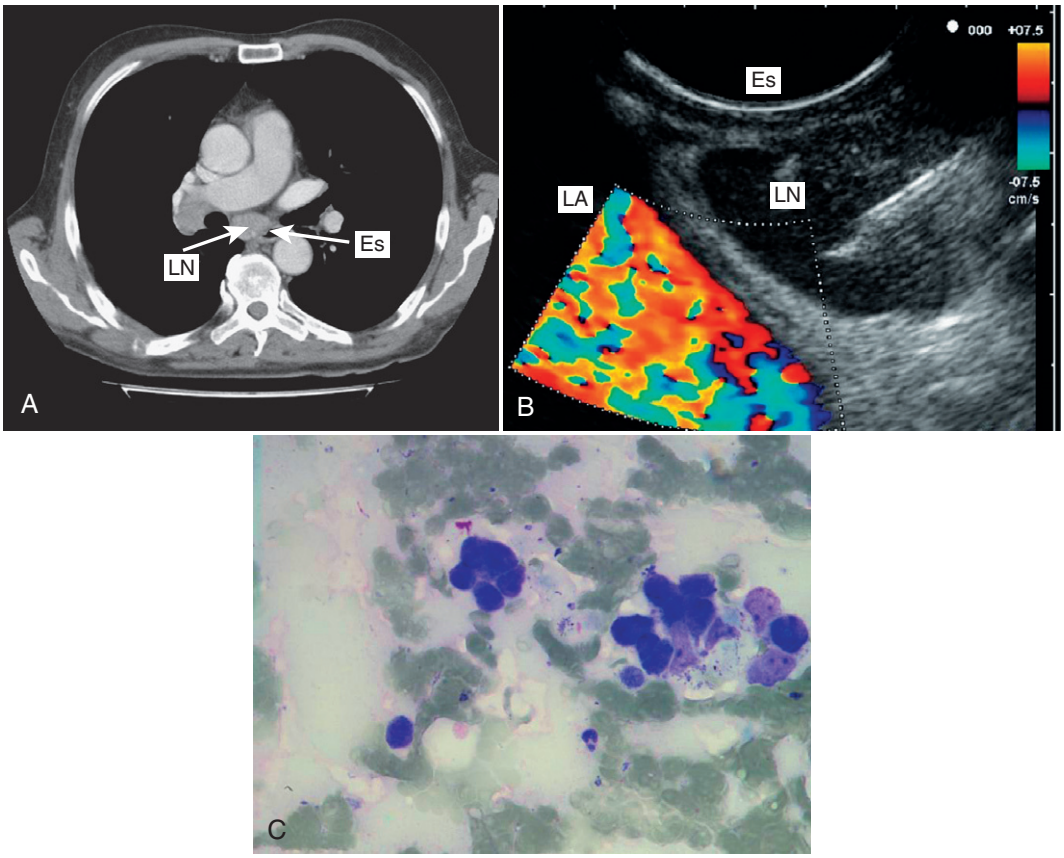


FIGURE 6.11 A 54-year-old man with proven non–small cell lung cancer who was fit for surgical resection. A, Computed tomography of the chest demonstrating a centrally located non–small cell lung carcinoma of the right lung and an enlarged subcarinal lymph node (LN). Es, esophagus. **B,** Real-time EUS-guided aspiration of the subcarinal lymph node (LN) located between the esophagus (Es) and the left atrium (LA). **C,** Cytologic appearance of a lymph node metastasis.

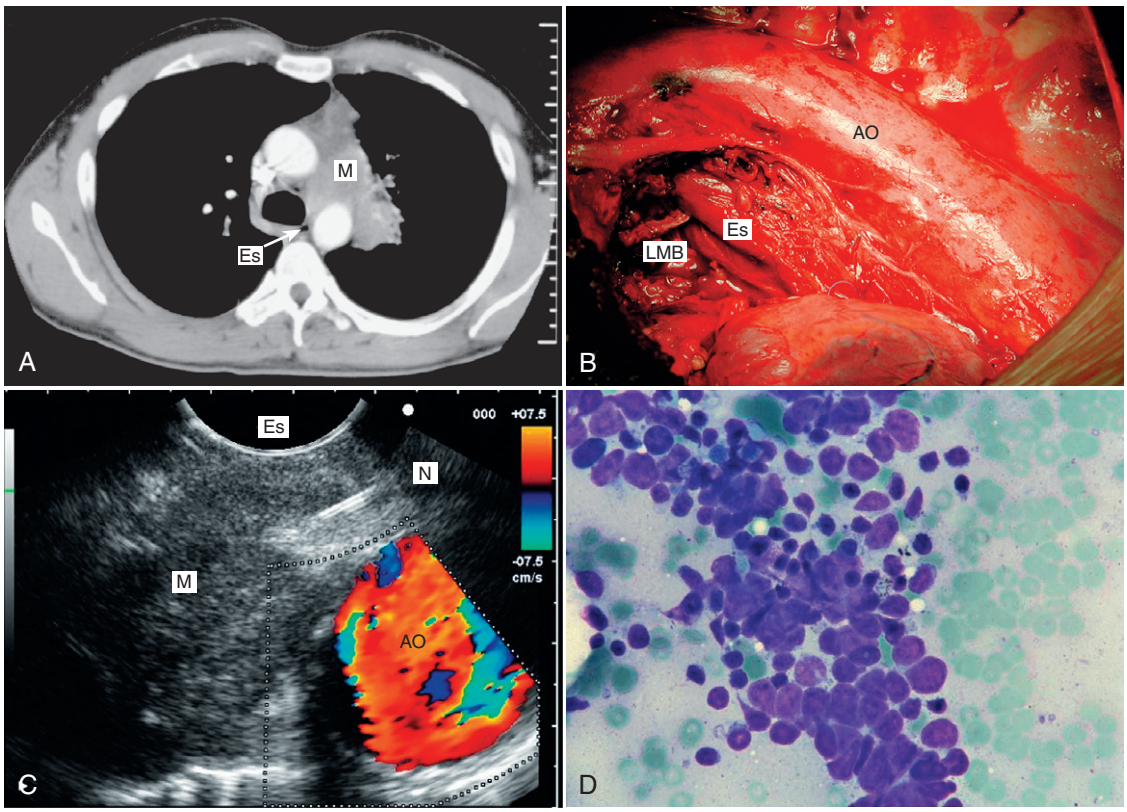
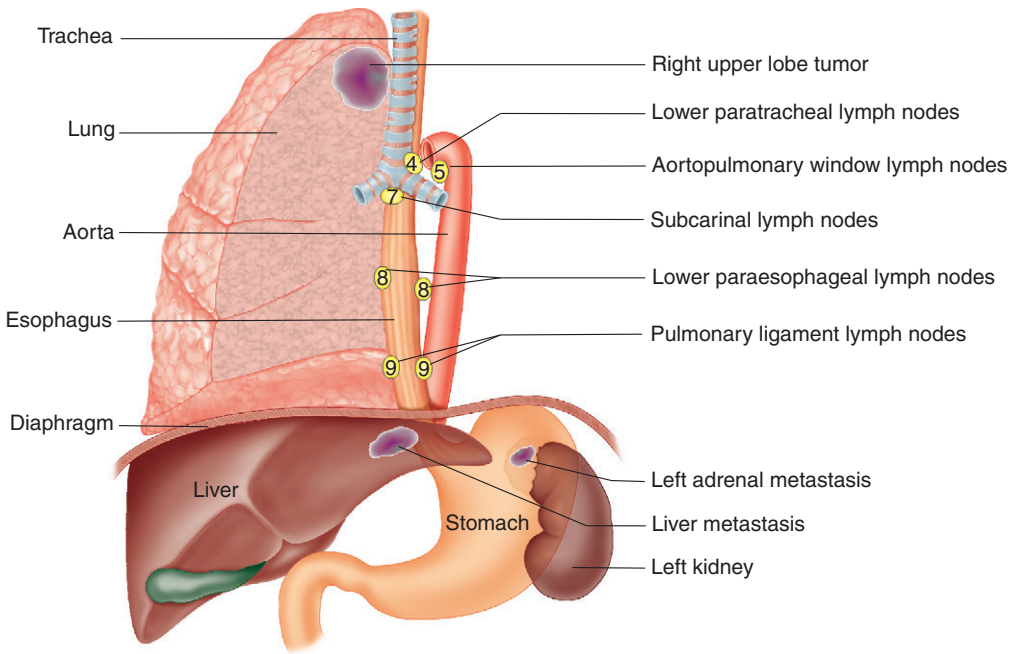


FIGURE 6.12 **A 66-year-old man, heavy smoker with suspected lung cancer, in whom bronchoscopy was nondiagnostic. A,** Computed tomography of the chest demonstrating a mass (M) in the aortopulmonary window. Es, esophagus. **B,** In another patient just after left-sided pneumonectomy, the close relationship between the esophagus (ES) and the aortopulmonary window. AO, aorta; LMB, left main bronchus. **C,** Corresponding EUS image with fine-needle aspiration of the mass (M) located between the esophagus (Es) and the aorta (AO) (with color Doppler). N, needle. **D,** Cytologic appearance of small cell carcinoma.

FIGURE 6.13 **EUS fine-needle aspiration (FNA) in non–small cell lung cancer.** EUS FNA in non–small cell lung cancer can sample intrapulmonary tumors for biopsy and detect mediastinal tumor invasion (T4), assess mediastinal lymph nodes, and identify distant metastases located in the left liver lobe and left adrenal gland.



EUS versus EUS Fine-Needle Aspiration

Specific ultrasonographic features of mediastinal lymph nodes (size [short axis >10 mm], round shape, homogeneous hypoechoic pattern, sharp distinctive borders) are associated with malignant involvement,[12,13] for which EUS has a sensitivity, specificity, and positive and negative predictive values of 78%, 71%, 75%, and 79%, respectively.[14] Elastography is a newer technical application that depicts the mechanical properties of tissue during endosonography. An accuracy of 85% for differentiating benign from malignant mediastinal nodes has been reported.[15] The value of elastography is investigational, and this technique may be helpful in selecting target lymph nodes for biopsy. EUS in combination with FNA is more accurate than is EUS imaging alone.[12,14,16,17] Therefore. FNA is always required before a lymph node can be designated as malignant (Video 6.1). For this reason, curved linear, not radial, ultrasound probes are required for mediastinal staging of NSCLC. Of the different needle sizes (19, 22, and 25 gauge) available for nodal staging, the 22 gauge is regarded as the standard size.

The recommended number of biopsies per lymph node depends on the presence or absence of on-site cytologic examination. If on-site cytologic examination is not available, three or five needle passes are recommended to obtain an optimal yield.[18,19] No benefit in diagnostic yield has been correlated with the position of the needle in the lymph node (central versus peripheral) or the application of suction.[19] In addition to conventional cytologic evaluation, cell blocks can be made of EUS fine-needle aspirates on which immunohistochemistry can be performed. EUS FNA of mediastinal lymph nodes is safe, and complications such as a mediastinitis are rare.[20]

Accuracy of Mediastinal Staging

Mediastinal nodal staging in patients with known or suspected lung cancer has been investigated in multiple studies.[19,21–38] In a meta-analysis of 18 studies of EUS FNA for the mediastinal staging of lung cancer, sensitivity was 83% (95% confidence interval [CI], 78% to 87%) and specificity was 97% (95% CI, 96% to 98%).[39] In those patients with enlarged lymph nodes, sensitivity was 90% (95% CI, 84% to 94%). Another meta-analysis, which partly discussed the same studies, of 1003 patients in whom the overall prevalence for mediastinal disease was 61%, EUS had a sensitivity of 84% and a false-negative rate of 19%.[3] Although positive predictive values were reported in most studies, tumor-positive findings were verified by surgical-pathologic staging in only one study.[22] Although false-positive EUS FNA findings have seldom been reported, they are possible when the primary tumor is located immediately adjacent to a lymph node, a situation in which the EUS images can be misinterpreted.[22] Most studies are performed in selected patients with enlarged (>1 cm) mediastinal lymph nodes at CT, and therefore the results apply only to patients in that category. Few studies have focused specifically on small (short axis ≤10 mm) nodes; sensitivity has varied between 35% and 93%.[30,34,36] The pooled sensitivity in a meta-analysis for this subgroup was 58% (95% CI, 39% to 75%).[39] Investigators have also reported that EUS FNA of lymph nodes in the lower mediastinum can be performed with a convex linear EBUS probe (Fig. 6.14).[40]

Mediastinal restaging after induction chemotherapy is an increasingly common indication for EUS FNA. Accurate restaging is important to identify those patients who are successfully downstaged because they benefit most from subsequent surgical resection.[41,42] The sensitivity (75%) of EUS FNA in mediastinal restaging is slightly inferior compared with conventional staging, mostly as a result of the sampling error of small residual tumor metastases.[43] In a study in 28 patients with locally advanced NSCLC, EUS had both an accuracy and negative predictive value of 92% for mediastinal restaging and was superior to fluorodeoxyglucose (FDG) PET.[44]

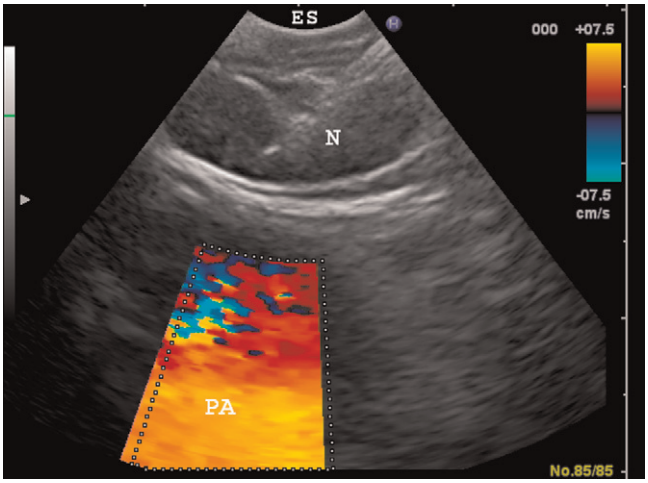


FIGURE 6.14 EUS fine-needle aspiration of a subcarinal lymph node (station 7) with an EBUS scope. Notice the smaller ultrasound range in comparison with an investigation with a conventional EUS scope (see Fig. 6.7). Es, esophagus; N, needle; PA, pulmonary artery.

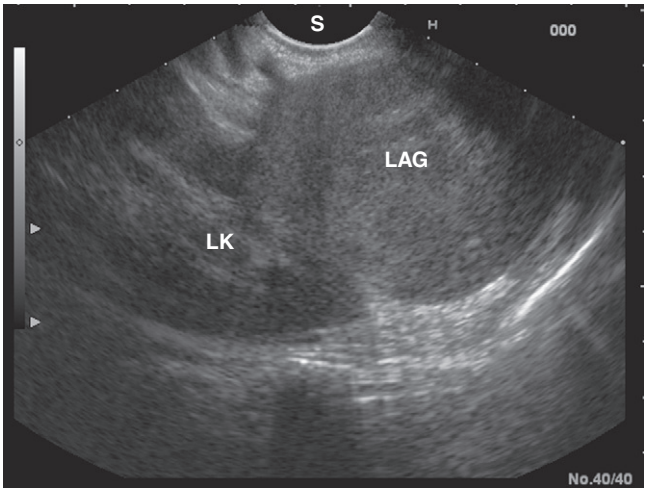


FIGURE 6.15 Transgastric EUS image of the left kidney (LK) and metastatic involved left adrenal gland (LAG). S, stomach.

Assessment of Distant Metastases

Approximately 40% of patients with lung cancer present with distant metastases, mostly in liver, brain, bone, and adrenal glands. Of these common locations of distant lung cancer metastasis, lesions located in the left liver lobe and left adrenal gland can be identified (Fig. 6.15) and sampled for biopsy by EUS (Video 6.2). In a study of highly selected patients (both with and without lung cancer) with enlarged left adrenal glands, EUS assessed malignant left adrenal involvement in 42% of patients.[45] In 40 patients with (suspected) lung cancer and an enlarged left adrenal

gland, EUS FNA altered TNM staging in 70% of patients after analysis of the left adrenal gland.[46] Whether the left adrenal gland should be examined routinely during EUS procedures in patients with lung cancer is the subject of debate.[47] Patients with disseminated lung cancer often present with liver metastases. The standard procedure for the detection of liver metastases is transabdominal ultrasonography. Investigators have reported that liver metastases can be assessed by EUS FNA using a transgastric approach.[48–50] Whether EUS FNA has additional benefits compared with transabdominal ultrasound–guided liver biopsy is unknown.

EBUS TRANSBRONCHIAL NEEDLE ASPIRATION FOR THE DIAGNOSIS AND STAGING OF LUNG CANCER

EBUS enables visualization of intrapulmonary lesions, mediastinal and hilar lymph nodes, and mediastinal masses located adjacent to the main airways (EBUS TBNA Examination Checklist). Similar to EUS in gastroenterology, EBUS development started with radial probes. With radial EBUS, lesions can be detected but not sampled under real-time ultrasound control. Radial EBUS is mainly used for the detection of peripheral lung lesions that can be subsequently sampled using fluoroscopy or guide sheets. Linear EBUS, commercially available since 2004, enables real-time controlled sampling of mediastinal or hilar nodes and centrally located lung tumors, similar to EUS FNA. In this chapter, only linear EBUS applications for the diagnosis and staging of lung cancer are discussed.

EBUS TBNA EXAMINATION CHECKLIST*

Upper left paratracheal region (station 2L)
Lower left paratracheal region (station 4L)
Upper right paratracheal region (station 2R)
Lower right paratracheal region (station 4R)
Subcarinal area (station 7)
Left hilar region (station 10L)
Left intrapulmonary region (station 11 L)
Right hilar region (station 10R)
Right intrapulmonary region (station 11R)
Intrapulmonary tumor visible?

*See also reference 4.

EBUS Procedure

Linear EBUS scopes (Olympus XBF UC 160 F, Pentax EB 1970 UK [Fig 6.16]) are modified bronchoscopes with an electronic linear ultrasound transducer (scanning range, 5 to 12 MHz) integrated in the distal end of the scope. A light source is also available and is positioned at a 30-degree angle. An EBUS investigation can be performed with the patient under conscious sedation with low-dose midazolam. The examination takes approximately 15 to 20 minutes. Before endoscopy, the pharynx is sprayed with lidocaine, and often codeine is administered to suppress the cough reflex. Patients are investigated while they are in a supine position, and the scope is introduced orally into the trachea. During an EBUS investigation, both white optical light and transbronchial ultrasound images are available. With the endobronchial view, the position of the EBUS scope in the tracheobronchial tree is evident (Fig. 6.17). When the ultrasound transducer is directed toward the airway mucosa, lymph nodes adjacent to the airway wall can be visualized (Fig. 6.18). Optionally, a water-filled balloon can be attached to the ultrasound head

FIGURE 6.16 Convex EBUS Pentax EB 1970 UK scope.

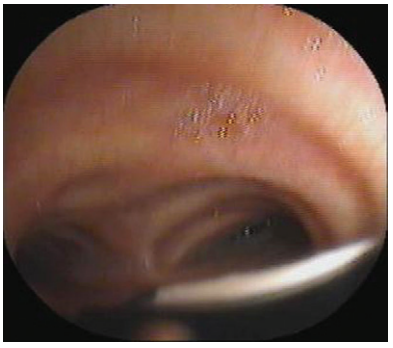


FIGURE 6.17 Optical image during EBUS demonstrating the position of the endoscope in the distal trachea. The main carina and ostia of the left and right main bronchi can be seen. Notice the white line at the bottom end of the image representing the ultrasound head of the scope.

to increase contact. During visualization of the lymph nodes, the endoscopic view is often limited because of the close proximity of the optical source to the airway wall (see Fig. 6.18). After positioning a sheet (see Fig. 6.16) that protects the working channel of the scope from the needle, lymph nodes can be aspirated in a real-time controlled fashion (see Fig. 6.18). Three needle passes are advised for an optimal yield.[51] Only 22-gauge needles are available, although larger, 19-gauge needles are in development. EBUS-related complications are very rare; a case of pneumothorax[52] and infections[53] have been reported.

Diagnosing Intrapulmonary Tumors by EBUS

Conventional bronchoscopy fails to detect the primary lung tumor in approximately 30% of patients.[54] Intrapulmonary tumors that are located immediately adjacent to the trachea or the main bronchi can be visualized (Fig. 6.19) and sampled by EBUS TBNA. In two studies in patients with a centrally located lung tumor without abnormalities noted on conventional bronchoscopy, the diagnosis was made by EBUS in 77%[55] and 94%[56] of patients, respectively. Biopsy of intrapulmonary tumors after a nondiagnostic conventional bronchoscopy is an important indication for EBUS because it is often difficult to procure tissue safely in centrally located lung lesions. In these patients, a CT-guided lung biopsy is often unattractive, given the close proximity of the tumor to centrally located vessels that pose an increased risk of pneumothorax and hemoptysis. For the primary diagnosis of lung cancer, and especially for

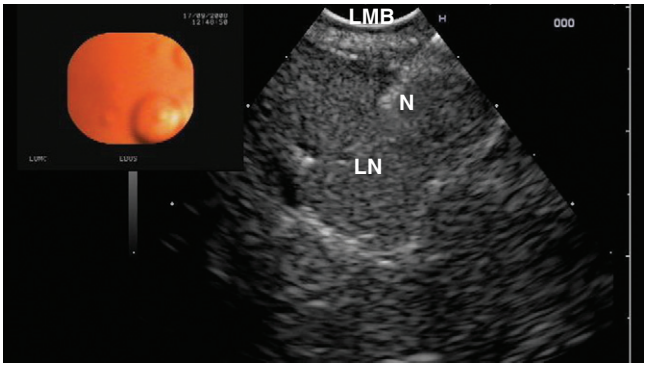


FIGURE 6.18 Real-time EBUS transbronchial needle aspiration of a subcarinal lymph node (station 7). Notice that when contact between the ultrasound transducer and the airway mucosa is made, the optical image disappears *(left upper corner).* LMB, position of the endoscope in the left main bronchus; LN, lymph node; N, needle.

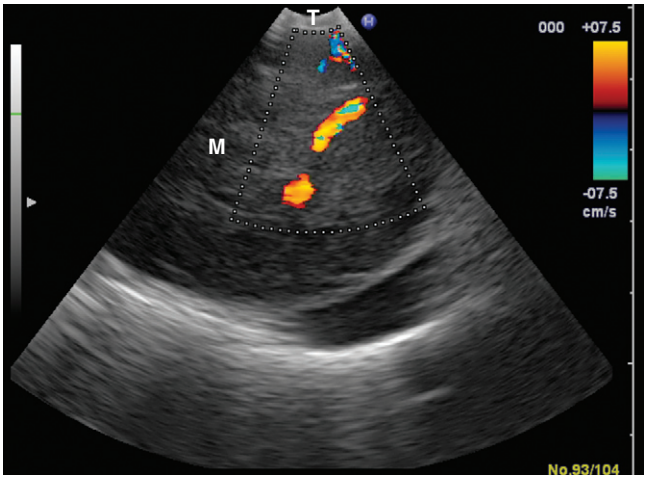


FIGURE 6.19 Adenocarcinoma (M) of the right upper lobe detected by EBUS from the trachea (T). Note the vessel running through the intrapulmonary tumor.

distinguishing among the different subtypes of adenocarcinoma, it remains to be seen how EBUS samples relate to histologic findings for accurate tumor subclassification. No data are available on the value of linear EBUS for mediastinal tumor invasion.

Nodal Staging by EBUS

Mediastinal nodal sampling is the major indication for EBUS TBNA (Video 6.3). Mediastinal lymph nodes that can be reached are located adjacent to the trachea (above the level of the aortic arch, stations 2L and 2R; below the aortic arch, stations 4L [Fig. 6.20] and 4R [Fig. 6.21]) or main bronchi (station 7, which can be reached from both the left and right main bronchi). Lymph nodes in the aortopulmonary window (station 5) can sometimes be detected but not safely sampled because of the intervening pulmonary artery. In addition to mediastinal nodes, EBUS can also be used to sample intrapulmonary lymph nodes (Fig. 6.22) or nodes located in the hilum of the lung (station 10). With the experimental elastography technique, the stiffness of a node can be assessed (Fig. 6.23). Whether elastography influences the biopsy procedure or diagnostic yield needs to be investigated. It is of critical importance that the lymph nodes identified by EBUS are given the appropriate number according to the revised seventh edition of the TNM classification,[5] in order to prevent understaging or overstaging.[4]

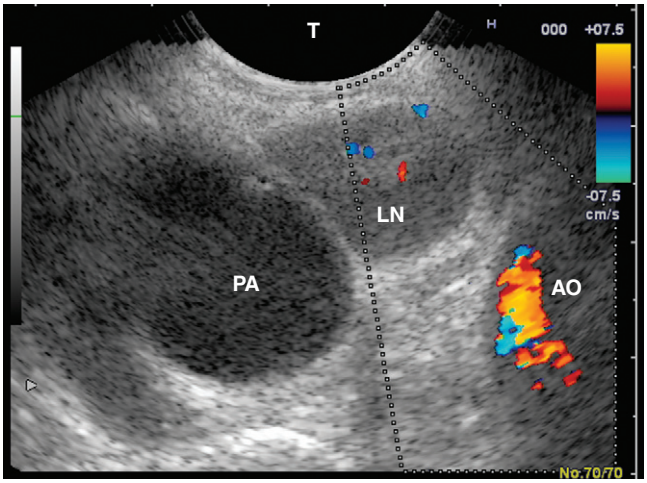


FIGURE 6.20 EBUS image of a left paratracheal lymph node (LN) (station 4L) detected by EBUS from the trachea (T). AO, aorta; PA, pulmonary artery.

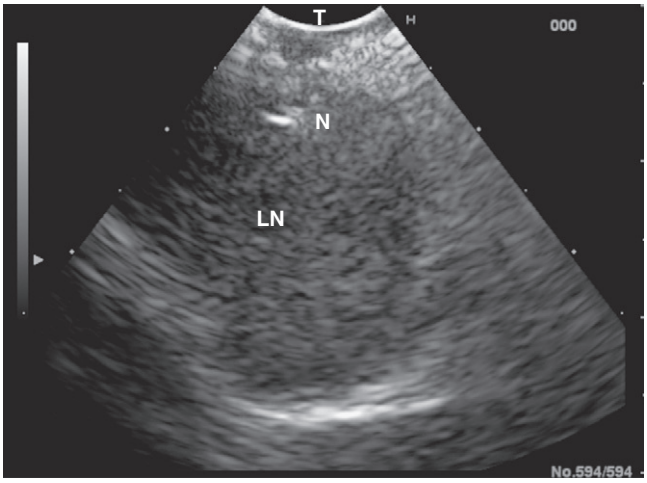


FIGURE 6.21 EBUS transbronchial needle aspiration image of a paratracheal node (LN) on the right (station 4R). N, needle; T, position of the scope in the trachea.

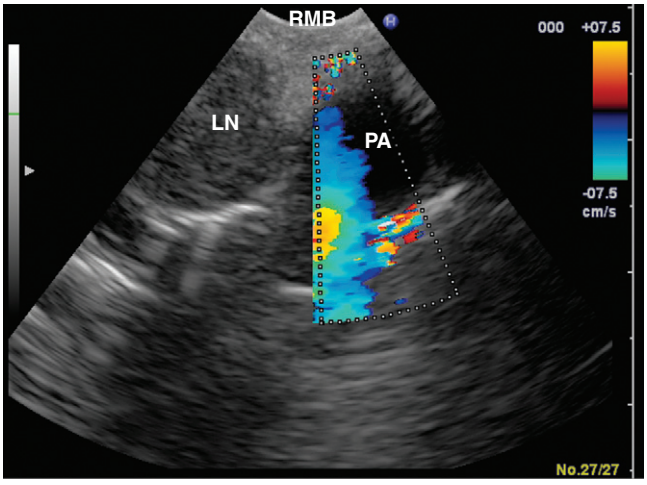


FIGURE 6.22 EBUS image of intrapulmonary node (LN) on the right detected from the right upper lobe carina (station 11R). The Doppler signal demonstrates a branch from the pulmonary artery (PA). RMB, position of the scope in the right main bronchus.

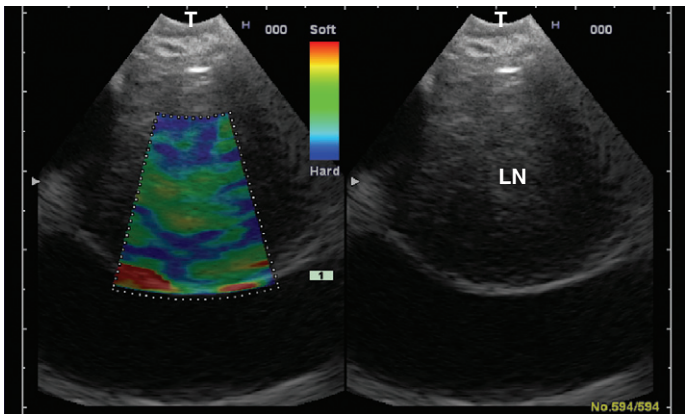


FIGURE 6.23 Enlarged right-sided lower paratracheal node. EBUS image (**B**) of an enlarged right-sided lower paratracheal node (station 4R). The blue color at elastography (**A**) shows the increased stiffness of the nodal tissue.

In 2009, three meta-analyses were published, partly discussing the same studies, on EBUS for mediastinal staging.[57–59] In 11 studies in 1299 patients, EBUS had a pooled sensitivity of 93% (95% CI, 91% to 94%) and a pooled specificity of 100% (95% CI, 0.99 to 1.0). Selected patients with either enlarged or PET-positive lymph nodes had a higher sensitivity, 0.94 (95% CI, 0.93 to 0.96), in comparison with those patients unselected by CT or PET, in whom sensitivity was 0.76 (95% CI, 0.65 to 0.85).[58] In this meta-analysis, no correlation was found between the prevalence of nodal metastases and sensitivity in the various studies. As in EUS, most studies were performed in selected patients with enlarged nodes.[51,60–66] In patients whose PET scans were suspected of showing nodal metastases, EBUS had sensitivities between 90% and 95% and negative predictive values between 60% and 97%.[52,67,68]

In a study in 100 patients with NSCLC without nodal enlargement at CT, sensitivity and negative predictive value were 92% and 96%, respectively.[69] In another series of 100 patients with NSCLC with small (mean diameter, 7.9 mm) and PET-negative nodes, EBUS detected mediastinal malignancy in 9% of patients and had a sensitivity and a negative predictive value of 89% and 99%, respectively.[70] EBUS is also the technique of choice for sampling lymph nodes located in the hilum of the lung. In 213 patients with either enlarged or FDG PET–active hilar nodes, EBUS had a sensitivity of 91%.[71] EBUS can also be used for mediastinal restaging after induction chemotherapy. Herth et al[72] found a sensitivity of 76% and a negative predictive value of only 20%. The low negative predictive value was mainly the result of sampling errors. In another mediastinal restaging study in 61 patients, EBUS had a sensitivity and a negative predictive value of 67% and 78%, respectively.[73]

IMPACT OF ENDOSONOGRAPHY ON PATIENT MANAGEMENT

The impact of endosonography on patient management depends on the prevalence of mediastinal metastases in the target population, the location of the primary tumor, and the extent and location of mediastinal disease.[38]

Preventing Mediastinoscopies

In a prospective study of 84 patients with mediastinal masses suspected of being malignant, EUS prevented thoracotomy or thoracoscopy in 48% and mediastinoscopy in 68% of patients by demonstrating lymph node metastases.[29] In a similar study population of 59 patients, all scheduled for mediastinoscopy, EUS FNA proved mediastinal metastases in 39% of patients, and mediastinoscopy was eventually performed in only 22%.[31]

In a prospective study of 242 patients with (suspected) NSCLC and enlarged mediastinal lymph nodes (all candidates for mediastinoscopy or mediastinotomy), EUS FNA demonstrated lymph node metastases, tumor invasion, or an alternative diagnosis in 70% of patients, and surgical interventions were thus prevented.[21] Routine use of EUS FNA in 152 patients with NSCLC (unselected by CT) reduced the need for surgical staging in nearly half the patients.[33]

In a randomized trial in patients with resectable NSCLC, EUS significantly reduced the need for surgical staging.[35] In other studies, EBUS omitted the need for surgical staging in half of patients with enlarged nodes at CT.[62,65] In patients with suspected nodal metastases based on PET, surgical staging was avoided in up to 71% of patients based on EBUS findings.[68] In a lung cancer staging strategy including PET, the diminished need for surgical staging based on EUS outcomes resulted in a cost reduction of 40%.[28]

Reducing Futile Thoracotomies

In a prospective study of 108 patients with NSCLC, staging by EUS added to mediastinoscopy identified significantly more patients with either tumor invasion or lymph node metastasis (36%) compared with staging by mediastinoscopy alone (20%). Had EUS results been taken into account, one of six thoracotomies could have been prevented.[22] Additionally, in a randomized study of 104 patients, routine staging by EUS FNA resulted in a 16% decrease in the number of futile thoracotomies compared with staging of selected patients by EUS.[74]

ENDOSONOGRAPHY VERSUS OTHER MEDIASTINAL STAGING METHODS

How do EUS FNA and EBUS TBNA compare with other mediastinal staging techniques? It is important to distinguish between imaging techniques that provide information about lymph node size (CT scan of the chest) or metabolic activity (PET) and those staging techniques by which tissue is obtained ("blind" transbronchial needle aspiration [TBNA], mediastinoscopy, mediastinotomy, or VATS).

In mediastinal staging, EUS FNA is more sensitive (88% versus 57%) and specific (91% versus 82%) than CT scan of the chest.[14,16] EUS FNA and PET have similar sensitivities (88% versus 84%) and specificities (91% versus 89%) in identifying mediastinal lymph node metastases.[14,16]

In a direct comparison study that had identification of inoperable patients as the outcome, EUS FNA and PET had comparable sensitivities (63% versus 68%) and negative predictive values (68% versus 64%), but EUS was more specific (100% versus 72%).[75] Obviously, tissue verification of PET-positive lymph nodes should occur, given the limited positive predictive value of FDG PET.[76] Analysis of PET-positive mediastinal nodes by either EUS[28,77] or EBUS[52,67,68] is a minimally invasive mediastinal staging strategy for NSCLC that has sensitivities of approximately 90%.

All available biopsy techniques have a different diagnostic reach, and, unfortunately, none can sample all mediastinal N2 to N3 lymph node stations. For the various sampling techniques, sensitivity and specificity are regularly based on the specific area that can be reached by the technique under investigation, and not on the mediastinum as a whole. Mediastinoscopy provides access to the upper and lower paratracheal regions (stations 2 and 4) and the ventral part of the subcarinal station (region 7) and has a sensitivity of 78%.[3] EUS is

complementary to mediastinoscopy because it provides access to both the ventral and the dorsal parts of station 7, the aortopulmonary window, the lower paraesophageal lymph nodes (station 8), and the nodes located in the pulmonary ligamentum (station 9; see Fig. 6.9). VATS has been shown to be more accurate than EUS FNA for lymph nodes located in stations 5 and 6.[78]

A limitation of EUS is its inability to detect upper paratracheal lesions as well as those located paratracheally on the right (see Fig. 6.10), because of the interposition of air in the trachea by which the ultrasound waves are reflected. As a result of their complementary diagnostic reach, the combination of EUS FNA and mediastinoscopy detects significantly more patients with lymph node metastases than either EUS FNA or mediastinoscopy alone.[22] EBUS TBNA has a diagnostic reach similar to that of mediastinoscopy (the paratracheal areas [station 2L, 4L, 2R, 4R] and the subcarinal space [station 7]), but it can additionally reach the hilar regions (station 10). In a comparison between EBUS and mediastinoscopy, a slight advantage for EBUS was found.[79] When EUS and EBUS are combined, virtually all mediastinal nodal stations can be investigated.[80–83]

COMPLETE ECHOENDOSCOPIC STAGING

In combination, EUS FNA and EBUS TBNA can reach virtually all mediastinal nodal stations. EBUS has access to the paratracheal zones (stations 2R, 4R, 2L, 4L), and EUS reaches the lower mediastinum (stations 8 and 9; see Fig. 6.9). The subcarinal area (station 7) and the left paratracheal station 4L can be reached by both methods. Herth et al[84] found that EUS and EBUS had an added value for the subcarinal station. Vilmann et al[82] proposed the concept of complete mediastinal staging of lung cancer by investigating patients with both EUS FNA and EBUS TBNA.

Two small series demonstrated the combined value of EUS FNA and EBUS TBNA for mediastinal staging.[82,85] In 138 patients with (suspected) lung cancer who were investigated by this combined approach, Wallace et al[83] found a sensitivity for lymph nodes of 93% and a negative predictive value of 97%. In 120 patients with NSCLC without nodal enlargement at CT, complete echoendoscopic staging of the mediastinum resulted in a sensitivity of 68% and a negative predictive value of 91%.[81] Complete echoendoscopic staging of the mediastinum with a single EBUS scope was reported in 84 patients.[40]

POSITION OF EUS AND EBUS IN LUNG CANCER STAGING ALGORITHMS

Where should endosonography (EUS or EBUS or both) be positioned in staging algorithms for the diagnosis and staging of lung cancer? The strength of endosonography is the minimally invasive confirmation of mediastinal lymph node metastases or mediastinal tumor invasion. Endosonography is complementary to PET, which has, under defined circumstances, a high negative predictive value in excluding advanced disease.[76]

Implementation of endosonography in local lung cancer staging protocols obviously depends on the availability and expertise of EUS and EBUS and its practitioners, the presence of imaging modalities such as integrated CT-PET, and surgical expertise. Current guidelines recommend the use of EUS or EBUS to confirm mediastinal metastases.[2,3] EUS and EBUS are advocated for use early in staging algorithms for NSCLC, especially in those patients with a high pretest probability of mediastinal disease.

In hospitals that have access to both endosonography and PET, the following strategy is proposed for patients with (suspected) lung cancer who are candidates for surgical resection: PET-CT followed by bronchoscopy, including conventional "blind" TBNA (Fig. 6.24). In patients with centrally located tumors or enlarged (>1 cm) or PET-positive mediastinal lymph nodes, further staging is required by EUS or EBUS (first) and mediastinoscopy (when EUS or EBUS does not provide proof of mediastinal metastasis or tumor invasion). In patients with a peripherally located tumor without enlarged or PET-positive mediastinal lymph nodes, thoracotomy can be performed directly because the probability of mediastinal metastases is very low.[76]

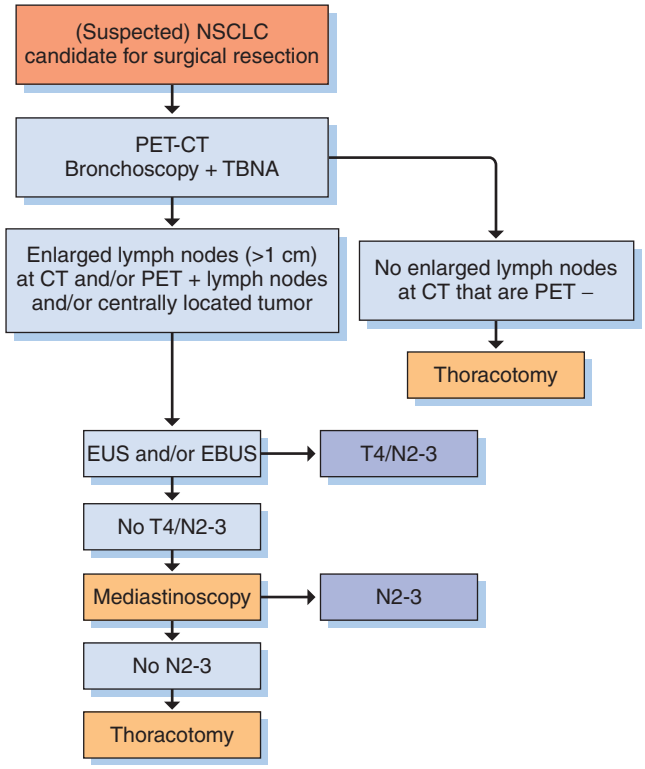


FIGURE 6.24 Proposed role of EUS fine-needle aspiration (FNA) and EBUS transbronchial needle aspiration (TBNA) in the mediastinal staging of non–small cell lung cancer (NSCLC) (with availability of positron emission tomography [PET]). CT, computed tomography.

In centers without access to PET, the recommendation is for staging of patients by EUS or EBUS, followed by mediastinoscopy in the absence of mediastinal metastases at endosonography (Fig. 6.25). Combined staging with EUS and mediastinoscopy significantly improves staging compared with EUS or mediastinoscopy alone.[22] The concept of complete echoendoscopic staging of NSCLC is very promising and currently under investigation.[81–83,85]

FUTURE PERSPECTIVES

A large body of evidence indicates that both EUS FNA and EBUS TBNA are accurate endoscopic methods for the diagnosis and staging of NSCLC. By demonstrating mediastinal lymph node metastases or tumor invasion, endosonography provides a minimally invasive alternative for surgical staging and therefore qualifies as the diagnostic technique of choice in many patients. Although the safety record of endosonography is impressive, monitoring for complications during these interventional techniques is recommended. Additionally, data on patient preferences for the various mediastinal tissue sampling methods are indicated. Further development of endoscopes (improved imaging) and needles (larger EBUS needles) is ongoing. It is expected that, where available, patients will be initially staged by

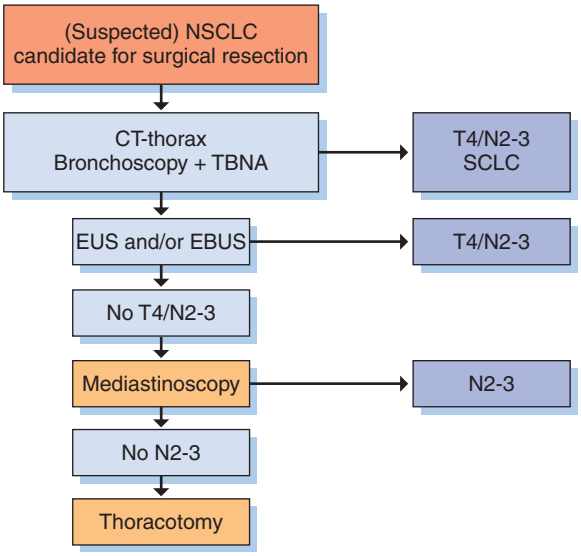


FIGURE 6.25 Proposed role of EUS fine-needle aspiration (FNA) and EBUS transbronchial needle aspiration (TBNA) in the mediastinal staging of non–small cell lung cancer (NSCLC) (without the availability of positron emission tomography). CT, computed tomography; SCLC, small cell lung cancer; TBNA, transbronchial needle aspiration.

endosonography. Whether a complete endosonography investigation (both EUS and EBUS) can be performed with a single EBUS scope[40] needs further investigation.

Targeted therapy, addressing specific treatments for different subtypes of NSCLC, will be more important in the years to come. Investigators will need to determine the extent to which the fine-needle aspirates and cell blocks obtained by EUS and EBUS can obtain the same molecular information (EGFR/K-ras receptor status[40,86,87]) as lymph node biopsies at surgical staging.

Regarding the high incidence of lung cancer, vast numbers of patients will qualify for mediastinal staging by endosonography. The dissemination of EUS and EBUS from specialized academic institutions to large regional hospitals is needed to facilitate general availability of these techniques. Investments in equipment, needles, training, and cytopathologic expertise are requirements for a successful endosonography service. To achieve this goal, key professionals in lung cancer care, including chest physicians and surgeons who perform lung surgery, should be aware of the indications of endosonography and the alternative it provides to surgical staging. Furthermore, specialists need to be trained to perform EUS and EBUS procedures. The fact that gastroenterologists are not generally familiar with lung cancer staging, and chest physicians are not used to performing EUS, may be a barrier. With a dedicated training and EUS implementation strategy, however, chest physicians have obtained results similar to those achieved by experts.[23] Training data regarding EBUS TBNA are needed; one study reported a plateau in diagnostic performance after 50 investigations.[62] The challenge will be to implement both EUS and EBUS in a short time span to guarantee general accessibility of these important diagnostic and staging methods for patients with NSCLC.

REFERENCES

1. Spira A, Ettinger DS. Multidisciplinary management of lung cancer. *N Engl J Med*. 2004;350(4):379–392.
2. De Leyn P, Lardinois D, Van Schil PE, et al. ESTS guidelines for preoperative lymph node staging for non–small cell lung cancer. *Eur J Cardiothorac Surg*. 2007;32(1):1–8.
3. Detterbeck FC, Jantz MA, Wallace M, et al. Invasive mediastinal staging of lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition). *Chest*. 2007;132(suppl 3):202S–220S.
4. Tournoy KG, Annema JT, Krasnik M, et al. Endoscopic and endobronchial ultrasonography according to the proposed lymph node map definition in the seventh edition of the tumor, node, metastasis classification for lung cancer. *J Thorac Oncol*. 2009;4(12):1576–1584.
5. Rusch VW, Asamura H, Watanabe H, et al. The IASLC lung cancer staging project: a proposal for a new international lymph node map in the forthcoming seventh edition of the TNM classification for lung cancer. *J Thorac Oncol*. 2009;4(5):568–577.
6. Annema JT, Veselic M, Rabe KF. EUS-guided FNA of centrally located lung tumours following a non-diagnostic bronchoscopy. *Lung Cancer*. 2005; 48(3):357–361.
7. Varadarajulu S, Hoffman BJ, Hawes RH, et al. EUS-guided FNA of lung masses adjacent to or abutting the esophagus after unrevealing CT-guided biopsy or bronchoscopy. *Gastrointest Endosc*. 2004;60(2):293–297.
8. Venuta F, Rendina EA, Ciriaco P, et al. Computed tomography for preoperative assessment of T3 and T4 bronchogenic carcinoma. *Eur J Cardiothorac Surg*. 1992;6(5):238–241.
9. Pieterman RM, van Putten JW, Meuzelaar JJ, et al. Preoperative staging of non–small-cell lung cancer with positron-emission tomography. *N Engl J Med*. 2000;343(4):254–261.
10. Varadarajulu S, Schmulewitz N, Wildi SF, et al. Accuracy of EUS in staging of T4 lung cancer. *Gastrointest Endosc*. 2004;59(3):345–348.
11. von Bartheld MB, Rabe KF, Annema JT. Transaortic EUS-guided FNA in the diagnosis of lung tumors and lymph nodes. *Gastrointest Endosc*. 2009; 69(2):345–349.
12. Bhutani MS, Hawes RH, Hoffman BJ. A comparison of the accuracy of echo features during endoscopic ultrasound (EUS) and EUS-guided fine-needle aspiration for diagnosis of malignant lymph node invasion. *Gastrointest Endosc*. 1997;45(6):474–479.
13. Catalano MF, Sivak Jr MV, Rice T, et al. Endosonographic features predictive of lymph node metastasis. *Gastrointest Endosc*. 1994;40(4):442–446.
14. Toloza EM, Harpole L, Detterbeck F, et al. Invasive staging of non–small cell lung cancer: a review of the current evidence. *Chest*. 2003;123(suppl 1):157S–166S.
15. Janssen J, Dietrich CF, Will U, et al. Endosonographic elastography in the diagnosis of mediastinal lymph nodes. *Endoscopy*. 2007;39(11):952–957.
16. Toloza EM, Harpole L, McCrory DC. Noninvasive staging of non–small cell lung cancer: a review of the current evidence. *Chest*. 2003;123(suppl 1):137S–146S.
17. Wiersema MJ, Vazquez-Sequeiros E, Wiersema LM. Evaluation of mediastinal lymphadenopathy with endoscopic US-guided fine-needle aspiration biopsy. *Radiology*. 2001;219(1):252–257.
18. Leblanc JK, Ciaccia D, Al Assi MT, et al. Optimal number of EUS-guided fine needle passes needed to obtain a correct diagnosis. *Gastrointest Endosc*. 2004;59(4):475–481.
19. Wallace MB, Silvestri GA, Sahai AV, et al. Endoscopic ultrasound-guided fine needle aspiration for staging patients with carcinoma of the lung. *Ann Thorac Surg*. 2001;72(6):1861–1867.
20. Aerts JG, Kloover J, Los J, et al. EUS-FNA of enlarged necrotic lymph nodes may cause infectious mediastinitis. *J Thorac Oncol*. 2008;3(10):1191–1193.
21. Annema JT, Versteegh MI, Veselic M, et al. Endoscopic ultrasound-guided fine-needle aspiration in the diagnosis and staging of lung cancer and its impact on surgical staging. *J Clin Oncol*. 2005;23(33):8357–8361.
22. Annema JT, Versteegh MI, Veselic M, et al. Endoscopic ultrasound added to mediastinoscopy for preoperative staging of patients with lung cancer. *JAMA*. 2005;294(8):931–936.
23. Annema JT, Bohoslavsky R, Burgers S, et al. Implementation of endoscopic ultrasound for lung cancer staging. *Gastrointest Endosc*. 2010;71(1):64–70.
24. Eloubeidi MA, Tamhane A, Chen VK, et al. Endoscopic ultrasound-guided fine-needle aspiration in patients with non–small cell lung cancer and prior negative mediastinoscopy. *Ann Thorac Surg*. 2005;80(4):1231–1239.
25. Fritscher-Ravens A, Sriram PV, Bobrowski C, et al. Mediastinal lymphadenopathy in patients with or without previous malignancy: EUS-FNA-based differential cytodiagnosis in 153 patients. *Am J Gastroenterol*. 2000;95(9): 2278–2284.
26. Fritscher-Ravens A. Endoscopic ultrasound evaluation in the diagnosis and staging of lung cancer. *Lung Cancer*. 2003;41(3):259–267.
27. Gress FG, Hawes RH, Savides TJ, et al. Endoscopic ultrasound-guided fine-needle aspiration biopsy using linear array and radial scanning endosonography. *Gastrointest Endosc*. 1997;45(3):243–250.
28. Kramer H, van Putten JW, Post WJ, et al. Oesophageal endoscopic ultrasound with fine needle aspiration improves and simplifies the staging of lung cancer. *Thorax*. 2004;59(7):596–601.
29. Larsen SS, Krasnik M, Vilmann P, et al. Endoscopic ultrasound guided biopsy of mediastinal lesions has a major impact on patient management. *Thorax*. 2002;57(2):98–103.

30. Leblanc JK, Devereaux BM, Imperiale TF, et al. Endoscopic ultrasound in non–small cell lung cancer and negative mediastinum on computed tomography. *Am J Respir Crit Care Med*. 2005;171(2):177–182.
31. Savides TJ, Perricone A. Impact of EUS-guided FNA of enlarged mediastinal lymph nodes on subsequent thoracic surgery rates. *Gastrointest Endosc*. 2004;60(3):340–346.
32. Silvestri GA, Hoffman BJ, Bhutani MS, et al. Endoscopic ultrasound with fine-needle aspiration in the diagnosis and staging of lung cancer. *Ann Thorac Surg*. 1996;61:1441–1445.
33. Talebian M, von Bartheld MB, Braun J, et al. EUS-FNA in the preoperative staging of non–small cell lung cancer. *Lung Cancer*. 2009; Sep 14 [Epub ahead of print].
34. Tournoy KG, Ryck FD, Vanwalleghem L, et al. The yield of endoscopic ultrasound in lung cancer staging: does lymph node size matter? *J Thorac Oncol*. 2008;3(3):245–249.
35. Tournoy KG, De Ryck F, Vanwalleghem LR, et al. Endoscopic ultrasound reduces surgical mediastinal staging in lung cancer: a randomized trial. *Am J Respir Crit Care Med*. 2008;177(5):531–535.
36. Wallace MB, Ravenel J, Block MI, et al. Endoscopic ultrasound in lung cancer patients with a normal mediastinum on computed tomography. *Ann Thorac Surg*. 2004;77(5):1763–1768.
37. Williams DB, Sahai AV, Aabakken L, et al. Endoscopic ultrasound guided fine needle aspiration biopsy: a large single centre experience. *Gut*. 1999; 44:720–726.
38. Witte B, Neumeister W, Huertgen M. Does endoesophageal ultrasound-guided fine-needle aspiration replace mediastinoscopy in mediastinal staging of thoracic malignancies? *Eur J Cardiothorac Surg*. 2008;33(6): 1124–1128.
39. Micames CG, McCrory DC, Pavey DA, et al. Endoscopic ultrasound-guided fine-needle aspiration for non–small cell lung cancer staging: a systematic review and metaanalysis. *Chest*. 2007;131(2):539–548.
40. Hwangbo B, Lee HS, Lee GK, et al. Transoesophageal needle aspiration using a convex probe ultrasonic bronchoscope. *Respirology*. 2009;14(6): 843–849.
41. Bueno R, Richards WG, Swanson SJ, et al. Nodal stage after induction therapy for stage IIIA lung cancer determines patient survival. *Ann Thorac Surg*. 2000;70(6):1826–1831.
42. Voltolini L, Luzzi L, Ghiribelli C, et al. Results of induction chemotherapy followed by surgical resection in patients with stage IIIA (N2) non–small cell lung cancer: the importance of the nodal down-staging after chemotherapy. *Eur J Cardiothorac Surg*. 2001;20(6):1106–1112.
43. Annema JT, Veselic M, Versteegh MI, et al. Mediastinal restaging: EUS-FNA offers a new perspective. *Lung Cancer*. 2003;42(3):311–318.
44. Stigt JA, Oostdijk AH, Timmer PR, et al. Comparison of EUS-guided fine needle aspiration and integrated PET-CT in restaging after treatment for locally advanced non–small cell lung cancer. *Lung Cancer*. 2009;66(2): 198–204.
45. Eloubeidi MA, Seewald S, Tamhane A, et al. EUS-guided FNA of the left adrenal gland in patients with thoracic or GI malignancies. *Gastrointest Endosc*. 2004;59(6):627–633.
46. Bodtger U, Vilmann P, Clementsen P, et al. Clinical impact of endoscopic ultrasound-fine needle aspiration of left adrenal masses in established or suspected lung cancer. *J Thorac Oncol*. 2009;4(12):1485–1489.
47. Ringbaek TJ, Krasnik M, Clementsen P, et al. Transesophageal endoscopic ultrasound/fine-needle aspiration diagnosis of a malignant adrenal gland in a patient with non–small cell lung cancer and a negative CT scan. *Lung Cancer*. 2005;48(2):247–249.
48. Prasad P, Schmulewitz N, Patel A, et al. Detection of occult liver metastases during EUS for staging of malignancies. *Gastrointest Endosc*. 2004;59(1): 49–53.
49. Hollerbach S, Willert J, Topalidis T, et al. Endoscopic ultrasound-guided fine-needle aspiration biopsy of liver lesions: histological and cytological assessment. *Endoscopy*. 2003;35(9):743–749.
50. Nguyen P, Feng JC, Chang KJ. Endoscopic ultrasound (EUS) and EUS-guided fine-needle aspiration (FNA) of liver lesions. *Gastrointest Endosc*. 1999;50(3):357–361.
51. Lee HS, Lee GK, Lee HS, et al. Real-time endobronchial ultrasound-guided transbronchial needle aspiration in mediastinal staging of non–small cell lung cancer: how many aspirations per target lymph node station? *Chest*. 2008;134(2):368–374.
52. Bauwens O, Dusart M, Pierard P, et al. Endobronchial ultrasound and value of PET for prediction of pathological results of mediastinal hot spots in lung cancer patients. *Lung Cancer*. 2008;61(3):356–361.
53. Haas AR. Infectious complications from full extension endobronchial ultrasound transbronchial needle aspiration. *Eur Respir J*. 2009;33(4):935–938.
54. Mazzone P, Jain P, Arroliga AC, et al. Bronchoscopy and needle biopsy techniques for diagnosis and staging of lung cancer. *Clin Chest Med*. 2002;23(1):137–158, ix.
55. Tournoy KG, Rintoul RC, van Meerbeeck JP, et al. EBUS-TBNA for the diagnosis of central parenchymal lung lesions not visible at routine bronchoscopy. *Lung Cancer*. 2009;63(1):45–49.
56. Nakajima T, Yasufuku K, Fujiwara T, et al. Endobronchial ultrasound-guided transbronchial needle aspiration for the diagnosis of intrapulmonary lesions. *J Thorac Oncol*. 2008;3(9):985–988.
57. Adams K, Shah PL, Edmonds L, et al. Test performance of endobronchial ultrasound and transbronchial needle aspiration biopsy for mediastinal staging in patients with lung cancer: systematic review and meta-analysis. *Thorax*. 2009;64(9):757–762.
58. Gu P, Zhao YZ, Jiang LY, et al. Endobronchial ultrasound-guided transbronchial needle aspiration for staging of lung cancer: a systematic review and meta-analysis. *Eur J Cancer*. 2009;45(8):1389–1396.
59. Varela-Lema L, Fernandez-Villar A, Ruano-Ravina A. Effectiveness and safety of endobronchial ultrasound-transbronchial needle aspiration: a systematic review. *Eur Respir J*. 2009;33(5):1156–1164.
60. Gilbert S, Wilson DO, Christie NA, et al. Endobronchial ultrasound as a diagnostic tool in patients with mediastinal lymphadenopathy. *Ann Thorac Surg*. 2009;88(3):896–900.
61. Herth FJ, Eberhardt R, Vilmann P, et al. Real-time, endobronchial ultrasound-guided, transbronchial needle aspiration: a new method for sampling mediastinal lymph nodes. *Thorax*. 2006;61(9):795–798.
62. Steinfort DP, Hew MJ, Irving LB. Bronchoscopic evaluation of the mediastinum using endobronchial ultrasound: a description of the first 216 cases performed at an Australian tertiary hospital. *Intern Med J*. 2009; Dec 4 [Epub ahead of print].
63. Szlubowski A, Kuzdzal J, Kolodziej M, et al. Endobronchial ultrasound-guided needle aspiration in the non–small cell lung cancer staging. *Eur J Cardiothorac Surg*. 2009;35(2):332–335.
64. Yasufuku K, Chiyo M, Sekine Y, et al. Real-time endobronchial ultrasound-guided transbronchial needle aspiration of mediastinal and hilar lymph nodes. *Chest*. 2004;126(1):122–128.
65. Yasufuku K, Chiyo M, Koh E, et al. Endobronchial ultrasound guided transbronchial needle aspiration for staging of lung cancer. *Lung Cancer*. 2005;50(3):347–354.
66. Omark PH, Eckardt J, Hakami A, et al. The value of mediastinal staging with endobronchial ultrasound-guided transbronchial needle aspiration in patients with lung cancer. *Eur J Cardiothorac Surg*. 2009;36(3): 465–468.
67. Hwangbo B, Kim SK, Lee HS, et al. Application of endobronchial ultrasound-guided transbronchial needle aspiration following integrated PET/CT in mediastinal staging of potentially operable non–small cell lung cancer. *Chest*. 2009;135(5):1280–1287.
68. Rintoul RC, Tournoy KG, El DH, et al. EBUS-TBNA for the clarification of PET positive intra-thoracic lymph nodes-an international multi-centre experience. *J Thorac Oncol*. 2009;4(1):44–48.
69. Herth FJ, Ernst A, Eberhardt R, et al. Endobronchial ultrasound-guided transbronchial needle aspiration of lymph nodes in the radiologically normal mediastinum. *Eur Respir J*. 2006;28(5):910–914.
70. Herth FJ, Eberhardt R, Krasnik M, et al. Endobronchial ultrasound-guided transbronchial needle aspiration of lymph nodes in the radiologically and positron emission tomography-normal mediastinum in patients with lung cancer. *Chest*. 2008;133(4):887–891.
71. Ernst A, Eberhardt R, Krasnik M, et al. Efficacy of endobronchial ultrasound-guided transbronchial needle aspiration of hilar lymph nodes for diagnosing and staging cancer. *J Thorac Oncol*. 2009;4(8): 947–950.
72. Herth FJ, Annema JT, Eberhardt R, et al. Endobronchial ultrasound with transbronchial needle aspiration for restaging the mediastinum in lung cancer. *J Clin Oncol*. 2008;26(20):3346–3350.
73. Szlubowski A, Herth FJ, Soja J, et al. Endobronchial ultrasound-guided needle aspiration in non–small-cell lung cancer restaging verified by the transcervical bilateral extended mediastinal lymphadenectomy: a prospective study. *Eur J Cardiothorac Surg*. 2009; Dec 18 [Epub ahead of print].
74. Larsen SS, Vilmann P, Krasnik M, et al. Endoscopic ultrasound guided biopsy performed routinely in lung cancer staging spares futile thoracotomies: preliminary results from a randomised clinical trial. *Lung Cancer*. 2005;49(3):377–385.
75. Fritscher-Ravens A, Davidson BL, Hauber HP, et al. Endoscopic ultrasound, positron emission tomography, and computerized tomography for lung cancer. *Am J Respir Crit Care Med*. 2003;168(11):1293–1297.
76. De WW, Stroobants S, Coolen J, et al. Integrated PET/CT in the staging of non–small cell lung cancer: technical aspects and clinical integration. *Eur Respir J*. 2009;33(1):201–212.
77. Annema JT, Hoekstra OS, Smit EF, et al. Towards a minimally invasive staging strategy in NSCLC: analysis of PET positive mediastinal lesions by EUS-FNA. *Lung Cancer*. 2004;44(1):53–60.

78. Cerfolio RJ, Bryant AS, Eloubeidi MA. Accessing the aortopulmonary window (#5) and the paraaortic (#6) lymph nodes in patients with non–small cell lung cancer. *Ann Thorac Surg*. 2007;84(3):940–945.
79. Ernst A, Anantham D, Eberhardt R, et al. Diagnosis of mediastinal adenopathy: real-time endobronchial ultrasound guided needle aspiration versus mediastinoscopy. *J Thorac Oncol*. 2008;3(6):577–582.
80. Rintoul RC, Skwarski KM, Murchison JT, et al. Endobronchial and endoscopic ultrasound-guided real-time fine-needle aspiration for mediastinal staging. *Eur Respir J*. 2005;25(3):416–421.
81. Szlubowski A, Zielinski M, Soja J, et al. A combined approach of endobronchial and endoscopic ultrasound-guided needle aspiration in the radiologically normal mediastinum in non–small-cell lung cancer staging: a prospective trial. *Eur J Cardiothorac Surg*. 2009; Dec 18 [Epub ahead of print].
82. Vilmann P, Krasnik M, Larsen SS, et al. Transesophageal endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) and endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) biopsy: a combined approach in the evaluation of mediastinal lesions. *Endoscopy*. 2005;37(9):833–839.
83. Wallace MB, Pascual JM, Raimondo M, et al. Minimally invasive endoscopic staging of suspected lung cancer. *JAMA*. 2008;299(5):540–546.
84. Herth FJ, Rabe KF, Gasparini S, et al. Transbronchial and transoesophageal (ultrasound-guided) needle aspirations for the analysis of mediastinal lesions. *Eur Respir J*. 2006;28(6):1264–1275.
85. Rintoul RC, Skwarski KM, Murchison JT, et al. Endoscopic and endobronchial ultrasound real-time fine-needle aspiration for staging of the mediastinum in lung cancer. *Chest*. 2004;126(6):2020–2022.
86. Garcia-Olive I, Monso E, Andreo F, et al. Endobronchial ultrasound-guided transbronchial needle aspiration for identifying epidermal growth factor receptor mutations. *Eur Respir J*. 2010;35(2):391–395.
87. Nakajima T, Yasufuku K, Suzuki M, et al. Assessment of epidermal growth factor receptor mutation by endobronchial ultrasound-guided transbronchial needle aspiration. *Chest*. 2007;132(2):597–602.

CHAPTER 7 EUS IN ESOPHAGEAL CANCER

Mohamad A. Eloubeidi

Key Points

Treatment and outcome in patients with esophageal cancer are stage dependent.

One important role for EUS is in the initial triage of patients to receive neoadjuvant therapy or to undergo immediate surgical resection or, in very early stages, endoscopic mucosal resection.

EUS is superior to computed tomography and positron emission tomography in celiac and peritumoral lymph node detection.

According to the American Joint Committee on Cancer (AJCC), the finding of a celiac lymph node is considered equivalent to metastatic disease, whether the tumor is in the distal (M1a) or proximal (M1b) esophagus.

Application of EUS after administration of adjuvant chemoradiotherapy in esophageal cancer may provide a general idea of response but cannot accurately differentiate residual tumor from radiation effect. EUS fine-needle aspiration can document persistent lymph nodes in the celiac axis area that may preclude curative surgical resection.

INTRODUCTION

Treatment and outcomes of patients with esophageal cancer are stage dependent. Since its introduction in the early 1980s, endoscopic ultrasonography (EUS) has played a central and growing role in the staging of patients with esophageal cancer. The purpose of this chapter is to review data pertaining to the accuracy of EUS in staging patients with esophageal cancer and to compare the operating characteristics of EUS with those of other staging modalities such as positron emission tomography (PET) and computed tomography (CT) scans. Data on the role of EUS in early and superficial esophageal cancer arising in Barrett's esophagus are reviewed, particularly in light of the development of ablative methods such as radiofrequency ablation. In addition, techniques of dilation of stricture to facilitate EUS and the use of alternative strategies are explored. The stepwise staging including celiac axis area and liver evaluation are described. Data on restaging after chemotherapy and radiation therapy are reviewed. Finally, the vital role of EUS fine-needle aspiration (FNA) in sampling celiac lymph nodes (CLNs) and peri-intestinal lymph nodes to complete the staging of patients with esophageal cancer is explored.

IMPORTANCE OF STAGING

Esophageal cancer is a leading health problem worldwide. In 2009, approximately 16,470 patients were diagnosed in the United States, of whom approximately 14,530 will die of the disease.[1] Survival has slightly improved in patients with esophageal adenocarcinoma in the United States, but overall 5-year survival remains dismal.[2] Treatment and outcomes of patients with esophageal cancer are stage dependent[2–5] (Figs 7.1 and 7.2 and Table 7.1). EUS plays a vital role in the management and treatment planning of patients with esophageal cancer by providing accurate T and N staging for triage of patients regarding therapy.[6] Perhaps the most important role for EUS is in the initial triage of patients to receive neoadjuvant therapy or undergo immediate surgical resection. Patients with any nodal involvement typically receive preoperative therapy, whereas patients with either T1 or T2 tumors (without nodal involvement) go directly to surgical resection (see Fig. 7.2).

The second important role for EUS is in restaging after patients receive chemotherapy and radiation therapy. Although EUS is less accurate in determining the true stage in these patients, it helps physicians to identify patients who would be less likely to benefit from surgical resection or those who could potentially benefit from additional chemotherapy before surgical resection, such as patients with recalcitrant lymph nodes in the celiac axis area or persistent T4 disease.

EUS, COMPUTED TOMOGRAPHY, AND POSITRON EMISSION TOMOGRAPHY

Numerous studies to date have shown that EUS is superior to CT scan in the individual detection of tumor stage (T stage) in patients with esophageal cancer[7] (Tables 7.2 and 7.3). Data also suggest that EUS retains its advantage when compared with spiral CT.[8] The reason for this superiority is that EUS enables one to determine and examine esophageal wall layers with histologic correlates.[9] In addition, EUS is superior to CT in the detection of peritumoral and celiac adenopathy[7,10] (see Tables 7.2 and 7.3; Table 7.4).

When compared with PET, which relies on metabolic imaging, EUS can better delineate the esophageal wall layers and hence has more favorable operating characteristics compared with PET for T staging. In addition, EUS is superior in detecting peritumoral lymph nodes and CLNs compared with PET.[11] In a systematic review of the literature, FDG PET showed moderate sensitivity and specificity for the detection of locoregional metastasis and reasonable sensitivity and specificity in the detection of distant lymphatic and hematogenous metastases.[12] In one study, false-positive results were found in 13, or 15%, of 86 patients.[13] Proper

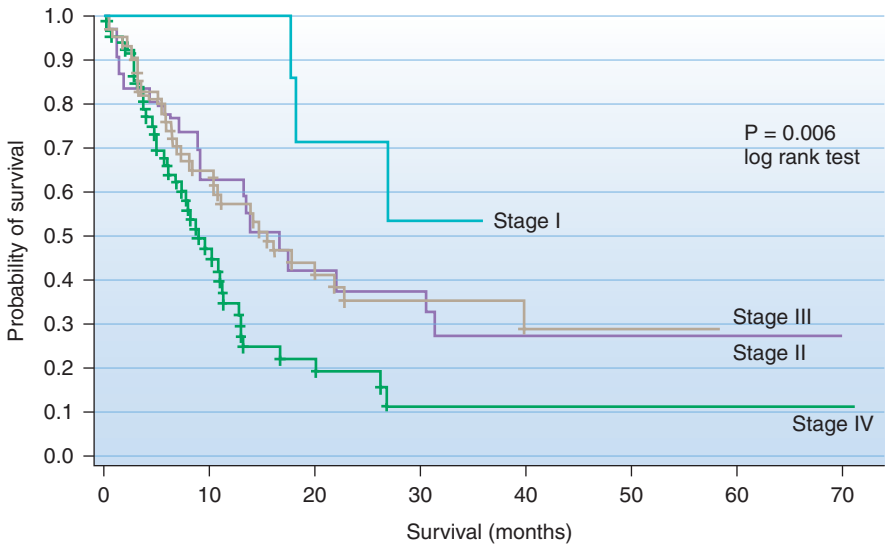


FIGURE 7.1 Survival of patients as staged by EUS. The overall staging is according to the American Joint Committee on Cancer system.

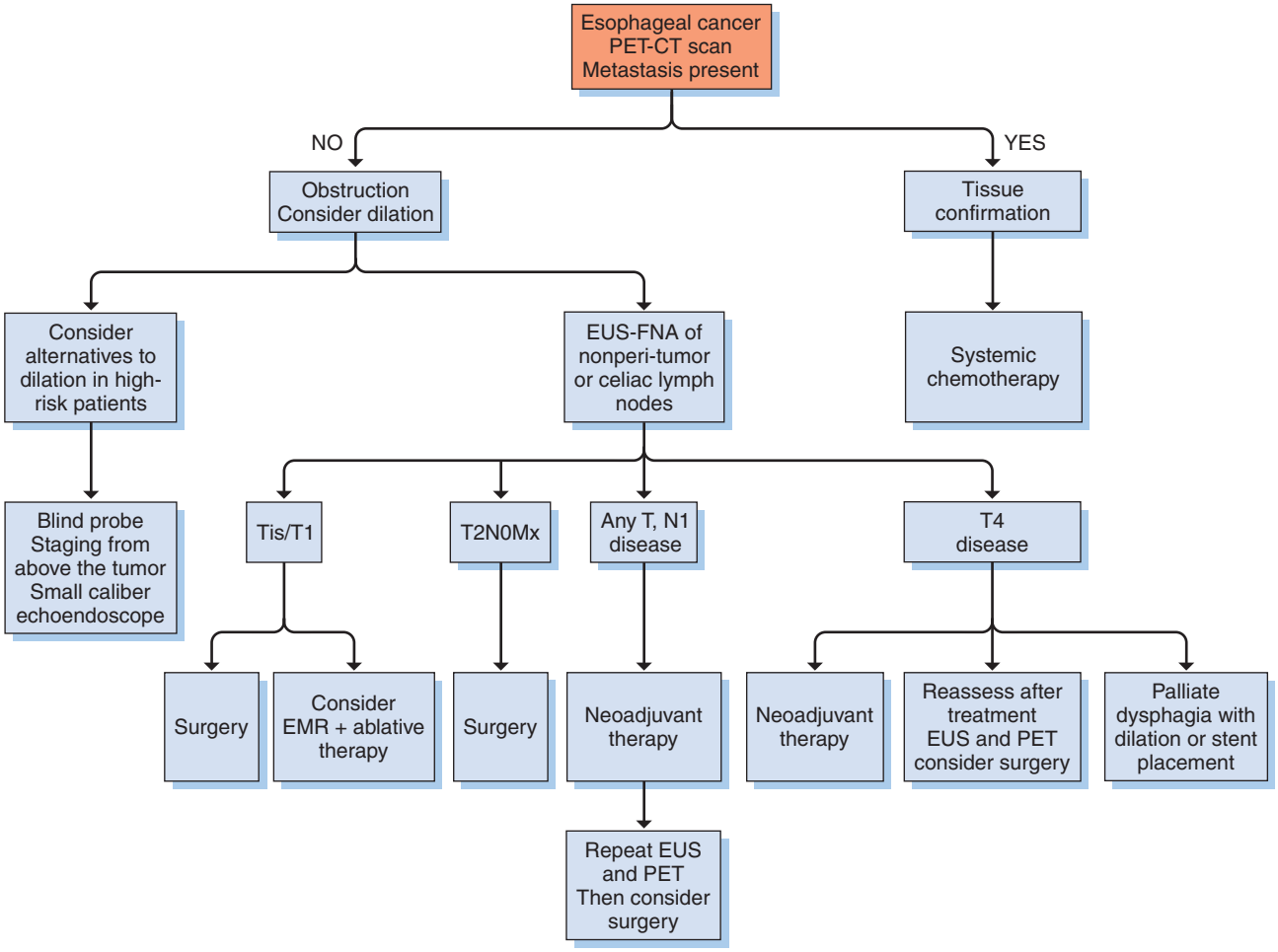


FIGURE 7.2 EUS-based algorithm for the management of esophageal cancer. CT, computed tomography; EMR, endoscopic mucosal resection; FNA, fine-needle aspiration; PET, positron emission tomography.

interpretation of fluorodeoxyglucose (FDG) PET findings in staging esophageal cancer is impeded by false-positive results; therefore, positive FDG PET findings must be confirmed by additional investigations.[13] EUS FNA can be used in this setting to confirm positive findings on PET scans.[14]

Although EUS is superior to PET and CT for locoregional recurrence, CT and PET are better for the detection of liver and lung metastases.[10,12] Therefore, it is logical to perform EUS in those patients whose CT and PET scans did not reveal distant metastasis. This approach helps in the triage of patients to surgery

TABLE 7.1

1997 American Joint Committee on Cancer (AJCC) TNM Classification

Stage	Description
Primary Tumor (T)	
Tx	Tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor invades lamina propria or submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades adventitia
T4	Tumor invades adjacent structures
Regional Lymph Nodes (N)	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
Distant Metastasis (M)	
Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
Tumors of the Lower Thoracic Esophagus	
M1a	Metastasis in celiac lymph nodes
M1b	Other distant metastasis
Tumors of the Midthoracic Esophagus	
M1a	Not applicable
M1b	Nonregional lymph nodes and/or other distant metastasis
Tumors of the Upper Thoracic Esophagus	
M1a	Metastasis in cervical nodes
M1b	Other distant metastasis
AJCC Stage Groupings	
Stage 0	Tis, N0, M0
Stage I	T1, N0, M0
Stage IIA	T2, N0, M0
	T3, N0, M0
Stage IIB	T1, N1, M0
	T2, N1, M0
Stage III	T3, N1, M0
	T4, any N, M0
Stage IV	Any T, any N, M1
Stage IVA	Any T, any N, M1a
Stage IVB	Any T, any N, M1b

TABLE 7.2

Comparison of Accuracy of Computed Tomography and EUS in the Locoregional Staging of Esophageal Cancer

Technique	Number of Patients	T Accuracy % (Range)	N Accuracy % (Range)
CT	1,154	45 (40-50)	54 (48-71)
EUS	1,035	85 (59-92)	77 (50-90)

CT, computed tomography.

Data from Rosch T. Endosonographic staging of esophageal cancer: a review of literature results. *Gastrointest Endosc Clin N Am.* 1995;5:537-547.

alone or to neoadjuvant therapy followed by surgery (see Fig. 7.2). Often, many investigations are needed in the same patient to complete staging. One study showed that the combination of CT, PET, and EUS reduced the number of unnecessary surgical procedures.[15] The number of unnecessary operations decreased from 44%, when CT alone was used, to 21%, when

TABLE 7.3

Comparison of Accuracy of Computed Tomography and EUS in the Locoregional Staging of Esophageal Cancer

Technique	Number of Studies	Sensitivity (%)	Specificity (%)
CT T stage	5	40-80	14-97
CT N stage	7	40-73	25-67
EUS T stage	13	71-100	67-100
EUS N stage	20	60-97	40-100

CT, computed tomography.

Data from Kelly S, Harris KM, Berry E, et al. A systematic review of the staging performance of endoscopic ultrasound in gastro-oesophageal carcinoma. *Gut.* 2001;49(4):534-539.

TABLE 7.4

Comparison of Operating Characteristics of Computed Tomography, EUS, and EUS Fine-Needle Aspiration in the Preoperative Lymph Node Staging of Esophageal Cancer

Technique	Sensitivity % (95% CI)	Specificity % (95% CI)	Accuracy % (95% CI)
CT	29 (17-44)	89 (72-98)	51 (40-63)
EUS	71 (56-83)	79 (59-92)	74 (62-83)
EUS FNA	83 (70-93)	93 (77-99)	87 (77-94)

CI, confidence interval; CT, computed tomography; FNA, fine-needle aspiration.

Modified from Vazquez-Sequeiros E, Wiersema MJ, Clain JE, et al. Impact of lymph node staging on therapy of esophageal carcinoma. *Gastroenterology.* 2002;125:1626-1635.

the three modalities were incorporated in the preoperative staging protocol. Moreover, the presence of celiac axis metastasis during surgical exploration was significantly reduced in patients who underwent EUS (13%) or PET (7%) compared with CT (32%).[15] Finally, although not statistically significant, patients who underwent the trimodality staging had better survival compared with those who underwent staging with CT alone (48 versus 28 months).[15] The integration of PET and CT promises better resolution and hence more accurate staging of patients with esophageal cancer.

EQUIPMENT

Echoendoscopes

EUS equipment is discussed fully in Chapter 2. This equipment consists of radial (mechanical or electronic) and curved linear array (CLA, electronic) echoendoscopes with their respective processors. The radial (electronic or mechanical) echoendoscope is the most popular instrument used in the United States for the staging of esophageal cancer, whereas the CLA echoendoscope is the most popular in Europe. The image created by the radial echoendoscope is in a 360-degree transverse plane perpendicular to the long axis of the echoendoscope. Recent-generation mechanical radial echoendoscopes (GF-UM 130 series, 60 series) have broadband frequencies ranging from 5 to 20 MHz. The electronic radial instrument provides a 270-degree (Pentax) or 360-degree (Olympus) ultrasound field of view (a portion of the image is obscured by the fiberoptic bundle in forward-viewing instruments) through an electronic multiple-element transducer. Image orientation is similar to that of radial mechanical instruments; however, the image is augmented by the addition of pulsed, color, and power Doppler techniques. The Olympus electronic radial echoendoscope has adjustable frequencies from 5 to 10 MHz.

CLA instruments scan along the long axis of the endoscope and thus permit real-time visualization of a needle passed through the biopsy channel. The field of view of CLA echoendoscopes is narrower than that of radial echoendoscopes. This characteristic appears to lengthen the learning curve for CLA endosonography and makes luminal tumor staging more tedious.

High-Frequency Catheter Probes

High-frequency transducers (12 to 30 MHz) can be incorporated into small catheters (2 to 3 mm in diameter). Currently, the best images are produced when the transducer is mechanically rotated 360 degrees, as is done during radial endosonography. The most commonly used catheters in the United States are manufactured by Olympus (UM-2R, 20 MHz; UM-3R, 30 MHz). These catheters produce very high-resolution images of the gut wall and are important adjuncts to endoscopic mucosal resection for early malignant tumors of the esophagus, stomach, and rectum. With the advent of the EUM-30S, a freestanding ultrasound unit, catheter probes are more accessible for use in general endoscopy units.

Blind Probes

Passing standard echoendoscopes past a tight stricture can be problematic. Perforation of the esophagus has been reported and can result from aggressive dilation or the application of too much force during passage through a malignant stricture. Characteristics that render echoendoscope use in esophageal strictures more difficult include the large diameter of the echoendoscope shaft, the oblique optics, and a long and rigid distal tip. The outer diameter of both radial and CLA echoendoscopes is approximately 13 mm; typically, the diameter of the lumen should be dilated to 45 Fr or more to allow predictable passage of the echoendoscope.[16] Earlier studies reported an unacceptably high perforation rate in patients with esophageal cancer when dilation was performed in conjunction with endosonography.[17] Several studies published since then confirmed that esophageal dilation before EUS is safe as long as the rules of sequential dilation are followed.[16,18,19] The use of a small-diameter nonoptic probe that can be inserted over a guidewire provides an alternative to esophageal dilation.[20,21] The ultrasonic esophagoprobe (Olympus MH-908) has an Eden-Puestow–shaped metal tip and is passed over a guidewire in a "monorail" fashion. The probe has an outer diameter of 7.9 mm and can usually be passed through an esophageal cancerous tumor without dilation.

TECHNIQUE

Patient Preparation

Endoscopic evaluation is an important step in the evaluation of patients with dysphagia and esophageal strictures (Examination Checklist). By the time a patient is referred for endosonography for the staging of esophageal cancer, the diagnosis is usually established. Review of the patient's prior barium swallow examination and recent endoscopy reports from referring colleagues, as well as assessment of the patient's degree of dysphagia, will allow optimal planning for performing the EUS. If the patient has difficulty swallowing soft (pureed) foods, one can predict that dilation will be required to pass the echoendoscope. This information should be communicated to the staff, so that dilation equipment and appropriate endoscopes can be prepared. An upper endoscopic procedure is a must before endosonography, even in patients without significant dysphagia, to assess the degree of stenosis and the distance of the stricture from the incisors and to look for tortuosity within the stricture that could affect the safety of EUS. Adequate landmarks, the extent of coexisting Barrett's esophagus, and the location of the lower and upper esophageal sphincter should be also noted to help the surgeon plan the surgical procedure.

EXAMINATION CHECKLIST

Liver
Celiac axis
Primary tumor
Periesophageal area above the aortic arch for lymph nodes
Relationship of tumor with carina
For distal esophageal tumors, invasion into the diaphragm
Full report: This should include the TNM stage, the length of the tumor, and the number of lymph nodes and their respective location. Finally, the extent of Barrett's esophagus and the location of the gastroesophageal junction and the upper esophageal sphincter should be included, to alert the surgeon to import landmarks before the operation.

Radial Endosonography

Initial passage of the echoendoscope should be done carefully, gently, and slowly. Once in the esophagus, the instrument is usually advanced past the tumor "by feel" rather by direct visualization of the stenosed lumen. When the echoendoscope is in position, the ultrasound unit is switched on, and imaging begins. In patients with esophageal cancer (see later), imaging actually begins in the duodenum and antrum of the stomach, to examine the liver for possible metastasis. The area surrounding the fundus and cardia of the stomach are scanned to look for perigastric and celiac axis lymphadenopathy. Once in the esophagus, attention is turned to the primary tumor, with particular attention to the wall layers. At frequencies raging from 5 to 10 MHz, the esophageal wall is imaged as a five-layer structure (first hyperechoic layer, superficial mucosa; second hypoechoic layer, deep mucosa; third hyperechoic layer, submucosa; fourth hypoechoic layer, muscularis propria; and fifth hyperechoic layer, adventitia).

Based on these special characteristics, EUS allows the endosonographer to assess the degree of tumor infiltration into the wall layers and subsequently determining the tumor stage (T stage). It is important to avoid tangential imaging because it may lead to overstaging of the tumor. Imaging with 12 MHz (GF-UM 130) or 20 MHz (GF-UM Q 130) allows superior resolution of the esophageal wall layers. After adequate interrogation of the tumor, several passes are performed at 5 or 7.5 MHz to evaluate the surrounding mediastinum to look for lymph nodes.

Data suggest that staging of more advanced esophageal cancer can be performed equally well with the CLA echoendoscope alone.[22] Using the CLA echoendoscope permits lymph node sampling without switching to a second echoendoscope. It is recommended that the CLA echoendoscope be used first if prior imaging suggests enlarged lymph nodes and liver lesions, situations in which T staging becomes less important. However, staging of the primary tumor is more complete and less cumbersome when the radial echoendoscope is used.

High-Frequency Catheter Probes

High-frequency catheter probes (HFCPs) provide high-resolution imaging of the gastrointestinal wall layers. They have proven indispensable in the staging of superficial esophageal cancer and in selection of patients for endoscopic mucosal resection (EMR). High-frequency mini-probes (20 MHz) provide a more detailed visualization and allow one to delineate nine layers in the esophageal wall (first and second layers, superficial mucosa [hyperechoic and hypoechoic, respectively]; third layer, lamina propria [hyperechoic]; fourth layer, muscularis mucosa [hypoechoic]; fifth layer, submucosa [hyperechoic]; sixth, seventh, and eighth layers [hypoechoic, hyperechoic, and hypoechoic, respectively], inner circular muscle and outer longitudinal muscle of the muscularis propria with intermuscular connective tissue; ninth layer, adventitia [hyperechoic]). Visualization of the muscularis

mucosa is important when evaluating superficial lesions and nonsurgical alternatives are being considered (EMR or ablative therapy such as radiofrequency ablation or photodynamic therapy).

Imaging of small superficial esophageal lesions with a radial echoendoscope is difficult because achieving proper positioning is cumbersome and balloon inflation compresses the lesion and causes inaccuracies in staging. High-quality esophageal wall imaging depends on maintaining a water-filled lumen (despite esophageal peristalsis), positioning the transducer perpendicular to the lesion, and being able to adjust the distance between the probe and the lesion.

The methods currently used to achieve safe imaging of the esophageal wall with HFCPs are the free-floating catheter technique, the condom technique, and, most recently, the balloon sheath technique.[23,24] The free-floating technique does not rely on a sheath or a condom to retain water in the esophagus. Although it is possible for the expert endosonographer to achieve a column of water in the distal esophagus, this technique is limited by its short duration as a result of peristalsis, which washes the water down to the stomach. Occasionally, suctioning some of the air out of a hernia sac can bring the column of water back up into the esophagus. If the lesion cannot be demonstrated in a short period of time, the distal esophagus will need to be refilled repeatedly. The most dreaded complication of the free-floating catheter technique is aspiration. Therefore, if this procedure is attempted, the head of the bed should be elevated to at least 45 degrees to minimize the risk of aspiration. Patients with Barrett's esophagus tend to tolerate this technique well. However, it is impossible to use this technique to image superficial lesions in the middle or upper esophagus. For these reasons, alternative methods were sought to image early esophageal lesions, hence the development of the condom and balloon sheath techniques.[23,24]

Fixing a condom to the end of a two-channel endoscope optimizes imaging by providing a contained column of water within the esophagus (that is not affected by peristalsis). This technique also permits perpendicular imaging and enables the examiner to adjust the position of the catheter relative to the lesion.[24] Additionally, condoms are soft and very compliant and thus do not compress the esophageal wall layers. Adequate preparation is important to the success of this technique. A standard, nonlubricated, translucent latex condom is attached to a two-channel therapeutic endoscope. One inch of condom extends beyond the endoscope tip. The condom is fixed to the endoscope shaft at three locations with a rubber band, and then strips of Tegaderm 2 cm wide are wrapped full circle around the condom. Because the condom is transparent, intubation can be performed under direct visualization, but one must avoid air insufflation during intubation. The endoscope is passed into the stomach, the condom is filled with water, and residual air and water are aspirated. The collapsed condom is then withdrawn into the esophagus, and water is gently instilled. The lesion should be visible through the condom. Once in position, the ultrasound catheter is passed down the second channel and is positioned against the lesion by visual contact. It is relatively easier to withdraw the scope, but if advancement is necessary, it is best to aspirate some water first. The limitation of this technique is the formation of air pockets between the condom and the esophageal wall that result in image artifacts (Video 7.1).

Another imaging method is the balloon sheath technique.[23,24] The HFCP is fitted with a sheath that has an acoustic coupling balloon at the distal end. The balloon can be filled with water and expanded by means of an adaptor at the proximal end outside the endoscope. With this device, standard endoscopy can be performed, and then the HFCP with balloon sheath can be advanced through the accessory channel of the endoscope and placed in the area of interest. With the balloon filled with water and enhanced acoustic coupling, high-resolution images can be obtained.

ESOPHAGEAL DILATION AND ALTERNATIVES

Up to one third of patients with esophageal cancer present with marked luminal stenosis that does not allow the passage of the 13-mm–tip echoendoscope[16] (Video 7.2). EUS examination from a position proximal to the tumor has been shown to result in inaccurate T staging and inadequate evaluation of the celiac axis. An earlier study using older model echoendoscopes and dilation practices that did not adhere to the "rule of 3s" reported an unacceptably high rate of esophageal perforation (24%) when dilation was employed before EUS.[17] Several more recent studies reported that dilation is safe and increases the yield of detection of CLN involvement.[16,19] Dilation to 45 Fr or 15 mm is usually needed to allow the passage of the echoendoscope. Repeated dilation over a 2-day period should be employed if necessary.

In patients with inadequate dilation or when dilation is either not preferred or impractical, a narrow-caliber, tapered-tip, wire-guided echoendoscope was shown to traverse high-grade malignant esophageal strictures with ease.[20,21] In addition, this probe has been shown to improve staging in these situations by evaluating both the primary tumor and the celiac axis. This esophagoprobe markedly reduced the occurrence of incomplete esophageal cancer staging and improved the detection of celiac disease in one study. However, the celiac axis could not be identified in 10% of the patients with esophagoprobe either because of an extremely stenotic tumor or because of retained gastric air. Obviously, this instrument lacks the image orientation to permit EUS-guided FNA. In T4 cancers (invasion into adjacent organs), FNA may not be required. However, if CLNs are seen, FNA is required to confirm that these lymph nodes are malignant.

Finally, in patients with esophageal stenosis that could not be overcome with dilation or patients with tumors with significant angulations, obtaining information from above the tumor (T3) can be enough to initiate chemotherapy and radiation therapy. In such situations, repeat EUS after neoadjuvant therapy may be appropriate to evaluate the presence of residual disease. Alternatively, a small-caliber echoendoscope used for endobronchial EUS (EBUS) can be useful in documenting nodal disease in patients with significant stenosis or whose risk of perforation is high or in whom perforation would be detrimental (personal observations).

FINDING AND EVALUATING THE CELIAC AXIS

CLN metastasis carries grave prognostic implications in patients with esophageal cancer.[4,25,26] Patients with esophageal cancer and CLN metastasis have shorter survival than do patients without CLN involvement[2] (Figs. 7.3 and 7.4). It is therefore crucial to both identify and inspect the celiac axis in all patients with esophageal cancer whenever possible. To identify and evaluate the celiac axis with the radial instrument, the echoendoscope is usually placed at the gastroesophageal junction, and the aorta (anechoic and posterior) is located. Once identified, the aorta is placed at the 6 o'clock position on the screen. As the echoendoscope is advanced forward, the aorta moves away from the echoendoscope toward the 5 o'clock position. With further advancement, the celiac axis emerges as a branching point from the descending aorta at the 7 o'clock position. Pushing 1 to 2 cm more usually demonstrates the bifurcation of the celiac axis into the splenic artery and the common hepatic artery ("whale's tail sign)," typically seen at approximately 45 cm from the incisors.

Sometimes it is not possible to locate the celiac axis by advancing the echoendoscope from the gastroesophageal junction (most commonly because of a hiatal hernia). In this case, beginning the examination in the gastric antrum and withdrawing slowly (while keeping the liver in the 11 o'clock position) will permit

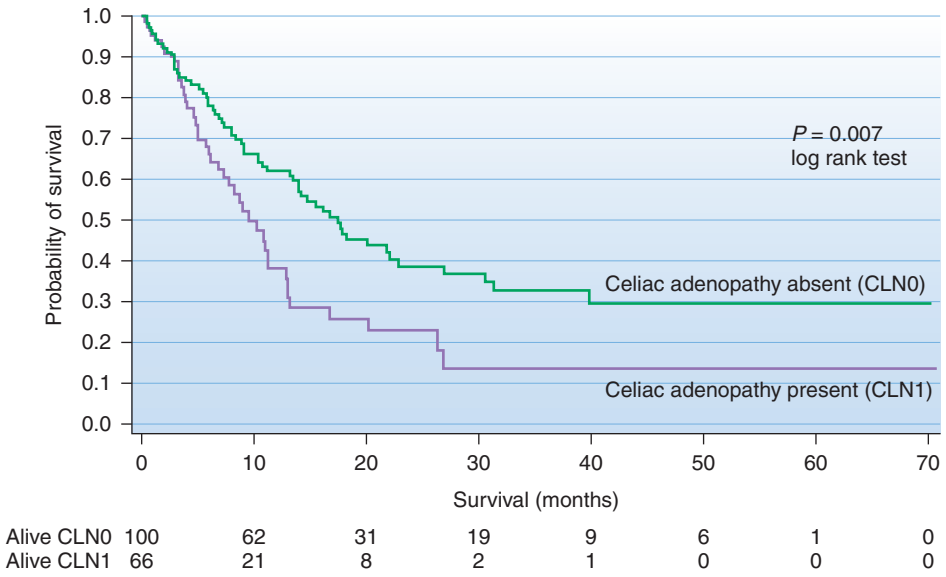


FIGURE 7.3 Survival of patients with esophageal cancer according to celiac lymph node (CLN) status as detected by EUS. Patients with nodal disease detected by EUS had worse survival than those without lymph nodes.

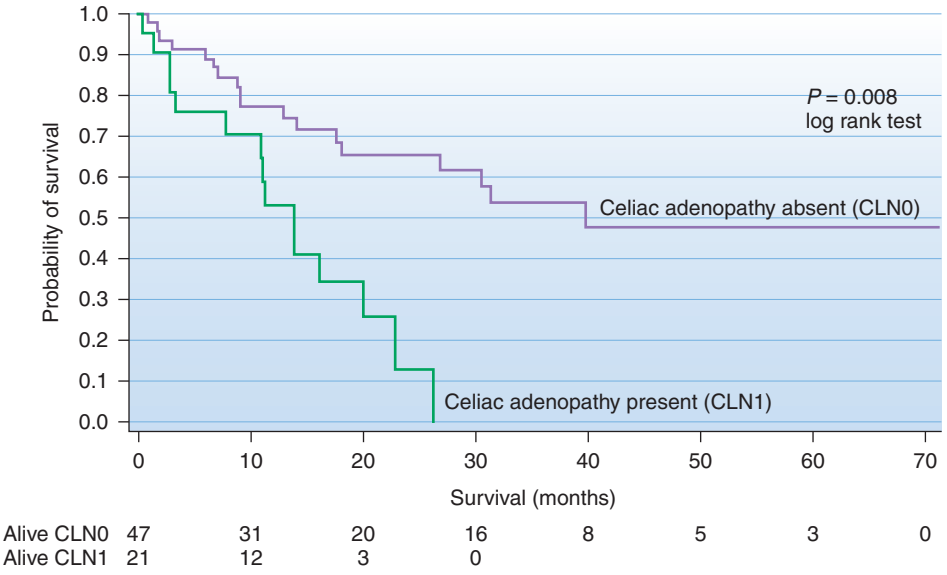


FIGURE 7.4 Survival of patients with esophageal cancer according to celiac lymphadenopathy status as detected by EUS. Patients with celiac lymph nodes (CLN) detected by EUS had worse survival than those without detectable CLN.

identification of the splenic-portal confluence. Then, with an additional 2- to 3-cm withdrawal, the celiac axis can be seen.[27]

To identify the celiac axis with the CLA echoendoscope, the aorta is found at approximately 35 cm from the incisors (distal esophagus) as a long, tubular structure (Videos 7.2 and 7.3). The endoscope is slowly advanced while the aorta is kept in view. The first branching artery from the descending aorta is the celiac axis trunk. (The superior mesenteric artery follows a few centimeters more distally.) When in doubt, one can use Doppler imaging for proper identification and verification of the celiac axis trunk. Careful interrogation is performed to assess for lymphadenopathy.

Certain lymph node characteristics are helpful in differentiating benign from malignant lymph nodes. Malignant lymph nodes tend to be larger than 1 cm, round, sharply demarcated, and hypoechoic.[28] The preponderance of these criteria enhances the likelihood that the lymph node is malignant.[29] In patients with esophageal cancer, the identification of CLNs is virtually synonymous with malignant involvement. Regardless of echo features and size, 90% of all detected CLNs were proven to be malignant in one study.[30] Moreover, 100% of all CLNs larger than 1 cm were malignant. The clinical impact of malignant CLNs on therapy mandates the use of EUS FNA, to provide a means of documenting nodal involvement before neoadjuvant therapy.[30,31]

Once lymph nodes are identified and deemed suitable for biopsy, EUS FNA is performed with a CLA echoendoscope.[27,30] The instrument is placed in the stomach lumen opposite the identified CLN. The FNA needle-sheath system is inserted through the biopsy channel of the echoendoscope and is screwed into the Luer lock or the channel hub of the echoendoscope. EUS FNA is then performed. Some investigators have suggested that suction during FNA of lymph nodes increases the bloodiness of the specimen but does not necessarily increase yield.[32] When this situation occurs, additional passes without suction are warranted. After 30 to 60 seconds, the needle is retracted. The aspirate is placed on a glass slide, is processed with a Diff-Quick stain (American Scientific Products, McGraw Park, Ill), and preferably is reviewed immediately by an on-site cytologist or pathologist to ensure that the specimen is adequate. The availability of on-site interpretation is variable from center to center. A diagnosis of

TABLE 7.5
Operating Characteristics of EUS Fine-Needle Aspiration in Celiac Lymph Nodes

Study and Year	Number of Patients	Sensitivity % (*n*)	Specificity % (*n*)	Accuracy % (*n*)
Giovannini et al[51] 1995	26	100 (21/21)	—	80 (21/26)
Reed et al[52] 1999	17	100 (15/15)	—	86 (15/17)
Williams et al[53] 1999	27	96 (25/26)	100 (1/1)	96 (26/27)
Eloubeidi et al[30] 2001	51	98 (45/46)	100 (5/5)	98 (50/51)

malignancy is usually obtained in the first two passes in the majority of malignant lymph nodes. Typically, four passes are performed in lymph nodes with benign EUS features, to ensure adequate sampling. The operating characteristics of EUS FNA for assessing CLNs are shown in Table 7.5.

EVALUATION OF THE LIVER

EUS can detect occult liver metastases in patients in whom noninvasive hepatic imaging studies are normal, although the frequency at which such lesions are detected is low. In addition, EUS FNA can be performed to document liver metastasis.[33,34] The echoendoscope is usually placed in the antrum of the stomach to evaluate the parenchyma of the left lobe of the liver. Because of anatomic restrictions, not all segments of the liver can be viewed with endosonography. The latex balloon is inflated with water to allow better acoustic coupling and more accurate imaging. Installation of water in the stomach is not necessary. Imaging begins by pulling the endoscope slowly from the antrum. Metastases usually appear as discrete, relatively hypoechoic areas in the liver. Once metastases have been identified, EUS FNA can be performed, to yield important diagnostic and prognostic information for patient management.[33,34]

STAGING OF MALIGNANT STRICTURES

Accurate preoperative staging of esophageal cancer allows appropriate selection of therapy and prognostication (see Fig. 7.2). After dilation of the tumor (if necessary), staging is performed according to the TNM classification[35] (see Table 7.1). The liver, the celiac axis, and the gastrohepatic ligament areas are inspected to assess the presence of liver metastasis and lymph nodes, respectively. Attention is then turned to the primary tumor and the mediastinum, to identify depth of tumor invasion and the presence of peritumoral and mediastinal adenopathy. The TNM system is based on the determination of depth of tumor invasion (T stage), the presence or absence of regional lymph node metastasis (N stage), and the presence or absence of distant metastasis (M stage). A global stage can be obtained by combining these components. An emerging body of data suggests that EUS staging, like surgical staging, predicts long-term survival in patients with esophageal cancer[4,36] (see Fig. 7.1).

T Stage

T stage is determined by the depth of tumor invasion and by involvement of the esophageal wall layers. The earliest stage, Tis, is present when the cancer is limited to the epithelium and the lamina propria is intact. This stage is detected by biopsy and cannot be imaged by EUS.

In T1 tumors, cancerous cells invade the lamina propria and the submucosa (Figs. 7.5 and 7.6). The advent of HFCPs made it possible to classify T1 tumors further into T1m (confined to mucosa) or T1sm (submucosal tumor invasion). This classification becomes important in countries where esophageal cancer is detected at early stages. These two tumor classes differ in their propensity for early spread to lymph nodes through a dense network of esophageal lymphatic vessels. This classification helps to identify appropriate therapy commensurate with stage of disease. For example, electromagnetic radiation (EMR) is appropriate treatment because local lymph nodes are rarely involved. T1sm disease has a 15% to 30% rate of lymph node metastasis, and therefore, surgery is the most appropriate treatment if lymph nodes are not detected.

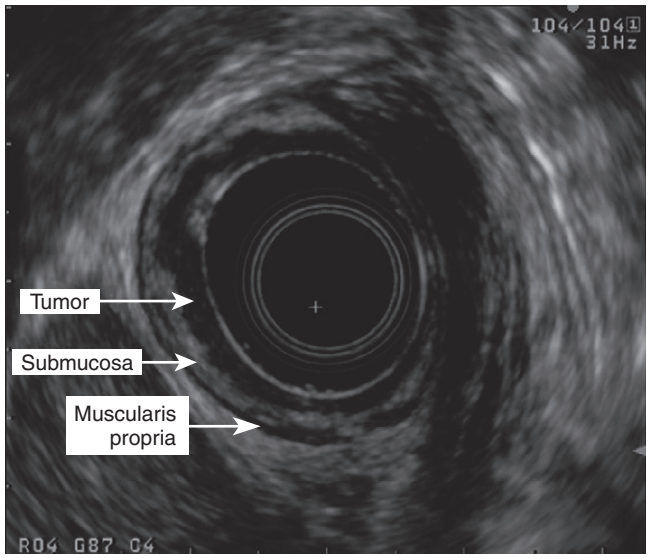


FIGURE 7.5 EUS staging showed a tumor that invaded into but not through the submucosa, consistent with a T1 tumor. Findings were confirmed at surgery. (Olympus electronic radial array scanning at 12 MHz.)

When the tumor invades the muscularis propria, the tumor is classified as T2 (Video 7.4). When the tumor progresses further to invade the adventitia, the tumor is classified as T3 (Figs. 7.7A and 7.8). Involvement of mediastinal structures, such as the aorta (Fig. 7.9), pleura, azygous vein (Video 7.5), or any adjacent structure, is classified as T4 disease. The accuracy of EUS and CT for detecting various T stages is shown in Tables 7.2 and 7.3. A systematic review of the literature that included 13 studies that met inclusion criteria found that EUS has a sensitivity range of 71.4% to 100% and a specificity range of 66.7% to 100% for T staging. The true positive rate was 89% (95% confidence interval [CI], 0.88 to 0.93). In articles that compared EUS directly with incremental CT, EUS performed better.[37]

T-stage accuracy depends in part on the learning curve of the endosonographer. A 1996 study showed that at least 100 examinations were required to provide accurate T staging in patients with esophageal cancer.[38] Appropriate hands-on and mentored training is mandatory to achieve safe, accurate, and reproducible results.

N Stage

Because of the rich esophageal lymphatic vessels, esophageal cancer has the propensity to spread early to local lymph nodes. It is clear that patients with N1 (nodal involvement) disease as

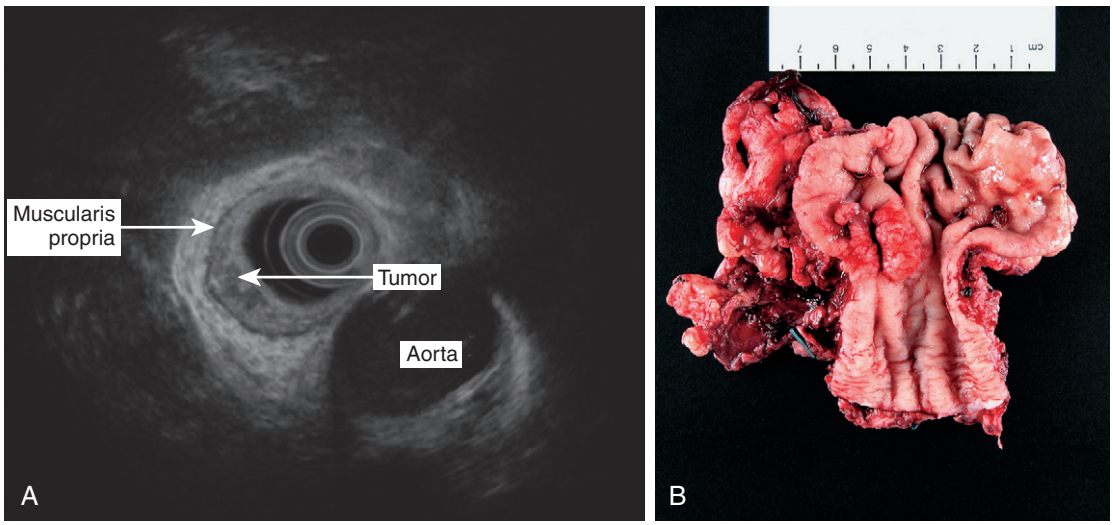


FIGURE 7.6 T1 tumor. A, EUS revealed a tumor limited to the submucosa (muscularis propria is intact) with no lymph nodes observed (T1N0). Surgery was recommended after EUS. **B,** Surgical resection confirmed no involvement of lymph nodes and disease that invaded the submucosa, consistent with T1 tumor.

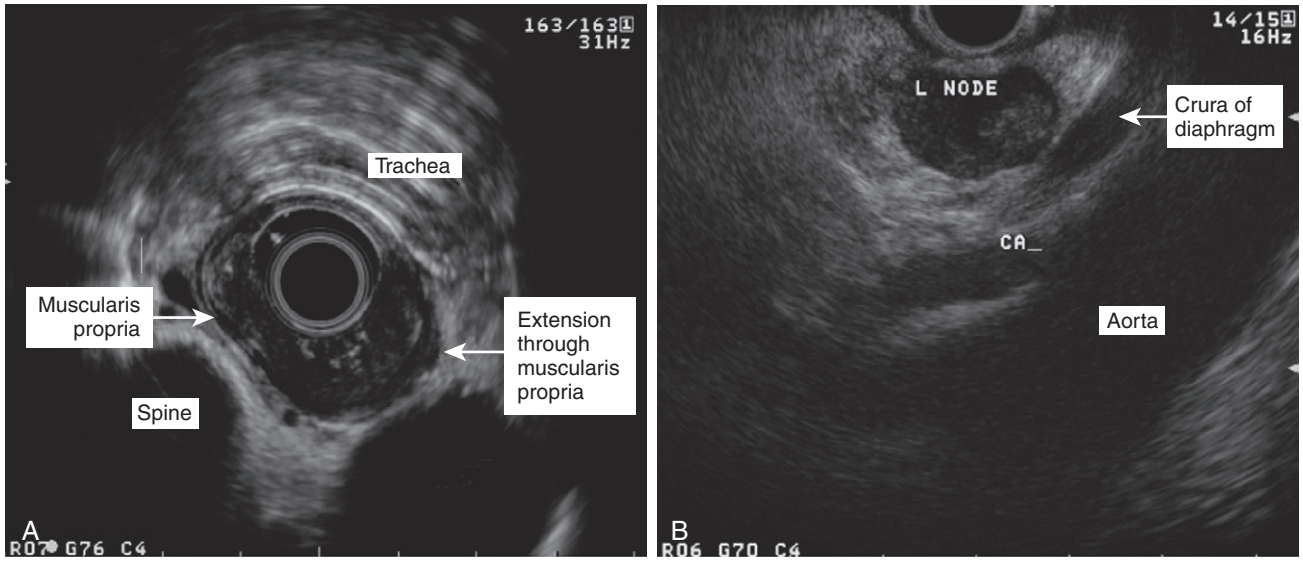


FIGURE 7.7 T3 tumor. A, EUS reveals a circumferential hypoechoic mass that invaded the muscularis propria to the adventitia, consistent with T3 disease. **B,** Inspection of the celiac axis (CA) area revealed an enlarged hypoechoic lymph node with sharp borders. Transgastric EUS-guided fine-needle aspiration confirmed the presence of malignant involvement. Neoadjuvant therapy was recommended after EUS. (Olympus UC-30P, frequency 5 MHz.)

classified by EUS have poorer survival compared with patients who have N0 (no lymph node involvement) disease (Fig. 7.10).[4,39] Furthermore, the number of lymph nodes detected is an important predictor of survival.[3] The advantage of EUS is that these lymph nodes can be accurately detected preoperatively. Certain lymph node characteristics are helpful in classifying benign from malignant lymph nodes. Malignant lymph nodes tend to be larger than 1 cm, round, sharply demarcated, and hypoechoic.[28] The more criteria a lymph node has, the more likely it is to be malignant.[29]

The location of the lymph node can help in determining whether it contains cancer cells. For example, unlike in the mediastinum, patients without upper abdominal disease generally do not have CLNs detectable by EUS. In patients with esophageal cancer, the identification of CLNs is synonymous with malignant involvement (see Fig. 7.7B).[30] Regardless of echo features and size, 90% of all detected CLNs were proven to be malignant in one study. Moreover, 100% of the CLNs larger than 1 cm were malignant.[30]

A systematic review of the literature that included 13 studies that met inclusion criteria found that EUS has a sensitivity range of 59.5% to 100% and a specificity range of 40% to 100% for N staging. The true positive rate was 79% (95% CI, 0.75 to 0.83).[37]

To eliminate or reduce uncertainty, EUS FNA provides a means of documenting nodal involvement before neoadjuvant therapy.[30,31,40] A major limitation of EUS FNA is that intervening tumor does not allow sampling of these lymph nodes without the risk of contamination. The 1997 American Joint Committee on Cancer (AJCC) TNM classification takes into account the location of the primary tumor for classification of lymph nodes as local disease (N1) or metastatic disease (M1).[35]

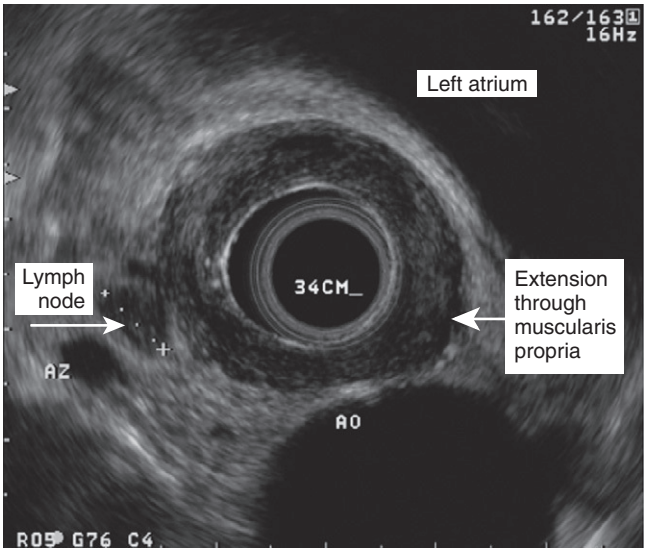


FIGURE 7.8 EUS appearance of a tumor that invaded muscularis propria to the adventitia. Few peritumoral lymph nodes are seen that are consistent with malignant involvement (T3N1MX0). These lymph nodes are not amenable to EUS fine-needle aspiration. AO, aorta; AZ, azygous vein. (Olympus electronic radial array scanning at 10 MHz.).

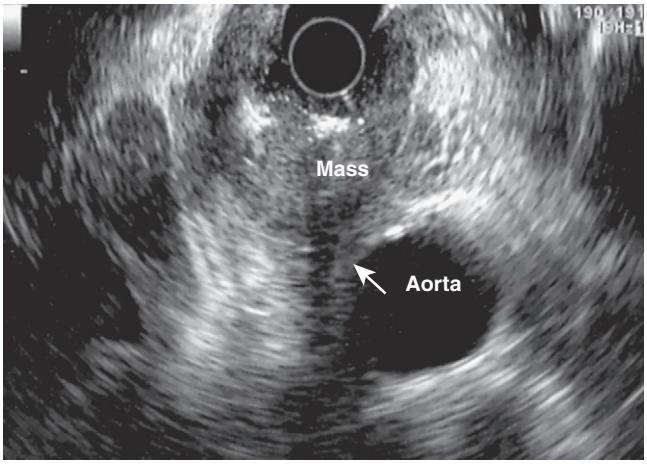


FIGURE 7.9 EUS reveals tumor adherence to the descending aorta, consistent with vascular invasion. (Olympus electronic radial array scanning at 7.5 MHz.)

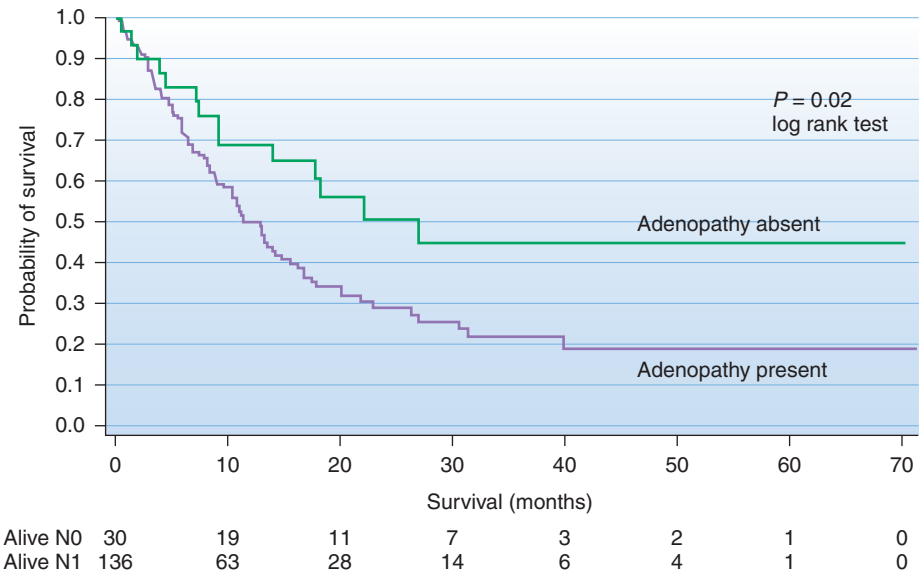


FIGURE 7.10 Survival of patients with esophageal cancer according to celiac lymphadenopathy status in the group who underwent operation. Patients who had persistent celiac lymph nodes at the time of operation had shorter survival.

M Stage

Involvement of distant sites from the primary tumor through hematogenous seeding of distant organs (liver, lung, bones) or distant lymph nodes is considered metastatic disease.[35] EUS provides excellent imaging of the medial two thirds of the liver, but it cannot exclude with certainty metastatic disease to all areas of the liver. Depending on the location of the tumor and the lymph nodes involved, metastasis to certain lymph nodes is classified as M1a or M1b disease (Video 7.6). For example, for tumors of the lower thoracic esophagus and the upper thoracic esophagus, metastasis to CLNs and to cervical lymph nodes is considered metastatic disease (M1a). The M1b designation denotes metastasis to distant organs for tumors of the upper and lower thoracic esophagus and metastasis to nonregional lymph nodes or other distant metastasis for tumors of the midthoracic esophagus.[35]

EUS IN SUPERFICIAL CANCER AND BARRETT'S ESOPHAGUS

With the advent of EMR and ablative procedures such as photodynamic therapy and radiofrequency ablation, accurate assessment of depth of tumor invasion is mandated before their application. Because the depth of tumor invasion correlates with lymph node metastasis, it is crucial to identify T stage before EMR. One study showed that cancer limited to the epithelium and lamina propria (m1 and m2) has a 5% chance of metastasis to lymph nodes. In contrast, cancer invading the muscularis mucosa or the submucosa has a 12% to 27% chance of metastasis to lymph nodes. Invasion of the deep submucosa that reaches the proper muscle leads to a 36% to 46% chance of lymph node metastasis.[41]

The accuracy of HFCP in distinguishing between mucosal cancer and cancer invading the submucosa is 81% to 100%.[42] The accuracy of EUS in patients with Barrett's esophagus and high-grade dysplasia or intramucosal carcinoma has been reported. The sensitivity, specificity, and negative predictive values of preoperative EUS for submucosa invasion were 100%, 94%, and 100%, and for lymph node involvement were 100%, 81%, and 100%, respectively.[43] A nodule or stricture noted by endoscopy was associated with an increased likelihood of submucosa invasion.[43] This study used the regular echoendoscope and not the HFCP. With the exception of patients with Barrett's esophagus, early esophageal cancer is rarely seen in the United States and therefore, HFCP is less frequently used compared with Japan.

EUS-GUIDED FINE-NEEDLE ASPIRATION BIOPSY OF CELIAC AND PERI-INTESTINAL LYMPH NODES

Before the advent of EUS FNA, endosonographers relied on lymph nodes echo features to identify malignancy in lymph nodes. Features included size larger than 1 cm, sharp borders, round shape, and hypoechoic echo texture. Studies suggested that EUS FNA improves the accuracy of lymph node staging and is superior to those of EUS alone.[29] EUS alone was only 33.3% accurate in differentiating between malignant and benign lymphadenopathy, whereas EUS FNA had a significantly higher accuracy of 99.4%.[29] This study also found that lymph node echo features were particularly unreliable in the mediastinum.

In patients with esophageal cancer, EUS FNA was found superior to helical CT and EUS for the preoperative staging of lymph nodes.[31] Because of the small numbers of cases, EUS was equivalent to CT for the detection of CLNs. However, EUS has been shown to be superior to both CT and PET for the detection of CLNs.[10] The operating characteristics of EUS FNA compared with those of CT and EUS and the accuracy of EUS FNA in sampling CLNs are shown in Tables 7.4 and 7.5, respectively.

CONTROVERSIES IN EUS STAGING

The role of EUS in the staging of esophageal cancer was challenged by a controversial study from the Cleveland Clinic in Ohio. Zuccaro et al[44] asserted that patients with advance-staged disease were overrepresented in previous studies. These investigators reviewed their cohort who went directly to surgery following EUS (without neoadjuvant therapy) between 1987 and 2001. The T stage was misclassified in 45% of patients, and the N stage was misclassified in 25% of patients. When T classification was dichotomized into tumors whose depth of invasion was not beyond the muscularis propria (pTis to pT2) and those beyond (pT3 and pT4), errors occurred in 42 patients (16%).[44] Investigators have suggested that the 14-year time period of the study may make it less reflective of contemporary methods and results.

Shimpi et al[45] designed a study with an equivalent standard of surgery immediately following EUS (without neoadjuvant therapy), but these investigators limited the duration to their cohort from 1999 to 2004. This group also emphasized the importance of dilating strictures to optimize evaluation. They reported a T-stage accuracy of 76% and an N stage accuracy of 89%, more consistent with what was previously reported in the literature. However, these investigators did observe that EUS may perform less accurately in assessing T1 and T2 stage compared with T3 and T4, although the high-frequency probe could improve yields for T1 staging. In the study by Zuccaro et al,[44] FNA was not routinely performed, and a critical strength of EUS compared with other staging modalities is the ability to confirm lymph node involvement with tissue confirmation.

ROLE AND LIMITATION OF EUS FOLLOWING NEOADJUVANT THERAPY

Because of its ability to image the gastrointestinal tract wall layers with accuracy and histologic correlates,[9] EUS is currently the best staging modality for locoregional disease in esophageal cancer. However, several studies showed that standard EUS criteria are not accurate after neoadjuvant chemoradiation therapy because EUS poorly differentiates tumor from necrosis or inflammatory reaction.[46,47]

One study evaluated the utility of EUS after neoadjuvant therapy.[48] These investigators studied 97 consecutive patients with esophageal cancer who were treated with preoperative chemoradiation therapy and a potentially curative surgical procedure. All patients had EUS examination before chemoradiation therapy, and 53 had a repeat EUS examination after chemoradiation but before surgery. Surgical resection specimens were analyzed for the absence or presence of residual tumor and its location. Patients with residual tumor in the esophagus and patients without residual tumor had similar cumulative survival rates. Patients with residual cancer in lymph nodes showed a trend toward shorter cumulative survival compared with patients without residual tumor in lymph nodes. The actuarial survival of the patients with involved lymph nodes was lower than that of the patients with no lymph node involvement at 1, 2, and 3 years. Patients with significant residual lymphadenopathy detected by EUS after therapy had significantly worse postoperative survival compared with patients with no residual lymphadenopathy.[48] In eight patients, the investigators reliably obtained cytologic specimens and were able to identify residual malignancy by EUS FNA after chemoradiation therapy. These investigators concluded that EUS and EUS-guided FNA can be helpful in identifying residual tumor in the lymph nodes after preoperative chemoradiation therapy in selected patients who benefit maximally from surgery.

Another study evaluated the accuracy of EUS in restaging 83 patients with esophageal adenocarcinoma after induction therapy.[49] T-stage classification was assessed correctly by EUS in 22 patients (29%). The proportion of individual T-stage classifications by EUS that were correct were 0% for T0 tumors, 19% for T1 tumors, 27% for T2 tumors, 52% for T3 tumors, and 0% for T4 tumors when comparing results from the EUS restaging examination with the findings at surgical pathology. Nineteen of 83 patients (25%) were assigned the correct stage by restaging EUS, 42 patients (55%) were overstaged, and 15 patients (20%) were understaged. The accuracy of restaging EUS examination for predicting the N classification of the tumor was 49%. The sensitivity of EUS for N classification was 48% for N0 disease and 52% for N1 disease. EUS FNA was not routinely performed in this study to assess for residual disease.

It is current practice to sample lymph nodes after chemoradiation therapy. Patients with residual disease, especially in the celiac axis, undergo more treatment before surgical resection is considered. Because neoadjuvant therapy was used initially to shrink and reduce the bulk of the tumor, perhaps it is more important to ask the question whether residual tumor is resectable, to enable the patient to undergo surgical resection. In addition, and more importantly, EUS FNA has the ability to sample lymph nodes after chemotherapy and therefore can identify persistent disease that would necessitate further chemotherapy. Many centers do not offer surgical resection to patients with residual lymph nodes, especially in the celiac axis area, who have persistent residual disease (Video 7.3 and Fig. 7.11).

Another useful measure of tumor response is reduction in cross-sectional area. Reduction in maximal cross-sectional area of tumor (MAX) offers better promise as a useful measure for assessing response to preoperative therapy.[46]

In one study, responders (patients who had a >50% reduction in MAX) as assessed by EUS were more likely to survive compared

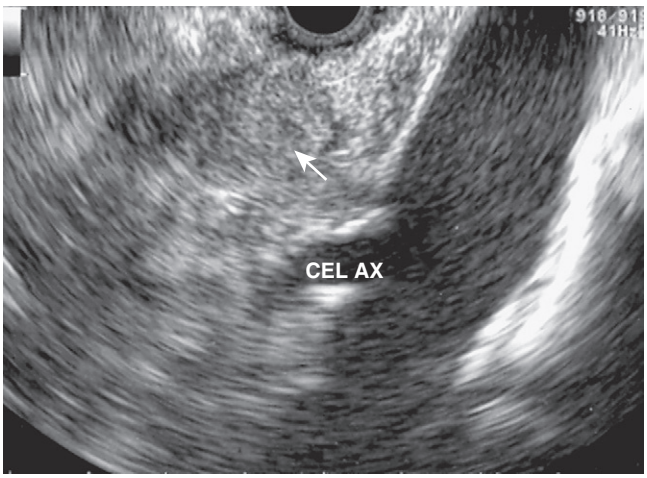


FIGURE 7.11 EUS performed after chemotherapy and radiation identified a soft tissue density in the celiac axis (CEL AX) area. EUS-guided fine-needle aspiration confirmed the presence of squamous cell carcinoma.

with nonresponders.[46] Moreover, it is apparent that responders with adenocarcinoma are more likely to survive compared with nonresponders. However, this finding did not hold true for patients with squamous cell carcinoma of the esophagus. Five of six patients in the R0 group were among the responders. None of the other clinical, endoscopic, or endosonographic variables studied predicted survival. This study was limited by a small sample size. The lack of effect of known important variables on survival, such as T stage, N stage, the presence of celiac adenopathy, or overall AJCC stage, is probably the result of a type 2 error (i.e., the study was underpowered to detect such a difference). Three-dimensional EUS that has the ability to measure the total volume of the tumor, rather than the cross-sectional area, may prove to be a superior modality in the assessment of response to multimodality therapy in patients with esophageal cancer.

IMPACT OF EUS ON SURVIVAL IN PATIENTS WITH ESOPHAGEAL CANCER

Because EUS provides accurate preoperative staging, initial data obtained at the time of EUS are predictive of survival. Eloubeidi et al[4] showed that EUS initial AJCC overall stage, the presence of adenopathy, and the presence of celiac adenopathy are all predictive factors of survival. More recently, a study showed that distinct survival advantages was seen in patients with fewer malignant-appearing regional lymph nodes noted on EUS.[50] The median survival rates were 66 months, 14.5 months, and 6.5 months for no, one to two, and more than two malignant-appearing lymph nodes, respectively. Survival was also influenced by the presence of CLNs and tumor length, both of which were associated with increased numbers of malignant lymph nodes.[50] The investigators concluded that the number of malignant-appearing periesophageal lymph nodes detected by EUS is associated with improved survival stratification in patients with esophageal adenocarcinoma and should be considered in the presurgical staging of esophageal cancer.[50] These findings were supportive of previous work from the Surveillance, Epidemiology, and End Results database suggesting that tumor length and the number of lymph nodes should be routinely reported as part of the staging system because these findings independently predicted survival in patients with esophageal cancer.[3]

SUMMARY

EUS is currently the only available modality that images the esophageal wall layers with histologic correlates. EUS is superior to CT and PET scan in the detection of peritumoral lymph nodes and CLNs. EUS FNA allows for documentation of locoregional and distant lymph node status before neoadjuvant therapy. EUS can aid in the selection of patients for surgical resection after neoadjuvant therapy. Future efforts should focus on implementing EUS as part of research protocols that evaluate therapies for esophageal cancer.

REFERENCES

1. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2009. *CA Cancer J Clin*. 2009;59(4):225–249.
2. Eloubeidi MA, Mason AC, Desmond RA, El Serag HB. Temporal trends (1973-1997) in survival of patients with esophageal adenocarcinoma in the United States: a glimmer of hope? *Am J Gastroenterol*. 2003;98(7):1627–1633.
3. Eloubeidi MA, Desmond R, Arguedas MR, et al. Prognostic factors for the survival of patients with esophageal carcinoma in the U.S.: the importance of tumor length and lymph node status. *Cancer*. 2001;95:1434–1443.
4. Eloubeidi MA, Wallace MB, Hoffman BJ, et al. Predictors of survival for esophageal cancer patients with and without celiac axis lymphadenopathy: impact of staging endosonography. *Ann Thorac Surg*. 2001;72:212–219.
5. Fockens P, Kisman K, Merkus MP, et al. The prognosis of esophageal carcinoma staged irresectable (T4) by endosonography. *J Am Coll Surg*. 1998;186:17–23.
6. Buxbaum JL, Eloubeidi MA. Endoscopic evaluation and treatment of esophageal cancer. *Minerva Gastroenterol Dietol*. 2009;55(4):455–469.
7. Rosch T. Endosonographic staging of esophageal cancer: a review of literature results. *Gastrointest Endosc Clin N Am*. 1995;5:537–547.
8. Romagnuolo J, Scott J, Hawes RH, et al. Helical CT versus EUS with fine needle aspiration for celiac nodal assessment in patients with esophageal cancer. *Gastrointest Endosc*. 2002;55:648–654.
9. Kimmey MB, Martin RW, Haggitt RC, et al. Histologic correlates of gastrointestinal ultrasound images. *Gastroenterology*. 1989;96:433–441.
10. Akdamar M, Eloubeidi MA. A prospective comparison of computerized tomography (CT), 18 fluoro-deoxyglucose positron emission tomography (FDG-PET) and endoscopic ultrasonography (EUS) in the preoperative evaluation of potentially operable esophageal cancer (ECA) patients. *Am J Gastroenterol*. 2005;98:S5.
11. Pfau PR, Perlman SB, Stanko P, et al. The role and clinical value of EUS in a multimodality esophageal carcinoma staging program with CT and positron emission tomography. *Gastrointest Endosc*. 2007;65(3):377–384.
12. van Westreenen HL, Westerterp M, Bossuyt PM, et al. Systematic review of the staging performance of 18F-fluorodeoxyglucose positron emission tomography in esophageal cancer. *J Clin Oncol*. 2004;22(18):3805–3812.
13. van Westreenen HL, Heeren PA, Jager PL, et al. Pitfalls of positive findings in staging esophageal cancer with F-18-fluorodeoxyglucose positron emission tomography. *Ann Surg Oncol*. 2003;10(9):1100–1105.
14. Eloubeidi MA, Cerfolio RJ, Chen VK, et al. Endoscopic ultrasound-guided fine needle aspiration of mediastinal lymph node in patients with suspected lung cancer after positron emission tomography and computed tomography scans. *Ann Thorac Surg*. 2005;79(1):263–268.
15. van Westreenen HL, Heeren PA, van Dullemen HN, et al. Positron emission tomography with F-18-fluorodeoxyglucose in a combined staging strategy of esophageal cancer prevents unnecessary surgical explorations. *J Gastrointest Surg*. 2005;9:54–61.
16. Wallace MB, Hawes RH, Sahai AV, et al. Dilation of malignant esophageal stenosis to allow EUS guided fine-needle aspiration: safety and effect on patient management. *Gastrointest Endosc*. 2000;51:309–313.
17. Van Dam J, Rice TW, Catalano MF, et al. High-grade malignant stricture is predictive of esophageal tumor stage: risks of endosonographic evaluation. *Cancer*. 1993;71:2910–2917.
18. Kallimanis GE, Gupta PK, al-Kawas FH, et al. Endoscopic ultrasound for staging esophageal cancer, with or without dilation, is clinically important and safe. *Gastrointest Endosc*. 1995;41:540–546.
19. Pfau PR, Ginsberg GG, Lew RJ, et al. Esophageal dilation for endosonographic evaluation of malignant esophageal strictures is safe and effective. *Am J Gastroenterol*. 2000;95:2813–2815.
20. Binmoeller KF, Seifert H, Seitz U, et al. Ultrasonic esophagoprobe for TNM staging of highly stenosing esophageal carcinoma. *Gastrointest Endosc*. 1995;41:547–552.
21. Mallery S, Van DJ. Increased rate of complete EUS staging of patients with esophageal cancer using the nonoptical, wire-guided echoendoscope. *Gastrointest Endosc*. 1999;50:53–57.

22. Siemsen M, Svendsen LB, Knigge U, et al. A prospective randomized comparison of curved array and radial echoendoscopy in patients with esophageal cancer. *Gastrointest Endosc*. 2003;58(5):671–676.
23. Vazquez-Sequeiros E, Wiersema M. High-frequency US catheter-based staging of early esophageal tumors. *Gastrointest Endosc*. 2002;55(1):95–99.
24. Wallace MB, Hoffman BJ, Sahai AS, et al. Imaging of esophageal tumors with a water-filled condom and a catheter US probe. *Gastrointest Endosc*. 2000;51:597–600.
25. Christie NA, Rice TW, DeCamp MM, et al. M1a/M1b esophageal carcinoma: clinical relevance. *J Thorac Cardiovasc Surg*. 1999;118:900–907.
26. Hiele M, De LP, Schurmans P, et al. Relation between endoscopic ultrasound findings and outcome of patients with tumors of the esophagus or esophagogastric junction. *Gastrointest Endosc*. 1997;45:381–386.
27. Eloubeidi MA, Vilmann P, Wiersema MJ. Endoscopic ultrasound-guided fine-needle aspiration of celiac lymph nodes. *Endoscopy*. 2004;36(10):901–908.
28. Catalano MF, Sivak MVJ, Rice T, et al. Endosonographic features predictive of lymph node metastasis. *Gastrointest Endosc*. 1994;40:442–446.
29. Chen VK, Eloubeidi MA. Endoscopic ultrasound-guided fine needle aspiration is superior to lymph node echofeatures: a prospective evaluation of mediastinal and peri-intestinal lymphadenopathy. *Am J Gastroenterol*. 2004;99(4):628–633.
30. Eloubeidi MA, Wallace MB, Reed CE, et al. The utility of EUS and EUS-guided fine needle aspiration in detecting celiac lymph node metastasis in patients with esophageal cancer: a single-center experience. *Gastrointest Endosc*. 2001;54:714–719.
31. Vazquez-Sequeiros E, Wiersema MJ, Clain JE, et al. Impact of lymph node staging on therapy of esophageal carcinoma. *Gastroenterology*. 2002;125: 1626–1635.
32. Wallace MB, Kennedy T, Durkalski V, et al. Randomized controlled trial of EUS-guided fine needle aspiration techniques for the detection of malignant lymphadenopathy. *Gastrointest Endosc*. 2001;54:441–447.
33. Prasad P, Schmulewitz N, Patel A, et al. Detection of occult liver metastases during EUS for staging of malignancies. *Gastrointest Endosc*. 2004;59(1):49–53.
34. tenBerge J, Hoffman BJ, Hawes RH, et al. EUS-guided fine needle aspiration of the liver: indications, yield, and safety based on an international survey of 167 cases. *Gastrointest Endosc*. 2002;55(7):859–862.
35. Esophagus. *AJCC Cancer Staging Manual*. 5th ed. Philadelphia: Lippincott-Raven; 2000:65–68.
36. Harewood GC, Kumar KS. Assessment of clinical impact of endoscopic ultrasound on esophageal cancer. *J Gastroenterol Hepatol*. 2004;19(4):433–439.
37. Kelly S, Harris KM, Berry E, et al. A systematic review of the staging performance of endoscopic ultrasound in gastro-oesophageal carcinoma. *Gut*. 2001;49(4):534–539.
38. Fockens P, Van den Brande JH, Van DH, et al. Endosonographic T-staging of esophageal carcinoma: a learning curve. *Gastrointest Endosc*. 1996;44:58–62.
39. Pfau PR, Ginsberg GG, Lew RJ, et al. Endoscopic ultrasound predictors of long term survival in esophageal carcinoma [abstract]. *Gastrointest Endosc*. 2000;51:136.
40. Penman ID, Williams DB, Sahai AV, et al. Ability of EUS with fine-needle aspiration to document nodal staging and response to neoadjuvant chemoradiotherapy in locally advanced esophageal cancer: a case report. *Gastrointest Endosc*. 1999;49:783–786.
41. Kodama M, Kakegawa T. Treatment of superficial cancer of the esophagus: a summary of responses to a questionnaire on superficial cancer of the esophagus in Japan. *Surgery*. 1998;123(4):432–439.
42. Murata Y, Napoleon B, Odegaard S. High-frequency endoscopic ultrasonography in the evaluation of superficial esophageal cancer. *Endoscopy*. 2003;35(5):429–435.
43. Scotiniotis IA, Kochman ML, Lewis JD, et al. Accuracy of EUS in the evaluation of Barrett's esophagus and high-grade dysplasia or intramucosal carcinoma. *Gastrointest Endosc*. 2001;54(6):689–696.
44. Zuccaro Jr G, Rice TW, Vargo JJ, et al. Endoscopic ultrasound errors in esophageal cancer. *Am J Gastroenterol*. 2005;100(3):601–606.
45. Shimpi RA, George J, Jowell P, et al. Staging of esophageal cancer by EUS: staging accuracy revisited. *Gastrointest Endosc*. 2007;66(3):475–482.
46. Chak A, Canto MI, Cooper GS, et al. Endosonographic assessment of multimodality therapy predicts survival of esophageal carcinoma patients. *Cancer*. 2000;88:1788–1795.
47. Isenberg G, Chak A, Canto MI, et al. Endoscopic ultrasound in restaging of esophageal cancer after neoadjuvant chemoradiation. *Gastrointest Endosc*. 1998;48:158–163.
48. Agarwal B, Swisher S, Ajani J, et al. Endoscopic ultrasound after preoperative chemoradiation can help identify patients who benefit maximally after surgical esophageal resection. *Am J Gastroenterol*. 2004;99(7): 1258–1266.
49. Kalha I, Kaw M, Fukami N, et al. The accuracy of endoscopic ultrasound for restaging esophageal carcinoma after chemoradiation therapy. *Cancer*. 2004;101(5):940–947.
50. Chen J, Xu R, Hunt GC, et al. Influence of the number of malignant regional lymph nodes detected by endoscopic ultrasonography on survival stratification in esophageal adenocarcinoma. *Clin Gastroenterol Hepatol*. 2006;4(5):573–579.
51. Giovannini M, Seitz JF, Monges G, et al. Fine-needle aspiration cytology guided by endoscopic ultrasonography: results in 141 patients. *Endoscopy*. 1995;27:171–177.
52. Reed CE, Mishra G, Sahai AV, et al. Esophageal cancer staging: improved accuracy by endoscopic ultrasound of celiac lymph nodes. *Ann Thorac Surg*. 1999;67:319–321.
53. Williams DB, Sahai AV, Aabakken L, et al. Endoscopic ultrasound guided fine needle aspiration biopsy: a large single centre experience. *Gut*. 1999;44:720–726.

CHAPTER 8

EUS IN THE EVALUATION OF POSTERIOR MEDIASTINAL LESIONS

Thomas J. Savides

Key Points

Criteria exist to differentiate benign from malignant mediastinal lymph nodes, but alone these criteria are not sufficiently accurate. EUS-guided fine-needle aspiration (FNA) is required to make sound clinical decisions.

The overall accuracy for the diagnosis of posterior mediastinal malignancies with transesophageal EUS FNA is greater than 90%.

The diagnosis of lymphoma in the posterior mediastinum is made by cytology and flow cytometry studies on EUS FNA specimens.

EUS FNA can be valuable in helping to establish a diagnosis of granulomatous disease involving the mediastinum (sarcoidosis, histoplasmosis, tuberculosis).

Most mediastinal cysts are benign, and because the risk of infection is high, EUS FNA should not be performed. If a high suspicion of malignancy exists, the cyst should undergo one puncture and be fully drained, and antibiotics should be administered.

INTRODUCTION

Transesophageal endoscopic ultrasonography (EUS) with fine-needle aspiration (FNA) offers a unique ability for the evaluation and biopsy of posterior mediastinal lesions. Usually these lesions are first detected with computed tomography (CT), but occasionally lesions are detected during passage of the echoendoscope through the esophagus on the way to image gastrointestinal or pancreatic disease. Transesophageal EUS is well suited to image the posterior mediastinum, but it cannot visualize the middle or anterior mediastinum. This chapter focuses on EUS diagnosis of posterior mediastinal masses, lymph nodes, and cysts. The role of EUS FNA in lung cancer staging is discussed in Chapter 6.

EUS EVALUATION OF ENLARGED POSTERIOR MEDIASTINAL LYMPH NODES

EUS Appearance of Benign Posterior Mediastinal Lymph Nodes

Mediastinal lymph nodes are commonly encountered during EUS for nonthoracic indications. The most common EUS feature of these benign lymph nodes is a triangular or crescent shape, with possibly an echogenic center (Fig. 8.1). The echogenic center represents the hilum of the lymph node. Intranodal blood vessels also suggest benign lymph nodes.[1,2]

The prevalence of posterior mediastinal adenopathy varies with geographic region of the world, depending on the risk of endemic pulmonary infections. The prevalence of benign posterior mediastinal adenopathy in a study from Indianapolis that evaluated patients undergoing EUS for nonthoracic indications was 86%, with an average of 3.6 periesophageal lymph nodes per patient.[3] These lymph nodes had mean short- and long-axis diameters of 5 and 10 mm, respectively. The high prevalence of lymph nodes in this study may be explained by the high rate of respiratory histoplasmosis in the state of Indiana. In contrast, a prospective study from England and Sweden revealed that only 62% of patients had posterior mediastinal lymph nodes, with a mean of 1.4 lymph nodes per patient. Nearly all of these lymph nodes had a short-axis diameter of 5 mm or less.[4]

EUS Appearance of Malignant Posterior Mediastinal Lymph Nodes

EUS findings associated with malignant lymph nodes include round shape, short-axis diameter greater than 5 mm, hypoechoic echotexture, and well-demarcated borders (Fig. 8.2).[3,5] If all four features are present in a lymph node, the chance of malignancy is 80% to 100%.[5,6] However, all four features are seen in only 25% of malignant lymph nodes.[6] For this reason, tissue sampling is important to obtain diagnostic cytopathologic material of enlarged mediastinal lymph nodes.

Elastography has been reported in the evaluation of mediastinal lymph node and masses.[7] However, the sensitivity and specificity (in the range of 80% to 90%) of this technique are lower than those of transesophageal or transbronchial EUS-guided FNA (>90% range). Therefore, elastography needs further assessment and improvement before widespread use of this method can be recommended.

Transesophageal EUS Fine-Needle Aspiration of Mediastinal Lymph Nodes

The first report of EUS-assisted FNA of mediastinal lymph nodes was in 1992, at Indiana University Medical Center.[8] A diagnostic radial EUS endoscope was used to mark the site on the esophageal wall adjacent to a mass lesion, followed by FNA using a sclerotherapy needle through a standard forward-viewing

endoscope.[8] The first use of a dedicated linear array echoendoscope to perform transesophageal EUS FNA of posterior mediastinal lymph nodes was reported in 1993.[9] Table 8.1 shows the types of pathologic lesions that can be diagnosed with transesophageal EUS FNA cytology.

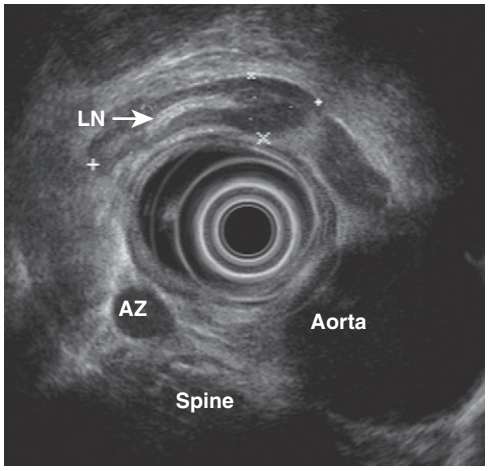


FIGURE 8.1 Benign mediastinal lymph node. Note the triangular appearance with a central hyperechoic stripe. AZ, azygous vein; LN, lymph node.

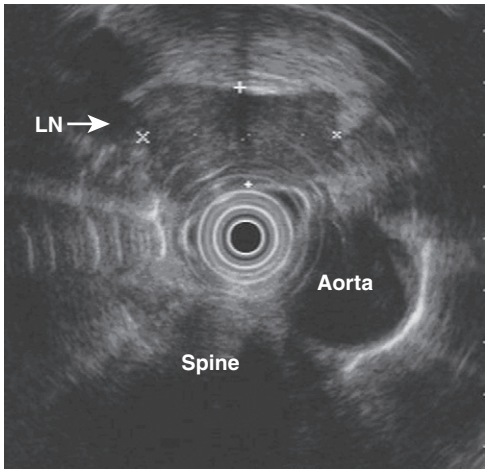


FIGURE 8.2 Malignant-appearing lymph node (LN). Note the round shape, well-demarcated border, hypoechoic echo pattern, and size larger than 5 mm.

TABLE 8.1

Posterior Mediastinal Lesions That Can Be Diagnosed with EUS Fine-Needle Aspiration

Malignant	Benign
Lung cancer	Reactive
Primary or metastatic	Granulomatous disease
Non–small cell (NSCLC)	Histoplasmosis
Small cell	Sarcoid
Mesothelioma	Tuberculosis
Lymphoma	Duplication cyst
Metastatic from nonlung primary	Leiomyoma
Gastrointestinal stromal tumor (GIST)	Mediastinitis/abscess
Spindle cell neoplasm	Pleural effusion

Technique for EUS Fine-Needle Aspiration of Posterior Mediastinal Lesions

Transesophageal EUS FNA is generally performed as an outpatient procedure. Patients are asked to stop taking antiplatelet medications, nonsteroidal anti-inflammatory drugs, and warfarin before the procedure. Patients usually receive intravenous moderate sedation using meperidine and midazolam. EUS can be performed first using a radial echoendoscope to identify lesions, followed by a linear array echoendoscope to perform the FNA, or directly with the linear array scope to find and biopsy a lesion based on prior CT findings. The echoendoscope is passed through the patient's mouth and into the stomach, and then ultrasound imaging is performed as the scope is withdrawn. The liver, celiac axis, left adrenal gland, and posterior mediastinum are evaluated for lesions.

The location of each lesion is documented in terms of the distance in centimeters of the transducer tip from the incisors and the anatomic site (e.g., subcarinal, left paraesophageal, right paratracheal, posterior aortopulmonic window). For each lesion, the short- and long-axis dimensions are measured, and the degree of demarcation is described (well demarcated or poorly demarcated). The shape is described in terms of round, oval, triangular, or draping. The echogenicity is described in terms of hypoechoic, hyperechoic, heterogenous, or anechoic.

Transesophageal EUS FNA is performed using a linear array echoendoscope and a 22- or 25-gauge aspiration needle. If there is more than one possible lesion to sample for biopsy, the lesion that is most likely to be malignant (i.e., rounder, larger, more demarcated) is chosen as the target.[10] If any question exists about whether the structure to undergo biopsy is vascular, color Doppler imaging can be used to assess for blood flow. Needle passage through an adjacent blood vessel can usually be avoided by displacing the esophagus with the scope tip to create a different needle path. However, in some reported cases, transaortic EUS FNA puncture with 22- and 25-gauge needles was successfully and safely used for biopsy of mediastinal lesions where the aorta was between the lesion and the esophagus.[11,12]

Once the lesion has been brought into view, the needle is passed through the esophageal wall and into the lymph node under constant ultrasound visualization. The internal stylet is then removed, intermittent suction is applied, and the needle is moved back and forth within the lesion to sample the edges as well as the center of the lesion. The needle is then pulled out of the scope, the stylet is slowly reintroduced into the needle, and the aspirated material is slowly expressed onto a microscope slide and into medium for cell block or flow cytometry.

In the United States, it is common for a cytotechnologist in the procedure room to prepare the slides using Quik-Dip stain (Mercedes Medical, Sarasota, FL). The cytopathologist then provides immediate cytologic evaluation of the slides under the microscope to determine whether there is adequate material on the slide for a preliminary diagnosis. The availability of immediate cytologic evaluation may increase the diagnostic yield.[13,14] If immediate cytologic evaluation raises the possibility of lymphoma, then additional passes may be obtained for flow cytometry. If immediate cytologic evaluation suggests infection, then additional passes may be made for microbiologic studies. A final diagnosis is provided only after the cytopathologist has evaluated all processed specimen slides and cell block material. In general, fewer EUS FNA passes are needed to obtain diagnostic material for posterior mediastinal lesions, on average approximately two to five passes for diagnostic material, in contrast to pancreatic masses, which usually require five to seven EUS FNA passes.[15–18]

EUS-guided 19-gauge Tru-Cut core biopsy can also be performed in mediastinal lesions. The advantages of this technique are the acquisition of a core of tissue for pathologic evaluation, the potentially shorter procedure duration, and perhaps reduced

cost when immediate cytologic evaluation is not used. However, the potential disadvantages are that the method is technically difficult, Tru-Cut needles are more expensive than standard FNA needles, and patients have a potentially increased safety risk. Tru-Cut FNA has especially been reported to increase the diagnostic yield in suspected lymphoma.[19]

Endobronchial Ultrasound

Endobronchial ultrasound (EBUS)–guided FNA has become increasingly widely available, especially as performed by interventional pulmonologists and thoracic surgeons.[20,21] EBUS provides unique access to lymph nodes and masses adjacent to the trachea, as well as the subcarinal and perihilar areas. The combination of transesophageal and transbronchial EUS provides nearly complete mediastinal evaluation.[22,23]

Accuracy of EUS Fine-Needle Aspiration for Diagnosing Posterior Mediastinal Lesions

The overall accuracy rate for diagnosing posterior mediastinal malignancy with transesophageal EUS FNA is approximately 93%.[10] A meta-analysis of 76 studies ($n = 9310$ patients) found a pooled sensitivity of 88% and specificity of 96%.[24] Table 8.2 shows a summary of the accuracy rates for EUS FNA for diagnosing malignancy in posterior mediastinal lesions. Several studies showed that the diagnostic accuracy of malignant posterior mediastinal lymph nodes increases with the use of EUS FNA cytology over simple EUS appearance alone.[24–27]

Risks of EUS Fine-Needle Aspiration of Posterior Mediastinal Lesions

EUS FNA of posterior mediastinal lesions is extremely safe, with few complications reported in the thousands of patients described in retrospective and prospective trials. However, several cases of mediastinitis have been reported after transesophageal EUS FNA.[28–37] Although most of these cases have involved mediastinal cysts, some patients with solid lesions (nodes or masses) have also developed post–EUS FNA mediastinitis.

There has been a single case of esophageal wall seeding with tumor after EUS FNA of a posterior mediastinal malignant node from a primary gastric cancer.[38] This occurred in the setting of several passes using a large 19-gauge needle, which may have contributed to the seeding. A case of esophagomediastinal fistula formation after EUS FNA of a posterior mediastinal lymph node resulting from tuberculosis has also been reported.[39]

EUS Fine-Needle Aspiration Compared with Other Modalities for Evaluation and Biopsy of Posterior Mediastinal Lymph Nodes or Masses

The noninvasive imaging modalities commonly used to evaluate enlarged mediastinal lymph nodes are CT scan and positron emission tomography (PET) scan. These modalities have mostly been compared with EUS FNA in the setting of suspected lung cancer. Both EUS alone and EUS FNA have been shown to be more accurate than CT alone (using short-axis lymph node diameter >10 mm) for diagnosing malignant posterior mediastinal lymph nodes.[25,40]

PET scanning detects increased uptake of the glucose analogue ^{18}F-2-deoxy-D-glucose. Increased uptake can occur both in malignancy and in inflammatory conditions. A meta-analysis comparing CT with PET scan for evaluation of mediastinal adenopathy in patients with lung cancer revealed that when the CT scan showed enlarged lymph nodes, the sensitivity of PET was 100%, but the specificity was only 78%, in contrast to when there were no CT findings of lymph node enlargement (sensitivity of 82% and specificity of 93%).[41] The low specificity of PET scan implies that 22% of patients with PET-positive enlarged mediastinal lymph nodes actually do not have malignancy (false-positive PET scan). Therefore, these PET-positive lymph nodes should undergo tissue biopsy if it is critical to be certain about the diagnosis of malignancy in the nodes.[41]

Several studies confirmed the poor specificity of PET compared with transesophageal EUS FNA.[40,42,43] One large study found that the EUS FNA positive predictive value of malignancy was 100% compared with 40% for PET.[43] One report noted an EUS FNA diagnosis of malignancy in an enlarged posterior mediastinal lymph node that had a false-negative PET scan result.[44] The combination of PET and EUS FNA can help improve the specificity and overall accuracy as compared with PET alone.[45,46]

The other modalities for obtaining tissue samples from posterior mediastinal lesions are percutaneous CT-guided transthoracic FNA, bronchoscopy with transbronchial biopsy, EBUS with transbronchial FNA, and mediastinoscopy with biopsy. Percutaneous transthoracic FNA is generally not used for biopsy of posterior mediastinal lesions because of the risk of pneumothorax or puncture of a major vessel. The diagnostic yield of transbronchial FNA without EBUS is lower than that of EUS FNA, whereas EBUS has a similar diagnostic yield in the biospying of adenopathy locations visualized by both transesophogeal EUS and EBUS.[23] Mediastinoscopy is associated with greater difficulty (and potentially increased risk) in accessing the lymph nodes in stations that are the most easily visualized and biopsied with transesophageal

TABLE 8.2

Summary of Studies Evaluating the Operating Characteristics of EUS Fine-Needle Aspiration for Diagnosing Malignant Posterior Mediastinal Lesions

Authors (yr)	*n*	Sensitivity (%)	Specificity (%)	Accuracy (%)	PPV (%)	NPV (%)
Giovannini et al[107] (1995)	24	81	100	83	—	—
Silvestri et al[108] (1996)	27	89	100	—	—	—
Gress et al[25] (1997)	52	95	81	96	—	—
Hunerbein et al[109] (1998)	23	89	83	87	—	—
Serna et al[110] (1998)	21	86	100	—	—	—
Wiersema et al[111] (2001)	82	96	100	98	94	100
Fritscher-Ravens et al[49] (2000)	153	92	100	95	—	—
Wallace et al[112] (2001)	121	87	100	—	—	—
Devereaux et al[54] (2002)	49	—	—	94	—	—
Larsen et al[78] (2002)	79	92	100	94	100	80
Hernandez et al[113] (2004)	59	—	—	84	—	—
Savides and Perricone[47] (2004)	59	96%	100	98	100	97
Eloubedi et al[43] (2005)	104	93%	100	97	100	97
Overall	91	97	100	97	99	94

NPV, negative predictive value; PPV, positive predictive value.

EUS FNA (subcarina, posterior aortopulmonic window, and periesophageal stations). Therefore, the less invasive EUS FNA and EBUS FNA are increasingly replacing mediastinoscopy at most referral centers.

DIFFERENTIAL DIAGNOSIS OF ENLARGED POSTERIOR MEDIASTINAL LYMPH NODES

Enlarged mediastinal lymph nodes are usually defined by CT findings of lymph nodes 10 mm diameter or larger. In the setting of a peripheral lung mass and mediastinal lymph nodes, the main concern is primary lung cancer with metastatic disease. The finding of numerous posterior mediastinal and hilar lymph nodes raises the question whether the diagnosis is benign (sarcoid, histoplasmosis, tuberculosis, reactive) or malignant (especially lymphoma). Often the clinical history suggests the origin.

MALIGNANT POSTERIOR MEDIASTINAL LYMPH NODES

The rate of diagnosis of malignancy with EUS FNA of posterior mediastinal nodes in patients without a known diagnosis of cancer varies depending on prior bronchoscopic evaluation and local referral patterns; however, it is approximately 50%, and most cancers are of pulmonary origin.[47–49] Table 8.2 shows the reported operating characteristics of EUS FNA for diagnosing malignancy in posterior mediastinal adenopathy. The overall sensitivity, specificity, and accuracy are greater than 90%.

Metastatic Disease from Thoracic Tumors

Lung Cancer

Most thoracic tumors originate as primary lung cancer. This disease is generally divided into small cell and non–small cell lung cancer (NSCLC) pathologic types, and 80% of lung cancer is NSCLC. EUS FNA cytology can diagnose and stage metastatic lung cancer to mediastinal lymph nodes from both small cell carcinoma and NSCLC.[10,25] Further discussion of EUS FNA for lung cancer staging is discussed in detail in Chapter 6.

Mesothelioma

Mesothelioma is a much rarer pleura-based tumor of the thoracic cavity associated with asbestos exposure. EUS FNA can diagnose mesothelioma metastases in posterior mediastinal lymph nodes.[50–52] The combination of transbronchial EBUS FNA and transesophageal EUS FNA may increase the sensitivity of diagnosed metastatic mesothelioma, especially because mesothelioma can also metastasize or directly extend below the diaphragm into the abdominal cavity, where EUS FNA can detect metastases.[53]

Metastatic Disease from Extrathoracic Malignancy

Various tumors result in metastases to the posterior mediastinum, and they appear as either a lymph node or a mass (Fig. 8.3). Metastatic lymph nodes from breast, colon, renal, testicular, laryngeal, pancreas, and esophageal cancers have been diagnosed by transthoracic EUS FNA.[54–57]

Lymphoma

EUS FNA can diagnose lymphoma in posterior mediastinal lymph nodes by obtaining material that can be evaluated with cytology, flow cytometry, and immunohistochemistry.[58] In one study, the sensitivity of lymphoma diagnosis increased from 44% to 86% with the addition of flow cytometry and immunocytochemistry.[58] Sometimes it can be difficult to obtain large quantities of adequate material during transesophageal EUS FNA to diagnose lymphoma, and therefore more needle passes may be needed than for NSCLC. Tru-Cut needle biopsies may provide additional material for architectural evaluation of low-grade lymphomas.[19,59]

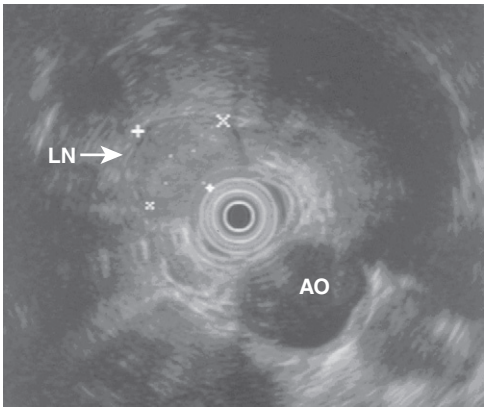


FIGURE 8.3 EUS of renal cell carcinoma metastatic to the mediastinum. AO, aorta; LN, lymph node.

BENIGN POSTERIOR MEDIASTINAL LYMPH NODES

Reactive Lymph Nodes

Reactive lymph nodes are usually the result of previous pulmonary infections. Cytologically, they appear as a mixture of lymphoid elements, with reactive and hyperplastic features.

Granulomatous Lymph Nodes

EUS FNA cytology is able to demonstrate granulomatous disease in lymph nodes. The cytologic appearance is that of histiocytes in a swirling pattern. The differential diagnosis usually includes sarcoid, histoplasmosis, tuberculosis, and coccidiomycosis. The presence or absence of caseating granulomas does not necessarily help with the diagnosis because caseation can be seen in all of the foregoing disorders. Sending EUS FNA cytology material for fungal stains and culture, acid-fast bacillus stain, and mycobacterial culture can help to determine whether the cause is infectious. Lymphoma is also rarely associated with granulomas.

Sarcoid

Sarcoid is a multisystemic granulomatous disease of unknown origin. It typically involves mediastinal lymph nodes. The final diagnosis is made by using clinical criteria and by excluding other causes of granulomatous disease. No pathognomic laboratory or pathologic finding exists for this disease. Elevated serum angiotensin-converting enzyme levels may suggest this diagnosis. The diagnosis of noncaseating granulomas in a mediastinal lymph node supports the diagnosis of sarcoid.

The usual endosonographic appearance of posterior mediastinal sarcoid is the presence of numerous enlarged lymph nodes (Fig. 8.4). EUS FNA can obtain granulomatous material to support the diagnosis of sarcoid with high accuracy (Table 8.3).[60–64] One retrospective study found the sensitivity and specificity of EUS FNA for diagnosing granulomas in suspected sarcoid to be 89% and 96%, respectively.[65] Another study found that EUS FNA demonstrated noncaseating granulomas in 41 of 50 patients (82%) with a final clinical diagnosis of sarcoidosis.[62] A study of patients with bilateral hilar lymphadenopathy, in whom EUS FNA was performed with a 19-gauge needle and whose material was sent for both cytologic and histopathologic examination, found that 94% of the histopathology specimens had noncaseating

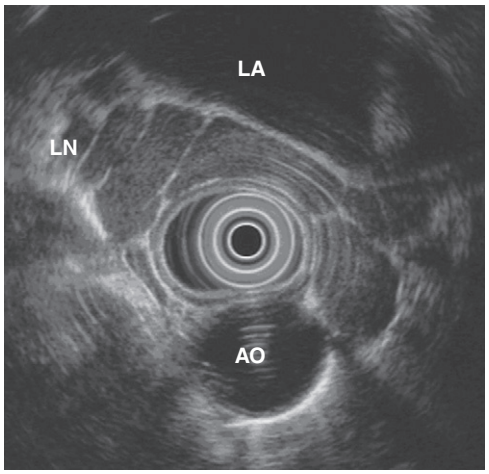


FIGURE 8.4 EUS image of presumed sarcoid lymph node (LN). Note that several lymph nodes are adjacent to each other. AO, aorta; LA, left atrium.

TABLE 8.3
Diagnostic Accuracy of EUS Fine-Needle Aspiration for Sarcoidosis

Authors (yr)	*n*	Sensitivity (%)	Specificity (%)
Fritscher-Ravens et al[61] (2000)	19	100	94
Wildi et al[65] (2004)	28	89	96
Annema et al[62] (2005)	50	82	—
Overall		90	95

granulomas, compared with 79% of the cytology specimens ($P = .04$).[36] EBUS FNA has been shown to be superior to blind transbronchial FNA in the diagnosis of sarcoid.[66,67]

Histoplasmosis

Histoplasmosis is caused by infection with *Histoplasma capsulatum*. Within the United States, infection is most common in the midwestern states located in the Ohio and Mississippi River valleys. The diagnosis is typically made by histopathology, serologic testing, or antigen testing.[68] Histoplasmosis usually is suspected either because of pulmonary symptoms or because of incidentally found mediastinal adenopathy on CT scan.

EUS FNA can diagnose granulomas in patients with suspected histoplasmosis.[69,70] Histoplasmosis should be suspected in patients with enlarged posterior mediastinal lymph nodes and granulomas on EUS FNA, particularly if these patients have spent time in areas endemic for *Histoplasma* infection.

Histoplasmosis can also cause dysphagia resulting from compression of the esophagus by enlarged, fibrosing lymph nodes (Fig. 8.5). The EUS appearance of mediastinal histoplasmosis that causes dysphagia includes the findings of a large mass of matted together, calcified lymph nodes that are adherent to a focally thickened esophageal wall.[70]

Tuberculosis

Mycobacterium tuberculosis can cause enlarged mediastinal lymph nodes, as well as a lymph node tuberculoma mass (Fig. 8.6). EUS FNA can obtain material for *M. tuberculosis* culture.[49,61,71–73] Patients with granulomas identified on EUS FNA should have material submitted for mycobacterial culture. The addition of polymerase chain reaction testing for *M. tuberculosis* in samples obtained by EUS FNA has been reported to increase the diagnostic yield compared with cytologic study and culture in patients suspected to have tuberculosis.[74]

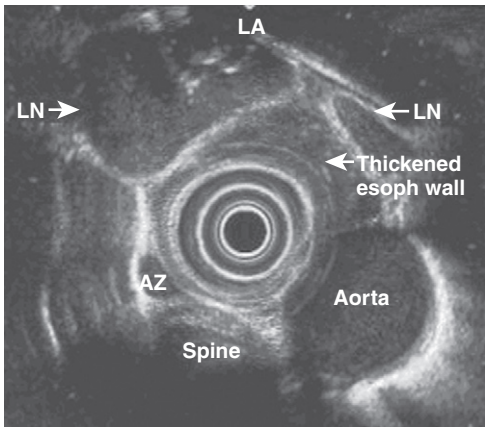


FIGURE 8.5 Lymph nodes (LN) in histoplasmosis. Note the matted together lymph nodes and calcification. AZ, azygos vein; LA, left atrium.

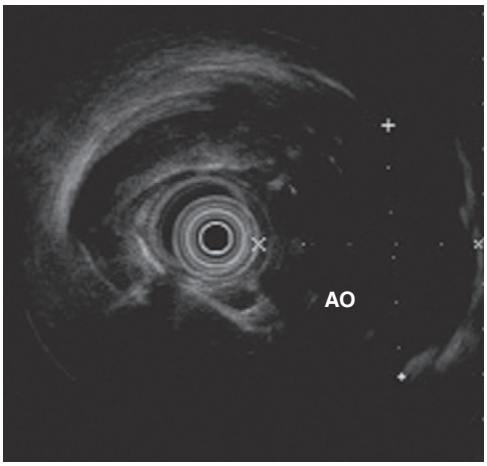


FIGURE 8.6 Posterior mediastinal tuberculoma. AO, aorta.

Other Infections

EUS FNA has also been reported to diagnosis infection with *Coccidioides immitis, Mycobacterium kansasii,* and *Nocardia.*[75,76]

Eosinophilic Esophagitis

Eosinophilic esophagitis is an increasingly recognized condition of diffuse esophageal strictures resulting from eosinophilic inflammation that may lead to dysphagia in adults. EUS often reveals thickening of the esophageal wall. One report noted patients with enlarged periesophageal lymph nodes who underwent EUS FNA after steroid treatment of eosinophilic esophagitis.[77] Results of the procedure revealed eosinophilic infiltrate of the lymph node, a finding suggesting that enlarged eosinophilic mediastinal lymph nodes may occur in the setting of eosinophilic esophagitis.[77]

IMPACT OF EUS FINE-NEEDLE ASPIRATION OF MEDIASTINAL LYMPH NODES ON SUBSEQUENT THORACIC SURGERY RATES

One study found that among 59 patients with mediastinal adenopathy who were referred for surgical mediastinoscopy but instead underwent EUS FNA first, only 22% of them eventually needed thoracic surgery.[47] Based on initial CT scan findings, 42% of the

patients who had a lung mass and mediastinal lymph nodes underwent surgery, compared with only 6% of patients with only mediastinal lymph nodes without an associated lung mass. The reason for this difference was that patients with lung masses and negative lymph nodes underwent surgical resection of the primary cancer, whereas those with only mediastinal adenopathy did not undergo surgery because either they had benign disease (i.e., sarcoid or reactive lymph nodes) or they had unresectable disease (i.e., lymphoma). Only 4% of patients with a positive EUS FNA result underwent subsequent surgery. These results are similar to those of a study from Denmark in which only 41% of patients who underwent EUS FNA subsequently underwent thoracic surgery.[78]

MEDIASTINAL MASSES

The distinction between a posterior mediastinal mass and a lymph node can be difficult because some lymph nodes are very large, whereas some masses are extremely small. Additionally, numerous lymph nodes matted together can form a "lymph node mass" (Fig. 8.7). Usually, a mass is larger than an enlarged lymph node (i.e., several centimeters in diameter), but no standardized terminology exists. Generally, when the term *mass* is used, there is only a single lesion, or one lesion that is significantly larger than adjacent lymph nodes. For the purpose of this section, only discrete, non–lymph node masses are discussed.

The differential diagnosis of a posterior mediastinal mass includes primary lung cancer extending into the posterior mediastinum, metastatic cancer (either primary lung cancer or nonthoracic cancer), neurogenic tumor, cyst, and infection. Transesophageal EUS FNA can easily sample large posterior mediastinal masses for biopsy.

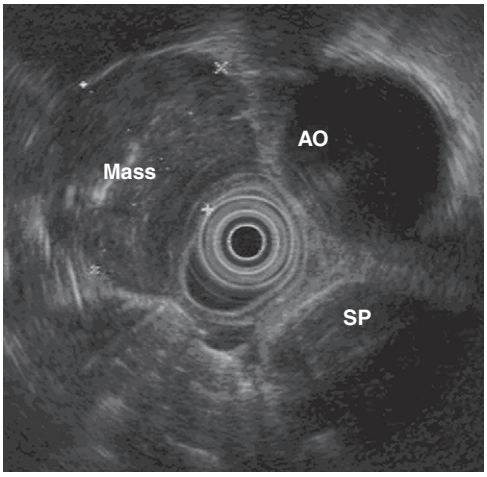


FIGURE 8.7 Mass of matted-together lymph nodes. "Lymph node mass." AO, aorta; SP, spine.

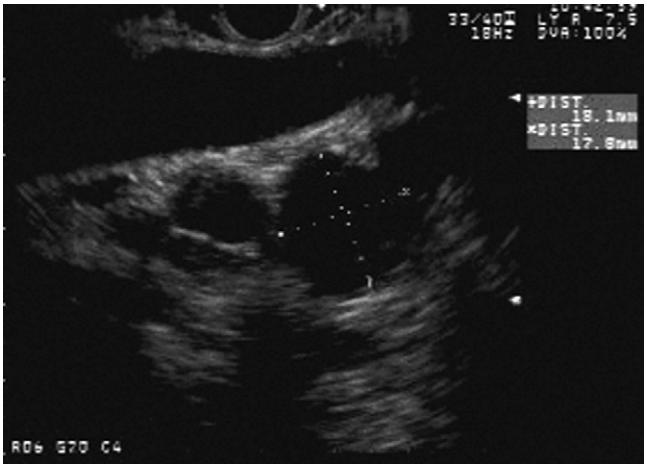


FIGURE 8.8 Posterior mediastinal schwannoma. Note the tumor located between the descending thoracic aorta and the spine.

Malignant Posterior Mediastinal Masses

Just as with mediastinal lymph nodes, approximately 50% of mediastinal masses that undergo EUS FNA are malignant.[54,55,79,80] Primary lung cancer masses that abut the esophagus can easily and safely undergo biopsy with transesophageal EUS FNA.[81] Mediastinal metastases from primary cancer of the lung, breast, colon, kidney, testicle, cervix, larynx, and esophagus have been diagnosed with transesophageal EUS FNA (see Fig. 8.3).[54,55,81] EUS FNA has also been reported to diagnose cases of primary mediastinal plasmacytoma and mediastinal granular cell tumor.[82,83]

Neurogenic Tumors

Primary neoplasms of the posterior mediastinum are rare. Neurogenic tumors account for approximately 75% of these primary posterior mediastinal neoplasms.[84] Neurogenic tumors may arise from peripheral nerves (schwannoma, neurilemoma, neurofibroma, nerve-sheath tumors), sympathetic ganglia (ganglioneuroma, ganglioneuroblastoma, neuroblastoma), or parasympathetic ganglia (paraganglionoma).[41] These are usually benign tumors, but approximately 10% to 20% may be malignant.[85] EUS FNA cytologic examination can diagnose mediastinal schwannoma (Fig. 8.8).[86]

Leiomyoma and Gastrointestinal Stromal Tumor

Gastrointestinal spindle cell tumors can arise from the muscularis propria of the esophagus and extend predominantly into the posterior mediastinum, rather than into the esophageal lumen. These tumors can have a CT and endoscopic appearance that more closely resembles that of a posterior mediastinal mass than an esophageal wall mass.[87–89] Esophageal spindle cell neoplasms are usually c-*kit*–negative leiomyomas, although occasionally they can be c-*kit*–positive gastrointestinal stromal tumors (GISTs).[87,88] These tumors have an EUS appearance of a hypoechoic mass with some internal signal and occasional acoustic enhancement, which sometimes makes them difficult to distinguish from cysts.[88] Because GISTs are highly metabolically active, they can often be diagnosed and followed with PET scans.[90] Although leiomyomas generally are PET-negative tumors, there have been reports of PET-positive esophageal or posterior mediastinal leiomyomas.[89] EUS FNA can be used to diagnose both posterior mediastinal leiomyomas and GISTs and can be considered when the distinction between a cyst and a GIST is uncertain.

Mesothelioma

Mesothelioma is a rare malignant tumor associated with asbestos exposure. This tumor is usually recognized as pleural thickening on CT, but sometimes the initial appearance is that of a mediastinal mass. The presence of metastatic lymphadenopathy is considered in the decision regarding surgical resection. EUS FNA has been used to diagnosis mesothelioma in both mediastinal masses and lymph nodes.[91,92]

Benign Posterior Mediastinal Masses

Benign causes of mediastinal "masses" that can be diagnosed with EUS FNA include histoplasmosis, sarcoidosis, leiomyoma, duplication cysts, and teratomas.[54] Tuberculosis can also appear

as a tuberculoma mass (see Fig. 8.6). A case of lymphangiohemangioma, a rare malformation of the lymphatic system, has been reported as a posterior mediastinal mass detected with EUS.[93]

Mediastinal Cysts

Congenital foregut cysts are the most common benign mediastinal cysts, and they account for 10% to 15% of mediastinal masses.[94–97] These cysts probably arise as a result of aberrant development of the primitive foregut. These foregut cysts may be categorized on the basis of the embryonic origin into bronchogenic or neuroenteric (esophageal duplication cysts and neuroenteric cysts). Esophageal duplication cysts are adherent to the esophagus, whereas those away from the esophageal wall are suggestive of bronchogenic cysts. The pathologic evaluation of duplication cysts reveals them to be typically lined by columnar epithelium.

Most patients with posterior mediastinal cysts are asymptomatic, and the cysts are discovered incidentally during other imaging studies. When symptoms occur, they can include chest pain, cough, dyspnea, and dysphagia. CT scan findings include well-defined, homogenous lesions ranging in size from 2 to 10 cm. These cysts are nonenhancing with intravenous contrast. They can sometimes be mistaken for a mass based on CT findings. Surgical resection may be indicated in symptomatic patients. Because the risk of malignancy is so rare, incidentally found lesions can usually be followed clinically.

The EUS appearance of a mediastinal cyst is usually a round or tubular anechoic structure with acoustic enhancement (Fig. 8.9).[98–101] Because it is usually difficult to determine whether the cyst is bronchogenic or esophageal in origin, the term *duplication cyst* is often used to describe the lesion. Some cysts appear to be mass lesions because of a more hypoechoic (rather than anechoic) echotexture and minimal acoustic enhancement. These mass-like cysts usually consist of thick, gelatinous cyst material.[30,32,101]

Mediastinal cysts can easily be aspirated with EUS FNA, but this is usually performed only when the EUS appearance is not compatible with a cyst and the lesion appears to be a possible mass.[28,32,98,101,102] Cytologic examination may reveal benign amorphous debris, degenerated cells, macrophages, needle-like crystals, mucinous material, or detached ciliary tufts.[102]

The risk of aspirating cystic mediastinal lesions was demonstrated by several reports of patients who developed mediastinitis after undergoing EUS FNA, including at least one patient who underwent Tru-Cut needle biopsy.[29,30,32,103] These patients required treatment with antibiotics, surgery, or endoscopic cyst drainage. None of the patients with reported bacterial mediastinitis after EUS FNA had received preprocedure or intraprocedure antibiotics. This situation raises the possibility that mediastinitis after EUS FNA of cysts may be prevented or minimized by the use of preprocedure or intraprocedure antibiotics. One series in which 22 patients underwent EUS FNA of posterior mediastinal cysts with 22-gauge needles and received intravenous ciprofloxacin followed by 5 days of oral ciprofloxacin reported no cases of mediastinitis.[104] This finding suggests that periprocedure antibiotics may prevent infection or mediastinitis when FNA of a cyst is performed.[104]

Despite the use of preprocedure antibiotics, in one reported case, EUS FNA of a duplication cyst resulted in *Candida albicans* infection of the cyst.[28] A 5-cm paratracheal cyst was aspirated, and gelatinous material was obtained. The patient subsequently underwent surgical resection, and culture grew *Candida albicans*, which was not present on the original EUS FNA. This organism was believed to have been introduced at the time of EUS FNA. The patient, who had been administered prophylactic antibiotics, did not develop mediastinitis. However, this finding again emphasizes the possible infectious risks in mediastinal cysts even with prophylactic antibiotics.

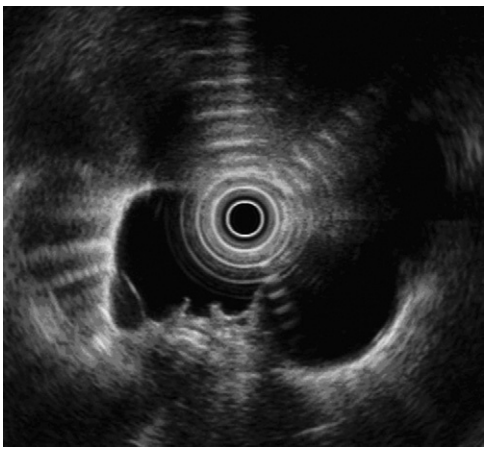


FIGURE 8.9 Mediastinal duplication cyst. Note the acoustic enhancement of the ultrasound signal.

Because of these reports of mediastinitis after aspirating posterior mediastinal duplication cysts, and given the benign nature of these cysts, any obvious posterior mediastinal duplication cyst should not be aspirated with EUS FNA. If there is a question that the lesion may be a cyst versus a malignant tumor, then the safest next diagnostic test may be thoracic magnetic resonance imaging or CT or PET scan to confirm the presence of a cyst and to exclude malignancy.[32] If EUS FNA is performed, a smaller-gauge (i.e., 25-gauge) needle ideally should be used to minimize introduction of infection into the cyst. If the lesion turns out to be a cyst (i.e., mucinous fluid), then the cyst should be completely drained if possible, and prophylactic antibiotics should be administered. A typical approach is to administer intravenous antibiotics during the procedure and oral antibiotics for the next 3 to 5 days afterward to minimize any risk of mediastinitis.[104] EUS-guided 19-gauge Tru-Cut needle biopsies should be avoided in suspected posterior mediastinal cysts because of the even higher risk of mediastinitis reported with the use of these larger needles.

Mediastinal Abscess and Mediastinitis

Acute mediastinitis and abscess occur most commonly after thoracic surgery or esophageal perforation. Patients generally have symptoms of sepsis. CT scan may show mediastinal fluid collections. Fritscher-Ravens et al[73] reported a series of 18 critically ill patients with clinical mediastinitis (mostly after thoracic surgery) who underwent EUS FNA. The EUS appearance of the abscesses were 2- to 4-cm, inhomogeneous, well-demarcated hypoechoic areas. Some lesions had hyperechoic 2- to 3-mm spots with shadowing that were thought to represent air. EUS FNA revealed purulent material and bacterial organisms on microbiology culture. No apparent complications resulted from performing EUS FNA in the mediastinal abscesses. EUS FNA has also been reported to diagnose candidal mediastinitis.[105] There has been a case report of a mediastinal abscess drained by EUS FNA aspiration, followed by placement of a transesophageal pigtail stent.[106]

SUMMARY

EUS is a very safe and effective means of visualizing and characterizing posterior mediastinal lesions. EUS FNA allows the ability to biopsy posterior mediastinal lesions accurately and safely, to determine malignancy. Because of the high rate of reported infectious complications after EUS FNA of mediastinal cysts, biopsy should not be undertaken if a cyst is suspected.

REFERENCES

1. Sawhney MS, Debold SM, Kratzke RA, et al. Central intranodal blood vessel: a new EUS sign described in mediastinal lymph nodes. *Gastrointest Endosc*. 2007;65:602–608.
2. Hall JD, Kahaleh M, White GE, et al. Presence of lymph node vasculature: a new EUS criterion for benign nodes? *Dig Dis Sci*. 2009;54:118–121.
3. Wiersema MJ, Hassig WM, Hawes RH, Wonn MJ. Mediastinal lymph node detection with endosonography. *Gastrointest Endosc*. 1993;39:788–793.
4. Kalaitzakis E, Sadik R, Doig L, Meenan J. Defining the lymph node burden in a northern European population without malignancy: the potential effect of geography in determining a need for FNA? *Dis Esophagus*. 2009;22:409–417.
5. Catalano MF, Sivak Jr MV, Rice T, et al. Endosonographic features predictive of lymph node metastasis. *Gastrointest Endosc*. 1994;40:442–446.
6. Bhutani MS, Hawes RH, Hoffman BJ. A comparison of the accuracy of echo features during endoscopic ultrasound (EUS) and EUS-guided fine-needle aspiration for diagnosis of malignant lymph node invasion. *Gastrointest Endosc*. 1997;45:474–479.
7. Janssen J, Dietrich CF, Will U, Greiner L. Endosonographic elastography in the diagnosis of mediastinal lymph nodes. *Endoscopy*. 2007;39: 952–957.
8. Wiersema MJ, Hawes RH, Tao LC, et al. Endoscopic ultrasonography as an adjunct to fine needle aspiration cytology of the upper and lower gastrointestinal tract. *Gastrointest Endosc*. 1992;38:35–39.
9. Wiersema MJ, Kochman ML, Chak A, et al. Real-time endoscopic ultrasound-guided fine-needle aspiration of a mediastinal lymph node. *Gastrointest Endosc*. 1993;39:429–431.
10. Wallace MB, Fritscher-Ravens A, Savides TJ. Endoscopic ultrasound for the staging of non-small-cell lung cancer. *Endoscopy*. 2003;35:606–610.
11. Wallace MB, Woodward TA, Raimondo M, et al. Transaortic fine-needle aspiration of centrally located lung cancer under endoscopic ultrasound guidance: the final frontier. *Ann Thorac Surg*. 2007; 84:1019–1021.
12. von Bartheld MB, Rabe KF, Annema JT. Transaortic EUS-guided FNA in the diagnosis of lung tumors and lymph nodes. *Gastrointest Endosc*. 2009;69:345–349.
13. Klapman JB, Logrono R, Dye CE, Waxman I. Clinical impact of on-site cytopathology interpretation on endoscopic ultrasound-guided fine needle aspiration. *Am J Gastroenterol*. 2003;98:1289–1294.
14. Tournoy KG, Praet MM, Van MG, Van Meerbeeck JP. Esophageal endoscopic ultrasound with fine-needle aspiration with an on-site cytopathologist: high accuracy for the diagnosis of mediastinal lymphadenopathy. *Chest*. 2005;128:3004–3009.
15. Emery SC, Savides TJ, Behling CA. Utility of immediate evaluation of endoscopic ultrasound-guided transesophageal fine needle aspiration of mediastinal lymph nodes. *Acta Cytol*. 2004;48:630–634.
16. LeBlanc JK, Ciaccia D, Al-Assi MT, et al. Optimal number of EUS-guided fine needle passes needed to obtain a correct diagnosis. *Gastrointest Endosc*. 2004;59:475–481.
17. Wallace MB, Kennedy T, Durkalski V, et al. Randomized controlled trial of EUS-guided fine needle aspiration techniques for the detection of malignant lymphadenopathy. *Gastrointest Endosc*. 2001;54:441–447.
18. Erickson RA, Sayage-Rabie L, Beissner RS. Factors predicting the number of EUS-guided fine-needle passes for diagnosis of pancreatic malignancies. *Gastrointest Endosc*. 2000;51:184–190.
19. Levy MJ, Wiersema MJ. EUS-guided Trucut biopsy. *Gastrointest Endosc*. 2005;62:417–426.
20. Herth FJ, Eberhardt R, Vilmann P, et al. Real-time endobronchial ultrasound guided transbronchial needle aspiration for sampling mediastinal lymph nodes. *Thorax*. 2006;61:795–798.
21. Gilbert S, Wilson DO, Christie NA, et al. Endobronchial ultrasound as a diagnostic tool in patients with mediastinal lymphadenopathy. *Ann Thorac Surg*. 2009;88:896–900.
22. Khoo KL, Ho KY, Nilsson B, Lim TK. EUS-guided FNA immediately after unrevealing transbronchial needle aspiration in the evaluation of mediastinal lymphadenopathy: a prospective study. *Gastrointest Endosc*. 2006; 63:215–220.
23. Wallace MB, Pascual JM, Raimondo M, et al. Minimally invasive endoscopic staging of suspected lung cancer. *JAMA*. 2008;299:540–546.
24. Puli SR, Batapati Krishna RJ, et al. Endoscopic ultrasound: its accuracy in evaluating mediastinal lymphadenopathy? A meta-analysis and systematic review. *World J Gastroenterol*. 2008;14:3028–3037.
25. Gress FG, Savides TJ, Sandler A, et al. Endoscopic ultrasonography, fine-needle aspiration biopsy guided by endoscopic ultrasonography, and computed tomography in the preoperative staging of non-small-cell lung cancer: a comparison study. *Ann Intern Med*. 1997;127:604–612.
26. Chen VK, Eloubeidi MA. Endoscopic ultrasound-guided fine needle aspiration is superior to lymph node echofeatures: a prospective evaluation of mediastinal and peri-intestinal lymphadenopathy. *Am J Gastroenterol*. 2004;99:628–633.
27. Vazquez-Sequeiros E, Wiersema MJ, Clain JE, et al. Impact of lymph node staging on therapy of esophageal carcinoma. *Gastroenterology*. 2003;125: 1626–1635.
28. Ryan AG, Zamvar V, Roberts SA. Iatrogenic candidal infection of a mediastinal foregut cyst following endoscopic ultrasound-guided fine-needle aspiration. *Endoscopy*. 2002;34:838–839.
29. Annema JT, Veselic M, Versteegh MI, Rabe KF. Mediastinitis caused by EUS-FNA of a bronchogenic cyst. *Endoscopy*. 2003;35:791–793.
30. Wildi SM, Hoda RS, Fickling W, et al. Diagnosis of benign cysts of the mediastinum: the role and risks of EUS and FNA. *Gastrointest Endosc*. 2003;58:362–368.
31. Varadarajulu S, Fraig M, Schmulewitz N, et al. Comparison of EUS-guided 19-gauge Trucut needle biopsy with EUS-guided fine-needle aspiration. *Endoscopy*. 2004;36:397–401.
32. Westerterp M, van den Berg JG, van Lanschot JJ, Fockens P. Intramural bronchogenic cysts mimicking solid tumors. *Endoscopy*. 2004;36: 1119–1122.
33. Pai KR, Page RD. Mediastinitis after EUS-guided FNA biopsy of a posterior mediastinal metastatic teratoma. *Gastrointest Endosc*. 2005;62: 980–981.
34. Savides TJ, Margolis D, Richman KM, Singh V. Gemella morbillorum mediastinitis and osteomyelitis following transesophageal endoscopic ultrasound-guided fine-needle aspiration of a posterior mediastinal lymph node. *Endoscopy*. 2007;39(suppl 1):E123–E124.
35. Aerts JG, Kloover J, Los J, et al. EUS-FNA of enlarged necrotic lymph nodes may cause infectious mediastinitis. *J Thorac Oncol*. 2008;3: 1191–1193.
36. Iwashita T, Yasuda I, Doi S, et al. The yield of endoscopic ultrasound-guided fine needle aspiration for histological diagnosis in patients suspected of stage I sarcoidosis. *Endoscopy*. 2008;40:400–405.
37. Diehl DL, Cheruvattath R, Facktor MA, Go BD. Infection after endoscopic ultrasound-guided aspiration of mediastinal cysts. *Interact Cardiovasc Thorac Surg*. 2010;10(2):338–340.
38. Doi S, Yasuda I, Iwashita T, et al. Needle tract implantation on the esophageal wall after EUS-guided FNA of metastatic mediastinal lymphadenopathy. *Gastrointest Endosc*. 2008;67:988–990.
39. von Bartheld MB, van Kralingen KW, Veenendaal RA, et al. Mediastinal-esophageal fistulae after EUS-FNA of tuberculosis of the mediastinum. *Gastrointest Endosc*. 2010;71(1):210–212.
40. Fritscher-Ravens A, Bohuslavizki KH, Brandt L, et al. Mediastinal lymph node involvement in potentially resectable lung cancer: comparison of CT, positron emission tomography, and endoscopic ultrasonography with and without fine-needle aspiration. *Chest*. 2003;123:442–451.
41. Gould MK, Kuschner WG, Rydzak CE, et al. Test performance of positron emission tomography and computed tomography for mediastinal staging in patients with non–small-cell lung cancer: a meta-analysis. *Ann Intern Med*. 2003;139:879–892.
42. Fritscher-Ravens A, Davidson BL, Hauber HP, et al. Endoscopic ultrasound, positron emission tomography, and computerized tomography for lung cancer. *Am J Respir Crit Care Med*. 2003;168:1293–1297.
43. Eloubeidi MA, Cerfolio RJ, Chen VK, et al. Endoscopic ultrasound-guided fine needle aspiration of mediastinal lymph node in patients with suspected lung cancer after positron emission tomography and computed tomography scans. *Ann Thorac Surg*. 2005;79:263–268.
44. Rosenberg JM, Perricone A, Savides TJ. Endoscopic ultrasound/fine-needle aspiration diagnosis of a malignant subcarinal lymph node in a patient with lung cancer and a negative positron emission tomography scan. *Chest*. 2002;122:1091–1093.
45. Kalade AV, Eddie Lau WF, Conron M, et al. Endoscopic ultrasound-guided fine-needle aspiration when combined with positron emission tomography improves specificity and overall diagnostic accuracy in unexplained mediastinal lymphadenopathy and staging of non–small-cell lung cancer. *Intern Med J*. 2008;38:837–844.
46. Bataille L, Lonneux M, Weynand B, et al. EUS-FNA and FDG-PET are complementary procedures in the diagnosis of enlarged mediastinal lymph nodes. *Acta Gastroenterol Belg*. 2008;71:219–229.
47. Savides TJ, Perricone A. Impact of EUS-guided FNA of enlarged mediastinal lymph nodes on subsequent thoracic surgery rates. *Gastrointest Endosc*. 2004;60:340–346.
48. Catalano MF, Nayar R, Gress F, et al. EUS-guided fine needle aspiration in mediastinal lymphadenopathy of unknown etiology. *Gastrointest Endosc*. 2002;55:863–869.
49. Fritscher-Ravens A, Sriram PV, Bobrowski C, et al. Mediastinal lymphadenopathy in patients with or without previous malignancy: EUS-FNA-based differential cytodiagnosis in 153 patients. *Am J Gastroenterol*. 2000;95: 2278–2284.
50. Kahi CJ, Dewitt JM, Lykens M, et al. Diagnosis of a malignant mesothelioma by EUS-guided FNA of a mediastinal lymph node. *Gastrointest Endosc*. 2004;60:859–861.

51. Bean SM, Eloubeidi MA, Cerfolio R, et al. Endoscopic ultrasound-guided fine needle aspiration is useful for nodal staging in patients with pleural mesothelioma. *Diagn Cytopathol*. 2008;36:32–37.
52. Tournoy KG, Burgers SA, Annema JT, et al. Transesophageal endoscopic ultrasound with fine needle aspiration in the preoperative staging of malignant pleural mesothelioma. *Clin Cancer Res*. 2008;14: 6259–6263.
53. Rice DC, Steliga MA, Stewart J, et al. Endoscopic ultrasound-guided fine needle aspiration for staging of malignant pleural mesothelioma. *Ann Thorac Surg*. 2009;88:862–868.
54. Devereaux BM, LeBlanc JK, Yousif E, et al. Clinical utility of EUS-guided fine-needle aspiration of mediastinal masses in the absence of known pulmonary malignancy. *Gastrointest Endosc*. 2002;56:397–401.
55. DeWitt J, Ghorai S, Kahi C, et al. EUS-FNA of recurrent postoperative extraluminal and metastatic malignancy. *Gastrointest Endosc*. 2003;58: 542–548.
56. Kramer H, Koeter GH, Sleijfer DT, et al. Endoscopic ultrasound-guided fine-needle aspiration in patients with mediastinal abnormalities and previous extrathoracic malignancy. *Eur J Cancer*. 2004;40:559–562.
57. Hahn M, Faigel DO. Frequency of mediastinal lymph node metastases in patients undergoing EUS evaluation of pancreaticobiliary masses. *Gastrointest Endosc*. 2001;54:331–335.
58. Ribeiro A, Vazquez-Sequeiros E, Wiersema LM, et al. EUS-guided fine-needle aspiration combined with flow cytometry and immunocytochemistry in the diagnosis of lymphoma. *Gastrointest Endosc*. 2001;53: 485–491.
59. Levy MJ, Jondal ML, Clain J, Wiersema MJ. Preliminary experience with an EUS-guided Trucut biopsy needle compared with EUS-guided FNA. *Gastrointest Endosc*. 2003;57:101–106.
60. Mishra G, Sahai AV, Penman ID, et al. Endoscopic ultrasonography with fine-needle aspiration: an accurate and simple diagnostic modality for sarcoidosis. *Endoscopy*. 1999;31:377–382.
61. Fritscher-Ravens A, Sriram PV, Topalidis T, et al. Diagnosing sarcoidosis using endosonography-guided fine-needle aspiration. *Chest*. 2000;118: 928–935.
62. Annema J, Veselic M, Rabe K. *Endoscopic ultrasound guided fine needle aspiration for the diagnosis of sarcoidosis*. 25th ed 2005:1–5.
63. Michael H, Ho S, Pollack B, et al. Diagnosis of intra-abdominal and mediastinal sarcoidosis with EUS-guided FNA. *Gastrointest Endosc*. 2008; 67:28–34.
64. Cooke JR, Behling CA, Perricone A, Savides TJ. Using trans-esophageal endoscopic ultrasound-guided fine needle aspiration to diagnose sarcoidosis inpatients with mediastinal lymph adenopathy. *Clin Pulm Med*. 2008; 15(1):13–17.
65. Wildi SM, Judson MA, Fraig M, et al. Is endosonography guided fine needle aspiration (EUS-FNA) for sarcoidosis as good as we think? *Thorax*. 2004;59:794–799.
66. Tremblay A, Stather DR, Maceachern P, et al. A randomized controlled trial of standard vs endobronchial ultrasonography-guided transbronchial needle aspiration in patients with suspected sarcoidosis. *Chest*. 2009;136:340–346.
67. Tournoy KG, Bolly A, Aerts JG, et al. The value of endoscopic ultrasound after bronchoscopy to diagnose thoracic sarcoidosis. *Eur Respir J*. 2010; 35(6):1329–1335.
68. Wheat LJ, Kohler RB, Tewari RP. Diagnosis of disseminated histoplasmosis by detection of Histoplasma capsulatum antigen in serum and urine specimens. *N Engl J Med*. 1986;314:83–88.
69. Wiersema MJ, Chak A, Wiersema LM. Mediastinal histoplasmosis: evaluation with endosonography and endoscopic fine-needle aspiration biopsy. *Gastrointest Endosc*. 1994;40:78–81.
70. Savides TJ, Gress FG, Wheat LJ, et al. Dysphagia due to mediastinal granulomas: diagnosis with endoscopic ultrasonography. *Gastroenterology*. 1995;109:366–373.
71. Hainaut P, Monthe A, Lesage V, Weynand B. Tuberculous mediastinal lymphadenopathy. *Acta Clin Belg*. 1998;53:114–116.
72. Kramer H, Nieuwenhuis JA, Groen HJ, Wempe JB. Pulmonary tuberculosis diagnosed by esophageal endoscopic ultrasound with fine-needle aspiration. *Int J Tuberc Lung Dis*. 2004;8:272–273.
73. Fritscher-Ravens A, Schirrow L, Pothmann W, et al. Critical care transesophageal endosonography and guided fine-needle aspiration for diagnosis and management of posterior mediastinitis. *Crit Care Med*. 2003;31: 126–132.
74. Sriram PVJ, Kaffes AJ, Rajasekhar P, et al. EUS features of mediastinal tuberculosis: a PCR based cytodiagnosis by trans-esophageal EUS-FNA. *Gastrointest Endosc*. 2004;59:AB216.
75. Chaya CT, Schnadig V, Gupta P, et al. Endoscopic ultrasound-guided fine-needle aspiration for diagnosis of an infectious mediastinal mass and/or lymphadenopathy. *Endoscopy*. 2006;38(suppl 2):E99–E101.
76. Naidu VG, Tammineni AK, Biscopink RJ, et al. *Coccidioides immitis* and *Mycobacterium tuberculosis* diagnosed by endoscopic ultrasound. *J S C Med Assoc*. 2009;105:4–7.
77. Bhutani MS, Moparty B, Chaya CT, et al. Endoscopic ultrasound-guided fine-needle aspiration of enlarged mediastinal lymph nodes in eosinophilic esophagitis. *Endoscopy*. 2007;39(suppl 1):E82–E83.
78. Larsen SS, Krasnik M, Vilmann P, et al. Endoscopic ultrasound guided biopsy of mediastinal lesions has a major impact on patient management. *Thorax*. 2002;57:98–103.
79. Catalano MF, Rosenblatt ML, Chak A, et al. Endoscopic ultrasound-guided fine needle aspiration in the diagnosis of mediastinal masses of unknown origin. *Am J Gastroenterol*. 2002;97:2559–2565.
80. Panelli F, Erickson RA, Prasad VM. Evaluation of mediastinal masses by endoscopic ultrasound and endoscopic ultrasound-guided fine needle aspiration. *Am J Gastroenterol*. 2001;96:401–408.
81. Varadarajulu S, Hoffman BJ, Hawes RH, Eloubeidi MA, EUS-guided FNA. of lung masses adjacent to or abutting the esophagus after unrevealing CT-guided biopsy or bronchoscopy. *Gastrointest Endosc*. 2004;60: 293–297.
82. Mallo R, Gottlieb K, Waggoner D, Wittenkeller J. Mediastinal plasmacytoma detected by echocardiography and biopsied with EUS-FNA. *Echocardiography*. 2008;25:997–998.
83. Bean SM, Eloubeidi MA, Eltoum IA, et al. Preoperative diagnosis of a mediastinal granular cell tumor by EUS-FNA: a case report and review of the literature. *Cytojournal*. 2005;2:8.
84. Macchiarini P, Ostertag H. Uncommon primary mediastinal tumours. *Lancet Oncol*. 2004;5:107–118.
85. Reed JC, Hallet KK, Feigin DS. Neural tumors of the thorax: subject review from the AFIP. *Radiology*. 1978;126:9–17.
86. McGrath KM, Ballo MS, Jowell PS. Schwannoma of the mediastinum diagnosed by EUS-guided fine needle aspiration. *Gastrointest Endosc*. 2001;53:362–365.
87. Lee JR, Anstadt MP, Khwaja S, Green LK. Gastrointestinal stromal tumor of the posterior mediastinum. *Eur J Cardiothorac Surg*. 2002;22:1014–1016.
88. Portale G, Zaninotto G, Costantini M, et al. Esophageal GIST: case report of surgical enucleation and update on current diagnostic and therapeutic options. *Int J Surg Pathol*. 2007;15:393–396.
89. Miyoshi K, Naito M, Ueno T, et al. Abnormal fluorine-18-fluorodeoxyglucose uptake in benign esophageal leiomyoma. *Gen Thorac Cardiovasc Surg*. 2009;57:629–632.
90. Van den Abbeele AD. The lessons of GIST-PET and PET/CT: a new paradigm for imaging. *Oncologist*. 2008;13(suppl 2):8–13.
91. Bakdounes K, Jhala N, Jhala D. Diagnostic usefulness and challenges in the diagnosis of mesothelioma by endoscopic ultrasound guided fine needle aspiration. *Diagn Cytopathol*. 2008;36:503–507.
92. Balderramo DC, Pellise M, Colomo L, et al. Diagnosis of pleural malignant mesothelioma by EUS-guided FNA (with video). *Gastrointest Endosc*. 2008;68:1191–1192.
93. Tang SJ, Sreenarasimhaiah J, Tang L, et al. Endoscopic injection sclerotherapy with doxycycline for mediastinal and esophageal lymphangiohemangioma. *Gastrointest Endosc*. 2007;66:1196–1200.
94. Ribet ME, Copin MC, Gosselin B. Bronchogenic cysts of the mediastinum. *J Thorac Cardiovasc Surg*. 1995;109:1003–1010.
95. Strollo DC, Rosado-de-Christenson ML, Jett JR. Primary mediastinal tumors: part II. Tumors of the middle and posterior mediastinum. *Chest*. 1997;112:1344–1357.
96. Snyder ME, Luck SR, Hernandez R, et al. Diagnostic dilemmas of mediastinal cysts. *J Pediatr Surg*. 1985;20:810–815.
97. Sirivella S, Ford WB, Zikria EA, et al. Foregut cysts of the mediastinum: results in 20 consecutive surgically treated cases. *J Thorac Cardiovasc Surg*. 1985;90:776–782.
98. Van DJ, Rice TW, Sivak Jr MV. Endoscopic ultrasonography and endoscopically guided needle aspiration for the diagnosis of upper gastrointestinal tract foregut cysts. *Am J Gastroenterol*. 1992;87:762–765.
99. Geller A, Wang KK, DiMagno EP. Diagnosis of foregut duplication cysts by endoscopic ultrasonography. *Gastroenterology*. 1995;109:838–842.
100. Bhutani MS, Hoffman BJ, Reed C. Endosonographic diagnosis of an esophageal duplication cyst. *Endoscopy*. 1996;28:396–397.
101. Faigel DO, Burke A, Ginsberg GG, et al. The role of endoscopic ultrasound in the evaluation and management of foregut duplications. *Gastrointest Endosc*. 1997;45:99–103.
102. Eloubeidi MA, Cohn M, Cerfolio RJ, et al. Endoscopic ultrasound-guided fine-needle aspiration in the diagnosis of foregut duplication cysts: the value of demonstrating detached ciliary tufts in cyst fluid. *Cancer*. 2004; 102:253–258.
103. Wiersema MJ, Vilmann P, Giovannini M, et al. Endosonography-guided fine-needle aspiration biopsy: diagnostic accuracy and complication assessment. *Gastroenterology*. 1997;112:1087–1095.

104. Fazel A, Moezardalan K, Varadarajulu S, et al. The utility and the safety of EUS-guided FNA in the evaluation of duplication cysts. *Gastrointest Endosc*. 2005;62:575–580.
105. Prasad VM, Erickson R, Contreras ED, Panelli F. Spontaneous candida mediastinitis diagnosed by endoscopic ultrasound-guided, fine-needle aspiration. *Am J Gastroenterol*. 2000;95:1072–1075.
106. Kahaleh M, Yoshida C, Kane L, Yeaton P. EUS drainage of a mediastinal abscess. *Gastrointest Endosc*. 2004;60:158–160.
107. Giovannini M, Seitz JF, Monges G, et al. Fine-needle aspiration cytology guided by endoscopic ultrasonography: results in 141 patients. *Endoscopy*. 1995;27:171–177.
108. Silvestri GA, Hoffman BJ, Bhutani MS, et al. Endoscopic ultrasound with fine-needle aspiration in the diagnosis and staging of lung cancer. *Ann Thorac Surg*. 1996;61:1441–1446.
109. Hunerbein M, Ghadimi BM, Haensch W, Schlag PM. Transesophageal biopsy of mediastinal and pulmonary tumors by means of endoscopic ultrasound guidance. *J Thorac Cardiovasc Surg*. 1998;116:554–559.
110. Serna DL, Aryan HE, Chang KJ, et al. An early comparison between endoscopic ultrasound-guided fine-needle aspiration and mediastinoscopy for diagnosis of mediastinal malignancy. *Am Surg*. 1998;64:1014–1018.
111. Wiersema MJ, Vazquez-Sequeiros E, Wiersema LM. Evaluation of mediastinal lymphadenopathy with endoscopic US-guided fine-needle aspiration biopsy. *Radiology*. 2001;219:252–257.
112. Wallace MB, Silvestri GA, Sahai AV, et al. Endoscopic ultrasound-guided fine needle aspiration for staging patients with carcinoma of the lung. *Ann Thorac Surg*. 2001;72:1861–1867.
113. Hernandez LV, Mishra G, George S, Bhutani MS. A descriptive analysis of EUS-FNA for mediastinal lymphadenopathy: an emphasis on clinical impact and false negative results. *Am J Gastroenterol*. 2004;99:249–254.

CHAPTER 9

How to Perform EUS in the Stomach

Robert H. Hawes | Shyam Varadarajulu | Paul Fockens

The two basic techniques for examining the stomach are the balloon inflation procedure and the water-filled stomach method. Both methods can be employed with either the linear or the radial echoendoscope, but examination with the radial scope is easier and more efficient because of the larger viewing field. The balloon inflation method is preferred for rapid screening for submucosal lesions and for examination of perigastric structures (Fig. 9.1). The water-filled method is best for examining the gastric wall layers and for careful and accurate evaluation of specific lesions (Fig. 9.2). With the balloon inflation technique, the tip of the echoendoscope is advanced to the immediate prepyloric antrum. The balloon is fully inflated, and continuous suction is applied to remove air from the gastric lumen. When the gastric wall is completely collapsed around the balloon, the balloon is centered as well as possible, and slow withdrawal is performed.

When learning EUS, it is critical that images are displayed in a standard orientation. In the case of gastric imaging, the liver is easily recognized and should be electronically rotated until it is positioned in the 9- to 12-o'clock space. This orientation will cause the pancreas to emerge at the 6-o'clock position on withdrawal, and the spleen and left kidney will appear between 12 and 4 o'clock. The examiner's eyes should then be fixed on both the gastric wall and the perigastric structures. If a lesion or abnormality is recognized, then specific maneuvers can be applied to obtain detailed imaging.

With the water-filled method, the stomach is collapsed (removing all air), and 200 to 400 mL of fluid are instilled into the gastric lumen (see Fig. 9.2). High-quality imaging of the gastric wall requires attention to detail on two points: (1) the transducer must be positioned at a perpendicular angle to the gastric wall or a specific lesion (Video 9.1) and (2) the tip of the echoendoscope must be positioned within the focal zone of the transducer (see Chapter 1). This second point is absolutely critical when using the mechanical radial echoendoscope but is less important with electronic radial instruments. To obtain superfine images with the water-filled method, one should consider using an agent to paralyze peristalsis and instill water into the gastric lumen in a way that minimizes the production of microbubbles (slow infusion versus a water jet technique).

The difficulty or impossibility of obtaining perpendicular images in some areas presents a significant challenge in gastric endoscopic ultrasonography (EUS). An example is the gastric antrum. It may be impossible to adjust the tip deflection in a way that positions the transducer perpendicular to the antral wall while at the same time not pressing the transducer against the wall. The consequence of an inability to achieve optimal orientation between the transducer and the surface of the stomach is tangential imaging. If the ultrasound waves pass tangentially across the gastric wall, the layers will appear abnormally thick. This appearance can lead to overstaging of early gastric cancer or

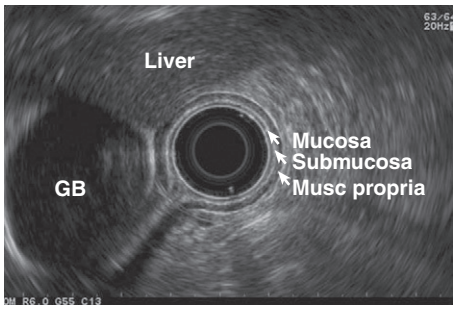


FIGURE 9.1 Balloon inflation method. Gastric wall layers as imaged using a radial echoendoscope. GB, gallbladder.

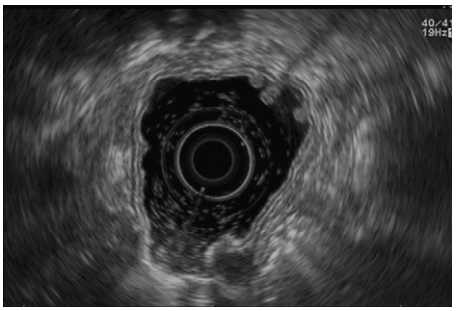


FIGURE 9.2 Water-filled method. With the radial echoendoscope positioned in the gastric lumen and the stomach filled with water, the individual layers of the gastric wall can be well visualized.

inaccurate determination of the layer of origin in submucosal masses. With large bulky tumors, in which one is trying to differentiate stage T3 from stage T4, this is less of an issue than with very superficial lesions in which one is trying to determine whether endoscopic mucosal resection (EMR) is appropriate. In the antrum, it is sometimes easier to use a dual-channel endoscope and a high-frequency catheter probe to achieve good positioning (Video 9.2; Fig. 9.3). However, if the lesion is large, the depth of penetration of the catheter probe will be insufficient for accurate staging.

SUMMARY

Two techniques are described for gastric imaging using standard echoendoscopes. Attention to proper technique is critical to accurate imaging. Evaluation of large lesions (>2 cm), global imaging of the stomach, and assessment of the perigastric space are best accomplished with standard echoendoscopes. Imaging of small lesions in which it is advantageous to obtain simultaneous endoscopic and ultrasound images is best accomplished with catheter probes in conjunction with dual-channel endoscopes.

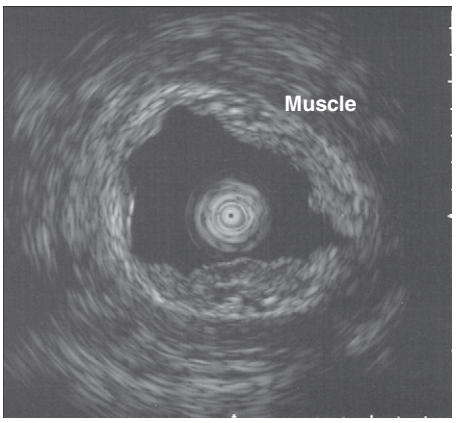


FIGURE 9.3 Imaging in the gastric antrum. Gastric wall layers as visualized using a high-frequency catheter probe with the water-filled technique.

CHAPTER 10 SUBMUCOSAL LESIONS

Eun Young (Ann) Kim

Key Points

EUS can accurately differentiate a mural lesion from extrinsic compression against the gut wall.

Determination of the cause of an intramural lesion is based on its layer of origin and internal echo characteristics.

The finding of an intact submucosal layer running deep into a mural lesion indicates that the lesion can be removed safely by endomucosal resection.

Carcinoid tumors can usually be diagnosed with standard mucosal biopsies because these tumors emanate from the deep mucosal layer.

*Leiomyomas can be differentiated from gastrointestinal stromal tumors by immunohistochemical staining for the c-*kit *proto-oncogene protein (also known as CD117).*

INTRODUCTION

The term *submucosal lesion* is used by endoscopists to describe any bulge covered with normal mucosa, usually found incidentally during gastrointestinal (GI) endoscopy or barium contrast radiography. Actually, this lesion could be either an intramural subepithelial mass or an impression caused by extramural structures. In the past, the prevalence of suspected gastric submucosal lesions at routine endoscopy was reported to be as low as 0.36%.[1] More recently however, the detection rate notably increased, especially with regard to small lesions, and the advances in technology and close attention paid to these lesions may be praised for this improvement.

To characterize the cause of protrusion, some noninvasive imaging methods, such as transabdominal ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI), have been used, but they are often insufficient. With endoscopic ultrasonography (EUS), however, the clinician can visualize the structure of gut wall layers clearly. Thus, EUS can not only differentiate subepithelial lesions from extramural structures, but also identify the layers of origin and endosonographic characteristics of intraluminal lesions.[2–7] EUS is now accepted as the modality of choice for visualization of submucosal lesions with high precision.

The differential diagnosis of submucosal lesions includes a wide variety of benign and malignant subepithelial neoplasms, as well as non-neoplastic lesions. To evaluate submucosal lesions, the transition zone (the area where the tumor arises from normal gut wall layers) should be examined carefully to determine the layer of origin. Next, the size and echo pattern of the tumor, such as the smoothness of the border, internal features, echogenicity, and vascularity, should be observed. In addition, the relationship with other adjacent organs and the presence of adenopathy nearby provide valuable information. From the information gathered, an educated guess on the submucosal tumor for the differential diagnosis can be made with reasonable accuracy (Table 10.1).[7] The reported accuracy of EUS in predicting the pathologic diagnosis of subepithelial lesions is 75% to 79%.[8,9] Diagnostic information on the submucosal mass, including the origin of the wall layer provided by EUS, also helps in deciding whether a lesion should be removed or followed in situ.[10,11] Lesions confined to the mucosal or submucosal layers can be safely removed endoscopically. Surgical resection, if needed, is generally recommended for lesions located in muscularis propria, although advances in endoscopic techniques such as endoscopic submucosal dissection (ESD) have made it possible for these lesions to be removed by experienced clinicians with no significant risk to the patient.[12,13]

COMPARISON OF ACCURACY BETWEEN EUS AND OTHER IMAGING MODALITIES

Differentiation of submucosal lesions is one of the main indications for EUS. Compared with endoscopy, barium contrast radiography, ultrasonography, CT, and MRI, EUS has a higher accuracy in detecting and assessing the size and location of subepithelial lesions.[14] When viewed endoscopically, the surface of submucosal lesions is usually smooth and has a color similar to that of the surrounding mucosa, without ulceration or erosion. Sometimes these lesions show a slight color change and certain morphologic characteristics, but it is often impossible to differentiate them by endoscopy alone. Ultrasonography provides diagnostic information only for very large submucosal lesions. In a study of patients with endosonographically diagnosed gastric submucosal lesions, 82.5% of tumors were visualized and measured by ultrasonography after the stomach was filled with water.[15] Like CT and MRI, ultrasonography can also provide useful information on perigastric structures. In one study using preoperative CT, large submucosal tumors previously identified by EUS were visualized in only two thirds of cases.[14] However, CT and MRI were able to detect large lipomas and malignant GI stromal tumors (GISTs), especially tumors with metastatic spread.[16–18]

In addition to detection, only EUS can establish the precise location of the lesion within the GI wall and provide information on the sonographic characteristics of the submucosal tumor.

TABLE 10.1

EUS Characteristics of Various Submucosal Tumors

Cause	EUS Layers*	EUS Appearance
Gastrointestinal stromal tumor	Fourth (rarely second)	Hypoechoic (irregular borders, echogenic foci, anechoic spaces suggest malignancy)
Leiomyoma	Fourth, second	Hypoechoic
Aberrant pancreas	Second, third, and/or fourth	Hypoechoic or mixed echogenicity (anechoic ductal structure may be present)
Lipoma	Third	Hyperechoic
Carcinoid	Second and/or third	Mildly hypoechoic, homogeneous
Granular cell tumor	Second or third	Homogeneous hypoechoic mass with smooth borders
Cyst	Third	Anechoic, round or oval (three- or five-layer walls suggest duplication cyst)
Varices	Third	Anechoic, tubular, serpiginous
Inflammatory fibroid polyp	Second and/or third	Hypoechoic, homogeneous or mixed echogenicity, indistinct margin
Glomus tumor	Third or fourth	Hypoechoic, smooth margin, internal heterogeneous echo mixed with high echoic spots
Lymphoma	Second, third, and/or fourth	Hypoechoic
Metastatic deposits	Any or all	Hypoechoic, heterogeneous

*First layer, interface of luminal fluid and mucosa; second layer, deep mucosa; third layer, submucosa; fourth layer, muscularis propria; fifth layer, serosa or adventitia.

The narrow differential diagnosis of subepithelial lesions afforded by the use of EUS enhances appropriate management decision making. Based on EUS, the clinician can decide between observation with re-examination, in patients with suspected benign lesions, and resection, when the lesion is likely to be malignant.

In the differentiation between submucosal lesions and extraluminal compression, EUS also demonstrates higher accuracy than endoscopy, ultrasonography, and CT. In a multicenter study, endoscopy was able to differentiate submucosal lesions from extraluminal compressions with sensitivity and specificity of 87% and 29%, respectively.[19] In another study,[20] ultrasonography and CT established the diagnosis in only 16% of cases, compared with 100% for EUS. Another comparison of ultrasonography, CT, and EUS reported an accuracy of 22%, 28%, and 100%, respectively, in differentiating submucosal tumors and extraluminal compressions.[21]

EXTRAMURAL LESIONS

EXAMINATION CHECKLIST

Check the integrity of the five wall layers between the lesion and the gut lumen.

Because EUS is able to visualize the gut wall layers in detail, it can readily differentiate the intramural and extramural nature of submucosal mass-like lesions. When EUS demonstrates the integrity of all gut wall layers between the gut lumen and the lesion, it is safe to say that the lesion is an impression caused by an extramural structure.

Although the extramural structures that compress the gut wall are on occasion pathologic masses, such findings are more likely to represent adjacent normal structures[19,22] (Table 10.2). A normal spleen usually makes an impression in the gastric fundus and upper body (Fig. 10.1), and the gallbladder compresses the gastric antrum. Transient gastric impression is often caused by bowel loops. Other causes of gastric impression include vessels in the splenic hilum, the pancreatic tail, and the left lobe of the liver. Abnormal structures such as pancreatic pseudocysts, splenic artery aneurysm, aortic aneurysm, cystic tumor of the pancreas or liver, colonic tumors, and lymphoma may also produce endoscopically visible impressions on the gastric wall. Adjacent structures, such as the aortic arch and vertebrae, can also press on the esophagus. Other potential causes of esophageal impression are vascular anomalies, such as a right descending aortic arch, anomalous branches of the aortic arch, aneurysm, and left atrial dilation.

TABLE 10.2

Causes of Extraluminal Compression Mimicking Submucosal Lesion

Normal Organ	Pathologic Condition
Liver	Pancreatic cystic tumor
Spleen	Pancreatic pseudocyst
Blood vessel	Hepatic cyst
Gallbladder	Vascular anomaly including aneurysm
Pancreas	Lymphoma
Bowel loop	Colonic tumor
Vertebra	Mediastinal tumor or lymphadenopathy
Kidney	Lung cancer

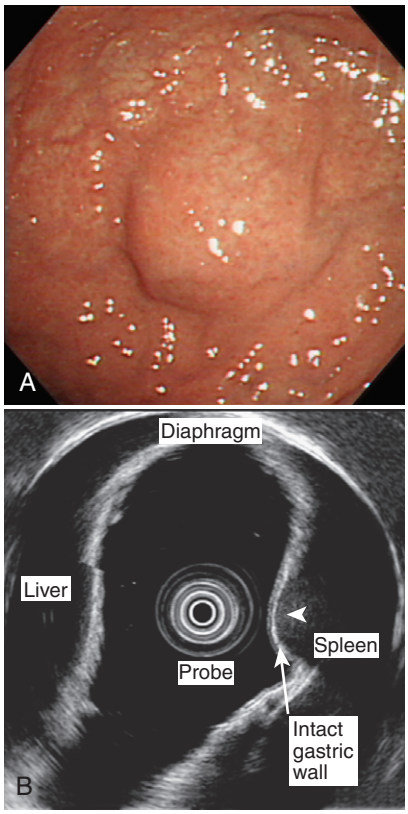


FIGURE 10.1 Extraluminal compression. A, Endoscopic image of gastric wall compression by normal spleen. An ill-defined, elevated area is seen at the gastric fundus. **B,** Endosonographic view of spleen *(arrow)* compressing the gastric wall.

Enlarged mediastinal lymph nodes or mediastinal tumors, lung cancer, and lymphomas are also known to compress the esophagus.

When using EUS, the suspected area of gastric impression should be observed by the two-step method. First, at a low frequency of 7.5 MHz, the examiner should survey the gross relationship between the extramural structure and the gut wall. Then, at a higher frequency of 12 MHz, the outer hyperechoic serosal layer should be observed carefully to determine whether it is intact or disrupted. This method allows reliable differentiation between gastric wall impression and gastric wall infiltration caused by an extragastric tumor. For examination of small lesions, a high-frequency catheter ultrasound probe is technically easier to use than is a conventional echoendoscope. In the esophagus, the endosonographer may encounter difficulties in this evaluation owing to interference from the air-filled bronchial system.

EVALUATION OF SUBMUCOSAL LESIONS

EXAMINATION CHECKLIST

Carefully examine the transition zone between the normal gut wall and the lesion, to determine the layer of origin.
Measure the size of the lesion and observe the echo pattern (e.g., echogenicity, internal features, vascularity, and smoothness of the border).
Check the presence of adjacent lymphadenopathy.
Small lesions measuring less than 1 to 2 cm may be better imaged using high-frequency catheter ultrasound probes.
For clear imaging of the wall layers and evaluation of submucosal lesions, it may be necessary to instill water or jelly in the luminal tract to obtain better acoustic coupling. Aspiration precautions should be taken under these circumstances.

GASTOINTESTINAL STROMAL TUMOR

DIAGNOSTIC CHECKLIST

Origin in second or fourth gastric wall layer
Well-circumscribed, hypoechoic, relatively homogeneous mass
If malignant, noticeable characteristics including large size, features of heterogeneous echo texture with hyperechoic foci and/or anechoic necrotic zones, irregular extraluminal border, and adjacent malignant-looking lymphadenopathy

GISTs are some of the most common mesenchymal tumors in the GI tract, and they are also the most commonly identified intramural subepithelial mass in the upper GI tract. Previously, these tumors were classified as GI smooth muscle tumors, such as leiomyomas and leiomyosarcomas, owing to histologic findings of circular palisades of spindle cells with prominent nuclei and apparent origin in the muscularis propria layer of the gut wall. However, with the development of newer molecular markers and an improved understanding of the biologic behavior of these tumors, GISTs are now classified as a distinct but heterogeneous group of mesenchymal tumors with varying differentiation. Interstitial cells of Cajal, also known as pacemaker cells of the GI tract, are now believed to be the precursor of GISTs that typically expresses KIT, transmembrane tyrosine kinase receptor. With immunohistochemical staining techniques, most GISTs stain positive for CD117, epitope of KIT protein, and, sometimes, CD34 but negative for desmin. Leiomyomas express smooth muscle actin and desmin, however, and schwannomas produce S-100 protein and neuron-specific enolase.[23]

According to the more recent classification, approximately 80% of GI mesenchymal tumors are GISTs, and approximately 10% to 30% of GISTs are malignant.[24] Leiomyomas are the most common mesenchymal tumors in the esophagus, but they rarely occur in the stomach and small bowel. In contrast, GISTs are rare in the esophagus and are more common in the stomach (60% to 70%) and small bowel (20% to 25%).[25]

The most common symptoms associated with GISTs are vague abdominal discomfort and pain, but most lesions are small (<2 cm) and asymptomatic. Larger lesions (>2 cm) may be ulcerated on top of the mass, and patients may present with bleeding or anemia. Occasionally, GISTs cause intestinal obstruction.

In defining the prognosis of patients with GIST, it has been recommended that a "grading as to the risk of aggressive behavior" be used instead of the term *benign*. This means that no GIST can be definitively labeled as benign, and all are considered to have some malignant potential. Pathologists classify GISTs as "very low risk," "low risk," "intermediate risk," and "high risk" according to the size of the mass and the mitotic count of the resected specimen.[26]

Endosonographically, a GIST is typically a well-circumscribed, hypoechoic, relatively homogeneous mass that can arise from either the second hypoechoic layer (muscularis mucosa) (Fig. 10.2) or, more frequently, the fourth hypoechoic layer (muscularis propria) (Fig. 10.3). In contrast, leiomyomas arise from muscularis mucosa more frequently than do GISTs. GISTs, leiomyomas, and schwannomas cannot definitely be differentiated with EUS without special immunohistochemical tissue staining. One study suggested that GISTs have a marginal hypoechoic halo and relatively higher echogenicity compared with the adjacent muscular layer.[27] Another study added inhomogeneity and hyperechoic spots to the foregoing features, and the presence of at least two of these four features predicted GISTs with 89.1% sensitivity and 86.7% specificity.[28] In addition to EUS, EUS-guided fine-needle aspiration (EUS FNA) and EUS-guided Tru-Cut biopsy (EUS TCB) can be performed for immunohistochemical examination to achieve better diagnostic accuracy (Table 10.3).[29–36]

When malignant changes occur (Box 10.1), GISTs commonly show heterogeneous echo texture with hyperechoic deposits or anechoic necrotic zones inside large tumors (Fig. 10.4). In one report, EUS findings of tumor size greater than 4 cm, an irregular extraluminal border, echogenic foci, and anechoic spaces were strong indicators of malignancy.[37] Sensitivity ranged between 80% and 100% in detecting malignancy when at least two out of four features were present.[37] Another study found a correlation with malignancy when irregular extraluminal margins, cystic spaces, and lymph nodes were seen. The presence of two out of these three features had a positive predictive value of 100% for malignant or borderline-malignant tumors.[38] Nonetheless, a lack of defined risk factors could not exclude a malignant potential. A multicenter study reported that malignancy or indeterminate GIST status correlated with the presence of ulceration, tumor size larger than 3 cm, irregular margins, and gastric location but not with hyperechoic or hypoechoic internal foci.[39] A major drawback of EUS FNA is its inability to differentiate with absolute certainty benign from malignant GISTs. However, staining for ki-67 (MIB-1), a marker of cell proliferation, may enable the discrimination of benign from malignant GIST with EUS FNA.[34,35] The role of EUS-guided FNA is described later.

Because small (<1 cm), asymptomatic mesenchymal tumors are rarely malignant, a policy of close follow-up with EUS may be justified, although an optimal surveillance strategy has not yet been established. Excision is advised when growth of the lesion, a change in the echo pattern, or necrosis is noted during yearly follow-up with EUS. Surgical treatment is indicated for lesions greater than 3 cm in diameter with features suggestive of malignancy. For lesions

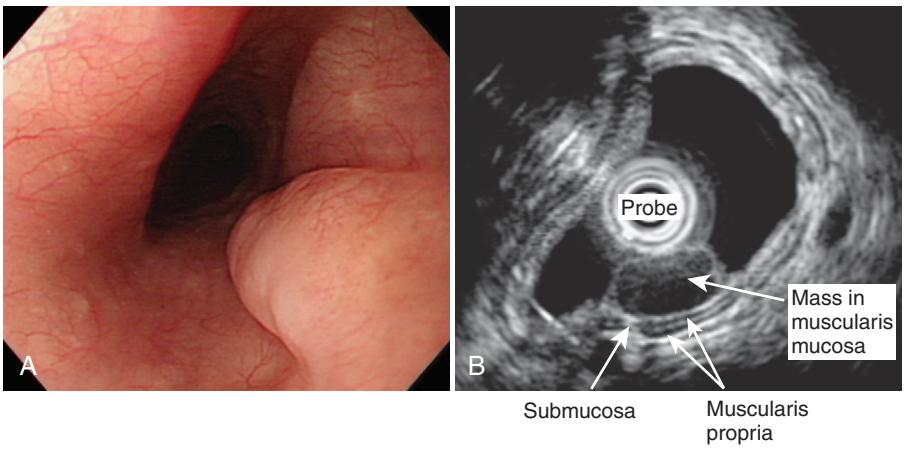


FIGURE 10.2 Esophageal leiomyoma. A, Endoscopic image shows an elongated submucosal lesion visible in the midesophagus. **B,** Endosonographic view using a 20-MHz catheter probe. The lesion is homogeneous, hypoechoic, and associated with muscularis mucosa.

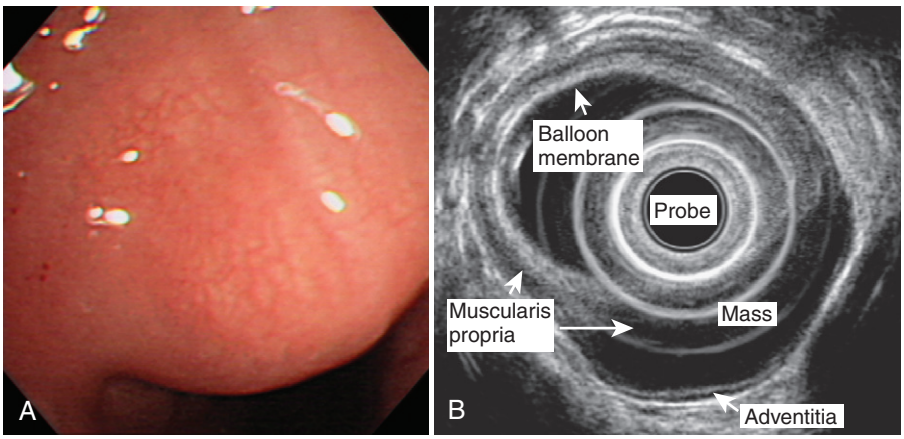


FIGURE 10.3 Esophageal benign gastrointestinal stromal tumor (GIST). A, Endoscopic finding of histologically proven esophageal benign GIST. **B,** Radial scanning EUS image showing a homogeneous, hypoechoic mass arising from the fourth sonographic layer, corresponding to the muscularis propria.

TABLE 10.3

Diagnostic Accuracy of EUS and EUS Fine-Needle Aspiration for Gastrointestinal Stromal Tumors

Authors (yr)	No. of Patients	Accuracy (%)	Diagnostic Method
Sepe et al[29] (2009)	37	78	EUS FNA*
Chatzipantelis et al[30] (2008)	17	100	EUS FNA*
Akahoshi et al[31] (2007)	28	97	EUS FNA*
Mochizuki et al[32] (2006)	12	83	EUS FNA*
Vander Noot et al[33] (2004)	28	94	EUS FNA*
Okubo et al[34] (2004)	14	79	EUS FNA†
Ando et al[35] (2002)	23	91	EUS FNA‡
Brand et al[36] (2002)	44	87	EUS*
Ando et al[35] (2002)	23	78	EUS‡

*For diagnosis of GISTs.
†For differentiating between low-grade and high-grade malignancy of GISTs.
‡For differentiating between benign and malignant GISTs.
FNA, fine-needle aspiration; GIST, gastrointestinal stromal tumor.

between 1 and 3 cm, EUS FNA can be recommended, or ESD can be chosen as a definite diagnostic and therapeutic tool with some risk of bleeding and perforation (2% to 3%, in specialized centers). When the lesion is confirmed to be a GIST, the risk of malignant transformation needs to be discussed with the patient; more careful follow-up or early resection should be considered.

BOX 10.1 EUS FEATURES SUGGESTIVE OF MALIGNANT GIST

Size >4 cm
Irregular borders
Mixed echogenicity
Cystic spaces
Adjacent lymph nodes

ABERRANT PANCREAS

DIAGNOSTIC CHECKLIST

Origin in the second, third, and/or fourth layers
Hypoechoic or mixed echogenicity with internal anechoic ductal structure

The term *aberrant pancreas* is used to describe ectopic pancreatic tissue lying outside its normal location with no anatomic or vascular connection to the pancreas proper. These lesions are also termed *ectopic pancreas, pancreatic rest,* and *heterotopic pancreas.* They are typically discovered incidentally during endoscopy, surgery, or autopsy. Aberrant pancreas is encountered in

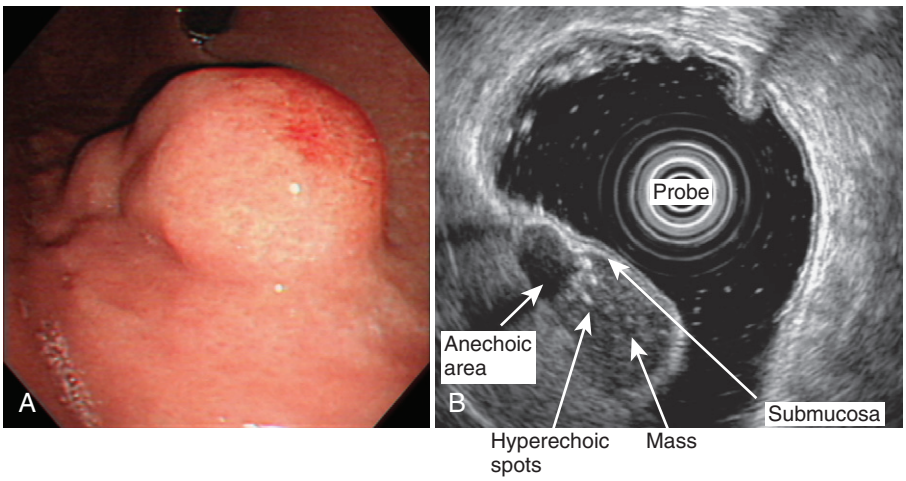


FIGURE 10.4 Malignant gastrointestinal stromal tumor (GIST) of the stomach. A, Endoscopy shows a submucosal mass in the body of the stomach. **B,** Radial scanning EUS image of histologically proven malignant GIST showing hyperechoic spots and an anechoic area. The mass is contiguous with the fourth sonographic layer.

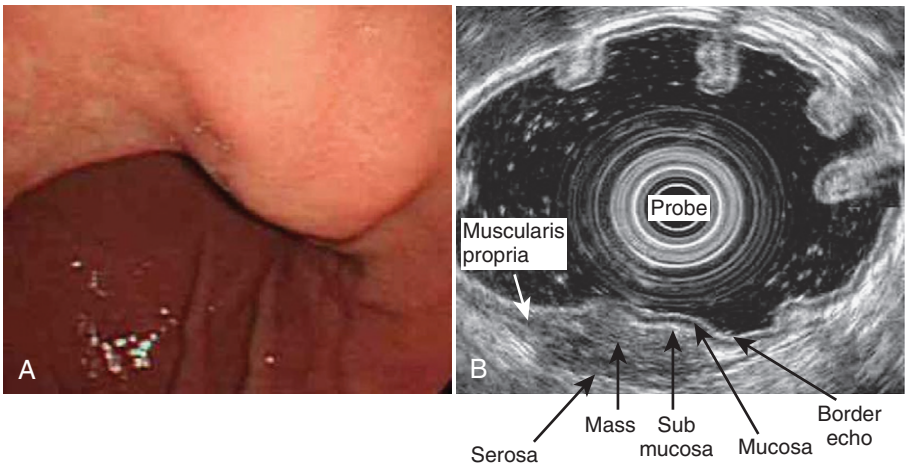


FIGURE 10.5 Aberrant pancreas. A, Endoscopic image of an indistinct submucosal lesion. **B,** Corresponding EUS image showing an ill-defined, slightly hypoechoic, inhomogeneous mass involving the third and fourth gastric layers.

approximately 1 of every 500 operations performed in the upper abdomen, and the incidence in autopsy series has been estimated to be between 0.6% and 13.7%.[40] Aberrant pancreas is usually located in the stomach wall (frequently along the greater curvature of the antrum), duodenum, small intestine, or anywhere in the GI tract. Patients with aberrant pancreas are usually asymptomatic, but rare complications are pancreatitis, cyst formation, ulceration, bleeding, gastric outlet obstruction, obstructive jaundice, and malignancy.[41]

On endoscopy, an aberrant pancreas appears as a submucosal nodule, usually small, with a characteristic central umbilication that corresponds to a draining duct. The characteristic EUS features of aberrant pancreas are heterogeneous lesions, mainly hypoechoic or intermediate echogenic masses accompanied by scattered small hyperechoic areas, with indistinct margins within the gut wall (Fig. 10.5). Generally, an anechoic area and fourth layer thickening accompany the lesions. Anechoic cystic or tubular structures within the lesion correlate with ductal structures. They commonly arise from the third and fourth layers.[42] However, lesions may develop in any location from the deep mucosal to the serosal layer.

The management of aberrant pancreas remains controversial. It should be guided by symptoms and the possibility of malignancy. Asymptomatic lesions do not necessarily require resection and can be followed expectantly. If needed, endoscopic removal is useful for both accurate diagnosis and treatment, although surgical resection is preferred to endoscopic resection when the muscularis propria is involved.

LIPOMA

DIAGNOSTIC CHECKLIST

Origin in the third layer
Hyperechoic, homogeneous lesion with regular margins

Lipomas are benign tumors composed of mature lipocytes. They are found incidentally in any part of the GI tract, more frequently in the lower tract. Lipomas are rarely symptomatic, but they may result in hemorrhage, abdominal pain, and intestinal obstruction.[43]

Endoscopically, most lipomas are solitary, with a smooth bulge and a yellow hue. They are soft and indented when pressed with biopsy forceps (pillow or cushion sign). On endosonography, lipomas characteristically appear as intensely hyperechoic, homogeneous lesions with clean regular margins arising from the third layer of the GI tract, which corresponds to the submucosa (Fig. 10.6).[44,45] The endoscopic and endosonographic characteristics make it possible to diagnose lipoma in most cases. Once lipoma has been confirmed, follow-up EUS is not recommended. The incidentally found lipoma does not require treatment, but local excision is advised for symptomatic lipomas associated with bleeding or obstruction. Resection is also recommended when it is impossible to distinguish between a lipoma

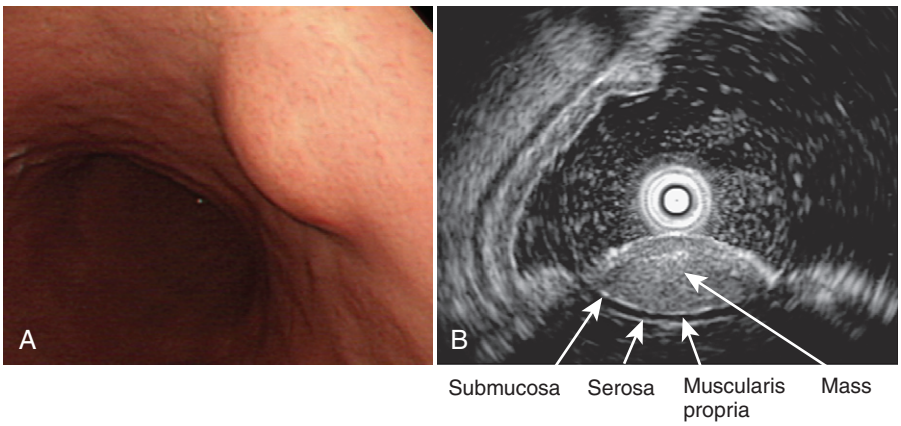


FIGURE 10.6 Gastric lipoma. A, Endoscopic view of a slightly elevated lesion covered with normal mucosa. **B,** Endosonogram showing a homogeneous, hyperechoic mass with smooth borders within the third gastric wall layer.

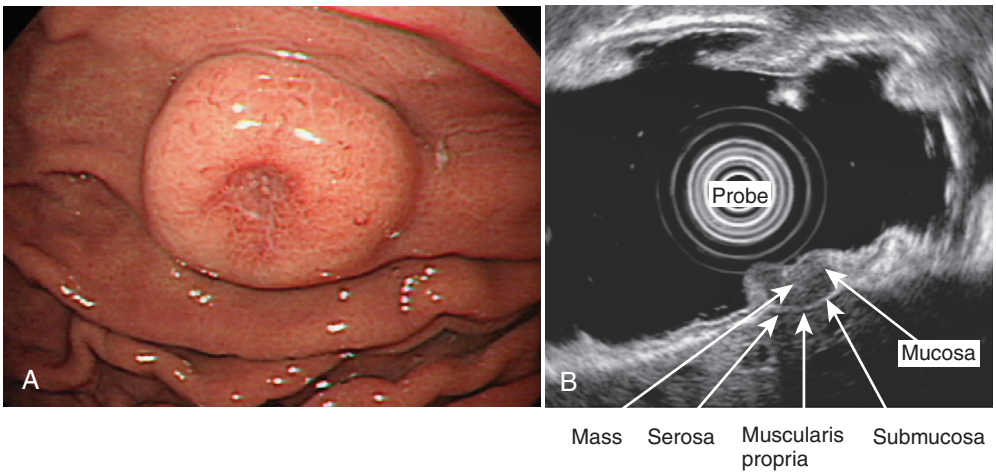


FIGURE 10.7 Gastric carcinoid tumor. A, Endoscopic image of a round, umbilicated, submucosal lesion in the gastric body. **B,** Endosonographic view of a homogeneous, hypoechoic, umbilicated mass within the second sonographic layer.

and a malignant neoplasm, such as a liposarcoma, even though this lesion is rare in the GI tract.[46]

CARCINOID TUMOR

DIAGNOSTIC CHECKLIST

Origin in the second layer
Homogeneous, well-demarcated, and mildly hypoechoic or isoechoic lesion

Carcinoid tumors are slow-growing neuroendocrine tumors with malignant potential. They may arise at various sites, most commonly the GI tract and lung. GI carcinoid tumors are generally discovered incidentally during endoscopy, surgery, or autopsy from the appendix, rectum, stomach, and small intestine. Rectal carcinoids are common and represent approximately 20% of all GI carcinoid lesions. Carcinoid tumors are usually asymptomatic, but rare complications include hemorrhage, abdominal pain, intestinal obstruction, and the endocrine carcinoid syndrome that results from secretion of functionally active substances.

Endoscopically, carcinoid tumors are small, round, sessile, or polypoid lesions with a smooth surface and a yellow hue. They usually have normal overlying mucosa and seldom ulcerate. Gastric and ileal carcinoids are commonly multiple, whereas those arising elsewhere are typically solitary. The endosonographic appearance of carcinoids is usually that of a homogeneous, well-demarcated, and mildly hypoechoic or isoechoic mass (Fig. 10.7). These lesions arise from the second layer of the GI tract and may invade beyond the third submucosal layer.[47] Deep mucosal biopsy is normally diagnostic. EUS accurately defines the size and extent of masses and can guide management. When the lesion is smaller than 2 cm, it does not invade further than the third layer, and no adenopathy is noted, endoscopic resection is possible.[8,48,49]

GRANULAR CELL TUMOR

DIAGNOSTIC CHECKLIST

Origin in the second or third layer
Hypoechoic, homogeneous lesion with smooth margins

Granular cell tumors (GCTs) are rare lesions of neural derivation, as supported by immunophenotypic and ultrastructural evidence. Granularity of tumor cells results from the accumulation of secondary lysosomes in the cytoplasm. Visceral involvement is encountered as mucosal or submucosal nodules anywhere in the GI tract, larynx, bronchi, gallbladder, and biliary tract. Approximately 2.7% to 8.1% of GCTs will involve the digestive tract, and these tumors are multiple in approximately 5% to 12% of patients. GCTs are usually found incidentally during endoscopy or colonoscopy and are located mostly in the esophagus; other locations include the stomach (10%) and rarely the colon or rectum.[50] GCTs are generally considered benign, but in 2% to 3% of cases they are malignant.[51]

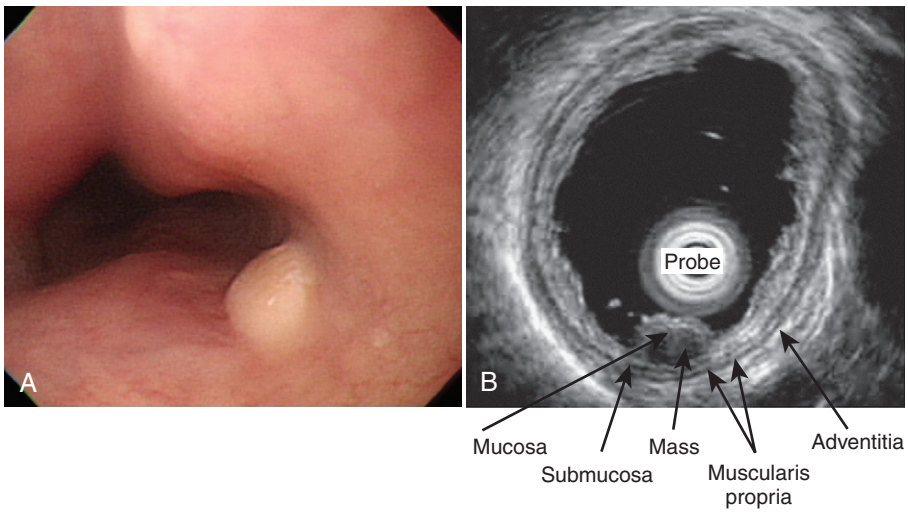


FIGURE 10.8 Granular cell tumor of the esophagus. A, Small, round, molar tooth–like, polypoid lesion in the esophagus. **B,** Endosonographic image acquired with a 20-MHz miniprobe shows the nine-layered structure of the esophageal wall. A homogeneous, hypoechoic lesion with smooth margins is noted within the fourth layer.

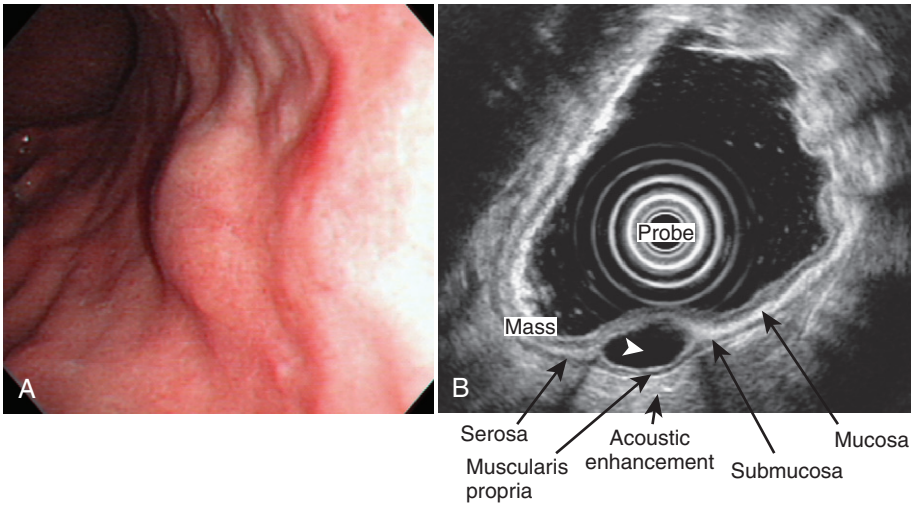


FIGURE 10.9 Gastric cyst. A, Endoscopic view of a smooth bulge in the body of the stomach. **B,** EUS revealed a sharply demarcated, anechoic, ovoid structure within the third gastric wall layer.

The endoscopic appearance of GCTs is that of small, isolated nodules or polyps resembling molar teeth, with normal overlying mucosa having a yellow hue. Most GCTs are small (<4 cm), but larger size is associated with malignant potential. At EUS, GCTs appear as hypoechoic, homogeneous lesions with smooth margins originating from the second or third layer of the GI tract (Fig. 10.8).[52] One study using EUS examined 15 patients with 21 GCTs and found that tumor size was less than 2 cm in 95% of cases. In all patients, echo patterns were hypoechoic and solid. The tumors arose in the inner layers in 95% (second layer, 15; third layer, 5).[53]

For asymptomatic GCTs that are not excised, surveillance EUS every 1 to 2 years is recommended to monitor changes in size. Local endoscopic snare excision can be performed for small tumors limited to the mucosa.

CYSTS INCLUDING DUPLICATION CYST

DIAGNOSTIC CHECKLIST

Origin in the third layer
Anechoic, round or oval lesion showing posterior acoustic enhancement (if the lesion has three- or five-layered walls, this suggests a duplication cyst)
Antibiotics indicated for EUS fine-needle aspiration of a bronchogenic cyst

Endosonographically, cysts in the GI tract appear as anechoic structures. Cystic submucosal tumors may be classified into three EUS types[54]: simple cystic, multicystic, and solid cystic tumors. The simple cystic type is frequently identified from cysts and, rarely, Brunner's gland hamartomas or heterotopic gastric mucosa. The multicystic type is common in lymphangiomas, gastric cystic malformations, hemangiomas, and Brunner's gland hamartomas. The solid cystic type includes duplication cysts, heterotopic gastric mucosa, aberrant pancreas, myogenic tumors with advanced cystic degeneration, and gastric tuberculomas.

Gastric cyst is a rare clinical entity and is usually asymptomatic. It may result from a resolved inflammatory process. Endosonographically, the cysts appear in the submucosal layer of the gastric wall as sharply demarcated, anechoic, rounded or ovoid structures with dorsal acoustic accentuation (Fig. 10.9). The inflammatory cyst always shows a single hyperechoic wall layer.

In adults, foregut cysts usually are asymptomatic and are discovered incidentally during radiographic or endoscopic examination. Foregut cysts are categorized on the basis of their anomalous embryonic origin into bronchogenic and neuroenteric cysts. Bronchogenic cysts represent 50% to 60% of all mediastinal cysts,[55] and they can be diagnosed easily with EUS (Fig. 10.10).

Duplication cysts may involve the entire GI tract, with the ileum the most common site. The stomach is the least common site for GI duplication cysts. When examined endoscopically, duplication cysts may have a slightly transparent appearance. EUS or EUS FNA (with antibiotic prophylaxis) is useful and safe

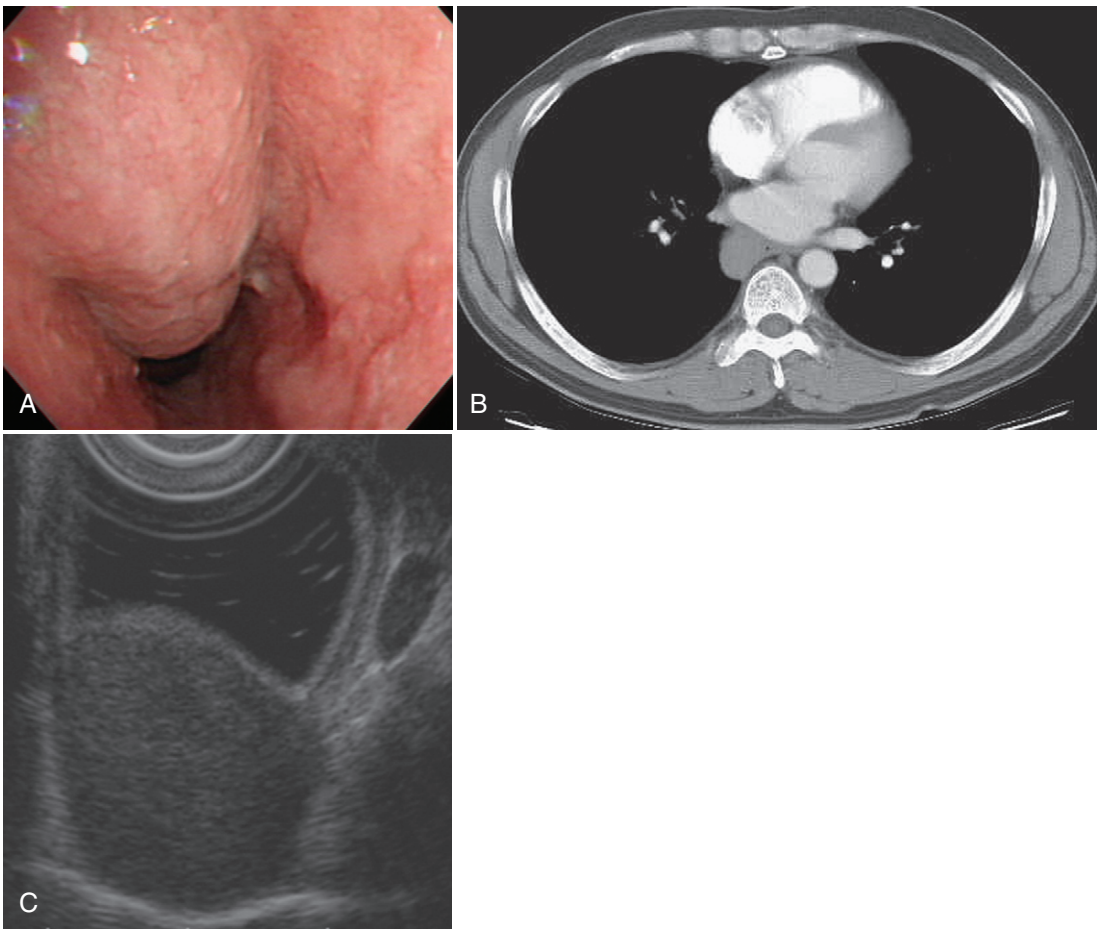


FIGURE 10.10 **Bronchogenic cyst. A,** Endoscopic view of a bulging mass lesion at the mid esophagus. **B,** The mass looks like a solid mass lesion on computed tomography. **C,** EUS demonstrates round homogeneous hypoechoic lesion in the mediastinum.

for the diagnosis of duplication cyst; some of these cysts are misdiagnosed as solid masses on CT or MRI.[56] Endosonographic findings of duplication cysts usually show anechoic, homogeneous lesions with regular margins arising from the third layer or extrinsic to the GI wall. The walls of duplication cysts may be shown as three- or five-layer structures because of the presence of the submucosa and muscle layer.[57,58] Duplication cysts are believed to have a low malignant potential, but case reports have described malignant transformation. Complications are rare and may include dysphagia, abdominal pain, bleeding, and pancreatitis when the cyst is located near the ampulla of Vater.

VARICES

DIAGNOSTIC CHECKLIST

Origin in the third layer
Anechoic, tubular, serpiginous lesion

Patients with portal hypertension may have varices. Gastric varices can be misdiagnosed endoscopically as submucosal tumors or thickened gastric folds. When varices are found incidentally during endoscopy in a patient with no relevant information, it is highly inappropriate and potentially hazardous to take a biopsy sample from such a lesion without EUS examination. On EUS, fundic varices appear as small, round to oval, and anechoic structures within the submucosa. They can be differentiated from submucosal cysts, which usually occur as solitary lesions, by their shape and easy compressibility using the ultrasound balloon. When gastric varices grow larger, they appear as anechoic, serpentine, tubular structures with smooth margins, accompanied by perigastric collateral vessels (Fig. 10.11). In severe portal hypertension, cross sections of multiple fundic varices may show a "Swiss cheese" pattern.[59] Demonstration of flow with Doppler examination is a definite clue for diagnosis.

In portal hypertensive gastropathy, EUS findings are often normal, and endosonographic intramural vessel changes are not usually observed. However, dilation of the azygos vein and thoracic duct and thickening of the gastric mucosa and submucosa have also been reported.[60] In comparative studies, EUS was inferior to endoscopy for detecting and grading esophageal varices, but it permitted detection of fundic varices earlier and more often than endoscopy in patients with portal hypertension.[61] EUS was used in the treatment of varices by making it possible to inject a sclerosing agent into perforating veins.[62]

INFLAMMATORY FIBROID POLYPS

DIAGNOSTIC CHECKLIST

Origin in the second and/or third layer
Hypoechoic, relatively homogeneous lesion with indistinct margins

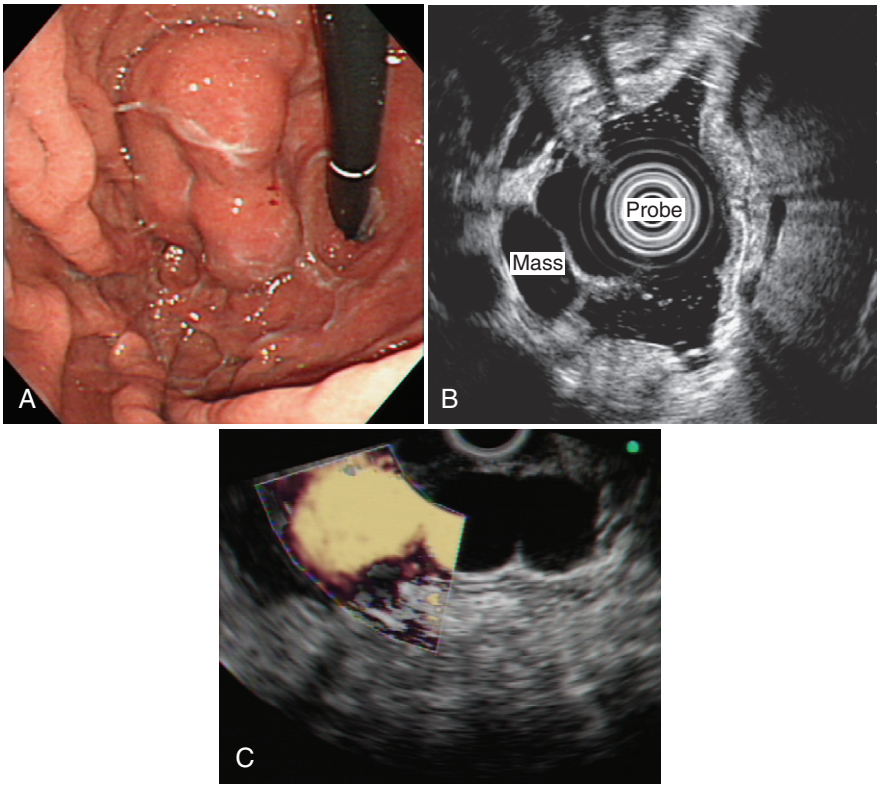


FIGURE 10.11 Gastric fundic varices. A, Endoscopic view of a large bulging mass lesion at the gastric fundus. **B** and **C,** EUS confirmed large, anechoic, tubular, submucosal vessels with multiple extramural collateral vascular structures.

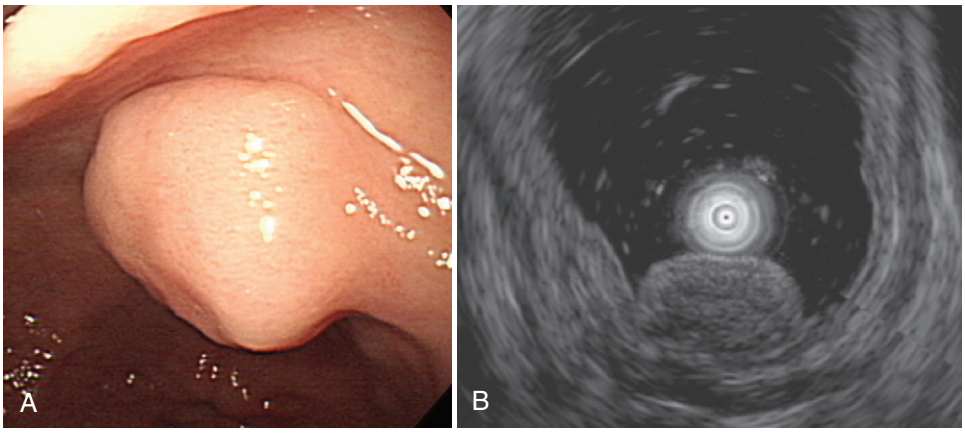


FIGURE 10.12 Inflammatory fibroid polyp. A, Endoscopic image of a small, round, polypoid lesion at the gastric antrum. **B,** Gastric EUS demonstrates a homogeneous hypoechoic lesion with indistinct margins located deep in the mucosal layer.

Inflammatory fibroid polyp is a rare benign polypoid lesion that is usually found in the stomach, occasionally in the small bowel, and rarely in the esophagus or large bowel.[63] The lesion is located in the second or third sonographic layer of the gastric wall, with an intact fourth layer. The usual echoendoscopic features of inflammatory fibroid polyp are indistinct margin and a hypoechoic and homogeneous echo pattern (Fig. 10.12). These findings correlate well with the histologic findings of proliferated, nonencapsulated fibrous tissue with vascular elements and eosinophilic infiltration, located in the deep mucosal and submucosal layers. Sometimes, the internal echo is heterogeneous or hyperechoic. In that case, the inner hyperechoic area and bright echoes correspond to the presence of many small blood vessels.[64]

The EUS patterns of leiomyomas originating from the muscularis mucosa and carcinoid tumors may be similar to that of inflammatory fibroid polyp. However, these tumors have a distinct margin.

RARE LESIONS

Many uncommon lesions have been reported in the endosonographic literature. The number of lesions is too small for their appearance on EUS to be described as characteristic. Some examples are provided here.

The glomus tumor of the stomach manifests as a circumscribed, low-echoic mass in the third or fourth layer; it has an internal heterogeneous echo mixed with high-echoic spots.[65] Glandular cysts appear as small, nodular to polypoid lesions in the body of the stomach. They create a uniform, relatively hyperechoic, internal echo pattern in the upper mucosa, but they do

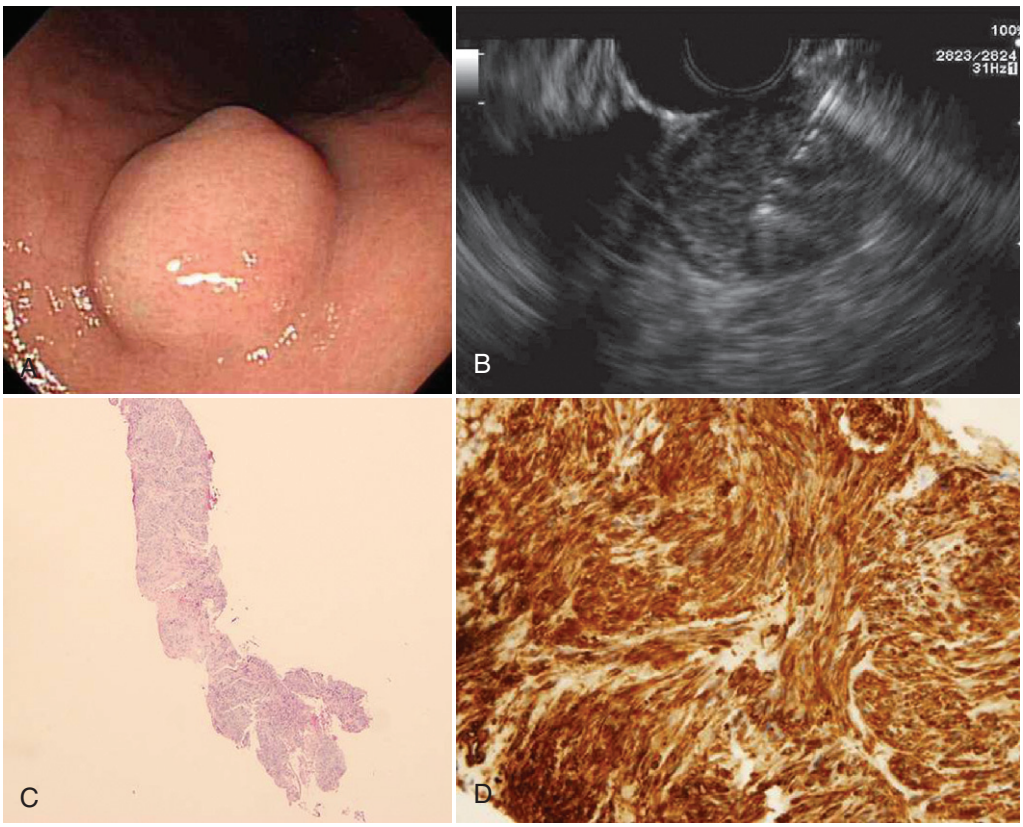


FIGURE 10.13 EUS-guided Tru-Cut biopsy of a gastric submucosal tumor. A, Endoscopic view shows round submucosal lesion at the lesser curvature side of gastric body. **B,** Tru-Cut needle is inserted into the mass with a linear echoendoscope. **C,** Gross finding of acquired tissue core. **D**, Immunohistochemical stains show a positive reaction of the tumor cells for CD117 and CD34.

not disrupt the normal layer pattern of the gastric wall.[59] Lymphoma may occasionally manifest as a submucosal mass. This mass typically appears as a homogeneous, hypoechoic lesion that is contiguous with the second and third gastric wall layers, but it can also invade down to deeper layers. Distant metastases may also appear as submucosal masses in the GI tract. At EUS, they are seen as hypoechoic, heterogeneous masses and may involve any or all of the sonographic layers.

Linitis plastica can sometimes be difficult to diagnose at endoscopy, and biopsy may be unrevealing. The mucosal and submucosal layers appear very thickened at EUS in these patients, who have poor distensibility of the GI lumen even with air insufflation. EUS FNA is diagnostic in most cases. Extrinsic malignant tumors that directly infiltrate the gut wall and manifest as submucosal lesions can be visualized easily by EUS.

TISSUE SAMPLING FOR HISTOLOGIC ASSESSMENT OF SUBEPITHELIAL LESIONS

During endoscopic examination of submucosal lesions, biopsy of the mucosa overlying the lesion is recommended to confirm the presence of intact epithelium. Nevertheless, when the lesion appears cystic or vascular, biopsy should not be attempted before EUS.

Some subepithelial masses arising from the lamina propria or muscularis mucosa may be diagnosed using standard endoscopic forceps biopsy. In particular, when the submucosal mass is ulcerated, careful biopsy provides an accurate diagnosis. However, for most submucosal lesions, the results of endoscopic biopsy are inconclusive. Trials with a bite-on-bite technique[66] or an unroofing and partial snaring technique[67] for submucosal lesions suggest better diagnostic yield than with standard forceps biopsy.

EUS FNA enables the procurement of tissue from submucosal masses for cytologic examination. However, the sensitivity, specificity, and accuracy of cytologic evaluation of intramural lesions are lower than are those of evaluations of lymph nodes or organs adjacent to the GI tract. In one study, the sensitivity of EUS FNA for mediastinal masses, mediastinal lymph nodes, celiac lymph nodes, pancreatic tumors, and submucosal tumors was 88%, 81%, 80%, 75%, and 60%, respectively.[68] To overcome some of the limitations of EUS FNA, EUS TCB was introduced. In EUS TCB, use of a needle with a guillotine tip yielded adequate tissue with no major complications in early reports (Fig. 10.13). [69,70] In some later prospective studies, however, the diagnostic yield of EUS TCB in patients with gastric submucosal lesions was not better than that of EUS FNA, and tissue core obtained with EUS TCB was not sufficient to examine mitotic index in GIST.[71,72] Complications of EUS FNA and EUS TCB include infection, bleeding, and perforation, but they are very rare.

The average reported accuracy of EUS FNA in the diagnosis of submucosal lesions is approximately 80% (Table 10.4).[8,31,33,70,72–76] EUS FNA with histologic and immunohistochemical analysis has a high reported accuracy in the differential diagnosis of mesenchymal tumors of the GI tract.[29–36] However, any form of needle biopsy carries the possibility of sampling error, and a negative finding does not exclude malignancy in GISTs. Because inoperable GIST can now be treated with imatinib, tyrosine kinase inhibitors that specifically block the KIT receptor, EUS-guided tissue diagnosis is useful for patients with GIST who have metastasis.

MANAGEMENT OF SUBEPITHELIAL LESIONS

Management of subepithelial lesions can be guided by EUS findings (Fig. 10.14). Extraluminal compression by adjacent organs and benign submucosal lesions such as lipoma or simple cyst do not need further treatment or follow-up. Pancreatic rest and inflammatory fibroid polyp can be followed in situ. Suspicious superficial lesions, such as carcinoid tumor, can be diagnosed with endoscopic biopsy. Biopsy should be avoided in lesions that are suspected varices. For deeply located hypoechoic lesions, EUS FNA or EUS TCB can be performed for tissue diagnosis. ESD can be used as a therapeutic tool for small mass lesions arising from the submucosal or inner circular muscularis propria layer, but attention should be paid to avoid tumor spillage.

Surveillance may be appropriate for subepithelial lesions without definite tissue diagnosis in patients who are at high operative risk. If the lesion is a suspected GIST, changes in size and echogenicity should be monitored. If the size increases or malignant features (echogenic foci, heterogeneity, internal cystic space, irregularity of extraluminal margins) develop, resection should be recommended. The follow-up interval depends on the index of suspicion of the examiner and is usually 1 year. When the characteristics of the lesion do not change for two consecutive follow-up examinations with EUS, a longer follow-up interval may be justified.[77]

TABLE 10.4

Diagnostic Accuracy of EUS and EUS Fine-Needle Aspiration for Gastrointestinal Submucosal Lesions

Authors (yr)	No. of Patients	Accuracy (%)	Diagnostic Method
Hoda et al[73] (2009)	112	84	EUS FNA
Polkowski et al[72](2009)	49	63	EUS TCB
Akahoshi et al[31] (2007)	51	82	EUS FNA
Chen and Eloubeidi[74] (2005)	42	98	EUS FNA
Vander Noot et al[33] (2004)	51	82	EUS FNA
Arantes et al[75] (2004)	10	80	EUS FNA
Levy et al[70] (2003)	5	80	EUS TCB
Kojima et al[8] (1999)	54	74	EUS
Matsui et al[76] (1998)	15	93	EUS FNA
Matsui et al[76] (1998)	15	60	EUS

FNA, fine-needle aspiration; TCB, fine-needle biopsy using a Tru-Cut needle.

SUMMARY

Subepithelial lesions involving the GI tract are difficult to diagnose definitively by conventional imaging methods such as GI radiography, ultrasonography, CT, and MRI. Endoscopic views are limited, and standard biopsy techniques have a low yield. EUS is an essential modality in the evaluation of these lesions. Any subepithelial lesion that appears to be larger than 1 cm on endoscopic examination, and is not regarded as a lipoma or cyst should be referred for EUS evaluation. With the unique ability of EUS to visualize the layers of the GI tract wall, to identify the layer of origin of the subepithelial lesion, and to assess the lesion's size, extent, and sonographic characteristics, a definitive diagnosis can be made in most cases.

Although a characteristic endosonographic appearance has been described for some submucosal lesions, EUS cannot reliably

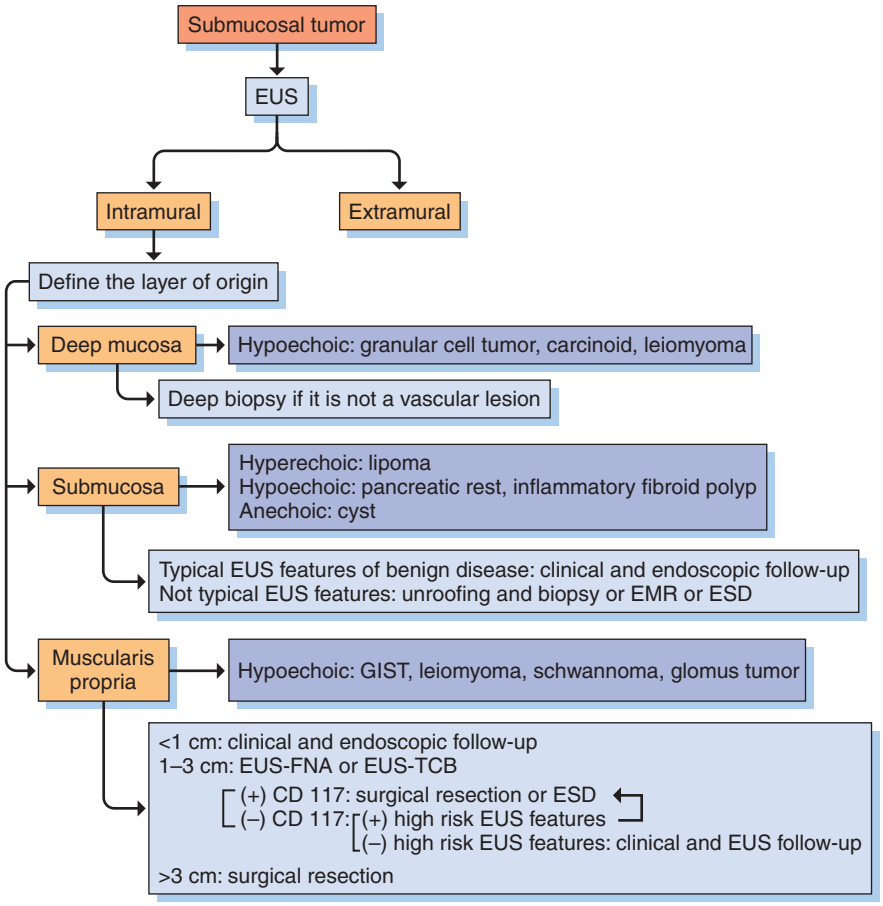


FIGURE 10.14 Algorithm for EUS-based management of different submucosal lesions based on appearance and wall layer origin. EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; FNA, fine-needle aspiration; GIST, gastrointestinal stromal tumor; TCB, Tru-Cut needle biopsy.

distinguish benign from malignant lesions, especially in terms of the malignant potential of GISTs. The addition of EUS FNA or EUS TCB can be helpful to obtain cytologic or histologic samples from submucosal lesions.

EUS is also helpful in the selection of patients for endoscopic resection because it can enable the examiner to determine the depth and originating wall layer of the lesion. EUS can also be used in the follow-up of submucosal tumors that are left in situ.

EXAMINATION CHECKLIST

Transition zone: Perpendicular imaging at the edge of the lesion produces an image that shows where the normal gut wall layers are merging into the lesion.

Overlying layers: Perpendicular imaging with the transducer positioned on top of the lesion (but not touching it) demonstrates which layers overlie the lesion.

REFERENCES

1. Hedenbro JL, Ekelund M, Wetterberg P. Endoscopic diagnosis of submucosal gastric lesions: the results after routine endoscopy. *Surg Endosc*. 1991;5:20–23.
2. Caletti G, Zani L, Bolondi L, et al. Endoscopic ultrasonography in the diagnosis of gastric submucosal tumor. *Gastrointest Endosc*. 1989;35:413–418.
3. Yasuda K, Nakajima M, Yoshida S, et al. The diagnosis of submucosal tumors of the stomach by endoscopic ultrasonography. *Gastrointest Endosc*. 1989;35:10–15.
4. Boyce GA, Sivak Jr MV, Rosch T, et al. Evaluation of submucosal upper gastrointestinal tract lesions by endoscopic ultrasound. *Gastrointest Endosc*. 1991;37:449–454.
5. Nesje LB, Laerum OD, Svanes K, et al. Subepithelial masses of the gastrointestinal tract evaluated by endoscopic ultrasonography. *Eur J Ultrasound*. 2002;15:45–54.
6. Van Stolk RU. Subepithelial lesions. In: Van Dam J, Sivak MV, ed. *Gastrointestinal Endosonography*. Philadelphia: Saunders; 1999:153–165.
7. Chak A. EUS in submucosal tumors. *Gastrointest Endosc*. 2002;56(suppl): S43–S48.
8. Kojima T, Takahashi H, Parra-Blanco A, et al. Diagnosis of submucosal tumor of the upper GI tract by endoscopic resection. *Gastrointest Endosc*. 1999;50:516–522.
9. Kwon JG, Kim EY, Kim YS, et al. Accuracy of endoscopic ultrasonographic impression compared with pathologic diagnosis in gastrointestinal submucosal tumors. *Korean J Gastroenterol*. 2005;45:88–96.
10. Shen EF, Arnott ID, Plevris J, et al. Endoscopic ultrasonography in the diagnosis and management of suspected upper gastrointestinal submucosal tumours. *Br J Surg*. 2002;89:231–235.
11. Nickl NJ, Bhutani MS, Catalano M, et al. Clinical implications of endoscopic ultrasound: the American Endosonography Club Study. *Gastrointest Endosc*. 1996;44:371–377.
12. Park YS, Park SW, Kim TI, et al. Endoscopic enucleation of upper-GI submucosal tumors by using an insulated-tip electrosurgical knife. *Gastrointest Endosc*. 2004;59:409–415.
13. Hoteya S, Iizuka T, Kikuchi D, Yahagi N. Endoscopic submucosal dissection for gastric submucosal tumor, endoscopic sub-tumoral dissection. *Dig Endosc*. 2009;21:266–269.
14. Rosch T, Lorenz R, Dancygier H, et al. Endosonographic diagnosis of submucosal upper gastrointestinal tract tumors. *Scand J Gastroenterol*. 1992;27:1–8.
15. Futagami K, Hata J, Haruma K, et al. Extracorporeal ultrasound is an effective diagnostic alternative to endoscopic ultrasound for gastric submucosal tumours. *Scand J Gastroenterol*. 2001;36:1222–1226.
16. Thompson WM, Kende AI, Levy AD. Imaging characteristics of gastric lipomas in 16 adult and pediatric patients. *AJR Am J Roentgenol*. 2003;181:981–985.
17. Hasegawa S, Semelka RC, Noone TC, et al. Gastric stromal sarcomas: correlation of MR imaging and histopathologic findings in nine patients. *Radiology*. 1998;208:591–595.
18. Scatarige JC, Fishman EK, Jones B, et al. Gastric leiomyosarcoma: CT observations. *J Comput Assist Tomogr*. 1985;9:320–327.
19. Rosch T, Kapfer B, Will U, et al. Accuracy of endoscopic ultrasonography in upper gastrointestinal submucosal lesions: a prospective multicenter study. *Scand J Gastroenterol*. 2002;37:856–862.
20. Motoo Y, Okai T, Ohta H, et al. Endoscopic ultrasonography in the diagnosis of extraluminal compressions mimicking gastric submucosal tumors. *Endoscopy*. 1994;26:239–242.
21. Zhang QL, Nian WD. Endoscopic ultrasonography diagnosis in submucosal tumor of stomach. *Endoscopy*. 1998;30(suppl):A69–A71.
22. Polkowski M, Butruk E. Submucosal lesions. *Gastrointest Endosc Clin N Am*. 2004;15:33–54, viii.
23. Miettinen M, Sobin LH, Lasota J. Gastrointestinal stromal tumors of the stomach: a clinicopathologic, immunohistochemical, and molecular genetic study of 1765 cases with long-term follow-up. *Am J Surg Pathol*. 2005;29:52–68.
24. Miettinen M, Sarlomo-Rikala M, Lasota J. Gastrointestinal stromal tumors: recent advances in understanding of their biology. *Hum Pathol*. 1999;30: 1213–1220.
25. Berman J, O'Leary TJ. Gastrointestinal stromal tumor workshop. *Hum Pathol*. 2001;32:578–582.
26. Fletcher CD, Berman JJ, Corless C, et al. Diagnosis of gastrointestinal stromal tumors: a consensus approach. *Hum Pathol*. 2002;33:459–465.
27. Okai T, Minamoto T, Ohtsubo K, et al. Endosonographic evaluation of c-kit-positive gastrointestinal stromal tumor. *Abdom Imaging*. 2003;28: 301–307.
28. Kim GH, Park DY, Kim S, et al. Is it possible to differentiate gastric GISTs from gastric leiomyomas by EUS? *World J Gastroenterol*. 2009;15: 3376–3381.
29. Sepe PS, Moparty B, Pitman MB, et al. EUS-guided FNA for the diagnosis of GI stromal cell tumors: sensitivity and cytologic yield. *Gastrointest Endosc*. 2009;70:254–261.
30. Chatzipantelis P, Salla C, Karoumpalis I, et al. Endoscopic ultrasound-guided fine needle aspiration biopsy in the diagnosis of gastrointestinal stromal tumors of the stomach: a study of 17 cases. *J Gastrointestin Liver Dis*. 2008;17:15–20.
31. Akahoshi K, Sumida Y, Matsui N, et al. Preoperative diagnosis of gastrointestinal stromal tumor by endoscopic ultrasound-guided fine needle aspiration. *World J Gastroenterol*. 2007;13:2077–2082.
32. Mochizuki Y, Kodera Y, Fujiwara M, et al. Laparoscopic wedge resection for gastrointestinal stromal tumors of the stomach: initial experience. *Surg Today*. 2006;36:341–347.
33. Vander Noot 3rd MR, Eloubeidi MA, Chen VK, et al. Diagnosis of gastrointestinal tract lesions by endoscopic ultrasound-guided fine-needle aspiration biopsy. *Cancer*. 2004;102:157–163.
34. Okubo K, Yamao K, Nakamura T, et al. Endoscopic ultrasound-guided fine-needle aspiration biopsy for the diagnosis of gastrointestinal stromal tumors in the stomach. *J Gastroenterol*. 2004;39:747–753.
35. Ando N, Goto H, Niwa Y, et al. The diagnosis of GI stromal tumors with EUS-guided fine needle aspiration with immunohistochemical analysis. *Gastrointest Endosc*. 2002;55:37–43.
36. Brand B, Oesterhelweg L, Binmoeller KF, et al. Impact of endoscopic ultrasound for evaluation of submucosal lesions in gastrointestinal tract. *Dig Liver Dis*. 2002;34:290–297.
37. Chak A, Canto MI, Rosch T, et al. Endosonographic differentiation of benign and malignant stromal cell tumors. *Gastrointest Endosc*. 1997;45: 468–473.
38. Palazzo L, Landi B, Cellier C, et al. Endosonographic features predictive of benign and malignant gastrointestinal stromal cell tumours. *Gut*. 2000;46: 88–92.
39. Nickl N. Decision analysis of hypoechoic intramural tumor study results. *Gastrointest Endosc*. 2002;56(suppl):S102.
40. Armstrong CP, King PM, Dixon JM, et al. The clinical significance of heterotopic pancreas in the gastrointestinal tract. *Br J Surg*. 1981;68: 384–387.
41. Jovanovic I, Knezevic S, Micev M, et al. EUS mini probes in diagnosis of cystic dystrophy of duodenal wall in heterotopic pancreas: a case report. *World J Gastroenterol*. 2004;10:2609–2612.
42. Matsushita M, Hajiro K, Okazaki K, et al. Gastric aberrant pancreas: EUS analysis in comparison with the histology. *Gastrointest Endosc*. 1999;49: 493–497.
43. Parmar JH, Lawrence R, Ridley NT. Submucous lipoma of the ileocaecal valve presenting as caecal volvulus. *Int J Clin Pract*. 2004;58:424–425.
44. Watanabe F, Honda S, Kubota H, et al. Preoperative diagnosis of ileal lipoma by endoscopic ultrasonography probe. *J Clin Gastroenterol*. 2000; 31:245–247.
45. Zhou PH, Yao LQ, Zhong YS, et al. Role of endoscopic miniprobe ultrasonography in diagnosis of submucosal tumor of large intestine. *World J Gastroenterol*. 2004;10:2444–2446.
46. Garcia M, Buitrago E, Bejarano PA, et al. Large esophageal liposarcoma: a case report and review of the literature. *Arch Pathol Lab Med*. 2004;128: 922–925.
47. Nakamura S, Iida M, Yao T, et al. Endoscopic features of gastric carcinoids. *Gastrointest Endosc*. 1991;37:535–538.
48. Ichikawa J, Tanabe S, Koizumi W, et al. Endoscopic mucosal resection in the management of gastric carcinoid tumors. *Endoscopy*. 2003;35: 203–206.

49. Matsumoto T, Iida M, Suekane H, et al. Endoscopic ultrasonography in rectal carcinoid tumors: contribution to selection of therapy. *Gastrointest Endosc*. 1991;37:539–542.
50. Yasuda E, Tomita K, Nagura Y, et al. Endoscopic removal of granular cell tumor. *Gastrointest Endosc*. 1995;41:163–167.
51. Nakachi A, Miyazato H, Oshiro T, et al. Granular cell tumor of the rectum: a case report and review of the literature. *J Gastroenterol*. 2000; 35:631–634.
52. Love MH, Glaser M, Edmunds SE, et al. Granular cell tumour of the oesophagus: endoscopic ultrasound appearances. *Australas Radiol*. 1999; 43:253–255.
53. Palazzo L, Landi B, Cellier C, et al. Endosonographic features of esophageal granular cell tumors. *Endoscopy*. 1997;29:850–853.
54. Hizawa K, Matsumoto T, Kouzuki T, et al. Cystic submucosal tumors in the gastrointestinal tract: endosonographic findings and endoscopic removal. *Endoscopy*. 2000;32:712–714.
55. Wildi SM, Hoda RS, Fickling W, et al. Diagnosis of benign cysts of the mediastinum: the role and risks of EUS and FNA. *Gastrointest Endosc*. 2003;58:362–368.
56. Fazel A, Moezardalan K, Varadarajulu S, et al. The utility and the safety of EUS-guided FNA in the evaluation of duplication cysts. *Gastrointest Endosc*. 2005;62:575–580.
57. Faigel DO, Burke A, Ginsberg GG, et al. The role of endoscopic ultrasound in the evaluation and management of foregut duplications. *Gastrointest Endosc*. 1997;45:99–103.
58. Geller A, Wang KK, DiMagno EP. Diagnosis of foregut duplication cysts by endoscopic ultrasonography. *Gastroenterology*. 1995;109:838–842.
59. Dancygier H, Lightdale CJ. Endoscopic ultrasonography of the upper gastrointestinal tract and colon. In: Stevens PD, ed. *Endosonography in Gastroenterology: Principles, Techniques, Findings*. New York: Thieme; 1999:76–89.
60. Faigel DO, Rosen HR, Sasaki A, et al. EUS in cirrhotic patients with and without prior variceal hemorrhage in comparison with noncirrhotic control subjects. *Gastrointest Endosc*. 2000;52:455–462.
61. Tio TL, Kimmings N, Rauws E, et al. Endosonography of gastroesophageal varices: evaluation and follow-up of 76 cases. *Gastrointest Endosc*. 1995;42: 145–150.
62. Lahoti S, Catalano MF, Alcocer E, et al. Obliteration of esophageal varices using EUS-guided sclerotherapy with color Doppler. *Gastrointest Endosc*. 2000;51:331–333.
63. Matsushita M, Hajiro K, Okazaki K, et al. Endoscopic features of gastric inflammatory fibroid polyps. *Am J Gastroenterol*. 1996;91:1595–1598.
64. Matsushita M, Hajiro K, Okazaki K, et al. Gastric inflammatory fibroid polyps: endoscopic ultrasonographic analysis in comparison with the histology. *Gastrointest Endosc*. 1997;46:53–57.
65. Imamura A, Tochihara M, Natsui K, et al. Glomus tumor of the stomach: endoscopic ultrasonographic findings. *Am J Gastroenterol*. 1994;89: 271–272.
66. Ji JS, Lee BI, Choi KY, et al. Diagnostic yield of tissue sampling using a bite-on-bite technique for incidental subepithelial lesions. *Korean J Intern Med*. 2009;24:101–105.
67. Lee CK, Chung IK, Lee TH, et al. Endoscopic resection using the unroofing technique: a simple method for pathologic confirmation of gastrointestinal subepithelial tumors that originate from the muscularis propria [abstract]. *Gastrointest Endosc*. 2009;69(suppl):330.
68. Giovannini M, Seitz JF, Monges G, et al. Fine-needle aspiration cytology guided by endoscopic ultrasonography: results in 141 patients. *Endoscopy*. 1995;27:171–177.
69. Kim EY. Linear array endoscopic ultrasonography. *Korean J Gastroendosc*. 2009;38:1–8.
70. Levy MJ, Jondal ML, Clain J, et al. Preliminary experience with an EUS-guided Trucut biopsy needle compared with EUS-guided FNA. *Gastrointest Endosc*. 2003;57:101–106.
71. Varadarajulu S, Fraig M, Schmulewitz N, et al. Comparison of EUS-guided 19-gauge Trucut needle biopsy with EUS-guided fine-needle aspiration. *Endoscopy*. 2004;36:397–401.
72. Polkowski M, Gerke W, Jarosz D, et al. Diagnostic yield and safety of endoscopic-ultrasound guided trucut biopsy in patients with gastric submucosal tumors: a prospective study. *Endoscopy*. 2009;41:329–334.
73. Hoda KM, Rodriguez SA, Faigel DO. EUS-guided sampling of suspected GI stromal tumors. *Gastrointest Endosc*. 2009;69:1218–1223.
74. Chen VK, Eloubeidi MA. Endoscopic ultrasound-guided fine-needle aspiration of intramural and extraintestinal mass lesions: diagnostic accuracy, complication assessment, and impact on management. *Endoscopy*. 2005; 37:984–989.
75. Arantes V, Logrono R, Faruqi S, et al. Endoscopic sonographically guided fine-needle aspiration yield in submucosal tumors of the gastrointestinal tract. *J Ultrasound Med*. 2004;23:1141–1150.
76. Matsui M, Goto H, Niwa Y, et al. Preliminary results of fine needle aspiration biopsy histology in upper gastrointestinal submucosal tumors. *Endoscopy*. 1998;30:750–755.
77. Hwang JH, Rulyak SD, Kimmey MB. American Gastroenterological Association Institute technical review on the management of gastric subepithelial masses. *Gastroenterology*. 2006;130:2217–2228.

CHAPTER 11

EUS IN THE EVALUATION OF GASTRIC TUMORS

Thomas Rösch | Shajan Peter | Shyam Varadarajulu

Key Points

EUS is useful for staging gastric cancer but is an ineffective modality for screening.

In patients without metastasis, EUS enables preoperative assessment of local tumor extent that will determine the choice of treatment.

Two methods for imaging can be used: water-filled stomach and balloon contact.

Endoscopic mucosal resection (EMR) can be applied to gastric cancer if the lesion is well differentiated and intramucosal (any size).

When gastric cancer extends into the superficial submucosa (<500 μm), EMR can be performed if the diameter of the tumor is less than 3 cm.

INTRODUCTION

Endoscopic ultrasonography (EUS) plays an important role in the diagnosis and staging of luminal gastrointestinal tumors. EUS is the most accurate modality for local-regional staging of gastric cancer. Advanced gastric cancer is staged using a combination of EUS and computed tomography (CT). The addition of fine-needle aspiration (FNA) for lymph nodes distant from the primary tumor improves the staging accuracy of EUS. Based on EUS staging, gastric cancer is managed by endoscopic mucosal resection, surgery, or chemotherapy. For other disease processes involving the stomach such as lymphoma, EUS, by virtue of its ability to evaluate individual gastric wall layers and to sample extramural lymph nodes, determines the best mode of therapy for individual patients. In addition, EUS plays an important role in evaluating patients with large gastric folds of unclear origin, with the aim of diagnosing lymphoma or other infiltrative diseases. This chapter focuses on EUS in the evaluation of gastric cancer, lymphoma, and large gastric folds.

GASTRIC CANCER

Despite decreases in incidence and mortality, gastric cancer remains the second leading cause of cancer-related deaths worldwide.[1] The treatment algorithm is based on accurate staging of gastric cancer that includes determination of tumor extent and nodal involvement.[2,3] Although the 5-year survival rate is greater than 75% for early gastric cancer confined to the mucosa or submucosa following resection, it is less than 30% for patients with distant spread (M1) or metastasis to more than 15 (N3) lymph nodes.[4,5] In general, for patients with localized gastric cancer, surgery is the mainstay of curative therapy, and endomucosal resection (EMR) is performed selectively in those with only mucosal involvement. Growing evidence also suggests that multimodal treatment involving chemoradiation is superior to surgery alone.[6,7] Therefore, it is important to stage gastric cancer accurately so that patients can undergo correct triage and receive appropriate therapy: EMR, surgery, adjuvant or neoadjuvant therapy, or palliation.

Role of EUS

Noninvasive imaging studies such as CT are widely available but lack accuracy for assessing the depth of tumor invasion or the presence of lymph node involvement.[8,9] Given its innate ability to differentiate the layers of the gastric mucosa, EUS is thought to be the most reliable nonsurgical method available for evaluating the depth of invasion of primary gastric cancers.[10,11] The procedure is relatively low risk and provides a more accurate prediction of T and N stage than does CT imaging.[8–14] Moreover, EUS-guided FNA of both regional and distant lymph nodes adds to the accuracy of nodal staging.[15,16]

The role of EUS in gastric cancer can be categorized as follows:

- Determination of treatment choice: In patients without distant metastasis, EUS enables preoperative assessment of local tumor extent that will determine the choice of treatment. Patients with mucosal or limited submucosal involvement may be candidates for EMR or primary resection. Although patients with T2 or T3 disease are treated surgically, those with T4 disease undergo palliative therapy.
- Detection of distant metastasis missed by CT: In some patients, EUS-guided FNA of small metastatic deposits in the left lobe of the liver or low-volume malignant ascites can be diagnosed by EUS-guided FNA. This finding obviates the need for staging laparoscopy. In addition, the diagnosis of metastatic disease at distant lymph nodes (e.g., the mediastinum) by EUS-guided FNA precludes operability.
- EUS has no role in patients with metastatic gastric cancer identified by CT. In most patients, the diagnosis is established by endoscopic biopsy. When these patients are proven to have metastasis on subsequent workup, no further role exists for staging by EUS.

Echoendoscopes

For staging gastric cancer, the radial echoendoscope is generally preferred because of its ease of manipulation and its ability to obtain 360-degree views and thus better evaluate the relationship between the lesion and adjacent organs. Alternatively, for evaluation of lesions smaller than 2 cm or small sessile lesions, an

ultrasonic mini-probe can be used because the lesion can be detected by endoscopy and visualized sonographically at the same time. In patients with nodal disease that requires confirmation to provide therapy or exclude surgery, one can perform the examination using a curvilinear echoendoscope.

A three-dimensional probe-based EUS system (Olympus Medical Systems Corporation, UM-DG20-25R [20 MHz] and UM-DG12-25R [12 MHz]) is commercially available that generates both real-time radial images and computer-reconstructed linear images displayed simultaneously on the monitor, as in helical CT scanning. The images generated using this three-dimensional system have a higher accuracy in determining the depth of gastric cancer invasion and also allow measurement of tumor volume.

Examination Techniques for Tumor Staging

Gastric lesions larger than 2 cm can be evaluated using the radial echoendoscope. Before gastric lesions are evaluated, de-aerated water is instilled into the stomach to submerge the lesion fully, and air is aspirated completely to obtain better acoustic coupling (Fig. 11.1). This maneuver permits ultrasonographic evaluation of the lesion without direct apposition of the echoendoscope balloon or probe tip over the lesion, a situation that could result in compression of tissue planes and inaccuracy in T staging (Videos 11.1 and 11.2). Occasionally, changing the patient to a prone, supine, or right lateral position permits complete immersion of the lesion under water and thereby makes the examination easier. To obtain optimal imaging, it is important to keep the echoendoscope transducer perpendicular to the lesion. When the radial echoendoscope is used, most examinations are performed at frequencies of 7.5 and 12 MHz, which allow a penetration of approximately 8 and 3 cm, respectively. Although the depth of penetration is lower at higher frequencies, it provides a greater resolution that is ideal for evaluating early-stage gastric cancer.

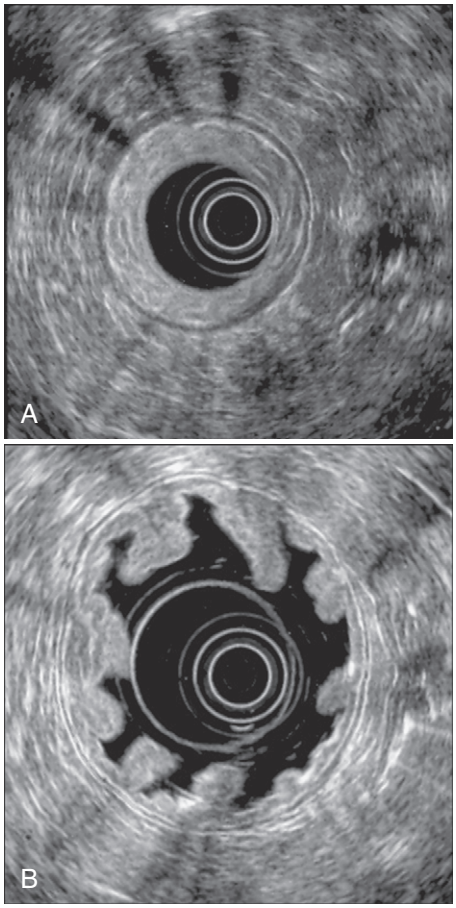


FIGURE 11.1 Evaluation of gastric wall layers. A, The gastric wall layers cannot be well evaluated at EUS in the absence of water instillation. **B,** After water instillation, the individual wall layers could be well examined using a radial echoendoscope.

T Staging

When the gastric wall is imaged using the radial echoendoscope, five distinct layers are seen, three hyperechoic and two hypoechoic, visible as an alternating bright-dark pattern (Fig. 11.2). The first two echo layers correspond histologically to the mucosa, the third corresponds to the submucosa, the fourth to the muscularis propria, and the fifth to the serosa. At EUS, T staging is classified as follows:

T1: Tumor involvement of the mucosal or both the mucosal and submucosal layers
T2: Tumor infiltration into the muscularis propria and subserosa
T3: Tumor penetration through the serosa but without involvement of adjacent organs
T4: Tumor invasion of adjacent organs or structures

Although tumors confined to the mucosa can be managed by EMR, those involving the submucosa usually require surgery because of the risk of nodal metastasis in nearly 20% of patients.[17] Therefore, it is imperative to stage these lesions accurately before determining treatment. If the lesion examined is small (<2 cm) or sessile, use of the high-frequency ultrasonic mini-probe is a better option (in conjunction with water-filled stomach) because this approach permits the lesion to be targeted under direct endoscopic visualization (Video 11.3). In addition, the high-frequency probes, by virtue of their superior resolution, can better evaluate the depth of tumor invasion. However, because of their limited depth of penetration, these probes should not be used for evaluating large gastric lesions. Studies have shown that the staging accuracy of these probes decreases as the tumor size increases.[18] When the high-frequency probes are used, the gastric wall appears as a nine-layer structure (Fig. 11.3). In addition

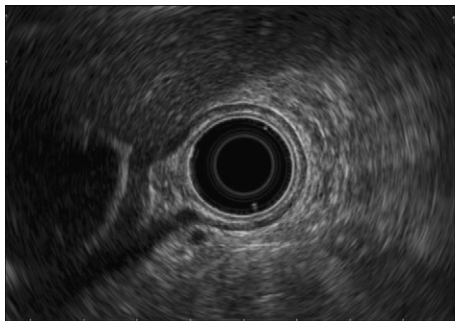


FIGURE 11.2 The five-layer gastric wall as examined using a radial echoendoscope at 7.5 MHz.

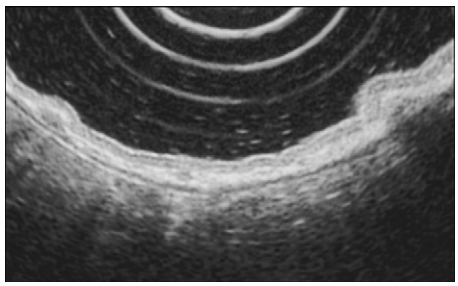


FIGURE 11.3 The nine-layer gastric wall as examined using a 20-MHz high-frequency EUS mini-probe.

to the normal five layers, a border echo (third layer) with the hypoechoic muscularis mucosa (fourth layer), a hypoechoic inner muscle layer (sixth layer), a border echo layer (seventh layer), and a hypoechoic outer muscle layer (eighth layer) are seen (Fig. 11.4).

N Staging

After the primary tumor is staged, the perigastric and regional lymph node stations should be surveyed for the presence of lymph nodes. Ultrasonographic features of lymph nodes such as low echogenicity (hypoechoic versus others), sharp versus irregular borders, round versus elliptical shape, and large size (>10 mm versus <10 mm) may be predictive of tumoral involvement. However, all four features may be present in only 25% of malignant lymph nodes, and no single feature can independently predict nodal metastasis.[19]

M Staging

Although EUS has limited usefulness in the detection of metastatic disease, it can provide vital information in a small subset of patients that can alter subsequent management. After the primary tumor and regional lymph node stations are evaluated, the echoendoscope is advanced to the gastric antrum, and a careful examination is undertaken on slow withdrawal. The left lobe of the liver, the peritoneum, the pleural layers of the lung, and the mediastinal lymph node stations should be carefully surveyed. The presence of malignant ascites or pleural effusion (Fig. 11.5) or the presence of metastasis in distant nodes such as the mediastinum can be easily detected by EUS; these findings preclude surgical treatment.[20,21] In addition, with EUS one can diagnose small metastatic deposits in the left lobe of the liver that are missed by staging CT.[22] EUS-guided FNA of these sites (Fig. 11.6) can be performed safely and can lead to subsequent changes in patient management.[21,22]

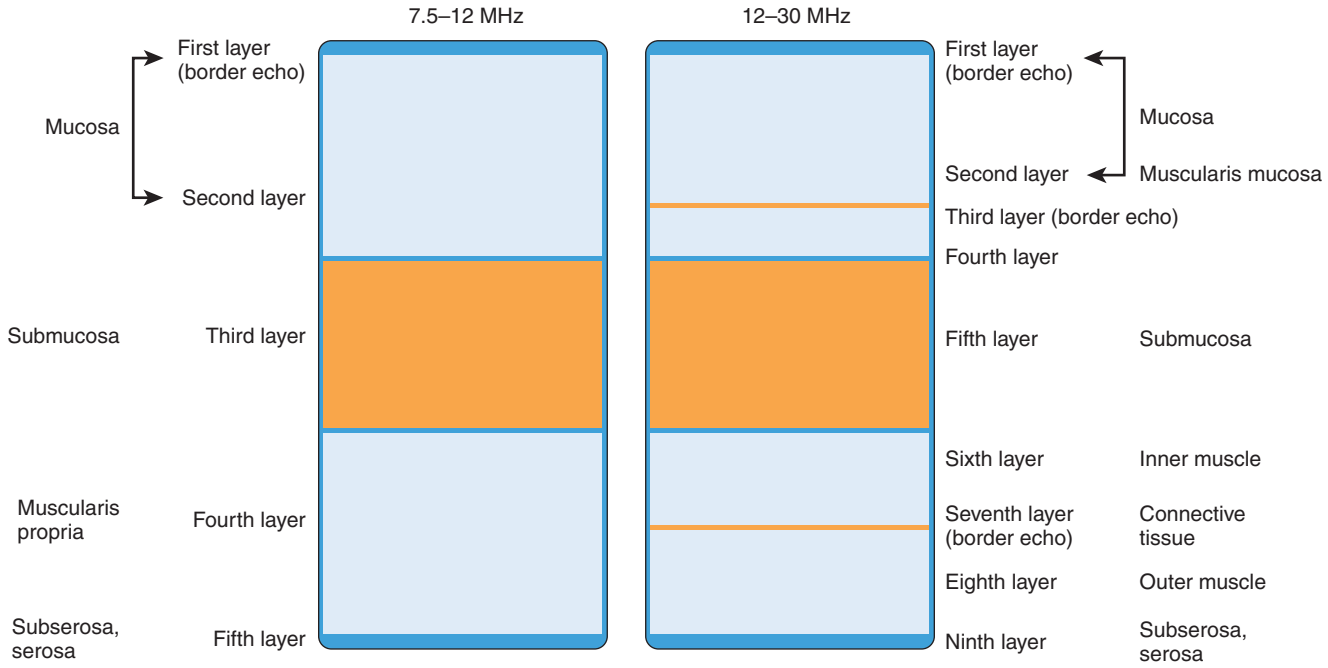


FIGURE 11.4 Schematic representation of the normal gastric wall as examined using a radial echoendoscope and a high-frequency mini-probe.

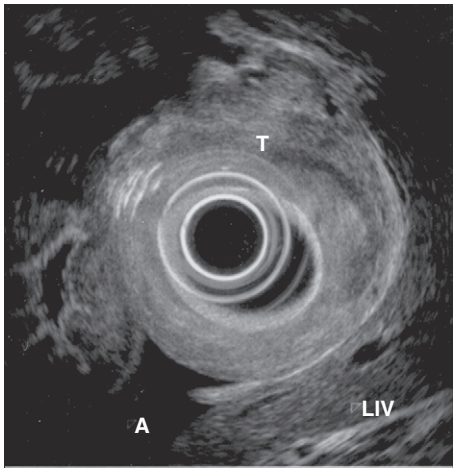


FIGURE 11.5 Presence of ascites (A) as diagnosed with a radial echoendoscope in advanced gastric cancer. LIV, liver; T, tumor.

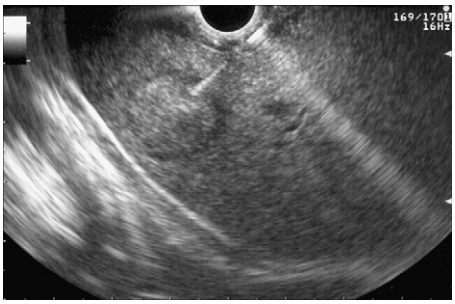


FIGURE 11.6 Hepatic metastasis of gastric cancer. EUS-guided fine-needle aspiration of a metastatic deposit in the left lobe of the liver in a patient with gastric cancer that was missed on computed tomography imaging.

TABLE 11.1

TNM Staging for Gastric Cancer

Tumor (T) Stage			
TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
T1s	Carcinoma in situ: intraepithelial tumor without invasion of the lamina propria		
T1	Tumor invades lamina propria or submucosa		
T2	Tumor invades muscularis propria or subserosa		
T2a	Tumor invades muscularis propria		
T2b	Tumor invades subserosa		
T3	Tumor penetrates serosa (visceral peritoneum) without invasion of adjacent structures*		
T4	Tumor invades adjacent structures*		
Nodal (N) Stage			
NX	Regional lymph node(s) cannot be assessed		
N0	No regional lymph node metastasis		
N1	Metastasis in 1 to 6 regional lymph nodes		
N2	Metastasis in 7 to 15 regional lymph nodes		
N3	Metastasis in more than 15 regional lymph nodes		
Metastasis (M) Stage			
Mx	Presence of distant metastasis cannot be assessed		
M0	No distant metastasis		
M1	Distant metastasis		
Stage Grouping			
Stage 0	Tis	N0	M0
Stage 1A	T1	N0	M0
	T1	N1	M0
Stage 1B	T2a/b	N0	M0
	T1	N2	M0
Stage II	T2a/b	N1	M0
	T3	N0	M0
Stage IIIA	T2a/b	N2	M0
	T3	N1	M0
	T4	N0	M0
Stage IIIB	T3	N2	M0
Stage IV	T1-3	N3	M0
	T4	N1-3	M0
	Any T	—	—

*The adjacent structures of the stomach include the spleen, transverse colon, liver, diaphragm, pancreas, abdominal wall, adrenal gland, kidney, small intestine, and retroperitoneum. Intramural extension to the duodenum or esophagus is classified by the depth of the greatest invasion in any of these sites, including the stomach.

From Greene FL, Page DL, Fleming ID, et al, eds. *AJCC (American Joint Committee on Cancer) Cancer Staging Manual*. 6th ed, New York: Springer-Verlag; 2002.

TABLE 11.2

Accuracy of EUS in Gastric Cancer with Respect to Overall T Staging

Authors (yr)	MHz	Patients (*n*)	T-Stage Accuracy (%)
Murata et al[116] (1988)	7.5–10	146	79
Tio et al[115] (1989)	7.5–12	72	81
Akahoshi et al[117] (1991)	7.5–12	74	81
Botet et al[8] (1991)	7.5–12	50	92
Caletti et al[76] (1993)	7.5–12	35	91
Dittler and Siewert[30] (1993)	7.5–12	254	83
Grimm et al[118] (1993)	7.5	147	78
Ziegler et al[39] (1993)	7.5–12	108	86
Massari et al[119] (1996)	7.5–12	65	89
Perng et al[120] (1996)	7.5–12	69	71
Wang et al[20] (1998)	7.5–12	119	70
Tseng et al[121] (2000)	7.5–12	74	85
Willis et al[122] (2000)	7.5–12	116	78
Habermann et al[123] (2004)	7.5–12	51	86
Tsendsuren et al[124] (2006)	5–7.5	41	69
Ganpathi et al[13] (2006)	7.5–20	126	80
Bentrem et al[125] (2007)	7.5–12	225	57
Lok et al[126] (2008)	5–20	123	64

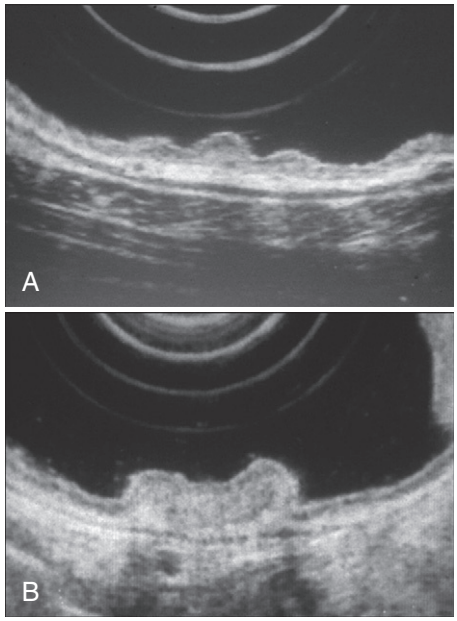


FIGURE 11.7 **Early-stage gastric cancer. A,** Early-stage gastric cancer confined to the mucosal layer. **B,** Early-stage gastric cancer extending to the submucosal layer.

Accuracy of EUS in Staging

After endoscopy, EUS is the most important diagnostic procedure for local staging in patients with gastric cancer. The EUS criteria for the depth of tumor and nodal invasions have changed, and current guidelines are based on the American Joint Committee on Cancer (AJCC) staging system (Table 11.1). Several studies have investigated the accuracy of EUS in tumor, node, metastasis (TNM) staging of gastric cancer (Table 11.2). Study results vary with respect to instrumentation, scanning frequency, and location of the tumor. In addition, the sensitivity of EUS has improved for differentiating mucosal disease from deeper invasion.

T Staging

The role of EUS in T category staging varies from early T1 lesions to deeper T4 invasion. The subset of T1 lesions that are confined to the mucosa and submucosa has been known as early-stage gastric cancer (Fig. 11.7). Accurate staging of this group is important because lesions confined to the mucosa can be removed by minimally invasive techniques such as EMR and endoscopic submucosal dissection rather than surgical resection. The type of EUS transducer and the transducer frequency help in precise delineation of the wall layers. Most studies have used the 7.5 and 12 MHz transducers but have not differentiated between mucosal and submucosal tumors in the T1 category. In contrast to conventional EUS transducers, high-frequency (≥15 to 20 MHz) mini-probes provide better-resolution images of the gastric wall.[22,23] As described earlier, these high-resolution mini-probes can target smaller lesions and provide a nine-layered spectral anatomy as compared with the standard five-layered anatomy seen using radial echoendoscopes.

TABLE 11.3

Accuracy of EUS in Gastric Cancer Staging in T Category

Authors (yr)	MHz	Patients (*n*)	T1 (%)	T2 (%)	T3 (%)	T4 (%)
Murata et al[116] (1988)	7.5-10	146	93	50	41	—
Tio et al[115] (1989)	7.5-12	72	77	93	81	88
Akahoshi et al[117] (1991)	7.5-12	74	93	57	100	60
Botet et al[8] (1991)	7.5-12	50	92		97	86
Caletti et al[76] (1993)	7.5-12	35	83	100	86	100
Dittler and Siewert[30] (1993)	7.5-12	254	81	71	87	79
Grimm et al[118] (1993)	7.5	147	74	73	85	85
Ziegler et al[39] (1993)	7.5-12	108	91	81	84	94
Massari et al[119] (1996)	7.5-12	65	100	86	85.7	88.8
Perng et al[120] (1996)	7.5-12	69	58	63	79	83
Wang et al[20] (1998)	7.5-12	119	68	67	81	53
Tseng et al[121] (2000)	7.5-12	74	100	74	87	86
Willis et al[122] (2000)	7.5-12	116	80	63	95	83
Habermann et al[123] (2004)	7.5-12	51	—	90	79	100
Tsendsuren et al[124] (2006)	7.5	41	83	60	100	25
Ganpathi et al[13] (2006)	7.5-20	126	79	74	86	73
Bentrem et al[125] (2007)	7.5-12	225	95		58	
Lok et al[126] (2008)	5-20	123	24	43	97	33

Several studies evaluated the use of high-frequency mini-probes for the staging of early gastric cancer. The overall accuracy was between 65% and 72%. These probes have a tendency to overstage T1 mucosal lesions as T1 submucosal lesions at a rate of 29% to 46%. The T1 submucosal understaging rates are lower, however, ranging between 6% and 48%.[18,24–26] The high-frequency mini-probes have an inherent disadvantage in that they are limited by their depth of penetration. Their accuracy is best for tumors that measure less than 2 cm. In the study by Okamura et al[18] using 20-MHz probes, the accuracy for lesions smaller than 20 mm was 85.7% compared with 50% for lesions larger than 20 mm. The accuracy of high-frequency mini-probes is also limited by attenuation of the probe by gastric folds, protruding lesions, or ulcerated lesions. Wall layer irregularity and a budding sign larger than 1 mm in depth in the third layer are other features suggestive of submucosal invasion in early gastric cancer.[27]

The overall accuracy of EUS in determining T stage ranges from 71% to 92%, with an average of 83% (see Table 11.2). The accuracy is best for T1, T3, and T4 lesions, whereas EUS is least accurate (range, 60% to 70%) for T2 lesions (Table 11.3). In a meta-analysis, the pooled sensitivity was 88% for T1 lesions, 82% for T2, 90% for T3, and 99% for T4 lesions.[28] These rates reflect the difficulty in differentiating T2 (muscularis propria and subserosal) from T3 (serosal) invasion (Fig. 11.8), a situation that provides room for both understaging and overstaging. Larger studies consistently showed overstaging of T2 lesions in 12% to 30% of tumors and understaging in 4% to 10%. Whereas microscopic invasion was the most frequent cause of understaging, overstaging was attributed to peritumoral fibrosis, ulceration, and inflammation. In addition, certain anatomic features can lead to inaccuracy in T staging. In areas such as the lesser curvature and the posterior wall of the fundus, which are not covered with serosa, tumors with complete transmural growth are histologically classified as T3. Although technically the serosa is free of tumor invasion, endosonographically these tumors appear as T3, thus potentially leading to overstaging. In other areas where the stomach is not covered completely by the serosa such as attachment sites of the gastrocolic ligament, gastrohepatic ligmanent, and omentum major and minor, tumors invading the fatty plane may appear endosonographically as T3 lesions when in fact histologically they are T2.

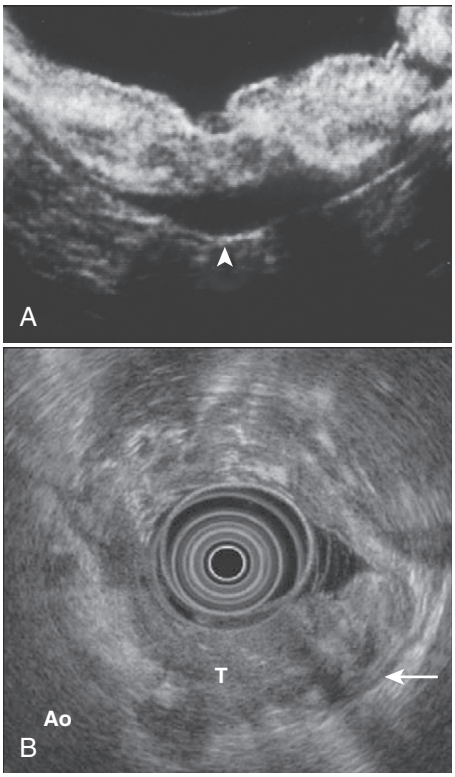


FIGURE 11.8 Staging of T2 and T3 gastric cancer. A, Gastric cancer staged as T2 where the tumor invades the subserosa *(arrowhead)*. **B,** Gastric cancer staged as T3 where the tumor invades the serosal layer of the stomach *(arrow)*. Ao, aorta; T, tumor.

N Staging

In the N category, the overall accuracy ranges from 65% to 90% (Table 11.4). The pooled sensitivity for N1 stage disease is 58.2%, and for N2 it is 64.9%.[28] In general, the accuracy for N staging is low because of the difficulty in differentiating malignant from benign inflammatory lymph nodes. Results among studies vary because different criteria were used to define nodes as malignant. In the description by Francois et al,[29] hypoechoic lymph nodes with well-defined margins and a ratio of largest to smallest diameter of less than 2 were considered to be malignant. Nonetheless, a strong correlation exists between increasing T stage and the presence of lymph node metastases, such that the

accuracy and sensitivity for diagnosing lymph node metastases are higher for T3 and T4 lesions. Dittler and Siewert[30] observed that when EUS did not show malignant lymph nodes in T1 or T2 stage, stage N0 could be assumed; when lymph nodes were visualized at EUS in stages T3 and T4, these nodes tended to be malignant. However, it is difficult to diagnose lymph node metastases in T1 stage because very few nodes are involved and they are difficult to detect. Other reasons for inaccuracy in nodal staging are the limited depth of penetration of the EUS transducer and the inability to visualize distant lymph nodes.

EUS can detect lymph node metastasis around the lesser curvature of the stomach more easily than near the greater curvature or when the lymph nodes are located more than 3 cm away from the primary lesion. The reason is that EUS has to follow a wide area along the greater curvature and has a maximum depth of penetration of approximately 5 to 7 cm, thus limiting its ability to detect lymph node metastasis around this area. The role of FNA in nodal staging has not been well evaluated. However, in situations where malignant lymph nodes can be difficult to distinguish from benign nodes, EUS-guided FNA cytology and biopsy may offer better diagnostic yield.

M Staging

EUS has a limited role in the detection of metastatic disease such as distant lymph nodes, ascites, and peritoneal and liver metastases, with an overall pooled sensitivity of 73.2%.[28] Ascites can be detected during endosonographic staging of gastric cancer. Using EUS-guided FNA, Chang et al[31] diagnosed malignant ascites as well as pleural effusion in two patients with gastric cancer.

Although the presence of ascites compares well with the depth of tumor invasion and lymph node metastases, it does not correlate with peritoneal carcinomatosis found at surgery. In a study of 301 patients with gastric cancer that compared the sensitivity of different diagnostic techniques for predicting peritoneal metastases, EUS was more sensitive (87.1%) than combined ultrasound with CT (16.1%) and laparoscopy or laparotomy (40.9%).[32] In another study by Chu et al,[33] 402 consecutive patients with histopathologically confirmed gastric adenocarcinoma underwent mini-probe EUS. The accuracy of mini-probe EUS for the detection of ascites was compared with subsequent findings at laparoscopy or laparotomy. Compared with laparoscopy or laparotomy, EUS was 60.7% sensitive and 99.4% specific for detecting ascites. In addition, peritoneal metastasis detected by EUS was noted in 63.9% of patients with ascites and in 11.3% of patients without ascites. These studies indicate that EUS is less sensitive but highly specific for the detection of ascites.

Limitations of EUS in Staging

Interpretation of EUS findings is an important factor that restricts staging accuracy. The true accuracy of EUS in staging gastric cancer is still unclear because true blinding of the endosonographer to relevant clinical information has not been done. This raises concern about whether the factual accuracy of EUS has been overstated. In a videotaped study of 33 patients who had undergone EUS for the evaluation of gastric cancer, the results were blindly reviewed and further compared with the initial, nonblinded EUS assessment obtained during routine clinical evaluation.[34] This study, by Meining et al,[34] found that the nonblinded initial evaluation yielded an overall accuracy for T staging of 66.7% compared with 45.5% when the evaluation was blinded. Moreover, interobserver variability exists in the interpretation of EUS findings. The same investigators subsequently performed a similar videotaped EUS study in 55 patients with gastric cancer to assess interobserver variability among five blinded experienced examiners in determining T and N staging.[35] Kappa (κ) values for assessing T1, T2, T3, and T4 lesions were 0.47, 0.38, 0.39, and 0.34, respectively, findings consistent with a substantial degree of interobserver variability. In the N category, the values were worse; the κ value was 0.46, 0.34, and 0.34 for N0, N1, and N2 stages, respectively. Moreover, studies have not assessed the learning curve for accurate staging of gastric cancer by individual endosonographers.

Diagnostic performance of EUS may also be affected by clinicopathologic features, such as tumor type, location, histologic type, and size. Kim et al[36] found that the diagnostic accuracy of EUS in overall T staging was significantly affected by histopathologic differentiation and size of the lesion. These investigators noted that undifferentiated histologic type and larger tumor size were more frequently associated with incorrect depth of tumor invasion at EUS. A tumor size of more than 3 cm was associated with overstaging by EUS, whereas tumors with poorly differentiated histologic features were associated with understaging. However, it needs to be determined whether these clinicopathologic features also affect the diagnostic performance of EUS in differentiating early from locally advanced gastric cancers. Microscopic tumor invasion is often difficult to assess on ultrasound images and therefore can be missed. Using conventional EUS or even the mini-probes, vertical invasion less than 500 μm in depth can be difficult to diagnose. Using pattern analysis, especially for ulcerated tumors and surrounding fibrosis, it may be possible to minimize the number of false-positive examination results.[37]

As stated previously, anatomic limitations also affect tumor staging by EUS. Areas of the cardia, the greater curve of the upper

TABLE 11.4

Accuracy of EUS in Gastric Cancer Staging in N Category

Authors (yr)	MHz	Patients (*n*)	N (%)	N0 (%)	N1 (%)	N2 (%)	N3 (%)
Tio et al[115] (1989)	7.5-12	72	68	50	62	90	—
Botet et al[8] (1991)	7.5-12	50	78	91	68	82	—
Caletti et al[76] (1993)	7.5-12	35	69	—	—	—	—
Dittler and Siewert[30] (1993)	7.5-12	254	66	93	65	52	—
Grimm et al[118] (1993)	7.5	148	83	79	46	91	—
Ziegler et al[39] (1993)	7.5-12	108	74	71	74	100	—
Massari et al[119] (1996)	7.5-12	56	68	58	65	73	—
Perng et al[120] (1996)	7.5-12	69	65	75	53	60	—
Wang et al[20] (1998)	7.5-12	119	68	73	69	52	—
Willis et al[122] (2000)	7.5-12	116	77	82	75	64	—
Habermann et al[123] (2004)	7.5-12	51	90	100	83	84	—
Tsendsuren et al[124] (2006)	7.5	41	66	100	41	—	—
Ganpathi et al[13] (2006)	7.5 -20	126	83	74	78	54	50
Bentrem et al[125] (2007)	7.5-12	225	71	72	69 (N+)		
Lok et al[126] (2008)	5-20	123	75	85	69 (N+)		

body of the stomach, the lesser curve at the incisura, and the pyloric channel remain technically challenging to examine. In addition, other factors such as pulsation, breathing, air bubbles, and mucus can result in imaging artifacts. Technologies such as three-dimensional EUS, which is still in evolution, have shown promise in improving the staging accuracy.[38]

Comparison of EUS with Other Imaging Modalities

CT has been the primary method for staging gastric cancer. EUS is superior to CT in its ability to study the gastric wall layers (T stage), but it is not accurate for the assessment of nodal disease and distant metastasis (Tables 11.5 and 11.6). In an early study by Ziegler et al,[35,39] CT scan failed to detect six lesions and overstaged T1 lesions in 12 of 22 patients. Newer studies using multidetector CT (MDCT) yielded better results.

A systematic review showed that the diagnostic accuracy of overall T staging for EUS, CT, and magnetic resonance imaging (MRI) was between 65% and 92.1%, 77.1% and 88.9%, and 71.4% and 82.6%, respectively.[40] Sensitivity for assessing T4 (serosal) involvement for EUS, CT, and MRI varied between 77.8% and 100%, 82.8% and 100%, and 89.5% and 93.1%, respectively. Specificity for assessing T4 (serosal) involvement for EUS, CT, and MRI varied between 67.9% and 100%, 80% and 96.8%, and 91.4% and 100%, respectively.[40] The same investigators systematically reviewed the role of imaging in lymph node status (N stage). The median sensitivities and specificities for each modality were as follows: EUS, 71% sensitivity and 49% specificity; MDCT, 80% sensitivity and 78% specificity; and MRI, 68% sensitivity and 75% specificity.[41] Although EUS, MDCT, and MRI achieved similar results in terms of diagnostic accuracy for T staging, for N staging, their individual role cannot be reliably adapted to confirm or exclude the presence of metastatic disease.

In summary, the most experience has been with EUS. Fewer studies are available for MDCT and even fewer for MRI or fluoro-d-glucose positron emission tomography (FDG PET). With this background, EUS remains superior in diagnosing the depth of gastric cancer invasion, and CT is preferred for the diagnosis of distant metastases. Therefore, these technologies are complementary for overall staging. The performance of integrated PET-CT scans and functional MRI in gastric cancer still needs to be determined.

EUS in the Management of Gastric Cancer

The role of EUS in the management of gastric cancer is outlined in Figure 11.9. In addition to staging, EUS can confer additional benefit in the following specific situations.

Improved Patient Selection for Staging Laparoscopy

Most patients with gastric cancer present with metastatic disease, often with peritoneal involvement that is not well visualized on CT imaging.[42] Therefore, laparoscopy is recommended as a staging procedure for patients with apparent localized gastric cancer.[43] In a prospective study of 94 patients with localized gastric cancer who underwent staging EUS followed by laparoscopy, metastatic disease was noted in 4% of patients with T1 or T2, N0 disease as compared with 25% of patients T3 or T4 or N+ disease.[10] The negative predictive value for metastatic disease in patients staged T1 or T2, N0 by EUS was 96%. This finding suggests that staging laparoscopy may not be needed for all patients undergoing surgical treatment of gastric cancer, but rather laparoscopy can be used selectively in those who T3 or T4 or N+ disease as staged by EUS.

Predictor of Survival after Neoadjuvant Chemotherapy

Studies have shown improved surgical outcomes for patients with gastric cancer who received preoperative chemotherapy.[44] The prognostic factors for survival after neoadjuvant therapy (R0 resection, pathologic stage, and response) are determined postoperatively and cannot be used to assess the effectiveness of neoadjuvant therapy before surgery. In a prospective study of 40 patients with locally advanced gastric cancer, patients underwent CT and EUS before and after neoadjuvant chemotherapy, followed by surgical treatment.[45] After chemotherapy, the accuracy of CT and EUS for T and N staging was 57% versus 47% for T staging and 37% versus 39% for N staging, respectively. The 3-year overall survival rate for patients downstaged with EUS for T or N classification was greater than that for patients

TABLE 11.5

Comparison of T Staging Accuracy of Gastric Cancer with EUS, Computed Tomography, and Magnetic Resonance Imaging

Authors (yr)	Patients (*n*)	EUS (%)	CT (%)	MRI (%)	Other CT Modalities
Botet et al[8] (1991)	50	92	42	—	—
Grimm et al[118] (1993)	118	82	11	—	—
Ziegler et al[39] (1993)	108	86	43	—	—
Kuntz and Herfarth[127] (1999)	82	73	51	48	—
Polkowski et al[14] (2004)	88	63	44	—	Helical CT
Bhandari et al[128] (2004)	63	88	83	—	Multidetector row CT
Arocena et al[129] (2006)	17	35	—	53	—

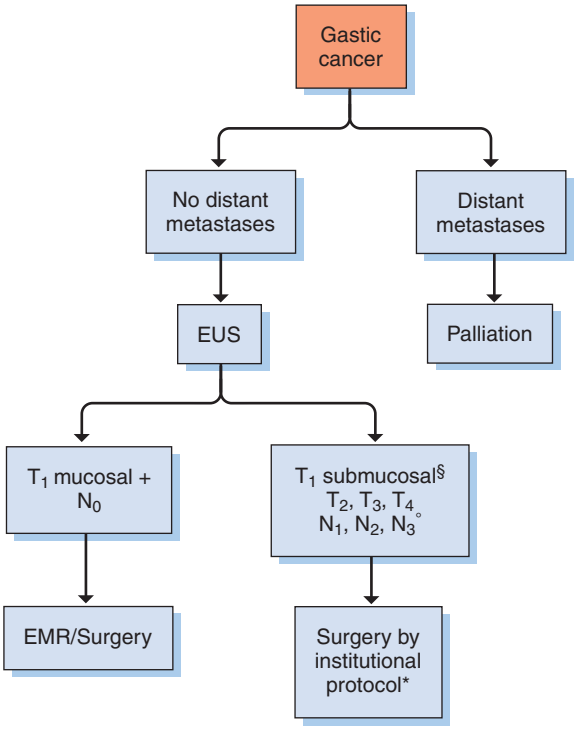
CT, computed tomography; MRI, magnetic resonance imaging.

TABLE 11.6

Comparison of N Staging Accuracy of Gastric Cancer with EUS, Computed Tomography, and Magnetic Resonance Imaging

Authors (yr)	Patients (*n*)	EUS (%)	CT (%)	MRI (%)	Other CT
Botet et al[8] (1991)	50	78	48	—	—
Grimm et al[118] (1993)	118	88	21	—	—
Ziegler et al[39] (1993)	108	74	51	—	—
Kuntz and Herfarth[127] (1999)	82	87	65	69	—
Polkowski et al[14] (2004)	60	30	47	—	Helical CT
Bhandari et al[128] (2004)	48	79	75	—	Multidetector row CT
Arocena et al[129] (2006)	—	54	—	50	—

CT, computed tomography; MRI, magnetic resonance imaging.



*Neoadjuvant/adjuvant therapy
§In Japan, some patients with T_1 submucosal N_0 disease undergo endoscopic submucosal dissection.
°N3 - staged as T4 disease

FIGURE 11.9 EUS-based algorithmic approach to the management of gastric cancer. EMR, endoscopic mucosal resection.

who were not downstaged (69% versus 41%). In addition, the 2-year recurrence-free survival rate was also better for the EUS-downstaged patients than for the patients who were not downstaged (77% versus 47%). Conversely, no difference in survival or recurrence-free survival rates were noted among patients downstaged or not downstaged using CT.

EUS-Detected Low-Volume Ascites as a Predictor of Inoperability

EUS has been shown to be more sensitive than transabdominal ultrasonography, CT, and operative findings of laparoscopy and laparotomy for the detection of intraperitoneal fluid.[32,46] In a study of 21 patients who underwent staging laparoscopy after detection of low-volume ascites at EUS, 11 patients were deemed inoperable at laparoscopy.[47] Of the remaining 10 patients who were deemed operable at laparoscopy and who underwent surgery, only 5 underwent curative surgical procedures; the other patients had incurable disease at surgery. Therefore, the presence of low-volume ascites on EUS was indicative of incurable disease in 76% of patients. Studies also showed that EUS-guided FNA of low-volume ascites can be performed safely, with an accuracy rate of nearly 80%.[48]

GASTRIC CANCER: EXAMINATION CHECKLIST

Primary tumor: depth of penetration
Regional lymph nodes: perigastric region, celiac axis, gastrohepatic ligament
Left lobe of the liver: metastatic deposits
Peritoneum: low-volume malignant ascites
Pleural lining: malignant effusion
Mediastinal lymph nodes: metastatic spread

PRIMARY GASTRIC NON-HODGKIN LYMPHOMA

The stomach, the most common extranodal site of non-Hodgkin lymphoma (NHL), accounts for nearly 70% of all lymphomas that involve the gastrointestinal tract.[49,50] The stomach can harbor primary NHL, or it may be involved secondarily by disseminated nodal disease. Most primary gastric lymphomas are either the extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) type or diffuse large B-cell lymphoma (DLBCL). Other rare types include mantle cell lymphoma, follicular lymphomas and peripheral T-cell lymphoma. The management of primary NHL is based on tumor staging, and EUS is regarded as the most accurate modality for local staging of gastric lymphoma.[51–55] Secondary gastric NHL, which occurs in 20% to 60% of newly diagnoses cases, reflects disseminated disease that requires extensive diagnostic and systemic treatment strategies. This chapter focuses mainly on the role of EUS in the evaluation of primary gastric NHL.

Diffuse Large B-Cell Lymphoma

DLBCL was previously known as high-grade MALT lymphoma. Patients with DLBCL tend to have a more advanced-stage disease at initial presentation and present with severe systemic symptoms such as abdominal pain, gastric outlet obstruction, bleeding, or perforation.[56,57] Upper endoscopy may reveal large, multiple ulcers or protruding exophytic tumors. Histologic examinations reveal confluent sheets or clusters of large cells that resemble centroblasts or immunoblasts.[58] These tumors are cytogenetically, biologically, and clinically different from MALT lymphoma and have a worse prognosis. The term *high-grade MALT lymphoma* should be avoided for DLBCL because it may lead to inappropriate undertreatment. Although EUS may help to determine the depth of tumor penetration into the gastric wall, local staging alone has a lesser impact, given the extent of disease and the multimodality treatment involved in the care of these patients.

Mucosa-Associated Lymphoid Tissue Lymphoma

MALT lymphoma is a low-grade disease that can occur anywhere in the gastrointestinal tract, but it is most commonly found in the stomach.[59,60] The stomach does not normally contain any appreciable amount of lymphoid tissue. However, stimulation by *Helicobacter pylori* may lead to the development of lymphoid tissue populated by B cells and $CD4^+$ lymphocytes that are recruited to the gastric mucosa and thus form MALT. Further stimulation by *H. pylori* leads to the formation of centrocyte-like cells that arise from the marginal zone of the lymphoid tissue and result in a monoclonal population of B cells known as MALT lymphoma.[61,62] More than 90% of patients with MALT lymphoma are known to be infected with *H. pylori*. Although several studies suggested a causative association between *H. pylori* and MALT lymphoma,[63–65] the strongest evidence comes from studies that demonstrated disease regression following eradication of *H. pylori*.[66–68]

Most patients with early-stage MALT lymphoma are asymptomatic or present with nonspecific symptoms such as epigastric pain or discomfort, anorexia, weight loss, nausea or vomiting, occult gastrointestinal bleeding, and early satiety.[50,59,60] The diagnosis of gastric lymphoma is usually established by upper endoscopy with biopsy. Findings on upper endoscopy are diverse and may include mucosal erythema, a mass or polypoid lesion with or without ulceration, benign-appearing gastric ulcer and nodularity, or thickened gastric folds.[69,70] In one study, 27 of 51 cases of MALT lymphoma were reported as benign based on biopsy results.[71] Therefore, multiple biopsy specimens should be obtained from the stomach, the duodenum, and the gastroesophageal junction, as well as from both normal- and abnormal-appearing gastric

TABLE 11.7

Treatment Response of MALT Lymphoma According to EUS Staging

Response	T1mN0	T1smN0	T2N0	T1mN1	T1smN1
Complete response	12 (75%)	11 (58%)	1 (25%)	2 (50%)	2 (50%)
Persistent disease or relapse	4 (25%)	8 (42%)	3 (75%)	2 (50%)	2 (50%)

From Caletti G, Zinzani P, Fusaroli P, et al. The importance of endoscopic ultrasonography in the management of low-grade gastric mucosa-associated lymphoid tissue lymphoma. *Aliment Pharmacol Ther*. 2002;16:1715-1722.

mucosa. When possible, every attempt should be made to obtain the largest biopsy specimen possible. Conventional pouch biopsies may miss the diagnosis because gastric lymphoma can infiltrate the submucosa without affecting the mucosa; this problem is most likely when no obvious mass is present. Jumbo biopsies, snare biopsies, biopsies within biopsies, and needle aspiration can all serve to increase the yield in such cases.[72,73]

Endoscopic biopsies are also important to determine whether the patient is infected with *H. pylori*. Once a diagnosis of MALT lymphoma is established, further workup includes serologic testing for any underlying viral illness, EUS for local staging of the tumor, and CT of the abdomen, pelvis, and chest. The disease pattern imaged by EUS may correlate with the type of lymphoma. In one series, for example, superficial spreading or diffuse infiltrating lesions on EUS were seen with MALT lymphoma, whereas mass-forming lesions were typical of DLBCL.[51] The need for PET scan or bone marrow biopsy depends on the disease extent.

In general, patients with early-stage (mucosal or submucosal disease and without lymph node involvement) *H. pylori*–positive lymphoma are initially treated with *H. pylori* eradication therapy. Patients without evidence of *H. pylori* infection and those with tumors that demonstrate the t (11;18) translocation are typically treated with local radiation therapy. Patients with more advanced stage (>T2, N+) disease are treated with *H. pylori* eradication therapy if they are *H. pylori* positive. These patients are then generally observed until the development of symptoms or are managed with more aggressive chemotherapy or immunotherapy.[74] Gastric resection is reserved for patients with complications such as perforation or obstruction.[75] Because the management of MALT lymphoma is stage dependent, accurate local staging is pivotal for optimal clinical outcomes. EUS is currently considered the most accurate modality for local staging of MALT lymphoma.

Role of EUS in MALT Lymphoma

The role of EUS in the management of MALT lymphoma can be categorized as follows:

- Local staging of disease: EUS accurately determines the level of involvement of individual gastric wall layers by the disease and the presence of perigastric lymphadenopathy. This feature is important because *H. pylori*–positive patients with mucosal or submucosal disease may respond to simple antimicrobial treatment, and those with T2 to T4 disease may require more aggressive treatment protocols. EUS alone has suboptimal accuracy in distinguishing benign from malignant lymph nodes.[76,77] When combined with FNA, the overall accuracy approaches 90% (versus 66% for EUS alone).[78] Even higher accuracy rates may be achievable when flow cytometry is performed on the aspirated material.[79]
- Tissue diagnosis: MALT lymphoma is best diagnosed by endoscopic biopsies. In the rare patient with thickened gastric folds in whom all endoscopic biopsy results are unrevealing, EUS-guided FNA or Tru-Cut biopsy of the deeper wall layers may be diagnostic.[80,81] It is important to procure more tissue to perform flow cytometry on the aspirated material.
- Predicting response to therapy: A direct relationship appears to exist between tumor grading by EUS and response to therapy.[82] Patients with disease confined to the mucosa and submucosa have better clinical outcomes compared with patients with involvement of deeper wall layers (Table 11.7).
- Post-treatment follow-up: EUS may reveal restoration of normal gastric wall layers or significant reduction in thickness of the wall layers following successful treatment.[83] Patients with persistently thick gastric wall layers on follow-up EUS examinations are more likely to have residual disease, even when results of endoscopic biopsy are negative. These patients most likely have persistent lymphoma that may warrant additional therapy.

TABLE 11.8

Ann Arbor Classification, Modified by Musshoff and Schmidt-Vollmer

Grade	Description
IE	Lymphoma restricted to GI tract on one side of diaphragm
IE1	Infiltration limited to mucosa and submucosa
IE2	Lymphoma extending beyond submucosa
IIE	Lymphoma additionally infiltrating lymph nodes on same side of diaphragm
IIE1	Infiltration of regional lymph nodes
IIE2	Infiltration of lymph nodes beyond regional nodes
IIIE	Lymphoma infiltrating gastrointestinal tract and/or lymph nodes on both sides of diaphragm
IVE	Localized infiltration of associated lymph nodes together with diffuse or disseminated involvement of extragastrointestinal organs

From Musshoff K, Schmidt-Vollmer H. Proceedings: prognosis of non-Hodgkin's lymphomas with special emphasis on the staging classification. *Z Krebsforsch Klin Onkol Cancer Res Clin Oncol*. 1975;83:323-341.

Examination Technique and Disease Correlates

The procedural technique for EUS evaluation of MALT lymphoma is similar to that described for evaluation of gastric cancer. Given the diffuse nature of the disease process, a radial echoendoscope is usually preferred for tumor staging with examinations performed at frequencies of 7.5 and 12 MHz. Another option is the use of a high-frequency ultrasonic mini-probe to study the gastric wall layers in greater detail, but these probes are limited in their ability to assess lymph node status.

T Staging

EUS assessment of the depth of lymphoma infiltration is based on the TNM classification. At EUS, tumor staging is determined by the extent of wall layer involvement.[84] The modified Ann Arbor classification has been frequently used to categorize the disease process in multiple studies (Tables 11.8 and 11.9).[85]

T1: Tumor located in the mucosa and/or submucosa (Fig. 11.10)
T2: Tumor located in the mucosa and submucosa with infiltration into the muscularis propria or subserosa (Fig. 11.11)
T3: Tumor penetration into the serosa (Fig. 11.12)
T4: Tumor infiltration into adjacent structures (Fig. 11.13)

TABLE 11.9

Comparison of Modified Ann Arbor and TNM Classifications

Ann Arbor	TNM	Comment
IE_1	T1m-smN0	
IE_2	T2-4N0	
IIE_1	T1-4N1	Perigastric lymph nodes
IIE2	T1-4N2	Regional lymph nodes
IIIE	T1-4N3	Lymph nodes on both sides of diaphragm
IVE	T1-4N0-3M1	Visceral metastases or second extranodal site

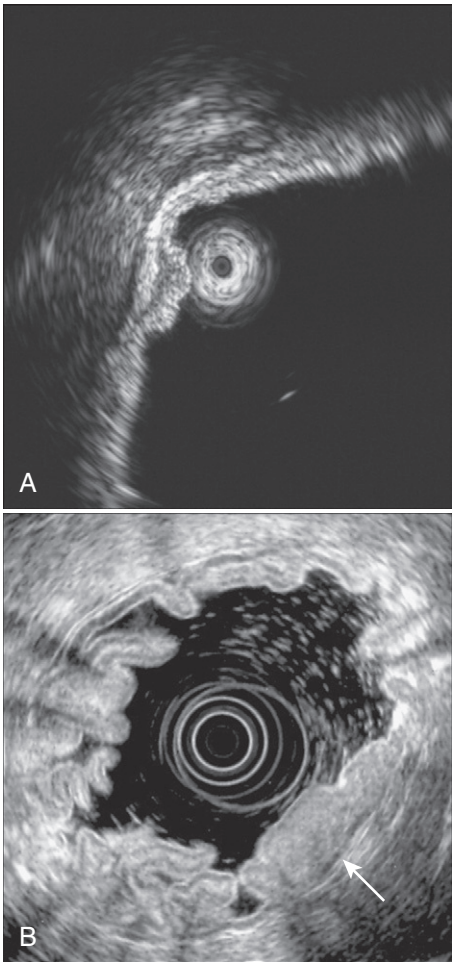


FIGURE 11.10 Staging of lymphoma. A, Small sessile lesion confined to the mucosal layer (T1m) as visualized using a 12-MHz mini-probe. **B,** Lymphomatous changes involving the submucosal layer (T1sm) but without infiltration of the muscularis propria *(arrow).*

N Staging

EUS can detect lymph nodes as small as 3 to 4 mm (see Fig. 11.12). However, it is not possible to differentiate benign from malignant lymph nodes by EUS imaging alone. In one study, the presence of rounded, sharply demarcated, homogeneous, hypoechoic lymph nodes greater than 1 cm in diameter were predictive of malignancy, whereas elongated, heterogeneous, hyperechoic lymph nodes with indistinct borders were more likely to be benign.[86] However, assessment of these features is highly operator dependent, and it may be impossible to differentiate them in the presence of micrometastases. EUS-guided FNA is more accurate than imaging alone for detecting tumor involvement in lymph nodes.

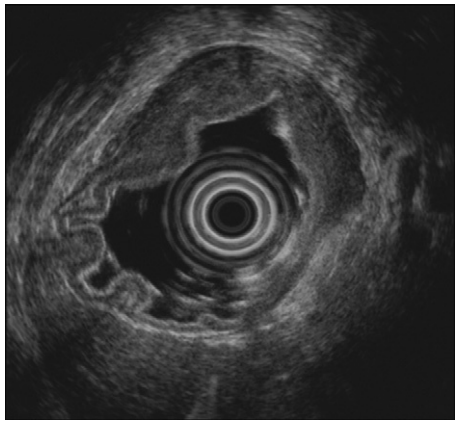


FIGURE 11.11 Radial scanning at 12 MHz revealing lymphoma infiltrating the muscularis propria (T2).

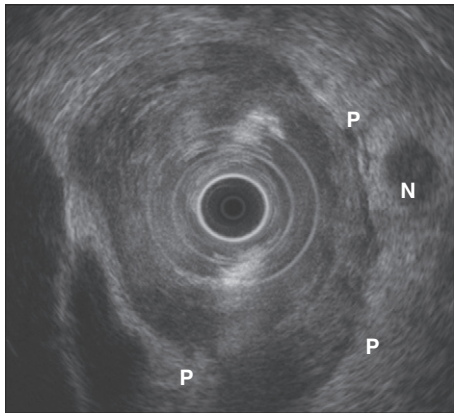


FIGURE 11.12 Radial image revealing infiltration of the serosa (pseudopodia, P) by the lymphoma and the presence of peritumoral lymph nodes (N) (T3N1).

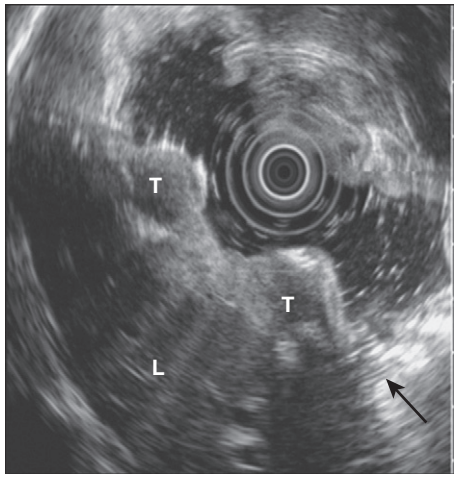


FIGURE 11.13 High-grade gastric lymphoma infiltrating all the wall layers *(arrow)* and into the perigastric structures (liver, *L*), consistent with T4 disease. *T,* tumor.

TABLE 11.10

Comparisons of Staging Classifications for MALT Lymphomas

Lymphoma Extension	TNM Modifications in the Paris System[88]	Adapted TNM Staging[66] System	Musshoff Modified Ann Arbor Staging[130]	Lugano Staging[87]
Mucosa	T1mN0M0	T1N0M0	IE_1	Stage I: confined to GI tract (single primary or multiple, noncontiguous)
Submucosa	T1smN0M0	—	IE_2	
Muscularis propria serosa	T2N0M0 T3N0M0	T2N0M0 T3N0M0		
Perigastric lymph nodes	T1-3N1M0	T1-3N1M0	IIE_1	Stage II: extending into the abdomen (stage II_1: local nodal involvement; stage II_2: distant nodal involvement)
More distant regional nodes	T1-3N2M0	T1-3N2M0	IIE_2	
Extra-abdominal lymph nodes	T1-3N3M0	—	—	
Invasion of adjacent tissues	—	T4N0M0	IE	Stage II_E: penetration of serosa to involving adjacent organs or tissues
Lymph nodes on both sides of the diaphragm, and/or additional extranodal sites with noncontinuous involvement of separate GI sites	T1-4N3M0	T1-4N3M0	IIIE	
Or noncontinuous involvement of non-GI sites	T1-4N0-3M1 T1-4N0-3M2	T1-4N0-3MI	IVE	Stage I: disseminated extranodal involvement or concomitant supradiaphragmatic nodal involvement
Bone marrow not assessed	T1-4N0-3M0-2 BX	—	—	
Bone marrow not involved	T1-4N0-3M0-2 B0	—	—	
Bone marrow involved	T1-4N0-3M2 B1	—	—	

GI, gastrointestinal.

Adapted from Ferrucci P, Zucca E. Primary gastric lymphoma pathogenesis and treatment: what has changed over the past 10 years? *Br J Haematol.* 2007;136:521-538.

Accuracy of EUS in Staging MALT Lymphoma

Some EUS features are specific for gastric lymphomas and also help in differentiating gastric cancer from lymphoma. These features are as follows: (1) whereas infiltrative carcinoma shows vertical growth (transmural) in the gastric wall, lymphoma grows horizontally; (2) the gastric wall thickening is typically more diffuse and homogeneous in lymphoma than in adenocarcinoma; (3) lymphoma rarely results in luminal narrowing and obstruction, even in the presence of diffuse infiltration, and it most commonly involves the distal half of the stomach; also, in contrast to gastric adenocarcinoma, lymphoma often involves more than one site within the stomach; (4) at an early stage, lymphomas can manifest with thickening of the second layer alone or separately in the second and third layers with preservation of layer architecture; in advanced stages, lymphomas show diffuse thickening with fusion of wall layers; and (5) diffuse and superficial infiltration is more often indicative of a low-grade MALT lymphoma, whereas the presence of masses is more frequently associated with aggressive high-grade histologic features.[71]

Once a diagnosis has been made (and before any therapeutic decision has been taken), it is important to establish the disease's anatomic extension because this is a crucial prognostic factor. The staging of gastric lymphoma is controversial even today. As previously described, several staging classifications for MALT lymphomas have been applied (Table 11.10). The commonly used classifications for EUS staging are the TNM and the modified Ann Arbor systems (see Table 11.9). TNM staging allows a detailed assessment of lymphoproliferative disease because it differentiates the degree of mural involvement layer by layer, whereas the modified Ann Arbor classification contemplates only two stages of mural involvement. Therefore, the modified Ann Arbor stage IE_1 corresponds to T1m and T1sm, and stage IE_2 corresponds to multiple stages including T2, T3, and T4. Compared with TNM staging, the modified Ann Arbor staging system is inadequate for proper staging of the layers of gastric lymphomatous infiltration. Therefore, the TNM system is more practical for prognostic staging. Further, the Lugano classification was introduced and incorporated stage IIE for penetration of serosa involving the adjacent organs into the modified Ann Arbor system.[87] Because TNM staging was primarily categorized for gastric cancers, it was modified as the Paris classification for primary gastrointestinal lymphomas.[88] This system adequately records the depth of the tumor infiltration into the gastric layers (T category), extent of nodal involvement (N category), and evidence of extranodal metastases (M category).

TABLE 11.11

Accuracy of EUS in Staging Gastric Lymphoma

Authors (yr)	Patients (*n*)	T Stage (%)	N Stage (%)
Fujishima et al[77] (1991)	11	91	82
Caletti et al[76] (1993)	44	92	77
Schüeder et al[131] (1993)	10	80	90
Palazzo et al[52] (1993)	24	91	83

(Adapted from Janssen J. The impact of EUS in primary gastric lymphoma. *Best pract res clin Gastroenterol.* 2009;23:671678)

Currently, EUS remains the most accurate imaging modality for the evaluation and staging of gastric lymphomas. Most studies were conducted in the era when surgical resection was the standard treatment modality as compared with the nonsurgical treatment strategies used currently. The reported accuracy of T staging by EUS was approximately 80% to 90% (Table 11.11). In a

single-center experience reported by Caletti et al,[76] the sensitivity and specificity of EUS were 89% and 97%, respectively. However, the results varied in a large study reported by Fischbach et al[67] that involved 34 centers using the modified Ann Arbor classification. Data from preoperative EUS procedures were compared with the histologic stage at resection. The sensitivities for stages IE1, IE2, and IIE2 were 67%, 83%, and 71%, respectively. However, in this study, only 5 of the 34 centers contributed more than two patients. This finding reflects the lack of experience in the remaining centers that resulted in the overall lower accuracy rates.

For staging of lymph nodes, EUS can detect nodes as small as 3 to 4 mm in diameter. In prior studies, the accuracy was 77% to 90% (see Table 11.11). However, the distinction between benign and malignant lymph nodes remains a gray area. The interpretation is operator dependent, and micrometastases to lymph nodes may be missed. EUS-guided FNA of suspicious lymph nodes may overcome this limitation.[78]

Yasuda et al[89] succeeded in diagnosing 48 of 50 lymphomas (96%) by using a 19-gauge EUS FNA needle system. When this approach was combined with flow cytometry and immunohistochemistry, the overall sensitivity, specificity, and accuracy of EUS-FNA for the diagnosis of lymphoma were 74%, 93%, and 81%, respectively.[79] The sensitivity was significantly higher for the combined technique when compared with regular EUS FNA-guided cytologic examination. However, these studies did not focus on primary MALT lymphomas of the stomach. Further studies will be necessary to define the role of these techniques, especially in early lymphomas, in which accurate staging is crucial to the choice of treatment.

EUS has a limited role in the evaluation of distant metastases. CT scan is superior to EUS in detecting metastatic disease. Comparative studies of other imaging modalities such as MRI and PET-CT scans with EUS in the staging of MALT lymphomas are lacking. The use of high-resolution mini-probes helps in better differentiating superficial gastric wall layers as well as in targeting smaller lesions. Lügering et al[90] studied the use of mini-probes (12 MHz) for staging of gastric lymphoma and reported a superior performance for mini-probes when compared with echoendoscopes. These investigators recommended the use of mini-probes in clinical practice because the examination can be performed as a single-step procedure during diagnostic endoscopy. However, mini-probes may not be optimal for lymph node staging.

Role of EUS in Predicting Response to Therapy

For low-grade MALT lymphomas, which account for approximately 35% of primary gastric lymphomas, the accuracy of EUS for staging and follow-up is decisive for optimal treatment. In fact, EUS can predict the outcome of treatment of MALT lymphoma by simple eradication of *H. pylori*. Although encouraging results of antibiotic treatment have been reported, many authors have failed either to include EUS in their staging methods or to correlate EUS staging results, when available, with remission rates. In fact, remission rates reported by different trials in which patients with MALT lymphoma were not differentiated according to EUS stage have shown striking disparities. Notably, few patients with deeper infiltration showed a complete response.[66,91] However, in patients with localized disease, EUS shows greater promise in predicting response to therapy.

In an early pilot study, Sackmann et al[92] studied whether staging by EUS predicted the outcome of treatment of MALT lymphoma by eradication of *H. pylori*. These investigators found complete eradication of *H. pylori* in all 22 patients with a 2-week course of oral omeprazole and amoxicillin. Twelve of 14 patients with lymphoma limited to the second or third layer (mucosa or submucosa) at EUS were in complete remission as compared with none of 10 patients with deeper stages of infiltration after a median follow-up period of 10 months. Thus, EUS appeared to be a reliable method for selecting patients with early superficial lymphomatous involvement who may benefit from antibiotics and for referring others for chemotherapy or surgery.

Another study, by Ruskoné-Fourmestraux et al,[93] evaluated predictive factors for regression of gastric MALT lymphoma following anti–*H. pylori* treatment. These investigators enrolled 44 consecutive patients with localized gastric MALT lymphoma (Ann Arbor stages IE and IIE), all of whom underwent EUS. All patients had *H. pylori* treatment with lansoprazole, amoxicillin, and clarithromycin for 14 days. Overall, histologic regression of the lymphoma was noted in only 43% of the patients; median follow-up for these 19 responders was 35 months. A significant difference was noted in the response rates between patients with disease restricted to the mucosa and those with more deep-seated lesions. In addition, the complete response rate for lymphoma clearance increased from 56% for patients with nodal involvement to 79% when no nodal involvement was found at EUS. The investigators concluded that the absence of lymph node involvement was predictive of successful treatment response.

Nakamura et al[3,94] found that 26 (93%) of 28 MALT lymphomas restricted to the mucosa regressed completely after therapy as compared with only 3 (23%) of 13 lymphomas that involved the submucosa. Other factors, such as the presence of a high-grade component, perigastric lymphadenopathy, or clinical staging before eradication therapy, had a poor correlation with the probability of lymphoma regression. Levy et al[95] noted a 69% overall complete response rate in 48 patients treated for *H. pylori* infection. These investigators found that the response rate did not correlate well with endoscopic features or the histologic grade. In contrast, when EUS features were taken into account, remission was achieved in 76% of patients who had no detectable perigastric lymph nodes as compared with only 33% of patients with detectable lymph nodes. Further remission was achieved with chlorambucil monochemotherapy in 58% of patients who did not respond to anti–*H. pylori* treatment. In the multicentric Italian study by Caletti et al,[96] 51 patients with low-grade MALT lymphomas were staged using the TNM classification. After antibiotic treatment, eradication of *H. pylori* was seen in 45 (88%) of the 51 patients. Two years after therapy, regression of lymphoma was noted in 28 (55%) of these 51 patients. Complete response was achieved in 12 (75%) of 16 patients with T1mN0 disease and in 11 (58%) of 19 patients with stage T1smN0 disease compared with only 4 (50%) of 8 patients with stage T1mN1 and T1smN1 and 1 of 4 (25%) patients with stage T2N0. None of the patients with stage T2N1 disease achieved a complete response (see Table 11.7).

A more recent trial aimed to determine the long-term outcome of patients undergoing only *H. pylori* eradication therapy.[67] Ninety patients with a low-grade gastric MALT lymphoma were enrolled in this multicenter study and were followed for at least 12 months. Successful eradication of *H. pylori* was achieved in 88 (98%) patients using a triple regimen. Long-term outcome was characterized by a complete response in 56 patients (62%), minimal residual disease in 17 (19%), partial remission in 11 (12%), no change in 4 (4%) and progressive disease in 2 patients (2%). The regression rate, as assessed by EUS, was higher in stage IE1 disease compared with stage IE2.

In conclusion, the ability of EUS to stage MALT lymphoma accurately is of paramount importance because it allows the clinician to determine the best mode of therapy for individual patients. From the current data, early-stage lesions (T1) may regress following anti–*H. pylori* therapy alone. More advanced lesions (T2 to T4) may require more aggressive treatment protocols, and it would be prudent to offer combination chemotherapy, radiation therapy, and surgery to these patients. In addition, the assessment of response to therapy requires long-term follow-up with interval upper endoscopy and mapping biopsies in combination with EUS. When biopsy results remain positive for lymphoma but EUS does not reveal any structural wall changes, it may be appropriate to use the "wait and watch" strategy because anti–*H. pylori* therapy may take up to 18 months to produce complete remission.[97]

Role of EUS in Clinical Follow-Up

The importance of EUS lies not only in its ability to stage MALT lymphoma before treatment, but also in systematic follow-up, because interval EUS may determine response to therapy and may detect early disease recurrence. During follow-up, EUS may show restoration of normal gastric wall layers before complete histologic remission, and at other times recurrent wall thickening or disruption may be seen in some patients who were previously documented to be in remission. In general, for patients who have a persistently thickened gastric wall on EUS despite adequate antibiotic therapy, other treatment modalities should be considered, even if endoscopic biopsy results are negative, because the likelihood of persistent lymphoma or recurrence is high.[96]

Most of the studies on EUS done for pretreatment staging of gastric MALT lymphoma agree on the importance of EUS for follow-up. However, given the relative lack of long-term follow-up series, issues of exactly when and how often to perform EUS, as well as exact clinical and histologic correlations with EUS, are still under debate. Püspök et al[98] evaluated 33 patients with primary gastric lymphoma and performed pretreatment and follow-up EUS every 3 to 6 months after nonsurgical treatment modalities. In this study, 158 EUS examinations were performed. A wall thickness less than or equal to 4 mm with preserved five-layer structure and the absence of suspicious lymph nodes were the criteria for endosonographic remission. At a median follow-up of 15 months, 82% of patients achieved histologic remission, whereas EUS remission was noted in only 64%. Eighteen patients achieved both histologic and EUS remission, and EUS remission occurred later than histologic remission (35 versus 18 weeks). Moreover, histologic relapse was demonstrated by EUS in only 1 of 5 cases. The investigators concluded that none of the tested endosonographic parameters were able to predict histologic remission. The reason for the lack of EUS concordance could be that the investigators did not use the TNM classification for EUS assessment of disease in the gastric wall. This situation may have led to underpowering of EUS parameters in predicting remission.

Yeh et al,[83] however, concluded differently in another trial evaluating the role of EUS in 20 patients with low-grade gastric MALT lymphoma before and after *H. pylori* eradication therapy. Of 17 patients who were *H. pylori* positive, 14 (82%) obtained histologic remission. The investigators found that, although pretreatment EUS performed with a 12-MHz mini-probe showed significantly greater wall thickness in patients with MALT lymphoma than in controls (6.1 versus 2.8 mm), follow-up showed a comparative and statistically significant reduction in wall thickness. For patients with a significant reduction in wall thickness just after *H. pylori* eradication, the probability of a complete response of the MALT lymphoma was 40% at 12 months and 84% at the end of 24 months. Despite the absence of endoscopic lesions, half the patients in the foregoing study had persistent changes noted on EUS. This finding may be interpreted in few ways: (1) EUS tends to overstage residual disease because it is unable to differentiate between tumor and fibrosis, (2) EUS is able to detect persistent lymphoma residue that is not evident histologically because the cells are limited to the submucosa or deeper layers, and (3) persistence of a B-cell monoclonal pattern of lymphoma cells in the gastric wall has been documented in roughly half of the patients who have had histologic remission using molecular markers.[99,100] The molecular pattern tends to disappear in a majority of patients during follow-up, although this process can be slow and varying, and the persistence of molecular markers can account for the EUS findings. The clinical significance with regards to detecting relapse is still unclear, and long-term follow-up studies are required.

Therefore, EUS should not be regarded as an alternative to endoscopic biopsies. On the contrary, both techniques are complementary to maximize the diagnostic yield for staging and follow-up of patients with gastric MALT lymphoma.

Limitations of Staging EUS

Given the strong correlation between EUS staging and prognosis, it is important that all observers agree on the same staging parameters. This is relevant because EUS is an operator-dependent technique. Good interobserver agreement is essential to compare clinical trials conducted at different centers, to stratify patients within studies, and to establish the best treatment strategy for individual patients, even when they are not included in clinical trials.

Interobserver agreement for judging gastric wall infiltration among different endosonographers was studied using photographs in a study by Fusaroli et al (Italian MALT Lymphoma Study Group).[101] In this multicenter evaluation of patients with MALT lymphoma of the stomach, evaluation was conducted before and after treatment, to assess interobserver agreement for EUS in the initial staging and in follow-up after therapy. In the baseline group, 54 patients were studied. In the follow-up group, 42 patients were re-evaluated 6 months after medical therapy. Overall, interobserver agreement for T stage was fair, both before and after treatment ($\kappa = 0.38$ and $\kappa = 0.37$, respectively). Interobserver agreement for N stage was substantial before treatment, but only fair after treatment ($\kappa = 0.63$ and $\kappa = 0.34$, respectively). The lowest values of agreement were for T1sm ($\kappa = 0.20$) and T2 lesions ($\kappa = 0.33$). The performance of each observer was further compared with that of the nine other endosonographers in the same study. It was shown that those with less EUS experience had the lowest rates of interobserver agreement. The investigators suggested that a minimum of 100 gastric EUS examinations may be required for better performance.

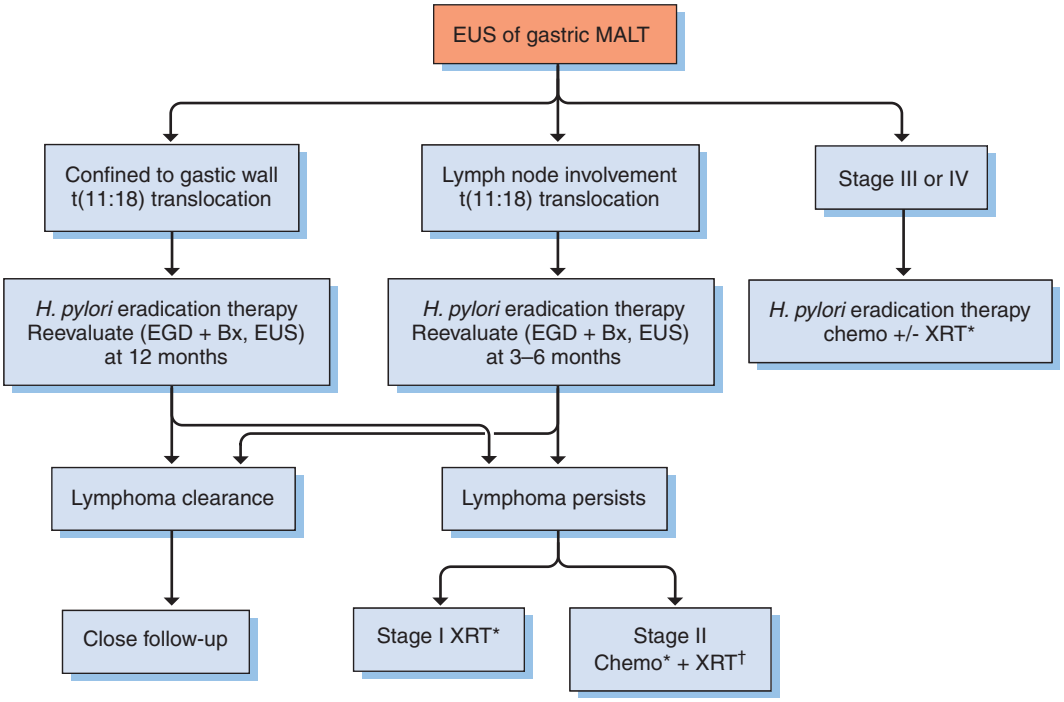
Several other factors limit the accuracy of EUS staging. Anatomic factors such as difficult areas of visualization including the cardia, lesser curve, antrum, and pylorus limit the 360-degree sweep view advantage of the EUS scope. Artifact errors may result from blood or mucus, body movements, breathing, and inadequate distention of the stomach. Inadequate gastric distention can limit assessment of the depth of infiltration, especially when large gastric folds are present. Moreover, accurate guidelines must be observed in patient preparation, sedation, administration of antispasmodics, and water filling of the stomach during the procedure. Technologic advances such as the three-dimensional reconstruction probes may help in enhancing the accuracy of staging in T and N categories.

EUS-Based Workup

Although *H. pylori*–positive patients diagnosed with early-stage disease (T1m and T1sm) by EUS may be treated with antimicrobial therapy, patients with advanced disease usually require more aggressive treatment protocols (Fig. 11.14). Following treatment, EUS also aids in determining response to therapy and in detecting early relapses. At times, EUS may show restoration of normal gastric wall layers before evident histologic remission, and at other times recurrent wall thickening or disruption may be seen in individuals who were previously in remission. For patients with a persistently thickened gastric wall on EUS despite antibiotic therapy, other treatment modalities should be considered, even if results of endoscopic biopsies are negative, because these patients are likely to have persistent lymphoma.

EVALUATION OF THICKENED GASTRIC FOLDS AT EUS

The range for normal gastric wall layer thickness at EUS is between 0.8 and 3.6 mm.[102] The diagnosis of gastric wall thickening is made when the overall thickness of the five layers exceeds 4 mm.[103] Although the possible causes of thickened gastric folds observed at endoscopy are myriad (Table 11.12), three disease entities are more



*Chemo: according to institutional protocol
†XRT: external radiation therapy according to institutional protocol

FIGURE 11.14 Algorithmic approach to the management of mucosa-associated lymphoid tissue (MALT) lymphoma. Bx, biopsy; EGD, esophagogastroduodenoscopy. (Adapted from Yoon S, Coit D, Portlock C, Karpeh M. The diminishing role of surgery in the treatment of gastric lymphoma. *Ann Surg.* 2004;240:28–37.)

TABLE 11.12
Differential Diagnosis for Thickened Gastric Folds Noted at Endoscopy

Category	Disorder
Malignant diseases	Adenocarcinoma, linitis plastica, lymphoma, metastases
Infections	Secondary syphilis, tuberculosis, cytomegalovirus infection, herpes simplex virus infection, histoplasmosis, cryptococcosis, aspergillosis, *H. pylori* infection, anisakiasis
Infiltrative disorders	Crohn's disease, sarcoidosis, amyloidosis, gastritis diseases (eosinophilic, granulomatous, and lymphocytic)
Vascular disorders	Portal hypertensive gastropathy, gastric varices
Other diseases	Ménétrier's disease, Zollinger-Ellison syndrome, hyperrugosity, gastritis cystica profunda

commonly encountered in clinical practice: linitis plastica, Ménétrier's disease, and lymphoma (described in the preceding section).

Linitis Plastica

Limited data are available on the endosonographic features of linitis plastica, also known as scirrhous-type gastric cancer. Thickened gastric folds are seen at endoscopy, and poor distensibility is a frequent finding. Histopathologically, linitis plastica is characterized by the diffuse growth of malignant cells with signet ring features and is usually associated with marked submucosal fibrosis and gastric wall thickening.[104] The diagnosis can sometimes be challenging because of the lack of a mucosal lesion and the scarcity of deeper diagnostic tissue in superficial biopsy material. It has been reported that in up to 30% of cases, particularly those without mucosal lesions, results of forceps tissue biopsy and brushings can be negative.[105] Although some investigators suggested diffuse thickening of all gastric wall layers at EUS in this disease,[105] others reported that the second, third, and fourth layers of the gastric wall are frequently thickened (Fig. 11.15).[106] Thickening of the fourth layer is rarely if ever seen in benign conditions, and the presence of a thickened fourth layer in the setting of large gastric folds should raise the concern of linitis plastica. Linitis plastica has been diagnosed successfully by EUS-guided FNA following negative

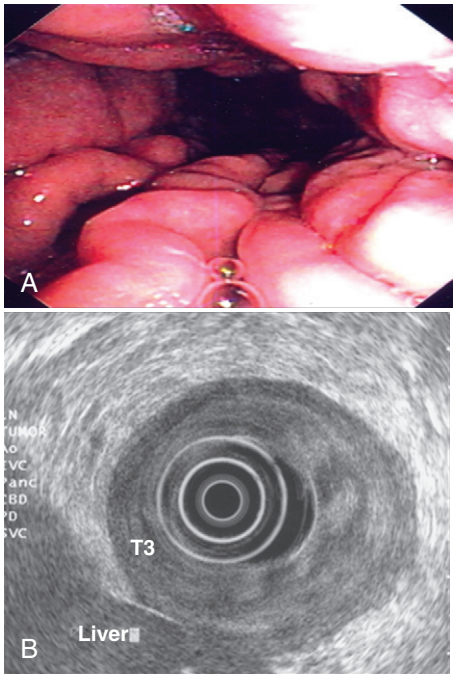


FIGURE 11.15 Linitis plastica. A, Thickened gastric folds that are poorly distensible at endoscopy. **B,** At radial scanning, the tumor is seen to involve the upper four layers of the gastric wall, consistent with linitis plastica.

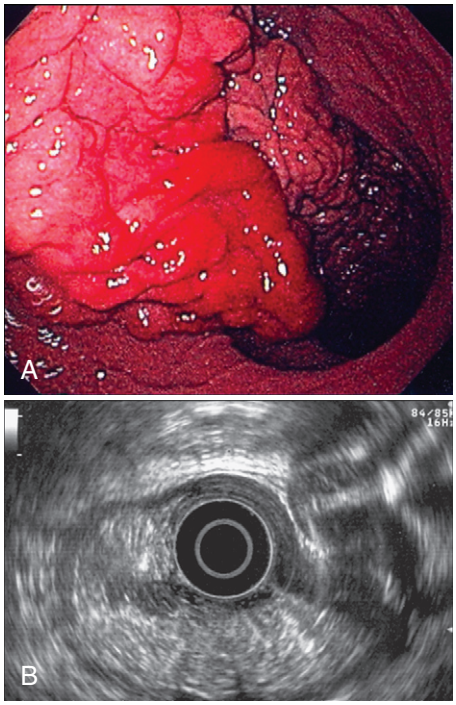


FIGURE 11.16 **Ménétrier's disease. A,** Hypertrophic gastric folds in the fundic region as seen on endoscopy. **B,** On EUS, the second layer of the gastric wall is found to be hyperechoic and thickened, consistent with Ménétrier's disease (proven by surgical resection).

endoscopic biopsy results.[104] On microscopy, malignant epithelial cells containing eccentric nuclei with foamy cytoplasm (resembling degenerated histiocytes) and rare cells with intracytoplasmic vacuoles and crescent-shaped, hyperchromatic nuclei, characteristic of signet ring cells are noted.

Ménétrier's Disease

Ménétrier's disease is characterized by epithelial hyperplasia involving the surface and foveolar mucous cells. The pathogenesis of Ménétrier's disease is incompletely understood but may involve transforming growth factor-alpha (TGF-alpha). TGF-alpha increases gastric mucus production and inhibits acid secretion.[107] Levels of TGF-alpha are markedly increased in the gastric mucous cells in patients with Ménétrier's disease. Patients typically present with epigastric pain, asthenia, anorexia, weight loss, edema, and vomiting. The enlarged folds are usually confined to the body and fundus of the stomach. The folds are usually enlarged symmetrically, although asymmetrical enlargement with a polypoid appearance may be encountered rarely. A full-thickness biopsy is usually required for diagnosis, which is established by the demonstration of extreme foveolar hyperplasia with glandular atrophy.[108,109] At EUS (Fig. 11.16), Ménétrier's disease displays a more localized thickening, which is hyperechoic rather than hypoechoic, and involves mainly the second layer of the stomach.[110]

EUS and Large Gastric Folds

The role of EUS in evaluating large gastric folds was assessed in 28 patients, most of whom had endoscopic biopsy results that were inconclusive for malignancy.[111] Because EUS demonstrated gastric varices, biopsies were not performed in four patients. In three others, biopsy results were negative for malignancy; however, because of ultrasonographic findings of wall thickening involving layers 3 and 4, the patients underwent laparotomy, which revealed primary gastric carcinoma. In the remaining 21 patients, large-forceps endoscopic biopsy revealed acute or chronic inflammation in 16 (67%), malignancy in 4 (17%), and Ménétrier's disease in 1 (4%). Malignancy did not develop in any of the patients with gastric wall thickening limited to layer 2 during a mean follow-up of 35 months. The investigators concluded that when EUS abnormalities involve only the mucosal layer, endoscopic biopsies are diagnostic. Abnormalities involving the muscularis propria in the absence of ulceration strongly suggest malignancy and should be investigated further if endoscopic biopsy findings are negative. Moreover, with EUS, potentially dangerous biopsies of gastric varices can be avoided.

Another study analyzed the EUS features of 35 patients with giant gastric folds and described some unique features that were characteristic of each type of lesion.[112] According to the investigators, when the second layer alone was thickened, Ménétrier's disease was one of the possible pathologic entities, whereas when the third layer alone was abnormally enlarged, anisakiasis was suspected. Most of the patients with scirrhous carcinoma showed an abnormally enlarged third and fourth layer. Although the second and third layers could be thickened in healthy subjects with simple hyperrugosity, these layers could also be thickened in patients with gastric lymphoma. The fourth layer was significantly thickened only in malignant conditions.

Gastritis cystic profunda is a rare cause of thickened gastric folds in which multiple small cysts are seen in the mucosa and submucosa of the stomach.[113] The diagnosis is usually established by findings at EUS and mucosectomy. EUS is not a histologic technique and must be used always in conjunction with endoscopic biopsy. EUS can help in determining the site at which to take a biopsy sample to avoid false-negative results, and sometimes the need for a larger biopsy sample can be suggested. Conversely, biopsy can be contraindicated when an EUS examination identifies gastric varices.

EUS-Based Workup

An algorithmic workup based on EUS findings can be suggested for patients with large gastric folds of unclear origin. For an early diagnosis, when the EUS pattern is normal and endoscopic findings are inconclusive, an adequate number of standard endoscopic biopsies should be performed and even repeated in multiple sessions. Large-forceps biopsy and snare biopsy must also be considered. When abnormalities involve layer 2, endoscopic biopsies are diagnostic. When abnormalities involve layers 2 and 3, large-forceps biopsy may be appropriate. When abnormalities involve layer 4, malignancy should be strongly suspected even if results of standard biopsies are negative; thus, FNA or Tru-Cut biopsy should be performed in these patients.

REFERENCES

1. Ferlay J, Bray F, Pisani P, Parkin DM. *Globacan 2000: Cancer Incidence, Mortality and Prevalence Worldwide*. Version 1.0. IARC Cancer Base No. 5. Lyon: IARC Press; 2001.
2. Siewert J, Böttcher K, Stein H, Roder J. Relevant prognostic factors in gastric cancer: ten-year results of the German Gastric Cancer Study. *Ann Surg*. 1998;228:449–461.
3. Nakamura K, Ueyama T, Yao T, et al. Pathology and prognosis of gastric carcinoma: findings in 10,000 patients who underwent primary gastrectomy. *Cancer*. 1992;70:1030–1037.
4. Middleton G, Cunningham D. Current options in the management of gastrointestinal cancer. *Ann Oncol*. 1995;6(suppl 1):17–25.
5. Agboola O. Adjuvant treatment in gastric cancer. *Cancer Treat Rev*. 1994; 20:217–240.
6. Macdonald J, Smalley S, Benedetti J, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med*. 2001;345:725–730.
7. Allum W, Hallissey M, Ward L, Hockey M. A controlled, prospective, randomised trial of adjuvant chemotherapy or radiotherapy in resectable gastric cancer: interim report. British Stomach Cancer Group. *Br J Cancer*. 1989;60:739–744.

8. Botet J, Lightdale C, Zauber A, et al. Preoperative staging of gastric cancer: comparison of endoscopic US and dynamic CT. *Radiology*. 1991;181: 426–432.
9. Sussman S, Halvorsen RJ, Illescas F, et al. Gastric adenocarcinoma: CT versus surgical staging. *Radiology*. 1988;167:335–340.
10. Power D, Schattner M, Gerdes H, et al. Endoscopic ultrasound can improve the selection for laparoscopy in patients with localized gastric cancer. *J Am Coll Surg*. 2009;208:173–178.
11. Mouri R, Yoshida S, Tanaka S, et al. Usefulness of endoscopic ultrasonography in determining the depth of invasion and indication for endoscopic treatment of early gastric cancer. *J Clin Gastroenterol*. 2009;43: 318–322.
12. Blackshaw G, Lewis W, Hopper A, et al. Prospective comparison of endosonography, computed tomography, and histopathological stage of junctional oesophagogastric cancer. *Clin Radiol*. 2008;63:1092–1098.
13. Ganpathi I, So J, Ho K. Endoscopic ultrasonography for gastric cancer: does it influence treatment? *Surg Endosc*. 2006;20:559–562.
14. Polkowski M, Palucki J, Wronska E, et al. Endosonography versus helical computed tomography for locoregional staging of gastric cancer. *Endoscopy*. 2004;36:617–623.
15. Sultan J, Robinson S, Hayes N, et al. Endoscopic ultrasonography-detected low-volume ascites as a predictor of inoperability for oesophagogastric cancer. *Br J Surg*. 2008;95:1127–1130.
16. Singh P, Mukhopadhyay P, Bhatt B, et al. Endoscopic ultrasound versus CT scan for detection of the metastases to the liver: results of a prospective comparative study. *J Clin Gastroenterol*. 2009;43:367–373.
17. Hölscher A, Drebber U, Mönig S, et al. Early gastric cancer: lymph node metastasis starts with deep mucosal infiltration. *Ann Surg*. 2009;250: 791–797.
18. Okamura S, Tsutsui A, Muguruma N, et al. The utility and limitations of an ultrasonic miniprobe in the staging of gastric cancer. *J Med Invest*. 1999;46:49–53.
19. Bhutani M, Hawes R, Hoffman B. A comparison of the accuracy of echo features during endoscopic ultrasound (EUS) and EUS-guided fine-needle aspiration for diagnosis of malignant lymph node invasion. *Gastrointest Endosc*. 1997;45:474–479.
20. Wang J, Hsieh J, Huang Y, et al. Endoscopic ultrasonography for preoperative locoregional staging and assessment of resectability in gastric cancer. *Clin Imaging*. 1998;22:355–359.
21. Prasad P, Schmulewitz N, Patel A, et al. Detection of occult liver metastases during EUS for staging of malignancies. *Gastrointest Endosc*. 2004;59:49–53.
22. Yoshida S, Tanaka S, Kunihiro K, et al. Diagnostic ability of high-frequency ultrasound probe sonography in staging early gastric cancer, especially for submucosal invasion. *Abdom Imaging*. 2005;30:518–523.
23. Yasuda K. Development and clinical use of ultrasonic probes. *Endoscopy*. 1994;26:816–817.
24. Yanai H, Noguchi T, Mizumachi S, et al. A blind comparison of the effectiveness of endoscopic ultrasonography and endoscopy in staging early gastric cancer. *Gut*. 1999;44:361–365.
25. Yanai H, Matsumoto Y, Harada T, et al. Endoscopic ultrasonography and endoscopy for staging depth of invasion in early gastric cancer: a pilot study. *Gastrointest Endosc*. 1997;46:212–216.
26. Akahoshi K, Chijiwa Y, Hamada S, et al. Pretreatment staging of endoscopically early gastric cancer with a 15 MHz ultrasound catheter probe. *Gastrointest Endosc*. 1998;48:470–476.
27. Matsumoto Y, Yanai H, Tokiyama H, et al. Endoscopic ultrasonography for diagnosis of submucosal invasion in early gastric cancer. *J Gastroenterol*. 2000;35:326–331.
28. Puli S, Batapati Krishna Reddy J, Bechtold M, et al. How good is endoscopic ultrasound for TNM staging of gastric cancers? A meta-analysis and systematic review. *World J Gastroenterol*. 2008;14:4011–4019.
29. François E, Peroux J, Mouroux J, et al. Preoperative endosonographic staging of cancer of the cardia. *Abdom Imaging*. 1996;21:483–487.
30. Dittler H, Siewert J. Role of endoscopic ultrasonography in esophageal carcinoma. *Endoscopy*. 1993;25:156–161.
31. Chang K, Albers C, Nguyen P. Endoscopic ultrasound-guided fine needle aspiration of pleural and ascitic fluid. *Am J Gastroenterol*. 1995;90: 148–150.
32. Lee Y, Ng E, Hung L, et al. Accuracy of endoscopic ultrasonography in diagnosing ascites and predicting peritoneal metastases in gastric cancer patients. *Gut*. 2005;54:1541–1545.
33. Chu K, Kwok K, Law S, Wong K. A prospective evaluation of catheter probe EUS for the detection of ascites in patients with gastric carcinoma. *Gastrointest Endosc*. 2004;59:471–474.
34. Meining A, Dittler H, Wolf A, et al. You get what you expect? A critical appraisal of imaging methodology in endosonographic cancer staging. *Gut*. 2002;50:599–603.
35. Meining A, Rösch T, Wolf A, et al. High interobserver variability in endosonographic staging of upper gastrointestinal cancers. *Z Gastroenterol*. 2003;41:391–394.
36. Kim J, Song K, Youn Y, et al. Clinicopathologic factors influence accurate endosonographic assessment for early gastric cancer. *Gastrointest Endosc*. 2007;66:901–908.
37. Kida M, Tanabe S, Watanabe M, et al. Staging of gastric cancer with endoscopic ultrasonography and endoscopic mucosal resection. *Endoscopy*. 1998;30(suppl 1):A64–A68.
38. Yoshimoto K. Clinical application of ultrasound 3 D imaging system in lesions of the gastrointestinal tract. *Endoscopy*. 1998;30(suppl 1): A145–A148.
39. Ziegler K, Sanft C, Zimmer T, et al. Comparison of computed tomography, endosonography, and intraoperative assessment in TN staging of gastric carcinoma. *Gut*. 1993;34:604–610.
40. Kwee R, Kwee T. Imaging in local staging of gastric cancer: a systematic review. *J Clin Oncol*. 2007;25:2107–2116.
41. Kwee R, Kwee T. Imaging in assessing lymph node status in gastric cancer. *Gastric Cancer*. 2009;12:6–22.
42. Kayaalp C, Arda K, Orug T, Ozcay N. Value of computed tomography in addition to ultrasound for preoperative staging of gastric cancer. *Eur J Surg Oncol*. 2002;28:540–543.
43. Burke E, Karpeh M, Conlon K, Brennan M. Laparoscopy in the management of gastric adenocarcinoma. *Ann Surg*. 1997;225:262–267.
44. Cunningham D, Allum W, Stenning S, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med*. 2006;355:11–20.
45. Park S, Lee J, Kim C, et al. Endoscopic ultrasound and computed tomography in restaging and predicting prognosis after neoadjuvant chemotherapy in patients with locally advanced gastric cancer. *Cancer*. 2008; 112:2368–2376.
46. Chen C, Yang C, Yeh Y. Preoperative staging of gastric cancer by endoscopic ultrasound: the prognostic usefulness of ascites detected by endoscopic ultrasound. *J Clin Gastroenterol*. 2002;35:321–327.
47. Fritscher-Ravens A, Schirrow L, Atay Z, et al. [Endosonographically controlled fine needle aspiration cytology: indications and results in routine diagnosis]. *Z Gastroenterol*. 1999;37:343–351 [in German].
48. DeWitt J, LeBlanc J, McHenry L, et al. Endoscopic ultrasound-guided fine-needle aspiration of ascites. *Clin Gastroenterol Hepatol*. 2007;5: 609–615.
49. Papaxoinis G, Papageorgiou S, Rontogianni D, et al. Primary gastrointestinal non-Hodgkin's lymphoma: a clinicopathologic study of 128 cases in Greece. A Hellenic Cooperative Oncology Group study (HeCOG). *Leuk Lymphoma*. 2006;47:2140–2146.
50. Koch P, del Valle F, Berdel W, et al. Primary gastrointestinal non-Hodgkin's lymphoma: I. Anatomic and histologic distribution, clinical features, and survival data of 371 patients registered in the German Multicenter Study GIT NHL 01/92. *J Clin Oncol*. 2001;19:3861–3873.
51. Suekane H, Iida M, Yao T, et al. Endoscopic ultrasonography in primary gastric lymphoma: correlation with endoscopic and histologic findings. *Gastrointest Endosc*. 1993;39:139–145.
52. Palazzo L, Roseau G, Ruskone-Fourmestraux A, et al. Endoscopic ultrasonography in the local staging of primary gastric lymphoma. *Endoscopy*. 1993;25:502–508.
53. Van Dam J. The role of endoscopic ultrasonography in monitoring treatment: response to chemotherapy in lymphoma. *Endoscopy*. 1994; 26:772–773.
54. Hordijk M. Restaging after radiotherapy and chemotherapy: value of endoscopic ultrasonography. *Gastrointest Endosc. Clin N Am*. 1995;5: 601–608.
55. Caletti G, Fusaroli P, Togliani T, et al. Endosonography in gastric lymphoma and large gastric folds. *Eur J Ultrasound*. 2000;11:31–40.
56. Paryani S, Hoppe R, Burke J, et al. Extralymphatic involvement in diffuse non-Hodgkin's lymphoma. *J Clin Oncol*. 1983;1:682–688.
57. Reddy S, Pellettiere E, Saxena V, Hendrickson F. Extranodal non-Hodgkin's lymphoma. *Cancer*. 1980;46:1925–1931.
58. De Paepe P, Achten R, Verhoef G, et al. Large cleaved and immunoblastic lymphoma may represent two distinct clinicopathologic entities within the group of diffuse large B-cell lymphomas. *J Clin Oncol*. 2005;23: 7060–7068.
59. Radaszkiewicz T, Dragosics B, Bauer P. Gastrointestinal malignant lymphomas of the mucosa-associated lymphoid tissue: factors relevant to prognosis. *Gastroenterology*. 1992;102:1628–1638.
60. Cogliatti S, Schmid U, Schumacher U, et al. Primary B-cell gastric lymphoma: a clinicopathological study of 145 patients. *Gastroenterology*. 1991;101:1159–1170.
61. Clark E, Ledbetter J. How B and cells talk to each other T. *Nature*. 1994; 367:425–428.

62. D'Elios M, Amedei A, Manghetti M, et al. Impaired T-cell regulation of B-cell growth in *Helicobacter pylori*–related gastric low-grade MALT lymphoma. *Gastroenterology*. 1999;117:1105–1112.
63. Eck M, Schmausser B, Haas R, et al. MALT-type lymphoma of the stomach is associated with *Helicobacter pylori* strains expressing the CagA protein. *Gastroenterology*. 1997;112:1482–1486.
64. Wotherspoon A, Ortiz-Hidalgo C, Falzon M, Isaacson P. *Helicobacter pylori*–associated gastritis and primary B-cell gastric lymphoma. *Lancet*. 1991;338:1175–1176.
65. Parsonnet J, Hansen S, Rodriguez L, et al. *Helicobacter pylori* infection and gastric lymphoma. *N Engl J Med*. 1994;330:1267–1271.
66. Steinbach G, Ford R, Glober G, et al. Antibiotic treatment of gastric lymphoma of mucosa-associated lymphoid tissue: an uncontrolled trial. *Ann Intern Med*. 1999;131:88–95.
67. Fischbach W, Goebeler-Kolve M, Dragosics B, et al. Long term outcome of patients with gastric marginal zone B cell lymphoma of mucosa associated lymphoid tissue (MALT) following exclusive *Helicobacter pylori* eradication therapy: experience from a large prospective series. *Gut*. 2004;53:34–37.
68. Carlson S, Yokoo H, Vanagunas A. Progression of gastritis to monoclonal B-cell lymphoma with resolution and recurrence following eradication of *Helicobacter pylori*. *JAMA*. 1996;275:937–939.
69. Spinelli P, Lo Gullo C, Pizzetti P. Endoscopic diagnosis of gastric lymphomas. *Endoscopy*. 1980;12:211–214.
70. Fork F, Haglund U, Högström H, Wehlin L. Primary gastric lymphoma versus gastric cancer: an endoscopic and radiographic study of differential diagnostic possibilities. *Endoscopy*. 1985;17:5–7.
71. Taal B, Boot H, van Heerde P, et al. Primary non-Hodgkin lymphoma of the stomach: endoscopic pattern and prognosis in low versus high grade malignancy in relation to the MALT concept. *Gut*. 1996;39: 556–561.
72. Komorowski R, Caya J, Geenen J. The morphologic spectrum of large gastric folds: utility of the snare biopsy. *Gastrointest Endosc*. 1986;32: 190–192.
73. Martin T, Onstad G, Silvis S, Vennes J. Lift and cut biopsy technique for submucosal sampling. *Gastrointest Endosc*. 1976;23:29–30.
74. Kuldau JG, Holman PR, Savides TJ. Diagnosis and management of gastrointestinal lymphoma. In: Faigel DO, Kochman ML, eds. *Endoscopic Oncology: Gastrointestinal Endoscopy and Cancer Management*. Totowa, NJ: Humana Press; 2006:139–149 [chapter 13].
75. Yoon S, Coit D, Portlock C, Karpeh M. The diminishing role of surgery in the treatment of gastric lymphoma. *Ann Surg*. 2004;240:28–37.
76. Caletti G, Ferrari A, Brocchi E, Barbara L. Accuracy of endoscopic ultrasonography in the diagnosis and staging of gastric cancer and lymphoma. *Surgery*. 1993;113:14–27.
77. Fujishima H, Misawa T, Maruoka A, et al. Staging and follow-up of primary gastric lymphoma by endoscopic ultrasonography. *Am J Gastroenterol*. 1991;86:719–724.
78. Harada N, Wiersema M, Wiersema L. Endosonography guided fine needle aspiration biopsy (EUS FNA) in the evaluation of lymphadenopathy: staging accuracy of EUS FNA versus EUS alone [abstract]. *Gastrointest Endosc*. 1997;45:31.
79. Wiersema M, Gatzimos K, Nisi R, Wiersema L. Staging of non-Hodgkin's gastric lymphoma with endosonography-guided fine-needle aspiration biopsy and flow cytometry. *Gastrointest Endosc*. 1996;44:734–736.
80. Vander Noot Mr, Eloubeidi M, Chen V, et al. Diagnosis of gastrointestinal tract lesions by endoscopic ultrasound-guided fine-needle aspiration biopsy. *Cancer*. 2004;102:157–163.
81. Caletti G, Brocchi E, Ferrari A, et al. Guillotine needle biopsy as a supplement to endosonography in the diagnosis of gastric submucosal tumors. *Endoscopy*. 1991;23:251–254.
82. Caletti G, Ferrari A, Bocus P, et al. Endoscopic ultrasonography in gastric lymphoma. *Schweiz Med Wochenschr*. 1996;126:819–825.
83. Yeh H, Chen G, Chang W, et al. Long-term follow up of gastric low-grade mucosa-associated lymphoid tissue lymphoma by endosonography emphasizing the application of a miniature ultrasound probe. *J Gastroenterol Hepatol*. 2003;18:162–167.
84. Shimodaira M, Tsukamoto Y, Niwa Y, et al. A proposed staging system for primary gastric lymphoma. *Cancer*. 1994;73:2709–2715.
85. Musshoff K, Schmidt-Vollmer H. Proceedings: prognosis of non-Hodgkin's lymphomas with special emphasis on the staging classification. *Z Krebsforsch Klin Onkol Cancer Res Clin Oncol*. 1975;83:323–341.
86. Catalano MF, Sivak Jr MV, Rice T, et al. Endosonographic features predictive of lymph node metastasis. *Gastrointest Endosc*. 1994;40:442–446.
87. Rohatiner A, d'Amore F, Coiffier B, et al. Report on a workshop convened to discuss the pathological and staging classifications of gastrointestinal tract lymphoma. *Ann Oncol*. 1994;5:397–400.
88. Ruskoné-Fourmestraux A, Dragosics B, Morgner A, et al. Paris staging system for primary gastrointestinal lymphomas. *Gut*. 2003;52:912–913.
89. Yasuda I, Tsurumi H, Omar S, et al. Endoscopic ultrasound-guided fine-needle aspiration biopsy for lymphadenopathy of unknown origin. *Endoscopy*. 2006;38:919–924.
90. Lügering N, Menzel J, Kucharzik T, et al. Impact of miniprobes compared to conventional endosonography in the staging of low-grade gastric MALT lymphoma. *Endoscopy*. 2001;33:832–837.
91. Pavlick A, Gerdes H, Portlock C. Endoscopic ultrasound in the evaluation of gastric small lymphocytic mucosa-associated lymphoid tumors. *J Clin Oncol*. 1997;15:1761–1766.
92. Sackmann M, Morgner A, Rudolph B, et al. Regression of gastric MALT lymphoma after eradication of *Helicobacter pylori* is predicted by endosonographic staging. MALT Lymphoma Study Group. *Gastroenterology*. 1997;113:1087–1090.
93. Ruskoné-Fourmestraux A, Lavergne A, Aegerter P, et al. Predictive factors for regression of gastric MALT lymphoma after anti-*Helicobacter pylori* treatment. *Gut*. 2001;48:297–303.
94. Nakamura S, Matsumoto T, Suekane H, et al. Predictive value of endoscopic ultrasonography for regression of gastric low grade and high grade MALT lymphomas after eradication of *Helicobacter pylori*. *Gut*. 2001;48: 454–460.
95. Levy M, Copie-Bergman C, Traulle C, et al. Conservative treatment of primary gastric low-grade B-cell lymphoma of mucosa-associated lymphoid tissue: predictive factors of response and outcome. *Am J Gastroenterol*. 2002;97:292–297.
96. Caletti G, Zinzani P, Fusaroli P, et al. The importance of endoscopic ultrasonography in the management of low-grade gastric mucosa-associated lymphoid tissue lymphoma. *Aliment Pharmacol Ther*. 2002; 16:1715–1722.
97. Zucca E, Cavalli F. Are antibiotics the treatment of choice for gastric lymphoma? *Curr Hematol Rep*. 2004;3:11–16.
98. Püspök A, Raderer M, Chott A, et al. Endoscopic ultrasound in the follow up and response assessment of patients with primary gastric lymphoma. *Gut*. 2002;51:691–694.
99. Thiede C, Wündisch T, Alpen B, et al. Long-term persistence of monoclonal B cells after cure of *Helicobacter pylori* infection and complete histologic remission in gastric mucosa-associated lymphoid tissue B-cell lymphoma. *J Clin Oncol*. 2001;19:1600–1609.
100. Bertoni F, Conconi A, Capella C, et al. Molecular follow-up in gastric mucosa-associated lymphoid tissue lymphomas: early analysis of the LY03 cooperative trial. *Blood*. 2002;99:2541–2544.
101. Fusaroli P, Buscarini E, Peyre S, et al. Interobserver agreement in staging gastric MALT lymphoma by EUS. *Gastrointest Endosc*. 2002;55:662–668.
102. Kimmey M, Martin R, Haggitt R, et al. Histologic correlates of gastrointestinal ultrasound images. *Gastroenterology*. 1989;96:433–441.
103. Botet J, Lightdale C. Endoscopic sonography of the upper gastrointestinal tract. *AJR Am J Roentgenol*. 1991;156:63–68.
104. Feng J, Al-Abbadi M, Kodali U, Dhar R. Cytologic diagnosis of gastric linitis plastica by endoscopic ultrasound guided fine-needle aspiration. *Diagn Cytopathol*. 2006;34:177–179.
105. Levine M, Kong V, Rubesin S, et al. Scirrhous carcinoma of the stomach: radiologic and endoscopic diagnosis. *Radiology*. 1990;175:151–154.
106. Fujishima H, Misawa T, Chijiwa Y, et al. Scirrhous carcinoma of the stomach versus hypertrophic gastritis: findings at endoscopic US. *Radiology*. 1991;181:197–200.
107. Dempsey P, Goldenring J, Soroka C, et al. Possible role of transforming growth factor alpha in the pathogenesis of Ménétrier's disease: supportive evidence form humans and transgenic mice. *Gastroenterology*. 1992;103: 1950–1963.
108. Wolfsen HC, Carpenter HA, Talley NJ. Menetrier's disease: a form of hypertrophic gastropathy or gastritis? *Gastroenterology*. 1993;104: 1310–1319.
109. Sundt 3rd TM, Compton CC, Malt RA. Ménétrier's disease: a trivalent gastropathy. *Ann Surg*. 1988;208:694–701.
110. Hizawa K, Kawasaki M, Yao T, et al. Endoscopic ultrasound features of protein-losing gastropathy with hypertrophic gastric folds. *Endoscopy*. 2000;32:394–397.
111. Mendis R, Gerdes H, Lightdale C, Botet J. Large gastric folds: a diagnostic approach using endoscopic ultrasonography. *Gastrointest Endosc*. 1994;40:437–441.
112. Songür Y, Okai T, Watanabe H, et al. Endosonographic evaluation of giant gastric folds. *Gastrointest Endosc*. 1995;41:468–474.
113. Okada M, Iizuka Y, Oh K, et al. Gastritis cystica profunda presenting as giant gastric mucosal folds: the role of endoscopic ultrasonography and mucosectomy in the diagnostic work-up. *Gastrointest Endosc*. 1994;40: 640–644.
114. Greene FL, Page DL, Fleming ID, et al. *AJCC (American Joint Committee on Cancer) Cancer Staging Manual*. 6th ed, New York: Springer-Verlag; 2002:99.
115. Tio T, Schouwink M, Cikot R, Tytgat G. Preoperative TNM classification of gastric carcinoma by endosonography in comparison with the

pathological TNM system: a prospective study of 72 cases. *Hepatogastroenterology*. 1989;36:51–56.
116. Murata Y, Suzuki S, Hashimoto H. Endoscopic ultrasonography of the upper gastrointestinal tract. *Surg Endosc*. 1988;2:180–183.
117. Akahoshi K, Misawa T, Fujishima H, et al. Preoperative evaluation of gastric cancer by endoscopic ultrasound. *Gut*. 1991;32:479–482.
118. Grimm H, Binmoeller K, et al. Endosonography for preoperative locoregional staging of esophageal and gastric cancer. *Endoscopy*. 1993;25:224–230.
119. Massari M, Cioffi U, De Simone M, et al. Endoscopic ultrasonography for preoperative staging of gastric carcinoma. *Hepatogastroenterology*. 1996; 43:542–546.
120. Perng D, Jan C, Wang W, et al. Computed tomography, endoscopic ultrasonography and intraoperative assessment in TN staging of gastric carcinoma. *J Formos Med Assoc*. 1996;95:378–385.
121. Tseng L, Mo L, Tio T, et al. Video-endoscopic ultrasonography in staging gastric carcinoma. *Hepatogastroenterology*. 2000;47:897–900.
122. Willis S, Truong S, Gribnitz S, et al. Endoscopic ultrasonography in the preoperative staging of gastric cancer: accuracy and impact on surgical therapy. *Surg Endosc*. 2000;14:951–954.
123. Habermann C, Weiss F, Riecken R, et al. Preoperative staging of gastric adenocarcinoma: comparison of helical CT and endoscopic US. *Radiology*. 2004;230:465–471.
124. Tsendsuren T, Jun S, Mian X. Usefulness of endoscopic ultrasonography in preoperative TNM staging of gastric cancer. *World J Gastroenterol*. 2006;12:43–47.
125. Bentrem D, Gerdes H, Tang L, et al. Clinical correlation of endoscopic ultrasonography with pathologic stage and outcome in patients undergoing curative resection for gastric cancer. *Ann Surg Oncol*. 2007;14: 1853–1859.
126. Lok K, Lee C, Yiu H, et al. Current utilization and performance status of endoscopic ultrasound in a community hospital. *J Dig Dis*. 2008;9: 41–47.
127. Kuntz C, Herfarth C. Imaging diagnosis for staging of gastric cancer. *Semin Surg Oncol*. 1999;17:96–102.
128. Bhandari S, Shim C, Kim J, et al. Usefulness of three-dimensional, multidetector row CT (virtual gastroscopy and multiplanar reconstruction) in the evaluation of gastric cancer: a comparison with conventional endoscopy, EUS, and histopathology. *Gastrointest Endosc*. 2004;59: 619–626.
129. Arocena M, Barturen A, Bujanda L, et al. MRI and endoscopic ultrasonography in the staging of gastric cancer. *Rev Esp Enferm Dig*. 2006;98: 582–590.
130. Musshoff K. [Clinical staging classification of non-Hodgkin's lymphomas (author's transl)]. *Strahlentherapie*. 1977;153:218–221 [in German].
131. Schüder G, Hildebrandt U, Kreissler-Haag D, et al. Role of endosonography in the surgical management of non-Hodgkin's lymphoma of the stomach. *Endoscopy*. 1993;25:509–512.

CHAPTER 12 How to Perform EUS in the Pancreas, Bile Duct, and Liver

Robert H. Hawes | Paul Fockens | Shyam Varadarajulu

PANCREAS

Successful pancreatic imaging requires the ability to image the entire gland. In general, the body and tail of the pancreas are imaged through the posterior wall of the stomach, and, in most cases, the transgastric approach provides images of the genu (neck) of the pancreas as well. Complete imaging of the pancreatic head, however, requires placement of the transducer in three different positions within the duodenum: the apex of the duodenal bulb (the apical view), directly opposite the papilla ("kissing the papilla"), and distal to the papilla to visualize the uncinate process. This organized, station-based approach to pancreatic imaging is critical for individuals who are just learning or who have limited experience with endoscopic ultrasonography (EUS). Although the stations are the same for radial and linear endosonography, the images produced are different, as are the techniques for maneuvering the echoendoscopes. As a result, representative images and illustrations from the various stations are presented for radial and linear echoendoscopes. As the reader is learning these techniques, it is also important to refer to the corresponding videos. Obtaining complete, accurate, and high-quality images of the pancreas and biliary tree represents the most difficult task facing the endosonographer.

Evaluation of the Body and Tail of the Pancreas

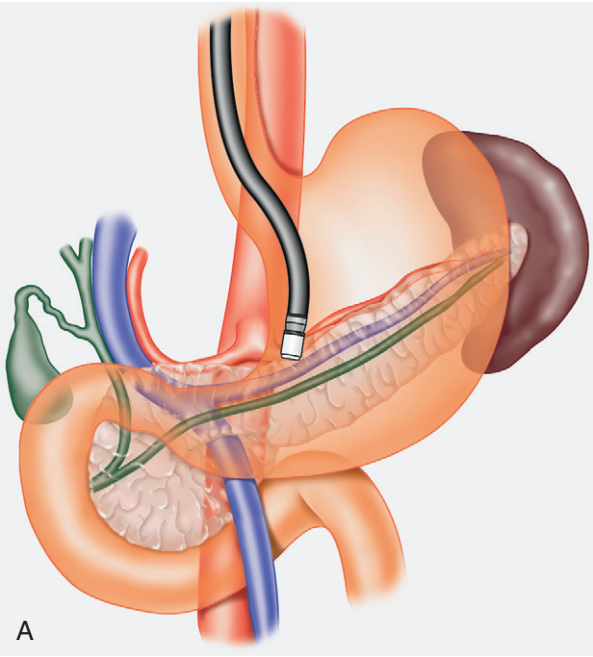
The examination of the body and tail of the pancreas begins by positioning the tip of the echoendoscope at the gastroesophageal junction, just distal the squamocolumnar junction. From this position, the aorta is easily located and becomes the "arrow" that points the way. When the radial scope is used, the aorta is round and anechoic. With the linear scope, the aorta fills the screen as a long, anechoic structure extending across the entire monitor.

Radial Echoendoscopes

With the tip of the endoscope just distal to the squamocolumnar junction, the endosonographer inflates the balloon and positions the transducer in the center. The aorta is located, and with the endosonographer in a comfortable position (neither body nor scope shaft twisted or torqued), the aorta is electronically rotated to the 6-o'clock position (Video 12.1). At this point, one usually sees a hypoechoic structure that moves from the esophageal wall and wraps partially around the aorta; this comprises the diaphragmatic crura. From here, one simply advances the echoendoscope while the aorta is kept in its cross-sectional conformation; the aorta must not be allowed to elongate. If the aorta is seen to elongate on advancement, this is an indication that the tip of the echoendoscope is being pushed laterally or is embedding in the gastric wall (often within a hiatal hernia pouch). If this occurs, the tip must be realigned and the maneuver repeated because it is important to keep the aorta in its round configuration. If this maneuver fails repeatedly, then the echoendoscope should be advanced beyond the hiatal hernia and withdrawn. This maneuver visualizes first the portal vein confluence (at the 6-o'clock position), and then the pancreas.

With advancement, when the crura disappear, the celiac trunk is seen to emerge from the aorta and tract toward the transducer (Fig. 12.1). In some cases with the radial scope, one first sees the splenic artery as a round, anechoic structure adjacent to the transducer. In this case, one just advances 1 to 2 cm, and the splenic artery traces into the celiac trunk. The celiac artery bifurcates into the hepatic and splenic arteries, and with the radial scope, the bifurcation can look like a whale's tail (Fig. 12.2). Slight advancement of the scope beyond the celiac artery takeoff produces images of the body of the pancreas. The pancreas is seen directly below the transducer. The pancreatic parenchyma is usually slightly hypoechoic relative to surrounding tissue and has a homogeneous "salt and pepper" appearance. From this position, deep to the pancreas is an anechoic structure that looks like the head of a golf club. This is the portal vein confluence and is often referred to as the *club head* (Fig. 12.3).

Once the club head has been identified, it becomes relatively straightforward to image the rest of the body and tail of the pancreas. Clockwise torque and withdrawal of the scope will trace the tail of the pancreas. During this maneuver, the left kidney comes into the picture as a large, oval structure with a hypoechoic, homogeneous outer "shell" (cortex) and an inhomogeneous, echo-rich central portion (medulla). The kidney roughly marks the body-tail junction of the pancreas (Fig. 12.4). On further withdrawal, one sees the splenic artery and vein course right below the transducer, and a homogenous, echo-poor bean-shaped structure occupies the right side of the image. This is the spleen, and the splenic vein and artery can be seen to insert into the splenic hilum. Once this image is seen, the examination of the distal body and tail is complete. From the tail of the pancreas, one simply reverses the maneuvers by advancing the scope, torquing counterclockwise, and returning to the portal vein confluence. From here, further advancement and counterclockwise torque allow imaging of the genu (neck) of the pancreas. The pancreatic duct is seen to dive away from the transducer as it courses through the neck. During the movements mentioned earlier, some left and right tip deflection may be required to obtain an



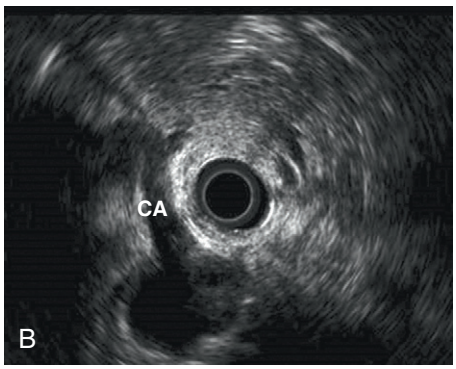


FIGURE 12.1 Pancreatic body and tail examination: radial echoendoscope. A, This illustration represents the starting point for imaging the pancreatic body and tail with the radial echoendoscope. The scope is advanced while the aorta is traced, starting at the gastroesophageal junction. The first branch of the aorta is the celiac artery. **B,** By tracing the celiac artery (CA), the pancreatic body and tail can be found.

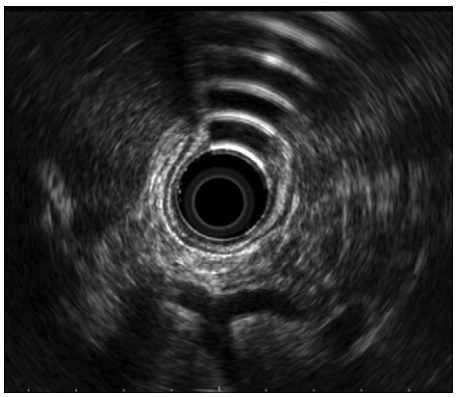


FIGURE 12.2 The celiac artery bifurcates into the hepatic and splenic arteries, which on endosonography can look like a whale's tail.

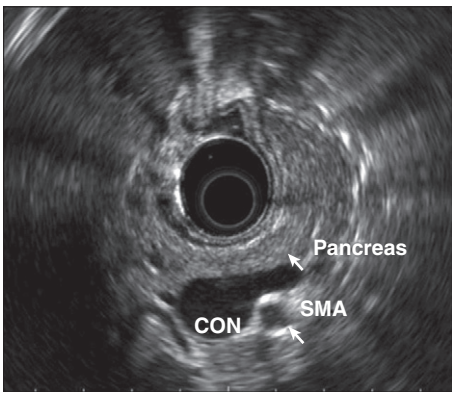


FIGURE 12.3 The portal vein confluence (CON) is referred to as *club head* because it looks like the head of a golf club and is located deep to the pancreas. In this view, the pancreas is located directly below the transducer and has a homogeneous "salt and pepper" pattern. SMA, superior mesenteric artery.

elongated view of the pancreas. Once the elongated view of the pancreas is achieved, very slow and purposeful advancement and withdrawal of the scope demonstrate the entire width of the pancreas, including the pancreatic duct.

An important principle of the station approach is that during the course of the examination (no matter what station one is working on), if one becomes lost and cannot see the typical landmarks that characterize the station, then it will be necessary to return immediately to the starting point for that station and repeat the standard maneuvers. In the case of the pancreatic body and tail, this means returning to the gastroesophageal junction, tracing the aorta until the celiac trunk is seen, and so forth. A particular station should be examined as many times as required until the endosonographer is comfortable that the examination is complete. Sometimes, however, despite repeated attempts, one cannot achieve the imaging goals of a particular station. In this case, the endosonographer can continue the examination by going to other stations and then come back later to the difficult station. Often, the return examination is successful.

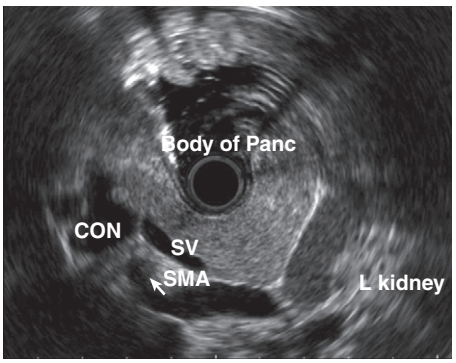


FIGURE 12.4 The left kidney has a hypoechoic outer cortex and an echo-rich medullary zone. This landmark roughly indicates the body-tail junction of the pancreas. CON, portal vein confluence; SMA, superior mesenteric artery; SV, superior mesenteric vein.

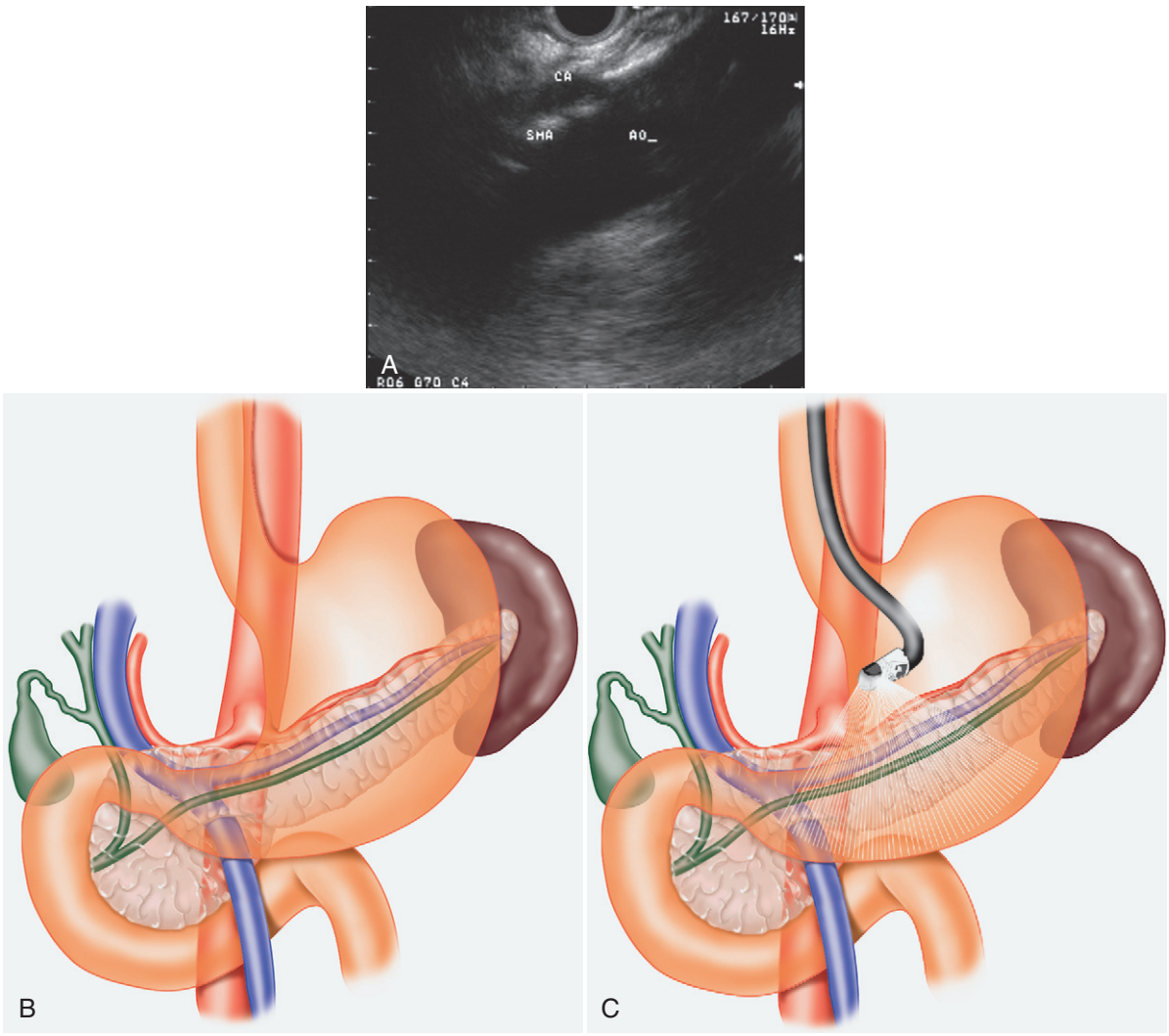


FIGURE 12.5 Pancreatic body and tail examination: linear echoendoscope. A to C, EUS image (**A**) and these illustrations (**B** and **C**) represent the starting point for imaging the pancreatic body and tail using the curvilinear echoendoscope.

The transducer is advanced while the aorta is traced, starting at the gastroesophageal junction. The first branch of the aorta represents the celiac axis; by tracing along the celiac axis, the pancreatic body can be found.

Linear Echoendoscopes

Examination of the pancreatic body and tail with the linear scope follows the same basic approach as with the radial instrument. The examination begins at the gastroesophageal junction (Video 12.2). In this case, however, the endosonographer must torque the scope shaft in a clockwise direction until the aorta is seen. Using the up-down dial, the aorta should gently slope down from right to left. Just as with the radial scope, the diaphragmatic crura are seen as a hypoechoic structure between the transducer and the aorta. This landmark is important because as one advances the scope, the celiac trunk takes off soon after the crura disappear (Fig. 12.5).

Unlike the radial scope, with which scope advancement is a passive maneuver (because of its 360-degree image), the linear scope must be gently torqued clockwise and counterclockwise to visualize the side of the aorta. Not uncommonly, the celiac trunk comes off the side of the aorta, and one can pass right by it if not systematically scanning back and forth. Once the celiac artery has been identified, it is traced until it bifurcates. Once the bifurcation is identified, and with 1 to 2 cm of further advancement combined with a gentle "down" on the up-down dial ("big dial away from you"), the pancreas and portal vein confluence come into view. From here, clockwise torque and withdrawal image the pancreatic body and tail (Fig. 12.6), and counterclockwise rotation and advancement provide images of the genu (Fig. 12.7). As with a radial echoendoscope, the pancreas should be traced all the way to the tail, confirmed when the splenic hilum is seen. As with all aspects of linear array imaging, gentle clockwise and counterclockwise torquing is mandatory throughout the examination to obtain complete imaging. Left and right tip deflection is of minimal importance when the linear echoendoscope is used.

Evaluation of the Head and Uncinate Regions of the Pancreas

To examine the entire head of the pancreas confidently, all three positions (the apex, the papilla, and distal to the papilla) should be achieved. The most efficient position is the apex of the duodenal bulb because from this position, most of the pancreatic head, distal bile duct, and portal vein can be seen together. As with other stations, positioning is the same with radial and linear scopes, but the subtle maneuvers to optimize imaging and the pictures produced are different.

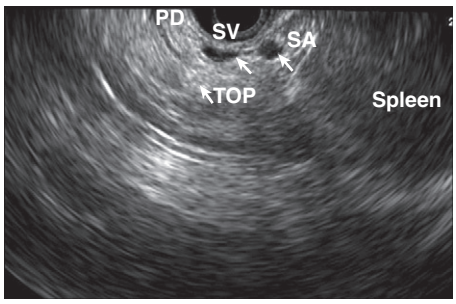


FIGURE 12.6 Clockwise torque from the portal confluence coupled with gradual scope withdrawal enables imaging of the body and tail regions of the pancreas. PD, pancreatic duct; SA, splenic artery; SV, splenic vein.

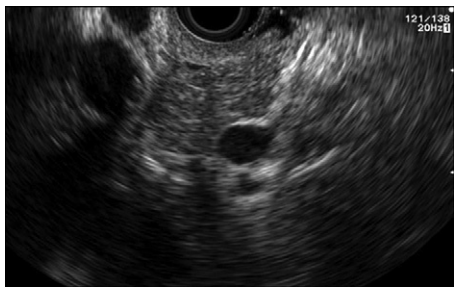
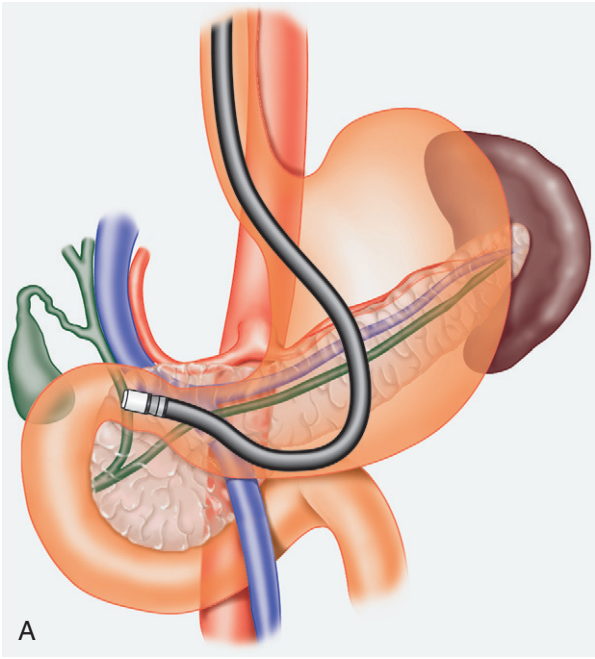
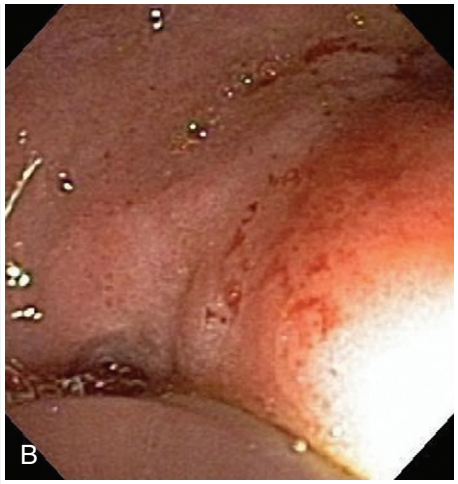


FIGURE 12.7 Counterclockwise rotation coupled with scope advancement enables visualization of the pancreatic genu.





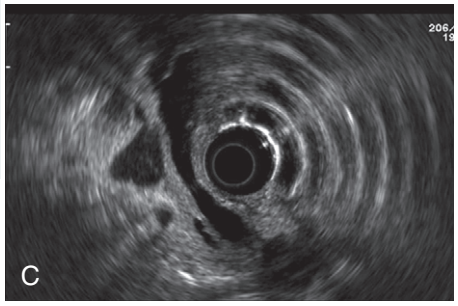


FIGURE 12.8 Pancreatic head examination: radial echoendoscope. A, Schema for evaluating the pancreatic head from the duodenal bulb. **B,** The balloon is inflated until it occludes the apex of the duodenal bulb. **C,** The liver is visualized at the left upper corner, the head of the pancreas is at the 6-o'clock position, and the bile duct will be seen as an anechoic tube closer to the transducer and coursing from the liver down to the 6-o'clock area.

Head of the Pancreas

Radial Echoendoscopes. This position allows imaging of the entire head of the pancreas (sometimes with the exception of the uncinate process) and also includes efficient imaging of the distal common bile duct. With the radial echoendoscope, the instrument should be slowly advanced through the stomach and allowed to bow along the greater curve. Once the pylorus has been visualized, the tip is advanced through the pylorus, at which point air is instilled into the duodenal bulb and some gentle downward deflection is applied to the tip of the echoendoscope (Video 12.3). This maneuver allows direct endoscopic visualization of the apex of the duodenal bulb. Once the apex is visualized, the tip of the echoendoscope should be advanced until it is at the level of the apex. The balloon is then inflated until it gently occludes the lumen of the duodenum (Fig. 12.8), and any residual air is aspirated from the duodenal lumen (all done under endoscopic control). At this point, EUS imaging commences, and the endosonographer turns his or her attention to the EUS image. The first order of business is to look for the liver.

Once the liver has been identified, the image should be electronically rotated *(do not torque the scope)* such that the liver is positioned in the upper left-hand corner of the screen. This technique provides uniform orientation and allows the endosonographer to identify the normal structures seen from this station and any abnormalities more easily. When the liver is in the upper left-hand corner, the head of the pancreas is at the 6-o'clock position, and the bile duct is seen as an anechoic tube lying close to the transducer and coursing from the liver down to the 6-o'clock area.

From this position, one should look for four landmarks (Fig. 12.9). The most important is the *duodenal falloff*. This is a hypoechoic line that represents the muscularis propria of the duodenal wall. It is seen to course down and away from the transducer. To the right of this line, the image is chaotic because it represents a mixture of air and fluid within the duodenal lumen. The second landmark is the *common bile duct*, a tubular anechoic structure that extends from at or near the duodenal wall toward the liver and courses closest to the transducer. This structure typically has a three-layer echo appearance. To trace the bile duct,

counterclockwise torque and withdrawal of the scope generally take the examiner toward the hilum, and clockwise torque and advancement of the scope take the endosonographer toward the papilla. The third landmark is the *pancreatic duct*. This may or may not be seen in the same plane of imaging as the bile duct. Often, gentle advancement of the scope combined with upward or downward tip deflection is required to see the pancreatic duct. During the entire process of imaging from the apical position, the endosonographer should be prepared to use some gentle upward or downward tip deflection to achieve complete imaging. The fourth landmark is the *portal vein*, which is seen to course in the far left of the imaging field and is the biggest tubular structure visible. One can use color Doppler imaging to identify the portal vein more easily.

Color Doppler imaging may also be required to differentiate the bile duct from the hepatic and gastroduodenal arteries. When the common bile duct, pancreatic duct, and portal vein are aligned in one view, they appear as though they are stacked on the top of each other. This image is known as the *stack sign*. Once the apical position is achieved, multiple small movements, which can include clockwise and counterclockwise torquing, forward advancement and withdrawal of the scope, upward and downward tip deflection, and left and right positioning of the tip, are all required to define the anatomic features thoroughly from this position.

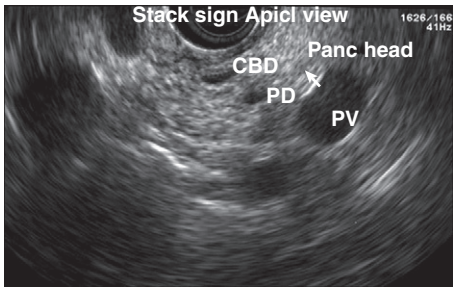
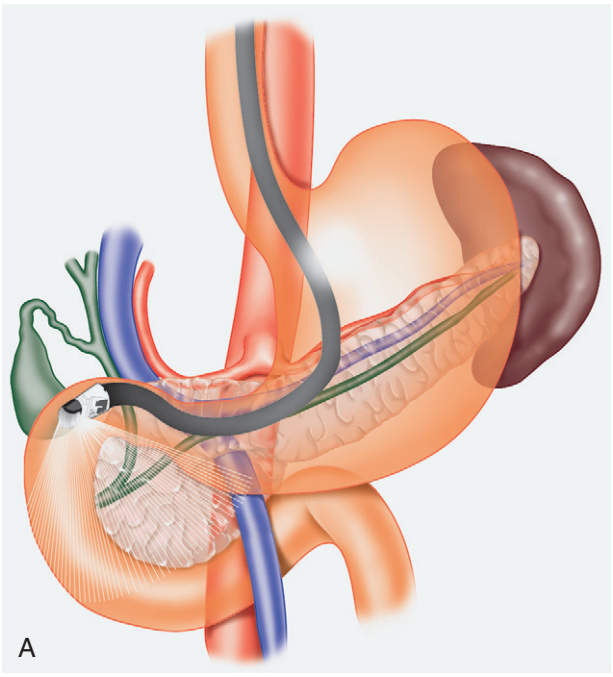


FIGURE 12.9 The stack sign. The stack sign is elicited during evaluation of the pancreatic head and is characterized by the common bile duct (CBD), main pancreatic duct (PD), and the portal vein (PV), which all appear "stacked" on top of each other. Also note the duodenal falloff, which represents the muscularis propria of the duodenal wall.

Linear Echoendoscopes. Positioning the linear scope for apical imaging is the same as with the radial scope. The scope should be advanced along the greater curve and through the pylorus, where air is instilled and gentle downward tip deflection is applied. Once the apex has been identified, the tip of the linear scope is nestled into the apex of the bulb, and gentle upward deflection is applied to the tip (Video 12.4). The balloon is less important with linear imaging, but some endosonographers like to inflate the balloon in the apex just as described with the radial scope. At this point, however, torquing is required, generally in a counterclockwise direction.

From this position, examination of the entire head of the pancreas (perhaps minus the uncinate process) can be achieved (Fig. 12.10). The most recognizable structure with the linear scope in this position is the portal vein. Color Doppler imaging can be used to confirm visualization. The bile duct courses along the portal vein (closer to the transducer). The bile duct can be traced to the liver and then down to the papilla through the pancreatic head by simply torquing the scope, with little to no need for advance or withdrawal of the instrument. The pancreatic duct runs parallel to the bile duct in the pancreatic head but may require gentle torquing to see it because it may not be in the exact same plane as the bile duct (Fig. 12.11). It is critical for the endosonographer to become very comfortable with this position with the linear scope. This position provides the best imaging to assess the relationship between a pancreatic head mass and the portal vein. It is also the position of choice for performing EUS-guided fine-needle aspiration of pancreatic head masses because the mass is close to the transducer, and the back wall of the duodenum prevents the scope from pushing away from the mass when the needle in inserted (especially important if the mass is very firm).



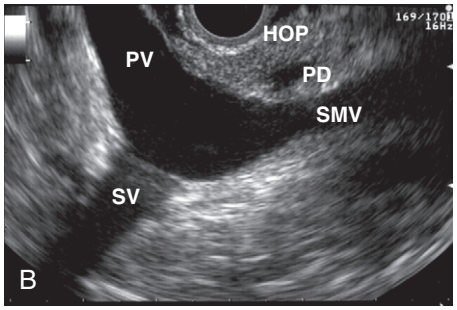


FIGURE 12.10 This is perhaps the most important station for viewing and performing fine-needle aspiration of the pancreatic head (HOP). A, The transducer is placed at the level of the apex of the duodenal bulb. **B,** After some manipulation of the scope tip, the neck of the pancreas can be viewed with the portal vein confluence deep to the pancreas. PD, pancreatic duct; PV, portal vein; SMV, superior mesentric vein; SV, splenic vein.

Papilla

Radial Echoendoscopes. The second position for pancreatic head imaging is from the level of the papilla. This position is best achieved by first using endoscopic visualization to localize the ampulla of Vater. Once that structure is seen, the balloon is inflated until it "kisses" the papilla (Fig. 12.12). It is best to try to orient the transducer perpendicular to the papilla and to position it so that upward tip deflection will cause the balloon to press against the papilla (Video 12.5). Once this position has been achieved, ultrasound imaging begins. The ultrasound image is rotated so that the papilla is located at the 6-o'clock position on the EUS image. From this point, the head of the pancreas is a crescent-shaped structure. As the transducer is moved gently in and out, one looks to see the bile duct and pancreatic duct coursing to the duodenal wall. The pancreatic duct is deep to the bile duct relative to the position of the transducer. Because of the usual appearance of the two ducts from this position, this image is termed *snake eyes*. From this position, it is easiest to see the differentiation between the ventral and the dorsal anlage. The ventral anlage is hypoechoic and has a heterogeneous echo architecture when compared with the dorsal pancreas (Fig. 12.13). The ventral anlage is triangular and occupies the left portion of the crescent-shaped pancreatic head, whereas the dorsal portion occupies the right portion. In addition to seeing the ventral and the dorsal anlage, this position also allows visualization of the superior mesenteric vein (closest to the pancreas) and the superior mesenteric artery (deeper and thicker wall when compared with the superior mesenteric vein).

This is also the position required for detailed imaging of the ampulla of Vater, either to assess an ampullary adenoma or cancer or to look for an impacted stone (in the case of gallstone pancreatitis). To image the papilla itself, the duodenum should be paralyzed with hyoscine butylbromide (Buscopan) or glucagon. Once the duodenum is paralyzed, water should be infused into the duodenum to achieve coupling of the ultrasound waves with the papilla without risking compression from the balloon. Exquisite views of the ampulla can be obtained if one can achieve

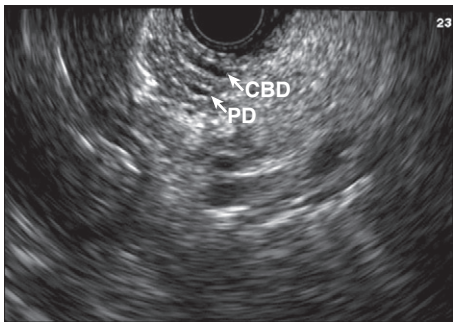


FIGURE 12.11 The pancreatic duct (PD) runs parallel to the common bile duct (CBD) in the head region of the pancreas. Gentle torquing may be required to identify and trace the ductal structures.

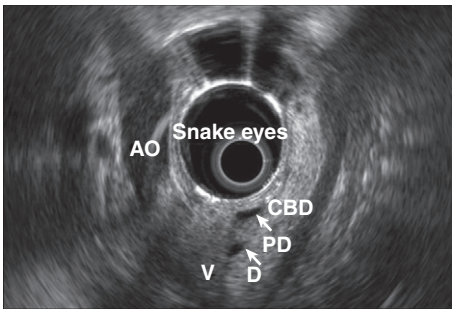
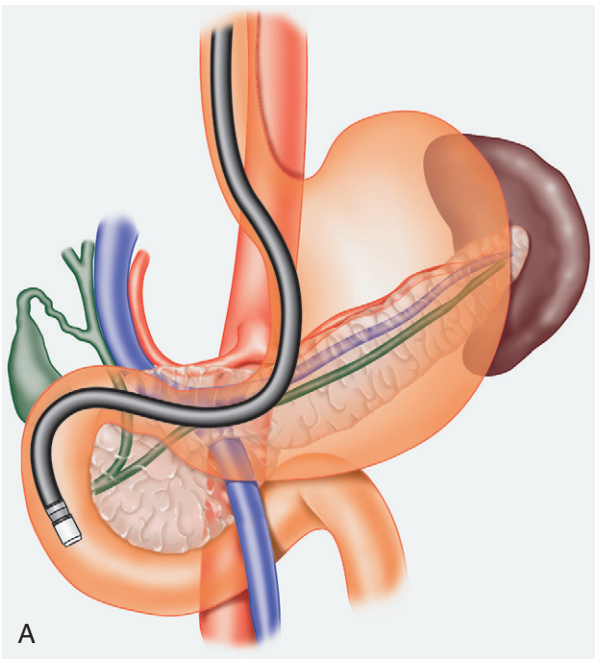
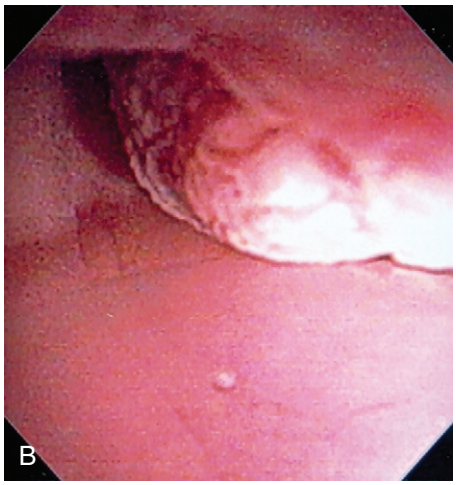


FIGURE 12.13 The ventral anlage is hypoechoic, triangular, and heterogeneous in echo architecture. It occupies the left portion of the crescent-shaped pancreatic head as compared with the dorsal pancreas, which occupies the right portion.





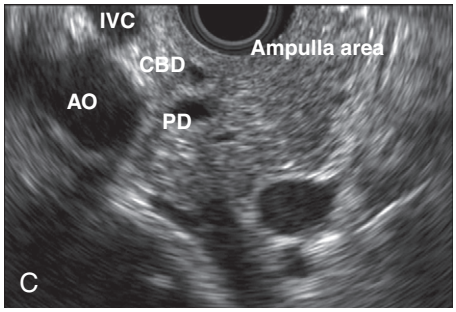


FIGURE 12.12 Papilla of Vater examination: radial echoendoscope. A, The position required for evaluating the papilla of Vater. **B,** The balloon is inflated so that it "kisses" the papilla but without causing mechanical compression. **C,** Gentle movement of the transducer enables visualization of the common bile duct (CBD) and the pancreatic duct (PD) coursing through the duodenal wall to the papilla. The presence of two ducts as imaged in this view is termed *snake eyes*. AO, aorta; IVC, inferior vena cava.

perpendicular positioning of the transducer relative to the papilla, obtain adequate water coupling, and keep the duodenum motionless (Fig. 12.14). The critical anatomic landmark when staging ampullary neoplasms is the muscularis propria of the duodenal wall. If the process disrupts this layer, tumor invasion can be predicted.

Linear Echoendoscopes. The ampullary position is exactly the same with the linear as with the radial echoendoscope. The papilla is visualized endoscopically, and then the transducer should be positioned perpendicular to the ampulla (Fig. 12.15). The orientation should be such that upward tip deflection should press the transducer against the papilla (Video 12.6). If detailed images of the papilla are required, the duodenum should be paralyzed and water infused into the duodenal lumen, just as with the radial instrument. In some circumstances, however, when either the radial or the linear echoendoscope is used, the curvature of the duodenum may be too acute to obtain perpendicular orientation between the transducer and the papilla despite maximal upward deflection of the endoscope tip.

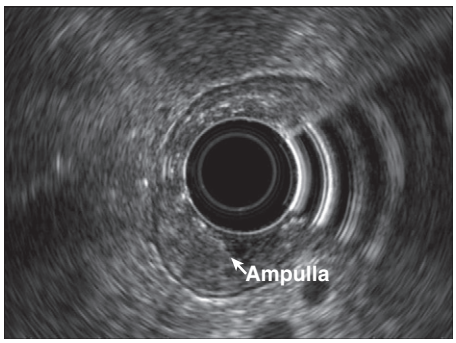


FIGURE 12.14 The ampulla is imaged best by perpendicular positioning of the transducer relative to the papilla coupled with water insufflation and a motionless duodenum.

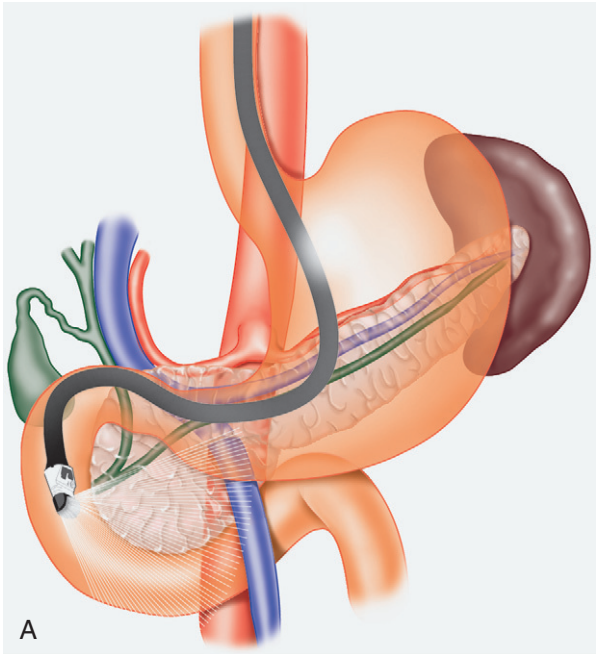
In this circumstance, imaging of the ampulla is somewhat tangential; this degrades the overall image quality and precision of interpretation. The pancreatic head appears crescent shaped, but unlike with the radial scope, with which the bile and pancreatic ducts are seen in cross section (snake eyes), the bile and pancreatic ducts are seen in their linear confirmation, with the bile duct more superficial and the pancreatic duct deep. Imaging is carried out by slow withdrawal and continuous gentle torquing clockwise and counterclockwise until the portal vein confluence is seen. This landmark signifies the completion of this station.

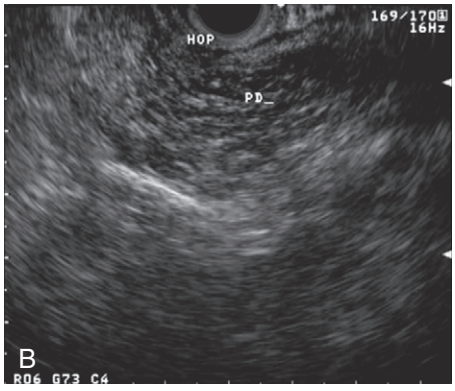
Uncinate

Radial Echoendoscopes. The uncinate process can be imaged by positioning the transducer distal to the ampulla of Vater. The critical anatomic structure in this position is the aorta. The up-down dial should be maximally "up," and the right-left control should be locked in the "right" position. Very gentle counterclockwise torque allows visualization of the aorta, which, if the transducer is deep enough in the duodenum, is seen initially in its longitudinal confirmation. At this point, electronic rotation is used, to position the aorta so that it courses top to bottom on the left side of the screen (Video 12.7). Slow withdrawal is then commenced. As the scope is withdrawn, the aorta slowly goes from linear to oval and ultimately to a cross-sectional (round) configuration. From this position, the inferior vena cava is usually visible as well and is typically superior to the aorta. At this point, if one looks to the right of the aorta, the uncinate process will emerge (Fig. 12.16). The pancreas is initially triangular but changes to a crescent shape as one withdraws to the level of the papilla. The aorta is critical for this position because if one does not see the pancreas right adjacent to the aorta, one cannot be sure that the uncinate process has been visualized.

One problem that can be encountered with withdrawal from this position is that the echoendoscope can suddenly flip back into the duodenal bulb. This problem can be avoided by manipulating the echoendoscope as one would a colonoscope: instead of slow, steady withdrawal, the echoendoscope is withdrawn a slight amount and then advanced a slight amount. If one can maintain one-to-one reaction of the echoendoscope to the manipulation of the shaft, then rapid uncontrolled withdrawal can be avoided.

FIGURE 12.15 Papilla of Vater examination: linear echoendoscope. A, The transducer is placed at a perpendicular angle to the papilla of Vater. **B,** From this position, the pancreas has a crescent shape, and the bile duct and pancreatic duct can be seen to emerge from the papilla.





Linear Echoendoscopes. The transducer should be passed just distal to the ampulla, and the instrument shaft should be rotated clockwise or counterclockwise, as necessary, to locate the aorta. Once the aorta has been visualized, the echoendoscope should be torqued (usually clockwise) and slowly withdrawn (Video 12.8). With this maneuver, the uncinate process comes into the image adjacent to the transducer and to the right of the aorta (Fig. 12.17). The endosonographer simply slowly withdraws the scope while gently torquing back and forth.

It is not possible to read a book and translate the reading to successful imaging of the pancreas. Successful imaging has innumerable nuances, and each patient's anatomy is different. Each case presents it own unique challenges, and no endosonographer, no matter how experienced, achieves successful and complete imaging in all patients. One is always limited by the patient's individual anatomic features, and these limitations must be accepted by the endosonographer.

BILE DUCT

EUS imaging of the bile duct is relatively straightforward, but overall it is easier and more efficiently performed with a radial scanning echoendoscope. Basically, two positions must be achieved to evaluate the extrahepatic portion of the bile duct fully. The first position, mentioned earlier, is the apical position. The second position, which is important for achieving full visualization of the bile duct, is one in which the transducer "kisses"

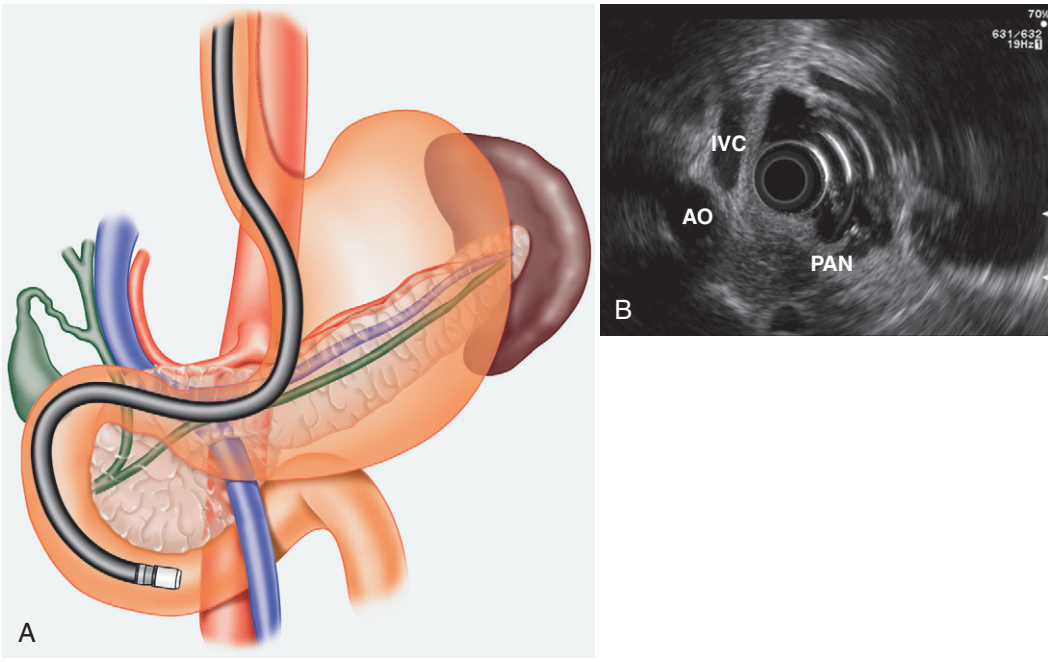


FIGURE 12.16 Uncinate examination: radial echoendoscope. A, This illustration reveals the echoendoscope in the second portion of the duodenum. **B,** At this station, by gradual scope withdrawal, the uncinate portion of the pancreas (PAN) is visualized to the right of the aorta (AO). IVC, inferior vena cava.

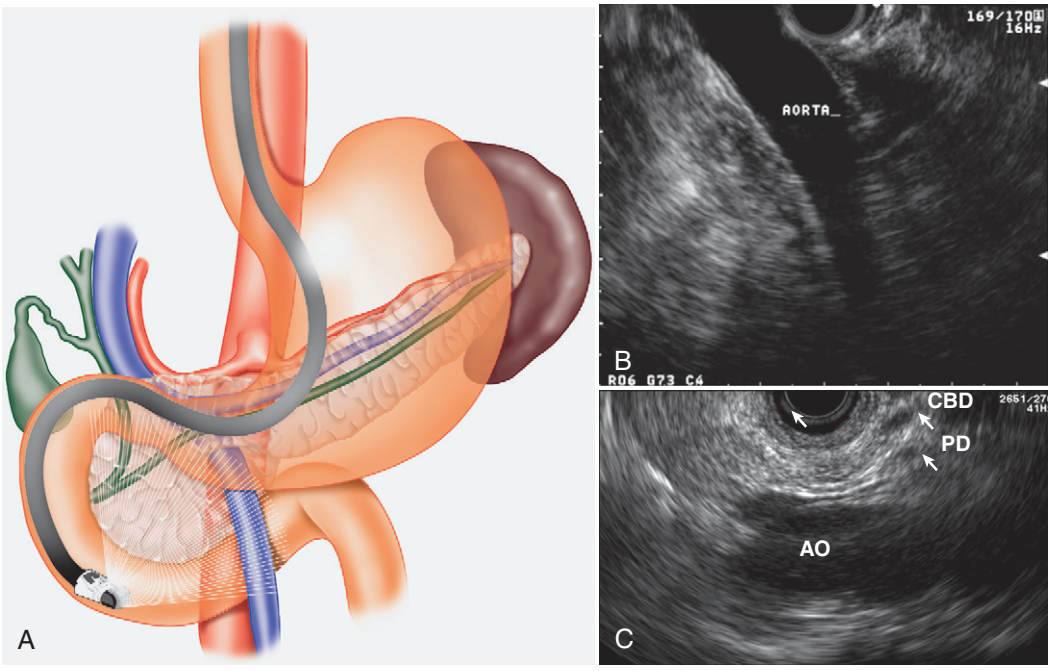


FIGURE 12.17 Uncinate examination: linear echoendoscope. A, The transducer is placed distal to the papilla, and the tip of the echoendoscope is moved upward. **B,** From this position, the aorta can be sought; the pancreas is viewed adjacent to it. **C,** Gradual withdrawal and torquing of the echoendoscope reveal the uncinate portion of the pancreas. Aorta (AO); CBD, common bile duct; PD, pancreatic duct.

the papilla. With a radial scanning echoendoscope, the apical position usually permits a very broad section of the bile duct to be visualized at one time.

Achieving the apical position begins with the tip of the instrument in the stomach. The echoendoscope is advanced along the greater curve of the stomach with a little downward tip deflection to enable visualization of the pylorus. Slight upward tip deflection is applied just before entering the pylorus, and, once within the duodenal bulb, air is instilled along with slight downward tip deflection to visualize the apex of the duodenal bulb (see Video 12.3). The tip of the scope is then positioned in the area of the apex, the balloon is inflated until it occludes the lumen, and slight clockwise torque is then applied to the instrument shaft. Ultrasound imaging then begins. The first structure to look for is the liver. The image should be rotated such that the liver is positioned in the upper left-hand portion of the screen. From this position, at least a portion of the bile duct can usually be visualized, although slight advancement or withdrawal of the echoendoscope may be required. The bile duct is seen as an anechoic tubular structure coursing right, adjacent to the transducer (see Fig. 12.9; Fig. 12.18).

The most important landmark of the apical position is the duodenal falloff. This represents the muscularis propria of the duodenum and is seen to course just adjacent to the transducer and then to fall away directly from it in the 6-o'clock position of the screen. Once the bile duct is visualized, one should recognize that it typically has three layers. Withdrawal and counterclockwise torque of the echoendoscope allow visualization of the bile duct toward the hilum, and clockwise torque and insertion of the endoscope shaft allow visualization of the distal bile duct as it enters the papilla.

The most common mistake made with apical imaging is that the endosonographer allows the transducer to slip back into the duodenal bulb. Some gentle pressure should be kept against the shaft of the instrument to prevent this problem. It is also possible that, if too much pressure is applied, the tip will slip around the apex into the second portion of the duodenum. If there is a tendency for this to occur, the balloon should be further inflated on the bulb side of the apex. Once one begins imaging from the apical position, if the bile duct is not recognized within 30 seconds, endoscopic control should be used to reposition the transducer in the apex, and ultrasound imaging should be restabilized. Three to four repositionings within the apex may sometimes be required to achieve proper imaging of the bile duct.

In some cases, a stone is impacted in the distal bile duct. In this circumstance, the only way to detect the stone may be to position the transducer directly perpendicular to the papilla (see Video 12.5).

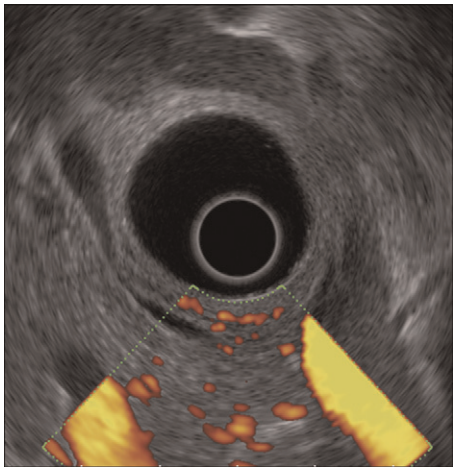


FIGURE 12.18 The use of color Doppler imaging distinguishes the bile duct from the surrounding vasculature.

This is achieved by advancing the echoendoscope into the second portion of the duodenum and then pulling back as one would do during an endoscopic retrograde cholangiopancreatography (ERCP), to achieve the straight scope position. The papilla should be visualized endoscopically, the duodenum paralyzed, and water instilled within the duodenal lumen. The balloon is then slightly inflated, but not enough to press firmly against the papilla. One then scans back and forth across the papilla and looks for the bile duct to emerge from the papilla (see Fig. 12.12C). One must look carefully because, if a small stone is impacted in the ampulla, only shadowing may be seen, without the intensely echogenic rim typically observed with stones in the bile duct or gallbladder. As always, complete imaging of the bile duct may require multiple attempts at each position.

The technique for imaging the bile duct with the linear echoendoscope is the same as that described for the radial instrument. The two positions remain the same: apical and opposite the papilla. Because the plane of imaging for the linear scope is more restricted than that of the radial scope, it may be difficult to obtain long views of the bile duct. The linear instrument should be positioned in the apex of the duodenal bulb, but usually counterclockwise torque is required to image the bile duct and some left-right tip deflection may be required (see Videos 12.4 and 12.6). The principle remains the same, however, that withdrawal of the instrument from this position generally gives views toward the hilum, whereas advancing the echoendoscope obtains views toward the papilla (see Fig. 12.11). Use of the linear scope for biliary imaging requires much more careful tracing because one single position provides only a small section of the bile duct. Sometimes it is easier to obtain perpendicular views of the papilla with the linear scope than with the radial scope. Of course, color Doppler imaging can be used to help differentiate the bile duct from surrounding vascular structures (see Fig. 12.18).

LIVER

There are basically three positions for EUS imaging of the liver. No matter how diligent the endosonographer, the extent to which the liver can be imaged depends largely on the patient's anatomy. In general, one should use the lowest frequency available with the instrument to maximize penetration, and the various liver imaging positions should be repeated several times before the examination is declared complete. Electronic scanning echoendoscopes, whether radial or linear, generally have deeper penetration in liver tissue than do mechanical rotating echoendoscopes.

The first liver position is in the duodenal bulb (see Fig. 12.8A; Fig. 12.19). If one is using the radial scope, the balloon should be overinflated so that one is "locked" in the bulb (Video 12.9).

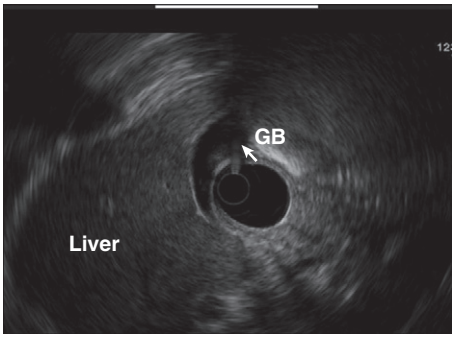
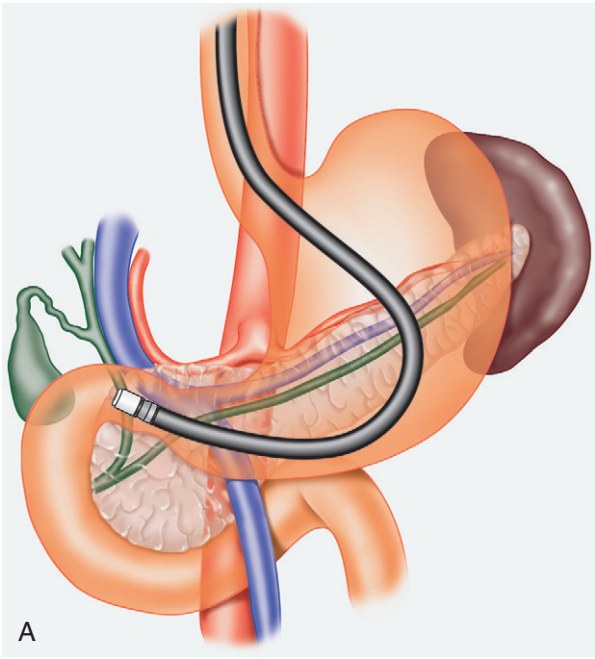


FIGURE 12.19 The echoendoscope is "locked" in the duodenal bulb, and the tip is deflected for obtaining images of the liver. Figure 12.8A reveals the positioning of the echoendoscope for visualizing the liver. GB, gallbladder.

From this position, the tip should be deflected so that it presses as firmly as possible against the liver. The echoendoscope is then advanced and withdrawn to its fullest extent, and at the same time clockwise and counterclockwise torquing is used. The instrument should be advanced until the liver disappears and withdrawn until firm pressure is felt against the pylorus. The duodenal bulb is also the best position for imaging the gallbladder, and the technique of balloon overinflation should be used to obtain full views of the gallbladder. Once imaging from this position has been exhausted, the balloon should be deflated and the transducer repositioned in the antrum. With the tip of the scope in the antrum and the balloon inflated (Fig. 12.20), the echoendoscope tip again should be pressed as firmly as possible against the wall of the stomach that lies next to the liver (Video 12.10).

Once again, the scope should be advanced and withdrawn to its fullest extent during continuous imaging of the left lobe of the liver. The third position is from the fundus of the stomach (Fig. 12.21). Beginning at the gastroesophageal junction, the transducer is pressed against the gut wall in the direction of the left lobe of the liver (Video 12.11). From this position, the scope is slowly advanced, and at the same time the endosonographer applies clockwise and counterclockwise torque to sweep across the extent of the liver. The scope should be advanced until no further imaging of the liver can be achieved.

The technique and positions are the same whether a radial or a linear instrument is used. With linear scopes, it takes more effort by torquing the scope shaft to accomplish as complete an examination as possible.



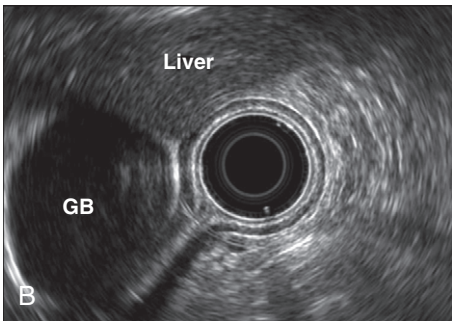
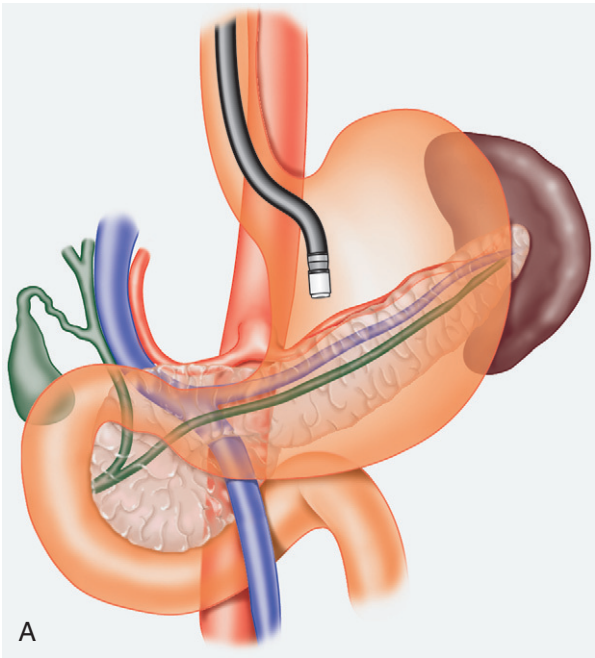


FIGURE 12.20 Examination of the liver. A, The echoendoscope positioned in the gastric antrum for visualizing the left lobe of the liver. **B,** The echoendoscope tip should be firmly against the gastric wall to image the liver. GB, gallbladder.



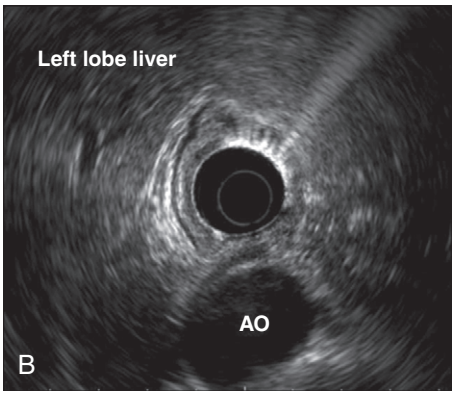


FIGURE 12.21 Examination of the liver. A, The echoendoscope in the proximal stomach. **B,** The scope is pressed firmly against the gut wall to image the left lobe of the liver. AO, aorta.

The anatomy of the liver is relatively simple. Branching structures with echogenic walls represent the portal venous system, whereas anechoic structures running alongside the portal venous system and without the echogenicity (and without color Doppler signal) represent branches of the biliary tree. Hepatic cysts are common and anechoic, and they have a characteristic echo enhancement along the border of the cyst further from the transducer. Hepatic metastases are generally echo poor, without a distinct border. They can be quite subtle, and thus the endosonographer should scan slowly and carefully. Hepatic veins also lack wall echogenicity and run toward the cranial part of the liver, where they can usually be seen entering the caval vein.

Liver imaging can be a frustrating aspect of endosonography because one cannot be sure that the liver has been imaged completely. As a result, the various positions mentioned earlier should be repeated until the endosonographer is satisfied that the extent of the examination has been as full as possible.

CHAPTER 13

EUS IN INFLAMMATORY DISEASES OF THE PANCREAS

Joseph Romagnuolo

Key Points

EUS is highly accurate in the diagnosis chronic pancreatitis when calcifications, or five or more of nine criteria, are present. The finding of two or fewer criteria has a high negative predictive value; the finding of three to four criteria lands on the borderline of a positive test, and so does not change the pretest suspicion of disease.

Fine-needle aspiration (FNA) does not appear to add helpful information to the diagnosis of chronic pancreatitis, and it creates an added risk of post-FNA pancreatitis.

Magnetic resonance cholangiopancreatography (MRCP) appears to have modest accuracy for chronic pancreatitis but, even with quantitative secretin flow dynamics, remains insensitive for mild disease.

Although not perfect, EUS is very useful in distinguishing inflammatory pseudotumors from neoplastic masses, even without FNA; positron emission tomography (PET) is also promising.

Autoimmune pancreatitis should be considered in unexplained inflammatory masses. Serum IgG4 is the test of choice, but in selected equivocal cases, trucut biopsy may be helpful.

EUS in the diagnosis or staging of acute pancreatitis has had limited study.

EUS appears to be accurate in the diagnosis of gallbladder sludge, tumors, and other causes of apparently "idiopathic" acute pancreatitis. It is most helpful in patients with a gallbladder still in place and in older patients for whom a tumor is a small possibility.

EUS has good accuracy in detecting pancreas divisum—at least as good as MRCP—but specificity is better than sensitivity. Attempting to follow the duct from the major papilla to the dorsal gland is most reliable.

Contrast-enhanced harmonic EUS and EUS with elastography are promising and emerging technologies to improve the accuracy of EUS; other types of image and backscatter analysis are also in early study.

INTRODUCTION

Endoscopic ultrasonography (EUS) is well suited to examination of the pancreas because of the proximity of the probe to the pancreatic parenchyma and was originally developed for this purpose in the early 1980s.[1–3] EUS boasts dynamic imaging, together with the fine resolution of parenchyma that characterizes real-time ultrasound imaging. These features give EUS a huge advantage over static cross-sectional imaging. At the same time, EUS avoids the intervening air and fat that degrade the quality of transabdominal ultrasound images. Because higher frequency means lower depth of penetration, transabdominal ultrasound is restricted to a lower frequency (with associated lower resolution) to overcome the distance between the skin and the retroperitoneum. Because of its noninvasive nature, EUS avoids the risk of pancreatitis associated with endoscopic retrograde cholangiopancreatography (ERCP), except when fine-needle aspiration (FNA) is added. The literature on chronic pancreatitis, as detailed later, suggests that EUS is likely at least as sensitive as the conventional imaging reference standard, ERCP, and may identify patients with earlier stages of disease that evade standard testing.

Grading of acute pancreatitis with EUS has not yet been studied. However, EUS appears to have a role in otherwise idiopathic recurrent pancreatitis, by identifying unrecognized chronic pancreatitis, biliary sludge, or pancreas divisum. Acute inflammatory masses can be distinguished from neoplasms to a greater extent than with other imaging options. The addition of FNA to EUS to sample equivocal masses and lymph nodes adds an invaluable dimension to the assessment of the pancreas that other imaging cannot match. However, EUS FNA appears neither safe nor accurate for the overall diagnosis of chronic pancreatitis, except perhaps in the subgroup of patients with suspected autoimmune disease. The novel adjuncts to EUS of elastography and

contrast-enhanced harmonic ultrasound may help to distinguish normal from abnormal tissue by using variations in tissue stiffness and perfusion, respectively.

This systematic review was derived from review of the existing literature. A PubMed search (from 1966 to December 2004), using the medical subject headings (MeSH) terms "endosonography" and "pancreatitis," revealed 148 abstracts (first edition), and an additional 451 articles were published from December 2004 until October 2009. These abstracts were individually reviewed for relevance, and relevant full manuscripts were then reviewed. Multiple topic reviews were also examined,[4–24] including bibliographies, to identify missing articles.

THE NONINFLAMED PANCREAS ON EUS

The technique for examining the pancreas by EUS is outlined in Chapter 12. Once good position and clear images have been obtained, the endosonographer needs to be able to recognize what is normal. Briefly, the normal noninflamed pancreas appears to be a homogeneous structure with a single anechoic (Doppler-negative) smooth ductular structure running within it that represents the main pancreatic duct. The body and tail of the pancreas have a fine, diffusely speckled ("salt and pepper") pattern that is, on average, more echogenic (brighter) than the liver because of its higher fat content (i.e., a small amount of fine, diffuse heterogeneity is normal). Caution should be exercised when making note of small echogenic foci or short echogenic strands when a high degree of magnification is used (as may be needed in an atrophic gland or a gland with a very small duct). The gland contour is generally smooth. The duct wall is barely perceptible, and its echotexture is similar to that of the surrounding pancreatic tissue.

With current technology, side branches can be seen in many patients. Even with older equipment, studies noted visible branches in half of control subjects,[25] with mean sizes of 0.7, 0.5, and 0.4 mm in the pancreas head, body, and tail, respectively.[26] Only side branches larger than 1 mm are now considered abnormal.[15] The course of the main pancreatic duct can be mildly tortuous, but beading should not be present (alternating sizes), and the duct should taper from the head to the tail; normal pancreatic duct sizes are 3, 2, and 1 mm in the head, body, and tail, respectively.[27,28] In patients who are more than 60 years old, an extra 1 mm for the main duct in each section is generally allowed because of expected atrophy of the surrounding parenchyma. However, control groups[26] composed of young individuals exceeded the foregoing duct diameters by up to a 1 mm in each site category. As such, a consensus group defined dilation as 3.5 mm in the body, or 1.5 mm in the tail, or greater dilation.[15] The anterior-posterior thickness of the pancreas is approximately 10 to 15 mm.[25,26] The importance of atrophy in the diagnosis of chronic pancreatitis is unclear.

The dorsal pancreas is generally more echogenic (brighter) than the embryologic ventral pancreas (the anlage). The ventral anlage, along with the transition zone from ventral to dorsal, can be seen in 45% to 75% of people examined with EUS,[25,26,29] more than twice as often as with computed tomography (CT).[30,31] Finally, the head of the pancreas is generally more heterogeneous than the body and tail.

CHRONIC PANCREATITIS DIAGNOSIS AND STAGING

The diagnosis of chronic pancreatitis is difficult. CT and magnetic resonance imaging (MRI) must rely for the diagnosis on main pancreatic duct dilation, moderate-sized cysts, and calcifications, all of which are markers of severe disease by the ERCP Cambridge criteria.[32] Magnetic resonance cholangiopancreatography (MRCP) can make some further inferences regarding main pancreatic duct irregularity and the presence of dilated side branches; unfortunately, the resolution is often too poor to be accurate in this assessment when the ducts are not dilated. Adding secretin can allow better ductal imaging and can permit functional assessments; atrophy and changes in parenchymal signal can also be seen.[24,33,34] ERCP carries the risk of causing further pancreatic damage, especially during filling of the pancreas to the tail and filling of side branches.[35] Furthermore, other than stones in the parenchyma large enough to be radiopaque on plain radiographs, only ductal imaging is possible.

In contrast, EUS can use parenchymal criteria in addition to ductal criteria to make a diagnosis of chronic pancreatitis. Smaller cysts and more subtly dilated or clubbed side branches can also be more reliably identified. Even calcifications a few millimeters in size can be readily identified as shadowing hyperechoic reflections.

Defining the Criteria and Identifying Them Reliably

The difficulty with interpreting the EUS literature on chronic pancreatitis is that, conventionally, the EUS diagnosis relied on tallying the number of criteria present. This approach generally assumed assigning equal weight to those criteria. Denominators (number of criteria sought) and criteria definitions were also variable (Table 13.1). There are generally now believed to be nine accepted criteria[36]: four parenchymal criteria (hyperechoic foci, hyperechoic strands, hypoechoic lobules, and cysts) and five ductal criteria (dilation, dilated side branches, main duct irregularity, hyperechoic duct margins, and stones). Hypoechoic lobules, in different publications, have also been referred to as "reduced echogenicity foci," "hypoechoic foci," and "pseudolobularity."

An American Society of Gastrointestinal Endoscopy (ASGE)–endorsed consensus conference of an international representation of expert endosonographers was convened in April of 2007 in Rosemont, Illinois, to attempt weighting some criteria as major and others as minor.[15] The results are summarized briefly in Tables 13.2 and 13.3.[15] It is not yet clear whether these criteria should be used widely yet, for either clinical purposes or for research, or whether the EUS community should wait for validation studies. Those studies would be needed to confirm that the newer system performs at least as well as the conventional criteria and has sufficient advantages to justify adopting the more complex Rosemont system and adding the confusion of switching to a new set of criteria.

Figure 13.1 shows a few examples of the normal pancreas body, with linear and radial views, and of the conventional criteria. The actual histologic correlates of these criteria are unknown,[15] but hypothetic correlations have been proposed (Table 13.4). Figure 13.2 provides examples of normal pancreas, periductal fibrosis that likely explains thickened hyperechoic duct walls, interlobular fibrosis that likely explains hyperechoic strands (and possibly foci, which may represent cross-sectional views of these strands), and clustered islands of (anatomic) lobules separated from other clusters of lobules by fibrotic strands that probably explain hypoechoic lobules (each single EUS lobule is really a cluster of multiple anatomic lobules).

The earliest comparative study of paid volunteers and patients with pancreatic pain[26] found the following 5 of 11 tentative criteria to be significant independent predictors of abnormal ERCP results when the sole patient with calcifications was excluded: (1) areas of reduced echogenicity, (2) irregular duct contour, (3) main duct dilation, (4) dilated side branches and (5) echogenic foci (>3 mm). Three other criteria, some of which are commonly used today, were not predictive in multivariate analysis (echogenic duct wall, accentuated lobular pattern, and cysts); echogenic strands were not assessed.

Some endosonographers believe that gland contour (lobular versus smooth) may be important, but many do not.[15] Either

TABLE 13.1

Criteria and Thresholds Used by Studies in Diagnosing Chronic Pancreatitis

		Parenchymal Criteria						Duct Criteria				
Authors (yr)	Threshold Number of Criteria	Hyperechoic Foci	Hyperechoic Strands	Hypoechoic Lobules, Foci, or Areas	Accentuation of Lobular Pattern	Irregular Gland Margin or Increased Size	Cyst	Irregular Duct Contour	Visible Side Branches	Hyperechoic Duct Margin	Dilated Main Duct	Stone
Chong et al[50] (2007)	Calcification; ≥3, if no calcification (by ROC)	x	x	x			x	x	x	x	x	x
Varadarajulu et al[52] (2007)	≥4 (noncalcific) (by ROC)	x	x	x			x	x	x	x	x	x
Pungpapong et al[85] (2007)	≥4 (by ROC)	x	x	x			x	x	x	x	x	x
Kahl et al[53] (2002)	≥1	x >3 mm	x*	x	*	x Increased gland size	x	x	x	x	x	x
Hollerbach et al[60] (2001)	≥2	x Hyperechoic lobules	x Septa				x	x				x
Hastier et al[84] (1999)	Unclear (possibly ≥1)	x		x			x	x	x	x	x	x
Catalano et al[25] (1998)	1-2 called mild; ≥3 used in comparison with ERCP	x†	x Septa	‡	‡	x Irregular margin	x	x	x			
	"Ectatic"	x	x	x								
Sahai et al[36] (1998)	<3 criteria rule out disease; >4 criteria rule in disease	x 1-2 mm	x	x 2-5 mm			x >2mm	x	x	x	x§	x
Buscail et al[76] (1995)	Not reported	‖	‖	x	‖		x	x	x	x‖	x	x
Wiersema et al[26] (1993)	≥3 (by ROC)	x¶ >3 mm		x¶	x		x	x¶	x¶	x	x¶	x

*Hypoechoic areas and hypoechoic areas surrounded by septa were considered two different criteria.
†Foci were called "calcifications" parenthetically in the article, but it is not clear whether acoustic shadowing was required.
‡Heterogeneous parenchyma was an additional criterion, separate from strands and foci.
§>3 mm in the head, >2 mm in the body, >1 mm in the tail.
‖Diffusely heterogeneous, diffusely hyperechoic, and hypertrophic were other parenchymal criteria used in this study, and "heterogeneous" appears to refer to hyperechoic strands and foci; echogenic duct wall was considered normal, but hyperechogenic duct wall was recorded as abnormal.
¶Significant in multivariate analysis.
ERCP, endoscopic retrograde cholangiopancreatography; ROC, receiver-operator characteristic curve analysis; x, this criterion was sought.

TABLE 13.2

Conventional and Rosemont EUS Criteria for Diagnosis of Chronic Pancreatitis

Conventional Criteria	Rosemont Criteria
Parenchymal Criteria	**Major Criteria A**
Hyperechoic foci	Hyperechoic foci (>2 mm in length or width with shadowing)
Hyperechoic strands	Major duct calculi (echogenic structure within the MPD with acoustic shadowing)
Hypoechoic lobules, foci, or areas	**Major Criteria B**
Cyst	Lobularity (≥3 contiguous lobules = honeycombing)
Duct Criteria	**Minor Criteria**
Irregular duct contour	Cyst (anechoic, round or elliptical with or without septations)*
Visible side branches	Dilated duct (≥3.5 mm in the body or >1.5 mm in the tail)*
Hyperechoic duct margin	Irregular duct contour (uneven or irregular outline and ectatic course)
Dilated MPD	Dilated side branch (>3 tubular anechoic structures each measuring ≥1 mm in width, budding from the MPD)*
Stone	Hyperechoic duct wall (echogenic, distinct structure >50% of entire MPD in the body and tail)
	Hyperechoic strands (≥3 mm in at least 2 different directions with respect to the imaged plane)
	Hyperechoic foci (>2 mm in length or width that are nonshadowing)*
	Lobularity (>5 mm, noncontiguous lobules)

*If any of these minor criteria are present, the patient cannot be classified as "normal."

MPD, main pancreatic duct.

Rosemont criteria adapted from Catalano MF, Sahai A, Levy M, et al. EUS-based criteria for the diagnosis of chronic pancreatitis: the Rosemont classification. *Gastrointest Endosc*. 2009;69(7):1251-1261.

TABLE 13.3

Classification of Patients Based on EUS Criteria

Conventional Criteria	Rosemont Criteria
Normal (Low Probability)	**Consistent With**
0-2 criteria	2 major A
Indeterminate or Intermediate Probability	1 major A + 1 major B
	1 major A + ≥3 minor
3-4 criteria	
High Probability	**Suggestive**
5-9 criteria	Major A + <3 minor
Calcifications/stones	Major B + ≥3 minor
	≥5 minor, no major
	Indeterminant
	Major B alone + <3 minor
	Normal
	<3 minor, no major

Rosemont criteria adapted from Catalano MF, Sahai A, Levy M, et al. EUS-based criteria for the diagnosis of chronic pancreatitis: the Rosemont classification. *Gastrointest Endosc*. 2009;69(7):1251-1261.

way, the term *lobularity* is best avoided because a lobular outer gland margin could be confused with hypoechoic lobules.[25] Loss of a distinct ventral anlage is usually not listed as a separate criterion and has not been tested as such, but this phenomenon occurs in inflammatory disorders of the pancreas more often than in control subjects (71% versus 25%).[29]

Minimal standard terminology (MST) has been developed for these criteria (currently, version 3.0) and for other EUS findings in the pancreas and other organs. MST is periodically updated by the World Organization of Digestive Endoscopy (OMED) Committee of Documentation and Standardization (Table 13.5).[37,38]

Reproducibility and Interobserver Agreement

The first assessment of a diagnostic test, after pilot studies that define what is normal and what is abnormal, involves measurement of reproducibility and interobserver reliability of the assessment and the criteria.[39] In the study by Wiersema et al,[26] concordance for the five criteria that achieved significance in multivariate analysis was seen in 83% to 94% for the three reviewers. Beyond reporting the proportion of observers agreeing, one can measure agreement using the kappa (κ) statistic as a measure of agreement beyond chance ($\kappa < 0$ is worse agreement than by chance, 0 is no more than chance agreement, and 1 is perfect agreement).[39] The minimum threshold for "fair" agreement varies from 0.20 to 0.40.[40–42]

Wallace et al[27] measured the interobserver reliability of 11 experienced endosonographers for the overall diagnosis of chronic pancreatitis at κ of 0.45; there was poorer reliability for individual criteria. Neither advanced training nor experience (>1000 procedures) improved agreement.[27] Only two of the nine had κ of more than 0.40: main duct dilation (0.61) and lobularity (0.51).[27] Ranking of importance of criteria was variable, except for stones ($\kappa = 0.38$), which were believed to be the most important.[27] Likely because of some variability in an endosonographer's tolerance for trivial dilation, and perhaps because of different age adjustments, even duct size[27] did not have complete agreement. Although these values for reliability appear poor at first glance, Wallace et al[27] pointed out that identification of bleeding ulcer stigmata ($\kappa = 0.34$ to 0.66),[43] stroke localization by radiologists using brain CT ($\kappa = 0.56$ to 0.62),[44] and interpretation of heart sounds ($\kappa = 0.05$ to 0.18)[45] have comparable or poorer interobserver reliability. MRCP may have slightly better agreement among experts, but community agreement is not known.[46]

Another dimension of a test's reliability is its test-retest reliability or intraobserver reliability. The latter, measure of how often one agrees with oneself when presented with the same images at a later time, was studied across multiple institutions. Intraobserver reliability was excellent (90% agreement; average κ, 0.75)[47] and at least as good as with ERCP images, which are consistent among individuals only 61% to 78% of the time.[48]

Many of the controversies surrounding interpreting the criteria that were raised in the last edition of this book[49] were temporarily settled to some extent by the more recent consensus Rosemont document.[15] These controversies include decisions on threshold sizes of abnormal side branches and sizes of foci and strands, on whether honeycombing (i.e., a combination of strands, foci, and lobules) should have extra weight or consideration, on whether a single lobule can be considered normal, and on whether minor degrees of duct dilation (e.g., 2.5 mm in the body) can be ignored (see Table 13.1). The Rosemont criteria are cumbersome to apply, however, and are not validated. Although they do settle some controversies regarding criteria definitions, no evidence indicates that, taken as a whole, they will achieve the goal of improved reliability. Finally, a few other controversies still remain, such as how best to diagnose chronic focal pancreatitis in the head (because findings isolated to the head of the pancreas are generally ignored), whether "lobularity" of the

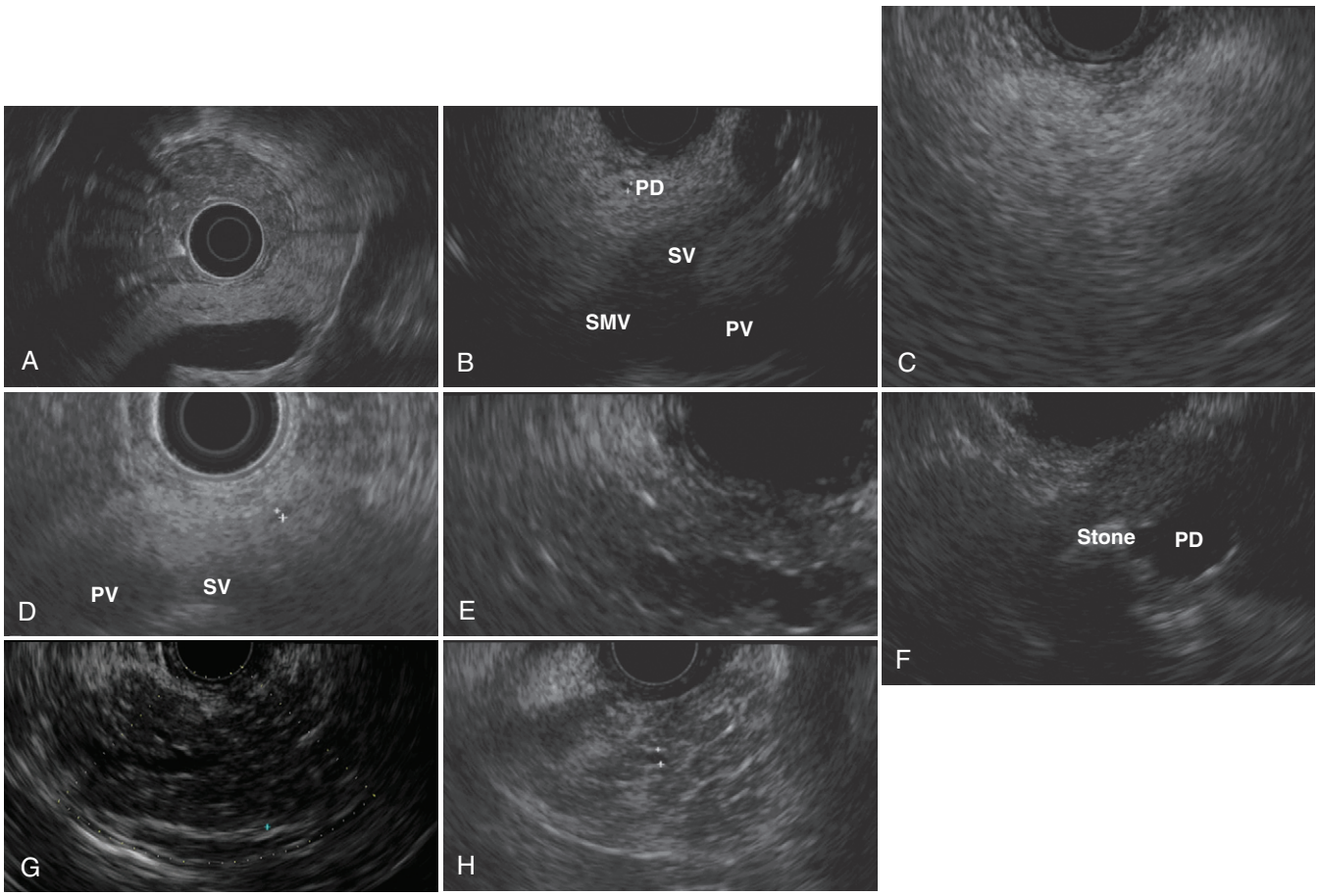


FIGURE 13.1 EUS views of normal pancreas versus chronic pancreatitis. A, Normal pancreas: electronic radial EUS. **B,** Normal pancreas: linear EUS. PD, pancreatic duct; PV, portal vein; SMV, superior mesenteric vein; SV, splenic vein. **C** and **D,** Fatty/snowstorm body of pancreas (BOP) on linear EUS (**C**) and electronic radial EUS (**D**): splenic artery and SV and PV blurry and barely discernible because of marked attenuation by the pancreas above them; a duct is difficult to see. **E,** Linear EUS of an irregular PD in BOP. **F,** Obstructing stone in the PD in the head of the pancreas on linear EUS, with a wedge of acoustic shadowing and upstream PD dilation. **G,** Dilated side branch *(thin arrow)* with small power Color Doppler–positive vessels mimicking branches in BOP on linear EUS. **H,** Hypoechoic (dark) lobules (*) surrounded by bright hyperechoic strands, with an echogenic duct wall (+ calipers) in BOP on linear EUS.

TABLE 13.4

Hypothesized Histologic Correlates of EUS Criteria for Chronic Pancreatitis and Their Alternate Explanations

EUS Finding	Proposed Histologic Correlate (and Alternative Non–Chronic Pancreatitis Explanations)
Hyperechoic or thickened duct margin	Periductal fibrosis (this "interface" can be accentuated [brighter or thicker] when changes in tissue density result in a more abrupt change in acoustic impedance between tissue and duct)
Dilated duct and/or side branches	Dilated duct and/or side branches (small vessels can mimic side branches; obstructed ducts)
Irregular duct contour	Irregularity resulting from fibrosis
Stones	Stones (pneumopancreatica and calcifications in splenic vessel walls)
Cysts	Cysts and/or cystic side branches (cysts and cystic side branches can represent cystic neoplasms)
Hyperechoic foci and strands	Focal or linear areas of interlobular fibrosis; round foci may also represent strands cut in cross section or small calcifications or protein plugs that are not dense enough to cause an acoustic shadow (changes in acoustic impedance cause linear reflections or strands; this artifact is less likely to explain strands that are not parallel to the probe)
Hypoechoic lobules	Groupings of anatomic lobules with focal edema, inflammation, or atrophy, often encapsulated by interlobular fibrosis (EUS lobules, especially in pancreatic cancer kindreds, can represent nodules of dysplasia or neoplasia)

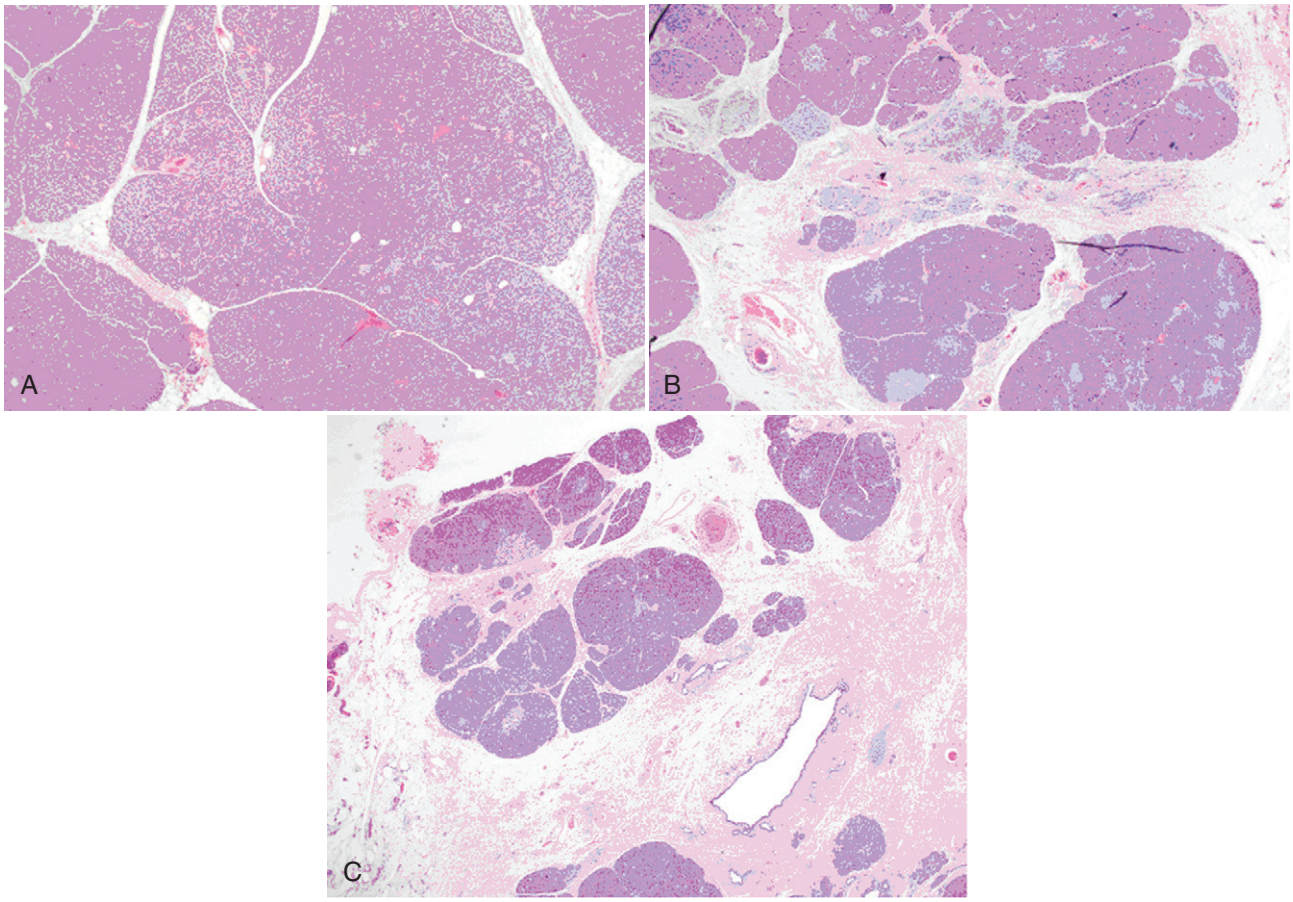


FIGURE 13.2 Histologic features of normal pancreas versus chronic pancreatitis. A, Normal pancreas histology. Low-power (2× objective) hematoxylin and eosin (H&E) stain of pancreas. Pancreatic acinar tissue is the predominant cellular component. There is limited fat (round clear spaces within the lobule *(white arrow)* and in a limited perilobular fibrous component; *black arrow*). No significant fibrosis is present. **B,** Mild chronic pancreatitis. Low-power (2× objective) H&E stain of pancreas. Lobular atrophy with interlobular fibrosis is visible *(black arrow)*. Prominent islets of Langerhans are present *(white arrow)*. **C,** Moderate chronic pancreatitis. Low-power (2× objective) H&E stain of pancreas. Lobular atrophy with interlobular fibrosis *(black arrow)* causes the "honeycombing" appearance of multiple adjacent "hypoechoic lobules" (multiple anatomic lobules in clusters, surrounded by strands of fibrosis). Prominent islets of Langerhans are present *(white arrow)*. A large pancreatic duct with periductal fibrosis is visible in the *lower right* of the image *(red arrow)*.

gland *margin* has any meaning, and whether atrophy should be considered a criterion (as it often is with MRI and CT).

How Many Criteria Should be Sought? How Many is Too Many?

A summary of the different criteria sought and of the thresholds used is presented in Table 13.1. Unfortunately, the thresholds for abnormality vary in studies from 1 or more to 6 or more, and the denominator of criteria sought also varies from 5 to 10 or more. The criteria with the most consistent use across studies are the ductal criteria. Of the parenchymal criteria, the most consistently used are hyperechoic foci (although the size criterion is not consistent), cysts, and hypoechoic lobules (also called *hypoechoic areas* or *hypoechoic foci* by some investigators).

Calcifications

Calcifications or *ductal stones* are considered diagnostic for chronic pancreatitis (Video 13.1). Because of this, and because patients with calcifications were largely excluded from threshold-seeking studies, this is not a criterion to be "counted." It stands on its own. However, some supporting findings should be sought, as suggested in the Rosemont document,[15] and care should be taken to ensure that the calcifications are not just associated with a splenic vessel. Air artifact (pneumopancreatica) can also mimic a ductal stone in patients who have had pancreatic sphincterotomy. Chong et al[50] showed that 30 of 71 patients in their surgical series had calcifications by EUS, but in only 16 (58%) were these calcifications detected preoperatively by CT or MRI. Another small study showed that 7 of 16 patients being evaluated were found to have small calcifications that were missed with other imaging techniques.[51] Therefore, EUS is arguably the most sensitive test for calcifications or stones, a finding that is very specific for chronic pancreatitis.

No Calcifications

In patients *without calcifications,* the number of criteria (out of the remaining eight) then becomes critical (Video 13.2). Wiersema et al[26] used receiver-operator characteristic (ROC) curve analysis and found three or more criteria to be best. Sahai et al[36] informally looked at different thresholds and showed that finding fewer than three criteria effectively excluded moderate and severe chronic pancreatitis on ERCP; the presence of five or more criteria strongly suggested at least mild chronic pancreatitis on ERCP. Neither of these studies included calcifications as a criterion, because those patients were excluded from analysis. Supporting these cutoffs, symptomatic controls had a mean of 1.9±1.8 criteria in a study conducted at the Medical University of South Carolina (MUSC) that looked at the prevalence of findings in dyspepsia; no controls had more than six criteria,[28] and 67%

TABLE 13.5

Definition of Inflammatory Pancreatic EUS Criteria Using Selected Minimum Standard Terms

Term*	Definition	Comment
Cyst	Abnormal anechoic (i.e., without echoes) round or oval structure	Specify size, septations, wall thickening or mural nodules, debris, connection with main duct or side branch, and associated solid mass Inflammatory cysts are generally thin walled, have single or no septations, often contain debris, and are often in communication with main pancreatic duct
Calcification	Hyperechoic lesion with acoustic shadowing (reduction in echo from strongly attenuating or reflecting structure) within parenchymal organ or mass	Generally not recommended for describing pancreas, unless describing components of cyst or mass
Stone	Hyperechoic lesion with acoustic shadowing (reduction in echo from strongly attenuating or reflecting structure) within duct or gallbladder	All calcifications in pancreas (excluding masses and cysts) are by definition intraductal, although side branch duct in which they reside may be too small to appreciate Generally stones and pancreatic "calcifications" are both considered "ductal" features Size measurement may be inaccurate because typically only hyperechoic proximal part of lesion is seen as echogenic Specify number, approximate size, location in gland (head/body/tail), and whether present within main duct
Hyperechoic foci	Small distinct reflectors	Some studies separate <3- and ≥3-mm sizes, but relative significance is not known Generally do not have acoustic shadowing Specify extent, location
Hyperechoic strands	Small, string-like, hyperechoic (echoes are brighter than normal and/or brighter than surrounding tissues) structures	Specify extent, location
Hypoechoic lobules	Rounded homogeneous areas separated by strands of another echogenicity	Almost by definition, lobules and strands coexist, and foci also frequently coexist "Lobulated" can be used to describe a gland with lobules but is sometimes confused with a lobular gland margin and is probably a term best avoided Care must be taken to ensure that lobules >1 cm are not in fact masses Specify extent, location
Irregular duct contour	Coarse, uneven outline of duct	Specify extent, location
Tortuous duct	Duct with numerous twists and bends	To be distinguished from irregular; not necessarily abnormal
Hyperechoic duct wall	Region of duct where echoes are brighter than normal and/or brighter than surrounding tissues	Normal pancreatic duct wall surrounded by normal tissue is barely perceptible on ultrasound and is essentially isoechoic to surrounding parenchyma
Dilated duct	Abnormal increase in caliber	Duct size should be measured from closest echo of wall closest to probe to closest echo of wall furthest from probe Size and location, beading (alternating small and large calibers), and localized narrowings (strictures) should be noted

*"Hypoechoic foci" and "accentuation of lobular pattern" are terms not listed in the Minimum Standard Terms.

Adapted from International Working Group for Minimum Standard Terminology for Gastrointestinal Endosonography. Reproduction of minimum standard terminology in gastrointestinal endosonography. *Dig Endosc*. 1998;10:158-184; World Organisation of Digestive Endoscopy (OMED) Committee of Documentation and Standardization. Minimum standard terminology (MST v 3.0). <http://www.omed.org/index.php/resources/re_mst/>; 3.0 ed; 2009 Accessed 05.19.10.

had fewer than four criteria. These findings would have been even more striking if the controls with a history of alcohol use (which had double the number of criteria on overage) had been excluded.

Chong et al[50] also compared EUS findings with those of surgical pathology in 71 patients. In patients without calcifications ($n = 41$), ROC curve analysis revealed that three or more EUS criteria provided the best balance of sensitivity and specificity. Another similar study (but with a higher histologic fibrosis score threshold) of 21 patients found four or more EUS criteria to be the best ROC-derived cutoff.[52]

Interpreting Levels of Certainty of Chronic Pancreatitis

Diagnostic tests with multiple values or continuous measures often have high levels that are considered diagnostic (e.g., lipase more than three times the upper limit of normal), low levels that are considered very reassuring (e.g., cyst fluid carcinoembryonic antigen <5), and values near or at the "best cutoff" that are indeterminate. The interpretation of the number of EUS criteria for chronic pancreatitis is no exception: having three or four criteria is considered equivocal because that result lands on or near the best cutoff. This finding essentially leaves the pretest suspicion of disease unchanged, with a likelihood ratio of near 1. Therefore, in the presence of risk factors that increase the pretest likelihood of disease, such as alcohol abuse, smoking, family history, or symptoms suggestive of pancreatic disease,[53] this value may represent chronic pancreatitis. Similar to other continuous measures, a low result (fewer than three criteria) is very reassuring, and a high result (five or more criteria) is very specific for disease. These levels are meant to represent *probability*, not *severity*.[15] There is only a modest correlation of increasing number of criteria with more severe fibrosis,[50,52] or more severe ERCP Cambridge score.

Adjusting Thresholds for Demographics

Making *special adjustments or allowances* for different age, gender, and risk factor groups is not supported.[15] Rajan et al[54] showed some relationship between age and number of criteria, but this was not significant in multivariate analysis when corrected for other factors,[55] and these investigators did not allow a higher duct size threshold for older patients. Another study showed a

significantly higher number of findings in alcoholic subjects versus subjects who did not have alcoholism, and EUS criteria for chronic pancreatitis predicted their alcohol history.[56] Yusoff and Sahai[57] also failed to find an age association. Both smoking and alcohol use were significant predictors of finding more criteria,[57] but because these are both known risk factors for chronic pancreatitis, allowances should not be made; instead, the higher number of criteria likely represents subclinical pancreatic disease in asymptomatic patients. Male gender was independently associated with more EUS features in both studies.[54,57] The reason for this finding is not clear. It could be that alcohol and smoking exposures were higher in men than in women, or such exposures were more likely to be underreported. It is also possible that a true gender-specific risk factor exists. In the end, no criteria threshold adjustments are recommended for these groups.

Accuracy and Test Performance

Reference Standards and Competing Technologies

After one is confident with the reliability of a test, the next step is to assess its accuracy against a reference standard.[39] Unfortunately, for chronic pancreatitis, the reference standard is also a problem. Although complex advanced statistical techniques exist to try to account for imperfect reference standards,[58] they have not been used in the literature to date. Even for *histology*, grading and diagnosis are unfortunately not standardized and are limited to small series.[59,60] The number of histologic criteria required is arbitrary and differs from study to study.[50,52] Disease can be patchy, just as it can be in cirrhosis,[61] FNA appears unreliable and does not increase accuracy significantly,[60] and it is not clear whether both chronic inflammation *and* fibrosis need to be present for the diagnosis (often, fibrosis is all that is seen). ERCP and secretin-stimulated pancreatic juice analysis have historically been considered the nonhistologic reference standards, but both techniques likely miss early disease.

Not all cases of chronic pancreatitis result in ductal disease sufficient to be seen at ERCP, and the pancreas has tremendous functional reserve, which results in false-negative secretin test results until late in the disease process. ERCP relies on ductal (main and side branch) irregularity and dilation, intraductal filling defects or stones, and inflammatory cysts that communicate with the main pancreatic duct, graded using the widely accepted, although consensus-derived, Cambridge classification (Table 13.6).[32] Fibrotic or inflammatory parenchymal changes cannot be assessed with ERCP until they cause ductal irregularity or obstruction.

Multiple types of noninvasive *pancreatic function tests* are available, including measurement of stool enzymes (e.g., fecal elastase),[16] as well as assessment of the cleavage of promarkers by proteases by measuring the markers in urine, blood, or breath.[16,62] Invasive tests involve measuring bicarbonate or fluid (hydrelatic) or enzyme (ecbolic) output after food or hormonal stimulation (e.g., secretin test). Although pancreatic function testing is viewed by some investigators as our most sensitive and reliable test for chronic pancreatitis and pancreatic insufficiency, with an accuracy of 80% to 90%,[16] sensitivity frequently drops to less than 40% in early disease.[6] One moderate-sized study from Japan that compared the secretin test with histologic findings (consensus-derived histology scoring system [grades 0 to 4] from the Japanese Society of Gastroenterology) in 108 patients (including 39 with abnormal histology) showed a sensitivity of less than 70%.[63,64] Other older comparisons with histologic findings found a similarly modest sensitivity.[65,66] Fecal elastase has a sensitivity of 45% to 63% for mild disease but 73% to 100% for severe[67–69] disease compared with ERCP[67] or invasive pancreatic function tests.[68,69]

Studies of MRCP have shown that the main pancreatic duct is seen well, especially with secretin, although resolution of side branches is inferior compared with ERCP.[70,71] Calvo et al[72] showed an 86% sensitivity and 94% specificity of MRCP compared with ERCP for ductal abnormalities in 78 patients. In contrast, Alcaraz et al[73] studied 81 patients undergoing both MRCP and ERCP but showed only a 50% sensitivity for MRCP in chronic pancreatitis (with 99% specificity). Another study found only a 25% sensitivity of MRCP for mild disease, versus 82% to 100% for severe disease.[24] Other adjuncts to MRCP that need further study and validation include noting of gland atrophy, lower T2 gland signal intensity,[74] secretory response (duct dilation or duodenal filling) to a test (Lundh) meal or secretin,[33,74] lower T1 (perfusion) intensity, (virtual) pancreatoscopy,[75] and diffusion-weighted secretin-MRCP (looking at water molecule movement to assess diffusion and microcirculation changes).[24]

Although the comparative literature on MRCP in chronic pancreatitis is far less extensive than that on EUS, newer comparative studies were published in 2007 and 2008. One study compared secretin-MRCP with pancreatic function tests (urinary pancreolauryl and fecal elastase-1). Secretin-MRCP results were abnormal in patients with steatorrhea, but many false-positive (4% to 18%) and false-negative (16% to 25%) results were noted compared with pancreatic function tests.[33] Another study showed that although secretin-stimulated flow was reduced in severe pancreatitis (5.6 mL/min), it was actually similar to controls (7.4 mL/min) in mild (7.5 mL/min) and moderate (7.0 mL/min) pancreatitis.[34] Other features such as T1/T2 intensity and atrophy have been proposed, and used by some investigators, but need further validation. In contrast to EUS, the MRCP literature does not propose a scoring system for counting or weighting features, but rather states that pancreatitis is "suspected" or "possible" when *any* of these features are found.

TABLE 13.6

Cambridge Classification of Chronic Pancreatitis by Endoscopic Retrograde Cholangiopancreatography

Class	Definition
0: Normal	Visualization of entire duct system with uniform filling of side branches without acinar opacification, with a normal main duct and normal side branches
1: Equivocal	Normal main duct 1-3 abnormal branches
2: Mild	Normal main duct >3 abnormal side branches
3: Moderate	Dilated main duct with irregularity >3 abnormal side branches Small cysts (<10 mm)
4: Marked/ severe	Large cysts (>10 mm) Gross irregularity of main pancreatic duct Intraductal calculus/calculi Stricture(s) Obstruction with severe dilation

From Axon AT, Classen M, Cotton PB, et al. Pancreatography in chronic pancreatitis: international definitions. *Gut*. 1984;25:1107-1112.

Test Performance and Study Limitations

EUS has been compared with both ERCP and secretin-stimulated pancreatic function testing as the best available reference standards for chronic pancreatitis, notwithstanding the foregoing limitations. The studies with and without clinical follow-up are summarized in Tables 13.7 and 13.8, and in Figure 13.3.

Pilot and Retrospective Studies

In 1993, Wiersema et al[26] compared a sample of 20 healthy volunteers with 69 patients with pancreaticobiliary pain. Thirty patients had chronic pancreatitis by ERCP (19), ERCP and secretin-stimulated pure pancreatic juice collection (PPJ) (3), PPJ alone (6), and clinical (2) criteria. The sensitivity and specificity of EUS in chronic pancreatitis compared with ERCP were 100% and 79%, respectively, and 80% and 86%, respectively, compared

TABLE 13.7

Review of Literature *without Clinical Follow-Up*, Regarding the Diagnostic Test Performance of EUS in Chronic Pancreatitis

Authors (yr)	Patients (*n*)	Design	Results	Comments
Wiersema et al[26] (1993)	69	20 controls examined 69 patients with pancreatic or biliary pain studied All 69 had ERCP, 16 had PPJ testing	30 had chronic pancreatitis by ERCP (19), ERCP and PPJ (3), PPJ alone (6), and clinical (2) SN 80%; SP 86% if ≥3 criteria of 11 used, as per ROC curve analysis SN 100%; SP 79% vs. ERCP SN 67%; SP 29% vs. PPJ for EUS SN 33%; SP 86% vs. PPJ for ERCP	11 total criteria, 5 significant in logistic regression Called foci >3 mm, 20 controls not used in accuracy, calculation
Buscail et al[76] (1995)	44	81 consecutive patients, 44 had ERCP, plus 18 controls	SN 88%; SP 100%	Nonconsecutive enrolment "Hand-picked" controls Called echogenic duct wall normal Nonstandard terms and criteria No threshold reported
Catalano et al[25] (1998)	80	Consecutive patients with recurrent pancreatitis	SN 86%; SP 95% vs. ERCP SN 84%; SP 98% vs. ERCP and PPJ testing 0 criteria: 100% NPV ≥6 criteria: 100% PPV 3-5 criteria: 92% positive ERCP, 50% positive PPJ 1-2 criteria: 17% positive ERCP, 13% positive PPJ	Even 1 criterion was considered abnormal Waited 6 weeks since last attack Blinded EUS (not ERCP)
Sahai et al[36] (1998)	126	Double-blind prospective Patients with unexplained pain or suspected pancreatitis referred for ERCP	<3 criteria: "NPV >85%" ≥6 criteria: "PPV >85%" No actual SN/SP specified	9 criteria used Head ignored Called foci <3 mm
Hollerbach et al[60] (2001)	37	Suspicion of chronic pancreatitis, with FNA in 27 patients	SN 97%; SP 60% vs. ERCP, without FNA SN 100%; SP 67% vs. ERCP, with FNA ($n = 27$) SN 52%; SP 75% vs. indirect pancreatic function tests	5 criteria total Weighted criteria 7% post-FNA pancreatitis
Chowdhury et al[79] (2005)	21	Retrospective review of patients undergoing EUS and secretin stimulation test	≥4 criteria ideal on ROC SN 57%, SP 64% for ≥4 criteria ≥6 criteria had SP 92%	9 EUS criteria Abnormal peak stimulated duodenal (bicarbonate) ≥80 mEq/L
Chong et al[50] (2007)	71	Retrospective review of patients undergoing surgery for pancreatic pain with preoperative EUS on record	Only 58% of 30 with calcifications had these seen on pre-EUS imaging 41 of 71 did not have calcifications ≥3 criteria ideal on ROC (noncalcific) SN 83%; SP 80% for ≥3 criteria ≥5 criteria: 100% SP 2 or fewer: 90% SN $r = 0.40$ for criteria vs. histologic severity	9 EUS criteria 12 histologic criteria (≥2 abnormal) Blinded GI pathologist Mass lesions excluded
Varadarajulu et al[52] (2007)	42	Prospective study of patients undergoing preoperative EUS, without calcifications, before pancreatic surgery for variety of indications	≥4 criteria ideal on ROC SN 91%; SP 86% for ≥4 criteria $r = 0.85$ for criteria vs. histologic severity	9 EUS criteria 12 histologic criteria (≥6 abnormal) Blinded GI pathologist Patients with resectable masses were included, examining pancreas "furthest from the mass"

ERCP, endoscopic retrograde cholangiopancreatography; FNA, fine needle aspiration; GI, gastrointestinal; NPV, negative predictive value; PPJ, secretin-stimulated bicarbonate testing on pure pancreatic juice; PPV, positive predictive value; ROC, receiver-operator characteristic; SN, sensitivity; SP, specificity.

with the final diagnosis (ERCP, secretin testing, or "clinical criteria") when three or more criteria were defined as abnormal, based on ROC analysis of the composite standard. EUS had a sensitivity and specificity of 67% and 29%, respectively, in the 16 patients who had PPJ (including nine abnormal results); ERCP had sensitivity of 33% and 86%, respectively. Because the cutoff for the diagnostic test was only internally validated, the cutoff determination and test performance characteristics were likely somewhat biased.[39]

Buscail et al[76] reviewed 81 consecutive patients referred for suspected pancreatic disease. The results in the 44 patients who had ERCP were compared with 18 controls. EUS definitions were somewhat nonstandard (an "echogenic wall" was considered normal, and nonstandard terms such as *diffusely heterogeneous, diffusely hyperechoic, hypoechoic areas*, and *hypertrophic* were used to describe abnormalities). The threshold number of criteria for diagnosis was vague, but sensitivity and specificity of 88% and 100%, respectively, were reported.

Although common and acceptable for pilot study designs, comparing "cases" with "controls" to assess diagnostic test performance is prone to spectrum bias. In other words, it is generally easier to separate frankly normal (control) patients from frankly abnormal (case) patients than it is to separate normal and abnormal patients in a series of consecutive real-life patients with clinical suspicion of disease.[39,77,78]

Another retrospective study, by Chowdhury et al[79] and performed at the University of Florida, examined how EUS

TABLE 13.8

Review of Literature *with Clinical Follow-Up*, Regarding the Diagnostic Test Performance of EUS in Chronic Pancreatitis

Authors (yr)	Patients (*n*)	Design	Results	Comments
Hastier et al[84] (1999)	18	72 patients with alcoholic cirrhosis without pancreatic symptoms 32 controls with abdominal pain and normal ERCP, without history of pancreatitis or alcohol use 18 had EUS parenchymal criteria only and either follow-up EUS or ERCP	None of patients with parenchymal criteria only on EUS had progression on follow-up EUS or new abnormalities on ERCP ($n = 10$)	8 criteria sought Denominator was 104 patients Selection bias likely from confounding by the clinical factors leading to repeat EUS or ERCP Kasugai ERCP grading No blinding
Chen et al[83] (2002) (abstract)	19	Retrospective study of normal EUS and ERCP repeated >12 months later	5 (83%) of 6 patients with normal ERCP but abnormal EUS had abnormal ERCP 1 (7%) of 13 with normal EUS and ERCP had abnormal ERCP in follow-up	Denominator was 299 patients Selection bias likely from confounding by the clinical factors leading to repeat ERCP
Kahl et al[53] (2002)	38	Symptomatic with suspected chronic pancreatitis but normal ERCP 32 had abnormal EUS 22 of the 32 who had follow-up ERCP were abnormal on second ERCP	Half of abnormal second ERCPs were Cambridge 1, half Cambridge 2 Using second ERCP as a gold standard in those with abnormal EUS, ERCP had 81% SN EUS had 100% SN; 16% SP (74% SP using second ERCP as gold standard)	10 criteria sought Cambridge ERCP grading No blinding Most ERCP progression was subtle
Singh et al[86] (2004) (abstract)	39	Retrospective study EUS patients with ≤3 criteria	18% developed diabetes over a mean of 5 years follow-up, many times higher than the age-sex expected rate	No data on whether ERCP was normal at baseline Suggests 1-3 criteria may mean structural damage

ERCP, endoscopic retrograde cholangiopancreatography; SN, sensitivity; SP, specificity.

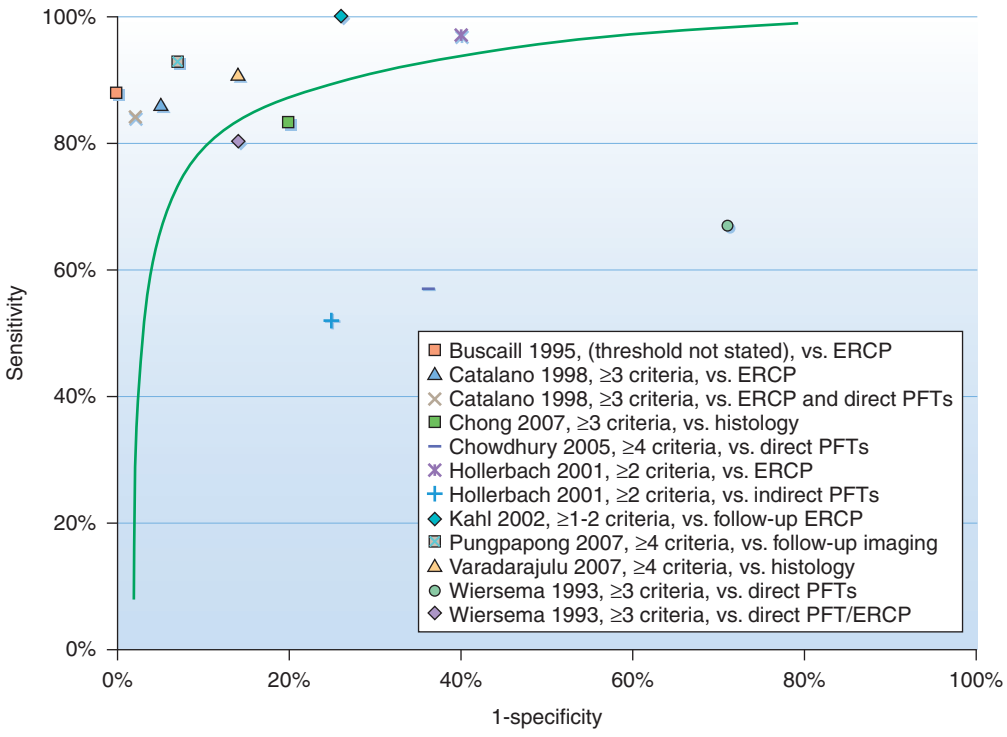


FIGURE 13.3 Test performance (receiver-operator characteristics) of various studies of EUS in chronic pancreatitis. Test performance is plotted as sensitivity against 1-specificity (false-positive rate). Most studies either did not include calcific pancreatitis, or had a very small number of patients with calcifications. A rough qualitative summary curve is provided. A quantitative curve is not calculated because of the inhomogeneity of the reference standard of the studies. ERCP, endoscopic retrograde cholangiopancreatography; PFT, pancreatic function test.

compared with invasive pancreatic function testing (secretin test, normal peak stimulated duodenal bicarbonate concentration ≥80 mEq/L). Using data from the 21 patients studied with both tests, a threshold of six or more criteria (out of nine) had a 92% specificity; ROC curve analysis showed that the best balance of sensitivity and specificity was achieved by using a cutoff of four or more criteria, but this approach had only modest performance (sensitivity 57%, specificity 64%).[79]

Prospective and Consecutive Series

Catalano et al[25] compared 80 consecutive patients who had recurrent pancreatitis in a prospective comparative trial. Patients waited at least 6 weeks after their last attack of acute pancreatitis before undergoing EUS, with ERCP and a secretin test. "Mild" chronic pancreatitis by EUS was defined (controversially) as having one to two diagnostic features; "moderate" disease had three to five criteria; and "severe" disease had more than five criteria,

of 10 criteria, including one termed "heterogeneity." A normal result was therefore defined as one having no diagnostic criteria. EUS had an 86% sensitivity and a 95% specificity compared with ERCP and had an 84% sensitivity and a 98% specificity when compared with ERCP plus a secretin test. Both normal EUS and "severe" disease EUS results had 100% agreement with normality or abnormality on ERCP and a secretin test, respectively; the grades also often agreed ($\kappa = .82$). The finding of three to five criteria ("moderate" disease) by EUS still had 92% agreement with ERCP, but only 50% with the secretin test. "Mild pancreatitis" (one to two criteria) had a 17% rate of abnormal ERCP and a 13% abnormal secretin test rate. This study suggested that a small percentage of patients with low numbers of criteria may actually have advanced chronic pancreatitis. The terms "mild," "moderate," and "severe" are more *grading* terms than they are indicators of *probability* of disease and are now usually avoided, including in the consensus document lead-authored by the same group.[15] A source of bias included that ERCP endoscopists were not necessarily blinded to the EUS result.

The largest prospective study to date is from MUSC, by Sahai et al[36] in 1998. In this study, 126 patients with unexplained abdominal pain or suspected pancreatitis who were referred for ERCP underwent EUS first and then ERCP blinded to EUS results. Nine fairly standard criteria were used, and size definitions for echogenic foci (1 to 2 mm), hypoechoic lobules (2 to 5 mm), ductal size (>3 mm in head, >2 mm in body, >1 mm in tail), and cysts (>2 mm) were given. An abnormal ERCP result was defined as Cambridge 3 (25%) or higher (21%); normal or equivocal (Cambridge <2) (24%) findings and "mild" chronic pancreatitis (Cambridge 2) (29%) on ERCP were considered normal (see Table 13.7). In this study, the finding of fewer than three criteria had a negative predictive value of "more than 85%," and the finding of more than six criteria had a positive predictive value of more than 85%. Other, more specific, performance numbers were not published. Neither individual criteria nor the number of criteria were apparently significant in multivariate analysis. In a secondary multivariate analysis (abnormal ERCP, defined as Cambridge 2 or higher), the number of parenchymal criteria were significant. In summary, this study illustrated that the presence of one to two criteria is uncommon in moderate or severe chronic pancreatitis (by ERCP) and that seven or more criteria are frequently associated with moderate or severe chronic pancreatitis on ERCP.

Studies Involving Fine-Needle Aspiration or Biopsy

In 2001, Hollerbach et al[60] studied 37 German patients suspected clinically of having chronic pancreatitis (31 [84%] had abnormal ERCP results). Patients underwent EUS with (n = 27) or without FNA, ERCP, and noninvasive pancreatic function testing (fecal chymotrypsin and elastase-1, and urinary pancreolauryl testing). Only five criteria were sought (hyperechoic lobules, hyperechoic strands ["septa"], ductal irregularity, calcifications, and cysts) and were weighted into 3 grades: grade 1, lobularity and strands; grade 2, grade 1 plus ductal irregularities; and grade 3, grades 1 to 2 plus stones or cysts. EUS had a sensitivity of 97% (100% with FNA) and a specificity of 60% (67% with FNA) compared with ERCP, and 52% and 75%, respectively, compared with pancreatic function tests. Two (7%) of 27 patients had complications of post-FNA pancreatitis requiring fluids and analgesia for 1 day.

Dewitt et al[80] attempted EUS-guided Tru-Cut biopsy in 16 patients with suspected (≥3 criteria) chronic pancreatitis on EUS, and in 13 of these patients, results were compared with ERCP. The agreement between the biopsy result and either the EUS or the ERCP result was poor (κ of 0 and 0.25, respectively). Of the five patients with a normal ERCP result, none had a normal Tru-Cut biopsy result (four had an abnormal Tru-Cut result; one was nondiagnostic). Of the eight patients with an abnormal ERCP result, only one had an abnormal Tru-Cut result (three had a normal Tru-Cut result; four were nondiagnostic). Two patients (13%) had pain requiring overnight admission.

It therefore seems that FNA and Tru-Cut biopsy either add little, or may be misleading, to the EUS-derived diagnosis, and they have a 5% to 15% adverse event (unanticipated hospital stay) rate. An ASGE practice guideline supports this position.[17]

Studies with Comparison to Surgical Pathology

Two groups,[50,52] including one at MUSC, compared EUS findings with surgical pathologic results. The MUSC study had 71 patients, who had undergone surgery for suspected chronic pancreatitis or pancreatic pain (e.g., refractory sphincter stenosis or pancreas divisum).[50] In patients without calcifications (n = 41), the presence of three or more EUS criteria (based on ROC curve analysis) had a sensitivity of 83% and a specificity of 80%. A cutoff of five or more criteria had 100% specificity; two or fewer criteria had a false-negative rate of less than 10% (sensitivity, 90%). In the subgroup of patients without calcifications, positive histologic findings ranged from 8 (67%) of 12 when a core or wedge biopsy was the sample, to 28 (97%) of 29 when a block of tissue (i.e., Whipple procedures, distal pancreatectomy) was sampled; sampling error in the reference standard is therefore a possible limitation.

Investigators at the University of Alabama studied the correlation between EUS and surgical pathology prospectively in 42 patients operated on for a variety of indications, including resectable cysts and tumors.[52] These investigators found four or more EUS criteria (ROC curve analysis) to have a 91% sensitivity and an 86% specificity.[52] Correlation between the number of EUS criteria and the histologic fibrosis severity score was higher (r = 0.85) than it was in the MUSC study (r = 0.40), although both were statistically significant. The MUSC investigators used a more conservative minimum fibrosis score threshold (2 of 12 on Ammann classification[81]) than did Alabama investigators (6 of 12). Finally, a study in dogs, using a pancreatic stent-induced pancreatitis model, showed some correlation between EUS findings and necropsy findings.[82]

Studies with Clinical or Radiologic Follow-Up

Because the "gold" reference standards are somewhat tarnished, a few studies aimed to follow up patients with "false-positive EUS" results to see whether early chronic pancreatitis (i.e., that may have been missed with the traditional gold standard methods) progresses to more overt disease. The results are conflicting (see Table 13.8 and Fig. 13.3).

In a 2002 study from MUSC by Chen et al,[83] 6 of 51 patients with normal ERCP but abnormal EUS results underwent repeat ERCP more than 1 year later. Five (83%) of the ERCP results became abnormal (i.e., a positive predictive value >80% despite normal ERCP). In contrast, 13 of 248 patients with both normal EUS and normal ERCP results underwent ERCP more than 1 year later, and only 1 (7%) result became abnormal (i.e., a negative predictive value of 93%).

Hastier et al[84] studied 72 French patients with alcoholic cirrhosis (without symptoms of pancreatitis) and 32 age- and sex-matched controls with abdominal pain and a normal ERCP result who had no history of pancreatitis or alcohol abuse. Eight criteria (five ductal and three parenchymal) were sought. Of these patients, 18 with one or more parenchymal criteria and either failed (n = 1) or normal (n = 18) ERCP underwent repeat EUS (n = 18), with (n = 10) or without repeat ERCP 12 to 38 months later. In all patients, EUS findings were unchanged; in the 10 patients who underwent repeat ERCP, ERCP results remained normal.

A second German study by Kahl et al[53] studied 32 symptomatic patients with suspected chronic pancreatitis and a normal ERCP result, although they had abnormal EUS findings (>1 criteria); 92 had normal ERCP. More than half (57%) of these patients drank alcohol during the follow-up period of 6 to 25 months. Ten criteria (five parenchymal, including "gland size," and five ductal) were sought; all patients had lobules and "septations." Twenty-two (69%) of the 32 patients had an ERCP in follow-up and all were abnormal (approximately half, Cambridge 1; half, Cambridge 2). If the abnormal second ERCP is used as a reference standard, the first ERCP was 81% sensitive, and EUS was 100% sensitive. Of note, although only one criterion was needed of a positive EUS in this study, accentuation of the lobular pattern (the most common finding)—as they defined it—is really two criteria: strands and lobules.

A study from the Mayo Clinic in Rochester, Minnesota, by Pungpapong et al,[85] used a combination of follow-up (nonblinded) ERCP, follow-up imaging (≥2 negative imaging tests when ERCP was normal [Cambridge I or 0]), and clinical follow-up (median, 15 months; minimum, 7 months) as their composite reference standard to assess the diagnostic performance of EUS showing four or more of nine criteria (derived by ROC curve) in 99 symptomatic patients. Sensitivity and specificity were 93% and 93%, respectively. MRI and MRCP, using one or more criteria, had a sensitivity and specificity of 65% and 90%, respectively.[85]

These study results conflict with one another, possibly because of different diagnostic criteria for chronic pancreatitis by EUS, different ERCP classifications (Kasugai[84] versus Cambridge[53,85]), asymptomatic[84] versus symptomatic[53,85] patient cohorts, varying proportions of ongoing alcohol use in the study groups, and relatively subtle findings on some ERCP tests.[53,85] A critical source of bias in all studies is that the physician interpreting the follow-up imaging was not blinded to the original assessments in all three studies.[39,77]

Comparison and follow-up with respect to endocrine pancreatic function have generally not been reported, mainly because endocrine insufficiency (impaired glucose tolerance or diabetes) is a late finding, given the tremendous endocrine reserve of the gland. An interesting study described follow-up of 39 patients with a low probability of chronic pancreatitis by EUS (≤3 criteria) and found that seven patients (18%) developed diabetes over 5 years,[86] an incidence that was higher than the 5-year age- and sex-matched standardized incidence.

Staging

EUS criteria thresholds and ranges have not been generally used to stage chronic pancreatitis *severity*, but rather to assess the *probability* of disease. That being true, EUS can detect the features (stones, strictures, and duct and side branch dilation) that comprise the ERCP Cambridge classification.[32] As such, one can likely use EUS to anticipate the Cambridge severity class.

Low, intermediate, and high numbers of criteria for chronic pancreatitis only loosely correlate with advancing histologic features[50,52] or advancing Cambridge class. Therefore, those cutoffs should generally not be used to stage severity of disease. Low probability should not be called "mild," and intermediate probability should not be called "moderate," and so forth. A consensus conference agreed with this principle.[15]

Differentiating Inflammatory Pseudotumors from Neoplastic Masses

Acute inflammatory exacerbations of chronic pancreatitis can result in focal edema. This focal edema on CT can be indistinguishable from a neoplastic mass; a 16% to 23% error rate has been reported in this setting.[87,88] Although the coexisting chronic pancreatitis features raise the suspicion of an inflammatory condition, cancer can still be present, because 2% to 4% of patients with nonfamilial chronic pancreatitis develop pancreatic cancer after 10 to 20 years.[89] False-negative results can have serious consequences (missed opportunities to remove a resectable cancer), as can false-positive results (unnecessary Whipple pancreatoduodenectomy).

Painless (versus painful) presentations, weight loss, frank jaundice, persistent or progressive (versus fluctuating) cholestasis, recent onset or worsening of diabetes, or vascular invasion on cross-sectional imaging can all be helpful in distinguishing benign from malignant causes of the mass. Absence of risk factors for pancreatitis, such as alcohol, is another red flag. Unfortunately, the presentation in patients with benign cases can uncommonly be accompanied by weight loss, especially in smoldering acute pancreatitis or in chronic pancreatitis associated with decreased intake, meal-induced nausea or pain, or pancreatic insufficiency. Diabetes can also worsen abruptly in a patient with benign, acute-on-chronic inflammation, or it can newly manifest if endocrine function was already borderline. Carbohydrate antigen (CA) 19-9 has tremendous overlap between benign and malignant disease, especially when biliary obstruction is present. Lymph nodes, including celiac nodes, can be evident in both benign and neoplastic pancreatic diseases. Biliary or pancreatic duct dilation (including the double duct sign) is unfortunately common in both benign and malignant disease. Pancreatic duct irregularity is also common in both types of disorders.[90] Benign pancreatic duct strictures can be similarly tight and irregular, and the yield of pancreatic duct cytology is low in neoplasia.[91,92] Because of this overlap, management decisions can be very difficult.

The accuracy of EUS, with or without FNA, for pancreatic cancer has been well studied,[93] as detailed in Chapter 14. Most of those studies, unfortunately, do not have a good mix of neoplastic and non-neoplastic cases. As an example, the study by Mallery et al[94] reported a 92% prevalence of malignancy.

EUS is uniquely able to show parenchymal detail in pancreatic tissue, and it does not solely rely on size, asymmetry of the gland, or upstream ductal dilation to assess pseudotumors. The usual parenchymal features and ducts are generally focally missing in neoplastic masses, which are usually more homogeneous and distinctly hypoechoic compared with surrounding tissue. Neoplastic masses are seldom calcified, and so masses with internal calcification are more likely benign. Malignant tumors within a calcified pancreas often push the calcified parenchyma aside. One significant limitation to EUS in calcific chronic pancreatitis is that acoustic shadowing from the calcifications can obscure variable proportions of the gland from assessment. Signs of vascular invasion are generally highly suggestive of malignancy. In some cases, however, inflammation-related compression of vascular structures, inflammatory adherence causing a loss of interface (see Fig. 13.6), or thrombosis can be present in benign inflammatory disease.

Barthet et al[95] claimed a 100% sensitivity for EUS, based on the workup of five patients (out of 85) with 2- to 3.5-cm masses in calcific chronic pancreatitis, all of whom had jaundice and weight loss. Two patients were FNA negative and had benign follow-up; the other three had adenocarcinoma. However, a sensitivity rate for EUS is biased here (verification bias),[77,96] because the investigators "verified" (i.e., gathered follow-up data on) only the EUS-positive patients. Kaufman and Sivak[97] studied 25 patients (10 with malignant disease): there was one false-negative result (90% sensitivity), and two false-positive results (87% specificity).

Nattermann et al[98] studied 130 consecutive patients (61 with malignant disease) and found several features that had different frequencies in cancer versus focal inflammation (7% versus 23% hyperechoic foci, 30% versus 7% loss of demarcation with the luminal wall, 28% versus 9% loss of separation between vascular structures, and 11% versus 0% frank invasion of a vessel), although none of these features were significant. Glasbrenner et al[99] studied 95 consecutive patients (50 with malignant disease): (unblinded) EUS, without FNA, had a 78% sensitivity and a 93% specificity.

A study by Varadarajulu et al[100] showed that the sensitivity of EUS FNA was significantly lower when chronic pancreatitis was present (25% of the 300 patients with pancreatic masses) than when it was absent (74% versus 91%; $P = .02$). Patients with chronic pancreatitis also required more EUS FNA passes in this study to establish a diagnosis (median, 5 versus 2; $P < .001$). These investigators also showed that the negative predictive value was lower (i.e., less reassuring when EUS results were negative) when the patient did not have evidence of chronic pancreatitis (89% versus 46%).

There appear to be genes that are overexpressed in pancreatic cancer,[101–110] whereas others are overexpressed or differentially expressed in chronic pancreatitis.[111–115] Therefore, the potential exists for reverse transcriptase polymerase chain reaction[116] to complement cytologic examination on FNA-acquired specimens in these diagnostic dilemmas as well. Pancreatic duct brushing does not increase yield.[91,92] Although one study showed great results,[117] k-ras analysis (sensitivity 42%) was no better than that of brush cytology.[118] p53 immunostain results are conflicting, but yield may be as low as 51%.[119]

Digital image analysis (DIA) and fluorescence in situ hybridization (FISH) have also been piloted to enhance diagnostic accuracy of EUS FNA; these techniques assess nuclear DNA content and the presence of aneuploidy to diagnose malignancy. In a 42-patient study, including 19 patients with pancreatic FNA, DIA/FISH had slightly lower sensitivity (87% versus 97%) but had comparable specificity to routine cytology.[120] Enhanced EUS with contrast harmonic imaging and EUS with elastography is discussed later. Autoimmune pancreatitis (AIP) is also discussed further later, and a diagnostic algorithm was proposed to help separate these inflammatory masses from cancer.[121]

Other competing imaging methods have been studied in this area. Intraductal ultrasound may be a helpful adjunct in some cases because of its high imaging resolution, but results are conflicting and poor overall. Fluorodeoxyglucose positron emission tomography (FDG PET) appears promising, with a reported sensitivity as high as 88%; however, this method uses metabolic activity to distinguish inflammatory and neoplastic lesions, and there is marked overlap in this marker.[122–125] In fact, in a review of more than 200 pancreatic masses, 8 false-negative results were seen.[125] In addition, up to 20% of cancers had decreased delayed uptake, which is a benign PET feature.[126] In another study, five of six cancerous tumors in patients with chronic pancreatitis were detected (sensitivity, 83%); the false-positive rate was 13%.[127] Study results are also often positive and misleading in AIP.[128]

Autoimmune Pancreatitis

AIP is a steroid-responsive inflammatory condition of the pancreas that accounts for less than 5% of patients investigated for acute and chronic pancreatitis[129] and can produce focal inflammatory masses that mimic cancer.[14] AIP is found in about 2% of pancreatoduodenectomy specimens for suspected pancreatic cancer. AIP can manifest with pancreatic insufficiency and weight loss, with minimal pain, and can also be associated with jaundice and malignant-looking biliary strictures.

Several publications detailed diagnostic criteria, including reports from Japan and Korea in collaboration,[19] the United States (Mayo Clinic),[130] and, more recently, Japan.[20] In the United States and Europe, type I AIP (lymphoplasmacytic sclerosing pancreatitis) is more common than type 2 (idiopathic duct-centric chronic pancreatitis, or AIP with granulocytic epithelial lesions).[18] Type 1 is more clearly an autoimmune disease, likely a pancreatic manifestation of systemic disease (including biliary strictures, retroperitoneal fibrosis, renal involvement, and salivary gland enlargement), with elevated serum immunoglobulin G_4 (IgG_4); it typically affects men who are more than 50 years old. Sensitivity and specificity of elevated serum IgG_4 (>140 mg/dL) for diagnosing AIP were 73% to 76% and 93%, respectively.[131,132] The specificity rose to 99% when IgG_4 was twice the upper limit of normal (>280 mg/dL).[131] Another serologic marker of AIP (antibody to plasminogen-binding protein [PBP]) was tested and was found to be approximately 95% sensitive and specific; it may be more accurate than IgG_4.[133] Patients with type 2 AIP have wider age and gender spectra and more often do not have elevated serum IgG_4 levels. Therefore, type 2 AIP is more likely to require a histologic diagnosis. However, both types can be associated with biliary strictures. When clinical suspicion is high, even a mildly elevated IgG_4 may be sufficient for diagnosis; in other cases, a negative FNA result of the mass and a more elevated (more than twice the upper limit) IgG_4 level may be needed.[18] IgG_4-associated disease present elsewhere is also supportive evidence, including ampullary involvement (ampullary biopsy staining positive for IgG_4).[134,135]

Tissue biopsy and ERCP have controversial roles in AIP (Figs. 13.4 and 13.5). FNA cytology is often nondiagnostic, showing nonspecific chronic inflammation, although high cellularity of stromal fragments may be suggestive.[136,137] The usefulness of Tru-Cut biopsy is unclear, and this procedure has a known risk of postprocedural pain and pancreatitis. The Mayo Clinic group[138] and others[139] found the Tru-Cut technique to be very helpful (and better than FNA) in small series (see Fig. 13.4). However, other investigators did not.[140] One study showed that only a quarter of cases of AIP were diagnosed histologically with ultrasound-guided cores; IgG_4-positive cells were also noted in 25% of patients with alcoholic pancreatitis and 10% of patients with cancer.[140] Although the Asian (Japanese-Korean) and Japanese consensus statements require ERCP for diagnosis, North Americans generally avoid diagnostic pancreatography and rely on the Histology, Imaging, Serology, other Organ involvement, and Response to steroid treatment (HISORt) protocol. ERCP was shown to have poor reliability in preliminary results of a multicenter trial.[141]

Classically, on cross-sectional imaging, diffuse pancreatic enlargement with delayed enhancement is noted, without pancreatic duct dilation, with or without a focal mass. The mass may demonstrate peripheral hypoattenuation and resemble a halo.[14] Similar features are seen on EUS: a diffusely enlarged, somewhat lobular, sausage-shaped gland with hypoechoic margins, sometimes with focal enlargement or a hypoechoic mass, without pancreatic duct dilation.[137,142] Pancreatic strictures (generally without upstream dilation) and biliary wall thickening and strictures can also be seen on EUS.

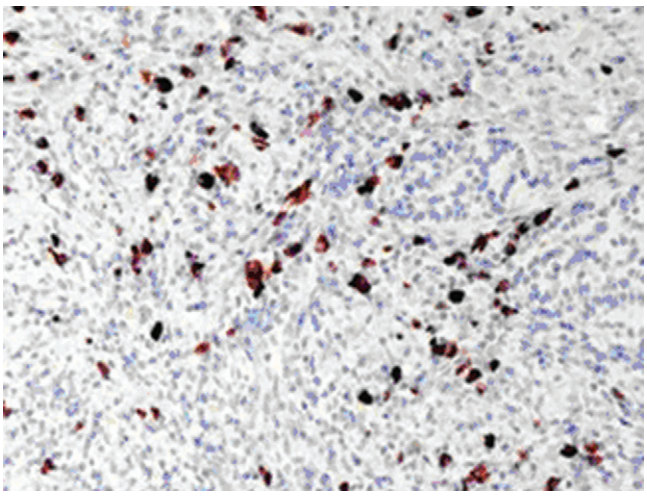


FIGURE 13.4 Autoimmune pancreatitis. Lymphoplasmacytic infiltrate with positive immunoglobulin G_4 immunostaining (>30 positive cells per high-power field) from an EUS-guided Tru-Cut biopsy specimen in autoimmune pancreatitis.

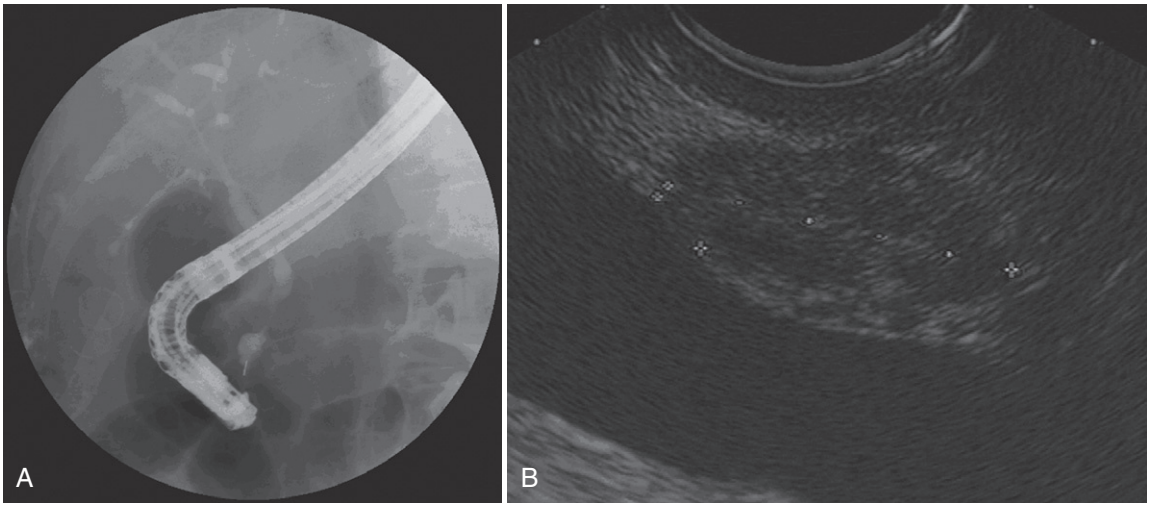


FIGURE 13.5 Biliary stricture and pancreas mass due to autoimmune chronic pancreatitis. A and **B,** Endoscopic retrograde cholangiopancreatography (ERCP) and linear EUS of a 70-year-old Asian man with painless jaundice, mild weight loss, and no past history of alcohol or pancreatitis. **A,** ERCP shows a tight-shouldered distal biliary stricture, but results of cytologic examination from biliary brushings were negative. Intrahepatic irregularities are also noted. Computed tomography scan of the pancreas was normal. **B,** A 5 × 25 mm hypoechoic mass, distinct from adjacent noninflamed parenchyma, is seen in the head of the pancreas and abutting the portal vein with a short loss of the interface *(curved bracket).* The rest of the pancreas appeared normal (no chronic pancreatitis criteria). Fine-needle aspiration showed benign cells without plasma cells. A serum immunoglobulin G_4 test was not requested, and surgical pathologic findings were consistent with focal chronic pancreatitis of the head, likely autoimmune.

Although AIP is generally a steroid-responsive disorder, investigators showed in a multicenter study of more than 500 patients that up to 74% of patients treated without steroids went into remission spontaneously, compared with 98% of those treated with steroids.[143] Response, generally seen in 2 to 4 weeks, is reassuring for the diagnosis; however, adenocarcinomas and lymphomas can also respond partially to steroids. Although some investigators have suggested prolonged steroid treatments, tapering over 3 to 6 months,[143] North American centers more commonly treat these patients with 30 to 40 mg/day of corticosteroids for 4 to 6 weeks, reassess clinical and radiologic response, and then taper the dose over the next 1 to 2 months.[144] Unfortunately, relapses occur in 30% to 40%; initial steroid use may be associated with lower relapse rates, as may normalization of IgG_4 levels and absence of proximal biliary involvement.[143,145] Most Japanese patients are treated with maintenance therapy (usually with low-dose steroids), whereas North American patients are usually given maintenance therapy (e.g., an immunomodulator like azathioprine) only if remission is not sustained throughout the drug tapering process.

Infectious Pancreatitis

Infection is an unusual cause of acute or subacute pancreatitis or of an inflammatory pancreatic mass. One case report showed that EUS FNA can detect *Giardia lamblia* infection.[146] Peripancreatic tuberculous lymphadenopathy has also been described.[147,148]

Chronic Pancreatitis Criteria in Kindreds at High-Risk for Pancreatic Cancer

The interpretation of chronic pancreatitis criteria in kindreds of familial pancreatic cancer and Peutz-Jeghers syndrome should be cautious. These same endosonographic findings may have very different histologic correlates. Canto et al[149] from Johns Hopkins University in Baltimore raised a concern that, in this group of patients, criteria for chronic pancreatitis may be associated with dysplasia rather than with inflammation and fibrosis. Of their cohort of 38 patients, 45% had three or more criteria, and 35% of the subgroup that did not drink any alcohol had this finding. Another study from Johns Hopkins University showed that pancreatic intraepithelial neoplasia and intraductal papillary mucinous neoplasm lesions were associated with so-called lobular pancreatic atrophy, mimicking chronic pancreatitis.[150] Brentnall et al[151] from Seattle found evidence of pancreatic intraepithelial neoplasia in high-risk patients with ERCP or EUS findings of "chronic pancreatitis." In contrast to recommendations in chronic pancreatitis (FNA is generally avoided), discrete lobules, cysts, or nodules in these patients likely require FNA, or at a minimum, close surveillance, with possibly even selective resection in some patients.

ACUTE PANCREATITIS

Acute Pancreatitis Diagnosis and Staging

Identification of fluid collections and estimation of the proportion of gland with necrosis are important predictors of outcome in acute pancreatitis and are generally performed by contrast-enhanced CT.[21] Except for calcifications, all the criteria used to detect and grade chronic pancreatitis can also be seen in acute pancreatitis (including cysts and mild ductal dilation). This is why it is generally recommended to wait at least 4 to 6 weeks after attacks of acute pancreatitis before looking for evidence of chronic pancreatitis. However, essentially no other published data exist on the ability of EUS to detect or stage acute pancreatitis. Contrast-enhanced EUS (discussed later) has not been studied to assess for focal hypoperfusion of the pancreas; this in theory could be possible. Assessing perfusion and detecting fluid collections appear feasible with MRI.[152,153] MRI and EUS may have limited roles in evaluating acute pancreatitis in selected patients, especially in those with renal failure or diabetes in whom intravenous CT contrast may be harmful, but further study is needed.

Idiopathic (Recurrent) Acute Pancreatitis and Pancreas Divisum

Acute pancreatitis is most commonly the result either of alcohol abuse or of sludge or stones obstructing the common bile duct; these features together make up the etiology in 80% of cases. The role of EUS in choledocholithiasis is discussed in Chapter 16. The other 20% of cases are generally considered idiopathic, but

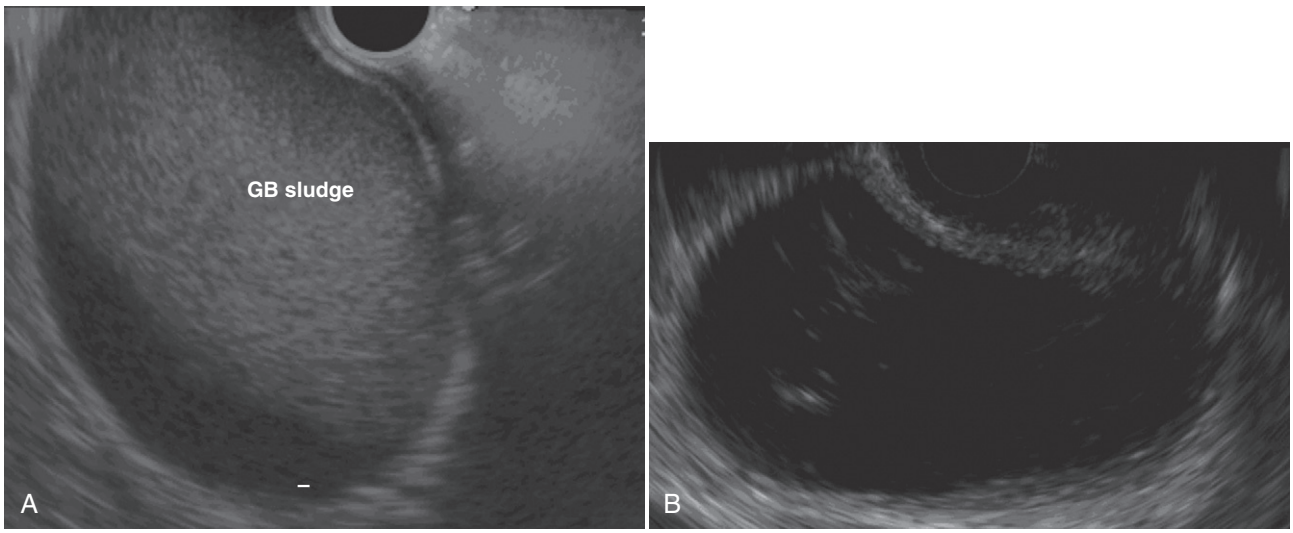


FIGURE 13.6 Gallbladder sludge missed on other image. A, Extensive sludge in the gallbladder (GB) on linear EUS (7.5 MHz) in a patient with acute idiopathic pancreatitis. Gallbladder sludge was missed on computed tomography scan and magnetic resonance imaging. **B,** Mobile, nonshadowing 1-mm reflections, seen on linear EUS (7.5 MHz), appreciated only after external palpation and shaking of the gallbladder (by pressing on the right upper quadrant of the abdomen).

up to half of them can be explained by a variety of causes, including medications, microlithiasis, tumors (especially in patients >60 years old), sphincter dysfunction (biliary or pancreatic), pancreas divisum, metabolic causes (hypercalcemia, hypertriglyceridemia), autoimmune disease, genetic causes, rare infections, and other conditions. Chronic pancreatitis is also present in up to half of these patients; calling this finding a cause is probably not correct, however, because this may simply be a sequela of damage from the intermittent acute attacks rather than a cause.

Because approximately 80% of "idiopathic" cases do not recur, after ruling out obvious causes (medications, metabolic causes, and in older patients, tumors), more extensive workup is generally not needed unless the problem recurs.[154] EUS is comparable to MRCP in detection of most causes of acute pancreatitis, so the two modalities can be used interchangeably for this purpose. However, EUS likely has a higher detection rate for tumors (in older patients) and for missed biliary lithiasis (in patients who still have a gallbladder, normal on conventional imaging), and it may even be helpful in those groups in addition to MRCP. Figure 13.6 shows an example of gallbladder sludge on EUS that was missed by CT and MRCP.

Yusoff et al[155] studied 370 patients in Montreal who had idiopathic pancreatitis referred for EUS; 169 (46%) had recurrent pancreatitis (i.e., 54% had only reported a single attack), and 124 (34%) had undergone cholecystectomy (i.e., 66% still had their gallbladder). Depending on gallbladder status (absent or present), 24% to 32% of patients had a possible explanation on EUS (considering chronic pancreatitis as a potential cause, these numbers rise to 51% and 63%). The rate of finding biliary stones was as low as 0% in the subgroup of patients with recurrent pancreatitis who had undergone cholecystectomy, but at the other extreme, it was as high as 9% in the single-attack patients who still had their gallbladder. Among patients who still had a gallbladder, 11% had gallbladder sludge found at EUS (missed on prior imaging). The rate of finding pancreas divisum also varied by gallbladder status, probably because biliary lithiasis is less relevant in patients with pancreas divisum: it was found in only 5% when the gallbladder was still present but in up to 11% when the pancreatitis had occurred despite cholecystectomy. Neoplasms were seen in 3% to 5% of patients. Limitations of the study included that EUS was performed as soon as 4 weeks after the last attack. The other main limitation was the possible inclusion of alcohol-related pancreatitis in this "idiopathic" group (≤12 alcoholic drinks [>120 g/day] within 14 days were allowed). Both these factors may have inflated the rate of finding chronic pancreatitis, especially in the group with recurrent disease.

Tandon and Topazian[156] reviewed their experience of EUS in 31 patients with idiopathic acute pancreatitis (half recurrent, 10% after cholecystectomy). Findings included microlithiasis (16%), pancreas divisum (7%), and cancer (3%). Chronic pancreatitis was found in 45%, but again, this is not necessarily a cause. One limitation was that this study included a large group of single-attack patients with a gallbladder still in place (almost 10% had not even had an ultrasound scan), and some patients may not have needed any advanced imaging investigations, except perhaps to rule out a tumor in the older subset. In addition, 16 (52%) patients had moderate to heavy alcohol use, and only 2 to 3 weeks were required after the last attack, perhaps thus accounting for the high rate of chronic pancreatitis findings.

Norton and Alderson[157] reported their results of 44 consecutive patients with idiopathic pancreatitis (23% recurrent, 18% after cholecystectomy). Findings included gallbladder stones (50%), choledocholithiasis (9%), pancreas divisum (2%), and tumor (2%). Chronic pancreatitis was noted in 9%.

Coyle et al[158] published results of a series of 90 patients with idiopathic pancreatitis (73% recurrent, 50% after cholecystectomy), of whom 56 had EUS with cholecystokinin (CCK)–stimulated duodenal sampling. Chronic pancreatitis was noted in 30%. Causes were found in 80% of patients by ERCP with manometry and selective bile sampling, including 31% with sphincter of Oddi dysfunction. Eighteen patients had a biliary cause; in three, only EUS found the abnormality. The concordance between CCK-stimulated duodenal sampling and direct biliary sampling for bile crystals was not reported.

Liu et al[159] prospectively evaluated the prevalence of occult cholelithiasis in 89 patients with idiopathic pancreatitis, after repeated ultrasound in 50%, and even ERCP in 72%. Cholelithiasis was noted in 14 of 18 patients (78%) with a gallbladder; 3 (17%) patients also had choledocholithiasis. All these cases were confirmed by ERCP and cholecystectomy. Another study showed a relatively high rate of cholelithiasis or choledocholithiasis at EUS (35%) in 42 patients with idiopathic recurrent acute pancreatitis, but the investigators did not note how many in their cohort still had their gallbladder at the time of EUS.[160]

Duodenal sampling at EUS, with or without CCK, is easy to do, but the accuracy is not well studied, and many institutions lack the infrastructure for and experience with centrifuging and detecting bile crystals. Lee et al[161] and Ros et al[162] showed the presence of crystals or sludge in duodenal aspirates of 73% to 74% of patients with unexplained pancreatitis. It appears that EUS itself may be more sensitive than duodenal fluid crystal analysis (96% versus 67%).[163] More study is needed to determine whether duodenal sampling is a useful adjunct to EUS for idiopathic pancreatitis, when sludge and stones are not seen.

The cost effectiveness of EUS in unexplained pancreatitis is unclear. One study[164] showed lower costs with EUS in patients with a gallbladder in place but assumed a 50% chance of finding missed cholelithiasis and that 1 in 20 patients would have a bile duct stone. These figures are much higher than those reported in at least three studies.[155,156,158] ERCP was preferred when cholelithiasis was present in less than 41%. A systematic review supported the usefulness of EUS in older patients (although the age cutoff is unclear) and in those with a gallbladder still in place, but the investigators agreed that younger patients with recurrent pancreatitis after cholecystectomy are probably better served by ERCP with manometry or with treatment of pancreas divisum, if present.[22]

Detection of Pancreas Divisum

EUS appears to have modest to high accuracy for pancreas divisum (Video 13.3). Although some early MRCP studies,[165] with large numbers of exclusions and verification biases (in terms of the gold standard selectively applied), show high accuracy, the accuracy of MRCP is probably modest as well. A small study by Bhutani et al[166] suggested that the inability to visualize a "stack sign" (a transduodenal view through the apex of the duodenum that results in a long-axis view of the portal vein, pancreatic duct, and bile duct simultaneously) because of a rudimentary ventral duct raises the possibility of pancreas divisum. In that study,[166] a stack sign was not able to be obtained in 67% of 6 patients with pancreas divisum, as opposed to 17% of 30 patients who did not have pancreas divisum. The 2 false-negative results were caused by a dilated ventral duct and a very long ventral duct, respectively.

Chen et al[167] also showed that the inability to obtain a stack sign was more likely to occur in pancreas divisum (49% of patients with pancreas divisum versus only 6% of patients without pancreas divisum). One must be cautious using this as the sole screening tool, however, because the foregoing studies clearly showed that a stack sign can still be obtained in one third to one half of patients with pancreas divisum. Other features included a prominent dorsal duct (16% versus 0%) and a cross-duct sign (8% versus 0%). The cross-duct sign represents seeing the Santorini crossing the common bile duct as it heads toward the minor papilla, but false-positive results can occur because of a prominent patent Santorini sometimes seen in normal patients.

A prospective study of 162 patients from Minneapolis,[168] with a high (14%) prevalence of pancreas divisum, showed that linear EUS had a high accuracy (95% sensitivity) for pancreas divisum. The main pancreatic duct was followed from the major papilla to the body of the pancreas or crossing the ventral-dorsal anlage to exclude pancreas divisum.[168] However, 35 (8%) examinations with incomplete visualization were excluded from analysis. If those cases had been classified as negative examinations, the sensitivity, specificity, and positive and negative predictive values would have been 82%, 98%, 86%, and 97%, respectively. False-positive EUS examinations included a pancreatic duct stricture between the head and body and two patients with ansa pancreatica. In comparison, 41 patients had MRCP, the sensitivity and specificity of which were only 60% and 89%, respectively. One case of pseudodivisum (correctly diagnosed as an adenocarcinoma by EUS FNA) gave a false-positive result on MRCP for pancreas divisum.

Vaughan et al[169] found a much lower sensitivity and specificity for EUS in a retrospective review of all MUSC patients checked for this diagnosis. Regarding MRCP, these investigators also noted a low accuracy for MRCP in detecting pancreas divisum in 111 patients: 32% sensitivity when results were read in the community and 67% (with or without secretin testing) when results were read in a tertiary center.[170]

Catalano et al[171] studied 22 patients with pancreas divisum and attempted to predict who would respond to pancreatic duct stenting by assessing response to secretin. Although these investigators showed an 81% sensitivity and 83% specificity, interobserver reliability was modest ($\kappa = 0.58$), and their definition of an abnormal response was not clear.

ENHANCED EUS IN PANCREATITIS

Secretin-stimulated EUS and intraductal ultrasound are discussed elsewhere, in other chapters of this book. This focuses on two adjuncts to conventional EUS: contrast-enhanced (harmonic) EUS and elastography. Other enhancements of EUS are digital analysis of the images and spectral analysis of ultrasound backscatter, but too few data are available on these techniques to dedicate a section to them. One study found that a postprocedural computer analysis of the hyperechoic portion of a region of interest appeared to correlate with the number of EUS features.[172] Another study looked at the usefulness of postprocedural processing of EUS images, and using a form of digital image analysis and an artificial neural network of the resulting gray-scale histogram plots (derived from a region of interest in the pancreas), investigators were able to separate normal examinations from chronic pancreatitis and cancer in a pilot study.[173] However, the investigators assigning the region of interest were not blinded to the final diagnosis. An older study showed poor specificity, in contrast to the foregoing findings.[174]

A validation study from Cleveland described spectrum analysis of backscattered radiofrequency ultrasound at EUS in which a digital oscilloscope was used to collect radiofrequency data.[175] The concept is that the backscattered signals (possibly different for different types or states of tissue) depend on the effective size and concentration of the scatterers within inhomogeneous tissue and are also a spatial function of the acoustic impedance of the tissue. This study of 24 patients showed 93% accuracy in differentiating normal from non-normal pancreas, and 77% accuracy in differentiating cancer from chronic pancreatitis; however, there were only three patients with chronic pancreatitis, and the patterns overlapped.[175] The foregoing techniques all involve interesting concepts that require further study.

Contrast-Enhanced EUS

Assessing differential perfusion among normal tissue, inflammatory tissue, and cancer is the most important part of a contrast-enhanced CT examination. Until recently, however, perfusion was not assessed at EUS. Assessing the perfusion of lesions with intravascular microbubbles has been studied in the evaluation of lymph nodes and masses.[90,176–180] The setting most relevant here is the differentiation of inflammatory from malignant masses of the pancreas. Microbubbles (bubbles with an inert shell and filling, smaller than 6- to 8-μm red blood cells, that can pass easily through pulmonary vasculature) are distorted by ultrasound waves; the asymmetrical compression and relaxation of the bubbles that occur under medium ultrasound "power" (or mechanical index) create "nonlinear" reflections that are detected with the capture of extended harmonics, as well as with other techniques. None of the agents are currently approved for abdominal imaging in the United States.

Becker et al[90] studied German patients with the addition of an intravenous contrast agent (albumin-based product, Optison, Mallinckrodt, St. Louis) to distinguish inflammatory from

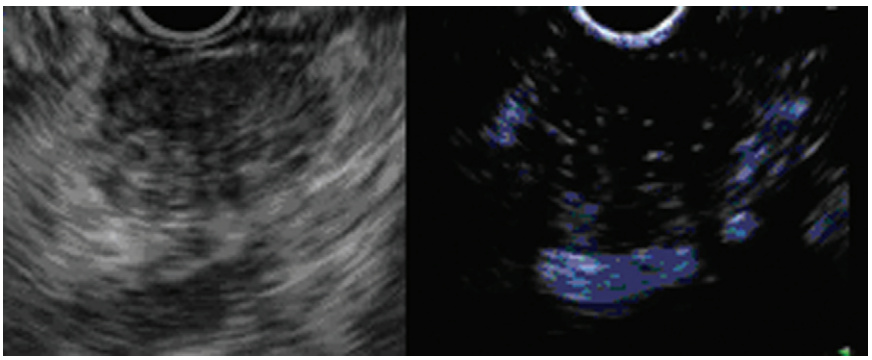


FIGURE 13.7 Pancreatic body cancer on contrast-enhanced harmonic EUS. Linear B-mode EUS of a pancreatic body cancer with the splenic vein *(left)* alongside a late portovenous phase contrast-enhanced harmonic EUS image using Definity *(right)*, with typical sparse perfusion and hypoperfused defects.

neoplastic masses in the pancreas. Surgical pathology or a 6-month period of lack of disease progression was considered the outcome. Of 23 patients with noncystic masses, 5 had a history of acute pancreatitis, 80% of whom had inflammatory masses as their final diagnosis. All 15 hypoperfused masses were malignant, and 7 of 8 hyperperfused masses were inflammatory (100% positive predictive value, 88% negative predictive value). Results of FNA were positive in the single hyperperfused mass that was malignant; CT also had shown a hyperperfused lesion. ERCP had two false-negative results and four false-positive results. More recently, EUS was used with second-generation agents, such as SonoVue (sulfur hexafluoride lipid microspheres, Bracco, Milan), and showed feasibility in an early pilot study assessing optimal settings (e.g., optimal mechanical index).[177] SonoVue has been widely used for abdominal ultrasonography outside the United States, especially because of its ability to detect and characterize liver masses,[178,179] but it is not available in the United States. A German study with EUS and SonoVue showed that the EUS sensitivity and specificity (73% and 83%) for pancreatic cancer rose to 91% (out of 56 patients) and 93% (out of 30 patients), respectively, with contrast-enhanced EUS.[180]

Investigators at MUSC piloted the use of Definity (Lantheus Medical Imaging, North Billerica, Massachusetts), a second-generation perflutren lipid microsphere contrast agent approved for cardiac ultrasound in the United States, and a prototype linear Olympus echoendoscope (XGF-UC180, Olympus) and the Aloka ProSound Alpha10 processor (Aloka, Tokyo, Japan) in 21 patients. Intermittent or continuous imaging was used with extended pure harmonic detection. EUS endoscopists were asked to rate the lesions on a Likert scale as to the suspicion of a malignant process, before and after contrast imaging. Positive and negative predictive values of contrast-enhanced harmonic EUS, without FNA, were greater than 80%, and it settled several undecided EUS cases while correcting others (Fig. 13.7). This technique differentiated solid from cystic lesions, and it also detected the unique vascular pattern of a liver hemangioma and distinguished it from pancreatic cancer metastasis. However, in the 16 masses imaged that were pancreatic, there was no significant disagreement with conventional EUS; therefore, in this small sample, the added value for pancreatic cases was unfortunately unclear.[176]

False-negative results (homogeneous perfusion in a tumor) can occur in neuroendocrine tumors and lymphomas, which can have normal perfusion or hyperperfusion. False-positive results (areas of hypoperfusion in a benign lesion) can occur in the presence of necrosis, scar, or small cystic areas because these areas will not perfuse.

EUS with Elastography

Elastography is an adjunct to EUS that allows one to assess and measure tissue elasticity. Malignant lymph nodes and tumors tend to be firmer and less elastic than benign lymph nodes and tissue. However, there is known overlap with inflammatory processes.[181] The technology is based on the detection of small structure deformations within the B-mode image caused by compression. The degree of deformation (speckle motion) is used as an indicator for the stiffness of the tissue.[181] Current software allows a color map of the lesion, according to elasticity (firm blue to soft red), and so the homogeneity, or pattern if heterogeneous, of the tissue "stiffness" can also be assessed.

A German pilot study of 20 normal subjects, 20 patients with chronic pancreatitis, and 33 patients with focal pancreatic masses found elastography to have tremendous overlap between chronic pancreatitis and tumors.[181] These investigators did not find this technique useful for distinguishing between the two disorders. Fibrosis should be stiffer than normal pancreas; however, although findings were not formally assessed, the investigators believed that elastography did not appear helpful in distinguishing normal pancreas from chronic pancreatitis, except in more advanced cases.[181] A multicenter European study of elastography in 222 patients (assessment of a pancreatic mass in 121) showed no improvement in sensitivity over conventional EUS (92% in both), but it showed a small improvement in specificity (80% versus 69%).[182]

The main limitations of elastography in differentiating inflammation from neoplasia are that not all tumors are hard or firm and chronic focal pancreatitis can be very hard.[181] This technique is limited for diagnosing chronic pancreatitis because the minimal fibrosis in early cases does not appear to change the elastography pattern. In addition, color coding of the image is performed by the software in relation to other tissue present in the image frame and is not "calibrated" to a known tissue stiffness.[181] The software tries to use the full color spectrum even if the lesion is homogeneously soft or homogeneously firm. Therefore, blood vessels and other structures in the field may affect the color spectrum used or the color assigned to a certain part of the image.

SUMMARY

EUS is highly accurate in the diagnosis of chronic pancreatitis: calcifications or five or more criteria correlate well with both ERCP and pancreatic exocrine function testing. The finding of fewer than three criteria, and especially no criteria, effectively rules out chronic pancreatitis. The presence of three or four criteria is the best overall cutoff; studies landing on or near this cutoff are essentially indeterminate and do not change one's pretest suspicion of disease. Obtaining histologic samples by FNA or Tru-Cut biopsy is not recommended. Using the number of criteria to stage the *severity* of chronic pancreatitis (i.e., mild, moderate, or severe disease) is not recommended. Functional MRCP is a competing technology but does not appear to be nearly as accurate for early disease.

EUS is useful for the identification of possible causes of idiopathic recurrent pancreatitis. The diagnostic yield of EUS is highest in older patients and in those with a gallbladder in place, and it may even be helpful in addition to MRCP in these patients. Yield is more limited in young patients without a gallbladder. Coexisting chronic pancreatitis can also be reliably diagnosed, and EUS may be especially relevant in those patients with chronic pain between attacks. Although more study is needed, the diagnosis of pancreas divisum by EUS appears specific and possibly more sensitive than MRCP (especially when MRCP results are read in the community setting). An inability to achieve a stack sign raises suspicion of pancreas divisum, but the ability to follow (or not follow) the pancreatic duct from the major ampulla to the genu (or from ventral to dorsal) is more reliable.

Although not perfect, EUS is one of the best techniques available to distinguish inflammatory (pseudotumors) from neoplastic masses in the pancreas. Often FNA is not required, because the EUS appearance of inflammatory changes alone or bulkiness without any perceptible mass has a strong negative predictive value. In patients with indeterminate pancreatic masses, FNA is definitely helpful. Most cases in this category require some type of follow-up imaging in approximately a month's time to detect the rare false-negative EUS results and to confirm the resolution or stability of benign masses. AIP can be suspected on EUS, and Tru-Cut biopsy can be helpful in selected cases, but serum IgG_4 testing is safer and more reliable in most cases. Secretin-stimulated EUS, EUS with image analysis, contrast-enhanced EUS, and EUS with elastography are promising adjuncts to EUS that require further study.

ACKNOWLEDGMENTS

I would like to acknowledge Dr. David Lewin (Professor, Department of Pathology, Medical University of South Carolina) for his help in working with me to obtain histologic figures displaying possible pathologic correlates of EUS findings and Dr. Michael Levy (Associate Professor, Department of Medicine, Mayo Clinic, Rochester, Minnesota) for his help in obtaining the microscopy figure depicting the histologic features typical of AIP from an EUS-derived sample.

REFERENCES

1. Hisanaga K, Hisanaga A, Nagata K, Ichie Y. High speed rotating scanner for transgastric sonography. *AJR Am J Roentgenol*. 1980;135:627–639.
2. DiMagno EP, Buxton JL, Regan PT, et al. Ultrasonic endoscope. *Lancet*. 1980;22:629–631.
3. DiMagno EP, Regan PT, Clain JE, et al. Human endoscopic ultrasonography. *Gastroenterology*. 1982;83(4):824–829.
4. Snady H. Endoscopic ultrasonography in benign pancreatic disease. *Surg Clin North Am*. 2001;81(2):329–344.
5. Inui K, Nakazawa S, Yoshino J, Okushima K, Nakamura Y. Endoluminal ultrasonography for pancreatic diseases. *Gastroenterol Clin North Am*. 1999;28(3):771–781.
6. Clain JE, Pearson RK. Diagnosis of chronic pancreatitis: is a gold standard necessary? *Surg Clin North Am*. 1999;79:829–845.
7. Raimondo M, Wallace MB. Diagnosis of early chronic pancreatitis by endoscopic ultrasound: are we there yet? *JOP*. 2004;5(1):1–7.
8. Etemab B, Whitcomb DC. Chronic pancreatitis: diagnosis, classification, and new genetic developments. *Gastroenterology*. 2001;120:682–707.
9. Bhutani MS. Endoscopic ultrasound in pancreatic diseases: Indications, limitations and the future. *Gastroenterol Clin North Am*. 1999;28: 747–770.
10. Wallace MB, Hawes RH. Endoscopic ultrasound in the evaluation and treatment of chronic pancreatitis. *Pancreas*. 2001;23(1):26–35.
11. Dancygier H. Endoscopic ultrasonography in chronic pancreatitis. *Gastrointest Endosc Clin N Am*. 1995;5:795–804.
12. Wiersema MJ, Wiersema LM. Endosonography of the pancreas: normal variation versus changes of early chronic pancreatitis. *Gastrointest Endosc Clin N Am*. 1995;5:487–496.
13. Kahl S, Glasbrenner B, Zimmerman S, Malfertheiner P. Endoscopic ultrasound in pancreatic diseases. *Dig Dis*. 2002;20:120–126.
14. Finkelberg DL, Sahani D, Deshpande V, Brugge WR. Autoimmune pancreatitis. *N Engl J Med*. 2006;355(25):2670–2676.
15. Catalano MF, Sahai A, Levy M, et al. EUS-based criteria for the diagnosis of chronic pancreatitis: the Rosemont classification. *Gastrointest Endosc*. 2009;69(7):1251–1261.
16. Forsmark CE. Chronic pancreatitis. In: Feldman M, Tschumy WOJ, Friedman LS, Sleisenger MH, eds. *Sleisenger & Fordtran's Gastrointestinal and Liver Disease*. 7th ed, Philadelphia: Elsevier; 2002:943–969.
17. Adler DG, Lichtenstein D, Baron TH, et al. The role of endoscopy in patients with chronic pancreatitis. *Gastrointest Endosc*. 2006;63(7):933–937.
18. Chari ST, Longnecker DS, Kloppel G. The diagnosis of autoimmune pancreatitis: a Western perspective. *Pancreas*. 2009;38(8):846–848.
19. Otsuki M, Chung JB, Okazaki K, et al. Asian diagnostic criteria for autoimmune pancreatitis: consensus of the Japan-Korea Symposium on Autoimmune Pancreatitis. *J Gastroenterol*. 2008;43(6):403–408.
20. Okazaki K, Kawa S, Kamisawa T, et al. Japanese clinical guidelines for autoimmune pancreatitis. *Pancreas*. 2009;38(8):849–866.
21. DiMagno EP, Chari S. Acute pancreatitis. In: Feldman M, Tschumy WOJ, Friedman LS, Sleisenger MH, eds. *Sleisenger & Fordtran's Gastrointestinal and Liver Disease*. 7th ed, Philadelphia: Elsevier; 2002:913–942.
22. Wilcox CM, Varadarajulu S, Eloubeidi M. Role of endoscopic evaluation in idiopathic pancreatitis: a systematic review. *Gastrointest Endosc*. 2006; 63(7):1037–1045.
23. Burns PN, Wilson SR. Microbubble contrast for radiological imaging: 1. Principles. *Ultrasound Q*. 2006;22(1):5–13.
24. Sugiyama M, Haradome H, Atomi Y. Magnetic resonance imaging for diagnosing chronic pancreatitis. *J Gastroenterol*. 2007;42(suppl 17):108–112.
25. Catalano MF, Lahoti S, Geenen JE, Hogan WJ. Prospective evaluation of endoscopic ultrasonography, endoscopic retrograde pancreatography, and secretin test in the diagnosis of chronic pancreatitis. *Gastrointest Endosc*. 1998;48(1):11–17.
26. Wiersema MJ, Hawes RH, Lehman G, et al. Prospective evaluation of endoscopic ultrasonography and endoscopic retrograde cholangiopancreatography in patients with chronic abdominal pain of suspected pancreatic origin. *Endoscopy*. 1993;25:555–564.
27. Wallace MB, Hawes RH, Durkalski V, et al. The reliability of EUS for the diagnosis of chronic pancreatitis: interobserver agreement among experienced endosonographers. *Gastrointest Endosc*. 2001;53(3):294–299.
28. Sahai AV, Mishra G, Penman ID, et al. EUS to detect evidence of pancreatic disease in patients with persistent or nonspecific dyspepsia. *Gastrointest Endosc*. 2000;52:153–159.
29. Savides TJ, Gress FG, Zaidi SA, et al. Detection of embryologic ventral pancreatic parenchyma with endoscopic ultrasound. *Gastrointest Endosc*. 1996;43:14–19.
30. Donald JJ, Shorvon PJ, Lees WR. A hypoechoic area within the head of the pancreas: a normal variant. *Clin Radiol*. 1990;41:337–338.
31. Atri M, Nazarnia S, Mehio A, et al. Hypoechogenic embryologic ventral aspect of the head and uncinate process of the pancreas: in vitro correlation of US with histopathologic findings. *Radiology*. 1994;190: 441–444.
32. Axon AT, Classen M, Cotton PB, et al. Pancreatography in chronic pancreatitis: international definitions. *Gut*. 1984;25:1107–1112.
33. Gillams A, Pereira S, Webster G, Lees W. Correlation of MRCP quantification (MRCPQ) with conventional non-invasive pancreatic exocrine function tests. *Abdom Imaging*. 2008;33(4):469–473.
34. Gillams AR, Lees WR. Quantitative secretin MRCP (MRCPQ): results in 215 patients with known or suspected pancreatic pathology. *Eur Radiol*. 2007;17(11):2984–2990.
35. Cheon YK, Cho KB, Watkins JL, et al. Frequency and severity of post-ERCP pancreatitis correlated with extent of pancreatic ductal opacification. *Gastrointest Endosc*. 2007;65(3):385–393.
36. Sahai AV, Zimmerman M, Aabakken L, et al. Prospective assessment of the ability of endoscopic ultrasound to diagnose, exclude, or establish the severity of chronic pancreatitis found by endoscopic retrograde cholangiopancreatography. *Gastrointest Endosc*. 1998;48(1):18–25.
37. International Working Group for Minimum Standard Terminology for Gastrointestinal Endosonography. Reproduction of minimum standard terminology in gastrointestinal endosonography. *Dig Endosc*. 1998;10: 158–184.
38. World Organisation of Digestive Endoscopy (OMED) Committee of Documentation and Standardization. *Minimum standard terminology (MST v 3.0)*. 3.0 ed. 2009. Available at http://www.omed.org/index.php/resources/re_mst/; Accessed May 19, 2010.
39. Romagnuolo J, Joseph L, Barkun AN. Interpretation of diagnostic tests. In: Rosenberg L, Joseph L, Barkun AN, eds. *Surgical Arithmetic: Epidemiological, Statistical, and Outcome-Based Approach to Surgical Practice*. Landes Bioscience: Georgetown, Tex; 2000:64–83.
40. Altman DG. *Practical Statistics for Medical Students*. London: Chapman and Hall; 1991.

41. Landis JR, Koch GG. An application of hierarchical kappa-type statistics in the assessment of majority agreement among multiple observers. *Biometrics*. 1977;33(2):363–374.
42. Fleiss JL. *Statistical Methods for Rates and Proportions*. 2nd ed, New York: John Wiley & Sons; 1981.
43. Lau JY, Sung JJ, Chan AC, et al. Stigmata of hemorrhage in bleeding peptic ulcers: an interobserver agreement study among international experts. *Gastrointest Endosc*. 1997;46:33–36.
44. von Kummer R, Holle R, Gizyska U, et al. Interobserver agreement in assessing early CT signs of middle cerebral artery infarction. *AJNR Am J Neuroradiol*. 1996;17:1743–1748.
45. Lok CE, Moragan CD, Ranganathan N. The accuracy and interobserver agreement in detecting the "gallop sounds" by cardiac auscultation. *Chest*. 1998;114:1283–1288.
46. Takehara Y, Ichijo K, Tooyama N, et al. Breath-hold MR cholangiopancreatography with a long-echo-train fast spin-echo sequence and a surface coil in chronic pancreatitis. *Radiology*. 1994;192(1):73–78.
47. Lieb J, Palma D, Leblanc J, et al. Intraobserver agreement and variability Among endosonographers for EUS features of chronic pancreatitis [abstract]. *Gastrointest Endosc*. 2009;69:AB239.
48. Reuben A, Johnson AL, Cotton PB. Is pancreatogram interpretation reliable? A study of observer variation and error. *Br J Radiol*. 1978;51(612): 956–962.
49. Romagnuolo J. EUS in inflammatory disease of the pancreas. In: Hawes RH, Fockens P, eds. *Endosonography*. Vol 1, London: Elsevier; 2006:155–176.
50. Chong AK, Hawes RH, Hoffman BJ, et al. Diagnostic performance of EUS for chronic pancreatitis: a comparison with histopathology. *Gastrointest Endosc*. 2007;65(6):808–814.
51. Morris-Stiff G, Webster P, Frost B, et al. Endoscopic ultrasound reliably identifies chronic pancreatitis when other imaging modalities have been non-diagnostic. *JOP*. 2009;10(3):280–283.
52. Varadarajulu S, Eltoum I, Tamhane A, Eloubeidi MA. Histopathologic correlates of noncalcific chronic pancreatitis by EUS: a prospective tissue characterization study. *Gastrointest Endosc*. 2007;66(3):501–509.
53. Kahl S, Glasbrenner B, Leodolter A, et al. EUS in the diagnosis of early chronic pancreatitis: a prospective follow-up study. *Gastrointest Endosc*. 2002;55(4):507–511.
54. Rajan E, Clain JE, Levy MJ, et al. Age-related changes in the pancreas identified by EUS: a prospective evaluation. *Gastrointest Endosc*. 2005; 61(3):401–406.
55. Chong AK, Romagnuolo J. Gender-related changes in the pancreas detected by EUS. *Gastrointest Endosc*. 2005;62(3):475.
56. Thuler FP, Costa PP, Paulo GA, et al. Endoscopic ultrasonography and alcoholic patients: can one predict early pancreatic tissue abnormalities? *JOP*. 2005;6(6):568–574.
57. Yusoff IF, Sahai AV. A prospective, quantitative assessment of the effect of ethanol and other variables on the endosonographic appearance of the pancreas. *Clin Gastroenterol Hepatol*. 2004;2(5):405–409.
58. Joseph L, Gyorkos TW, Coupal L. Bayesian estimation of disease prevalence and the parameters of diagnostic tests in the absence of a gold standard. *Am J Epidemiol*. 1995;141:263–272.
59. Fekete PS, Nunez C, Pitlik DA. Fine-needle aspiration biopsy of the pancreas: a study of 61 cases. *Diagn Cytopathol*. 1986;2:301–306.
60. Hollerbach S, Klamann A, Topalidis T, Schmiegel WH. Endoscopic ultrasonography (EUS) and fine-needle aspiration (FNA) cytology for diagnosis of chronic pancreatitis. *Endoscopy*. 2001;33(10):824–831.
61. Regev A, Berho M, Jeffers LJ, et al. Sampling error and intraobserver variation in liver biopsy in patients with chronic HCV infection. *Am J Gastroenterol*. 2002;97(10):2614–2618.
62. Romagnuolo J, Schiller D, Bailey RJ. Using breath tests wisely in a gastroenterology practice: an evidence-based review of indications and pitfalls in interpretation. *Am J Gastroenterol*. 2002;97:1113–1126.
63. Hayakawa T, Kondo T, Shibata T, et al. Relationship between pancreatic exocrine function and histological changes in chronic pancreatitis. *Am J Gastroenterol*. 1992;87:1170–1174.
64. Research Committee for Chronic Pancreatitis, Japanese Society of Gastroenterology. Yamagata S, ed. *Clinical Diagnostic Criteria for Chronic Pancreatitis*. Igakutosho: Tokyo; 1984.
65. Heij HA, Obertop H, van Blankenstein M, et al. Relationship between functional and histological changes in chronic pancreatitis. *Dig Dis Sci*. 1986;31:1009–1013.
66. Heij HA, Obertop H, van Blankenstein M, et al. Comparison of endoscopic retrograde pancreatography with functional and histologic changes in chronic pancreatitis. *Acta Radiol*. 1987;28:289–293.
67. Hardt PD, Marzeion AM, Schnell-Kretschmer H, et al. Fecal elastase 1 measurement compared with endoscopic retrograde cholangiopancreatography for the diagnosis of chronic pancreatitis. *Pancreas*. 2002;25(1):e6–e9.
68. Loser C, Mollgaard A, Folsch UR. Faecal elastase 1: a novel, highly sensitive, and specific tubeless pancreatic function test. *Gut*. 1996;39(4):580–586.
69. Lankisch PG, Schmidt I, Konig H, et al. Faecal elastase 1: not helpful in diagnosing chronic pancreatitis associated with mild to moderate exocrine pancreatic insufficiency. *Gut*. 1998;42(4):551–554.
70. Lomas DJ, Bearcroft PW, Gimson AE. MR cholangiopancreatography: prospective comparison of a breath-hold 2D projection technique with diagnostic ERCP. *Eur Radiol*. 1411;9(7):1411–1417.
71. Manfredi R, Costamagna G, Brizi MG, et al. Severe chronic pancreatitis versus suspected pancreatic disease: dynamic MR cholangiopancreatography after secretin stimulation. *Radiology*. 2000;214(3):849–855.
72. Calvo MM, Bujanda L, Calderon A, et al. Comparison between magnetic resonance cholangiopancreatography and ERCP for evaluation of the pancreatic duct. *Am J Gastroenterol*. 2002;97:347–353.
73. Alcaraz MJ, De la Morena EJ, Polo A, et al. A comparative study of magnetic resonance cholangiography and direct cholangiography. *Rev Esp Enferm Dig*. 2000;92(7):427–438.
74. Czako L, Endes J, Takacs T, et al. Evaluation of pancreatic exocrine function by secretin-enhanced magnetic resonance cholangiopancreatography. *Pancreas*. 2001;23(3):323–328.
75. Kalapala R, Sunitha L, Nageshwar RD, et al. Virtual MR pancreatoscopy in the evaluation of the pancreatic duct in chronic pancreatitis. *JOP*. 2008;9(2):220–225.
76. Buscail L, Escourrou J, Moreau J, et al. Endoscopic ultrasonography in chronic pancreatitis: a comparative prospective study with conventional ultrasonography, computed tomography, and ERCP. *Pancreas*. 1995;10:251–257.
77. Begg CB. Biases in the assessment of diagnostic tests. *Stat Med*. 1987;6: 411–423.
78. Lachs MS, Nachamkin I, Edelstein PH, et al. Spectrum bias in the evaluation of diagnostic tests: lessons from the rapid dipstick test for urinary tract infection. *Ann Intern Med*. 1992;117(2):135–140.
79. Chowdhury R, Bhutani MS, Mishra G, et al. Comparative analysis of direct pancreatic function testing versus morphological assessment by endoscopic ultrasonography for the evaluation of chronic unexplained abdominal pain of presumed pancreatic origin. *Pancreas*. 2005;31(1): 63–68.
80. DeWitt J, McGreevy K, LeBlanc J, et al. EUS-guided Trucut biopsy of suspected nonfocal chronic pancreatitis. *Gastrointest Endosc*. 2005;62(1):76–84.
81. Ammann RW, Heitz PU, Kloppel G. Course of alcoholic chronic pancreatitis: a prospective clinicomorphological long-term study. *Gastroenterology*. 1996;111(1):224–231.
82. Bhutani MS, Ahmed I, Verma D, et al. An animal model for studying endoscopic ultrasound changes of early chronic pancreatitis with histologic correlation: a pilot study. *Endoscopy*. 2009;41(4):352–356.
83. Chen RYM, Hino S, Aithal GP, et al. Endoscopic ultrasound (EUS) features of chronic pancreatitis predate subsequent development of abnormal endoscopic retrograde pancreatogram (ERP) [abstract]. *Gastrointest Endosc*. 2002;55:AB242.
84. Hastier P, Buckley MJ, Francois E, et al. A prospective study of pancreatic diseases in patients with alcoholic cirrhosis: comparative diagnostic value of ERCP and EUS and long-term significance of isolated parenchymal abnormalities. *Gastrointest Endosc*. 1999;49:705–709.
85. Pungpapong S, Wallace MB, Woodward TA, et al. Accuracy of endoscopic ultrasonography and magnetic resonance cholangiopancreatography for the diagnosis of chronic pancreatitis: a prospective comparison study. *J Clin Gastroenterol*. 2007;41(1):88–93.
86. Singh P, Vela S, Agrawal D, et al. Long term outcome in patients with endosonographic findings suggestive of mild chronic pancreatitis [abstract]. *Gastrointest Endosc*. 2004;59:AB231.
87. Delhaze M, Jonard P, Gigot JF, et al. [Chronic pancreatitis and pancreatic cancer: an often difficult differential diagnosis]. *Acta Gastroenterol Belg*. 1989;52:458–466 [in French].
88. DelMaschio A, Vanzulli A, Sironi S, et al. Pancreatic cancer versus chronic pancreatitis: diagnosis with CA 19-9 assessment, US, CT, and CT-guided fine-needle biopsy. *Radiology*. 1991;178:95–99.
89. Lowenfels AB, Maisonneuve P, Cavallini G, et al. Pancreatitis and the risk of cancer. *N Engl J Med*. 1993;328:1433–1437.
90. Becker D, Strobel D, Bernatik T, Hahn EG. Echo-enhanced color- and power-Doppler EUS for the discrimination between focal pancreatitis and pancreatic carcinoma. *Gastrointest Endosc*. 2001;53(7):784–789.
91. McGuire DE, Venu RP, Brown RD, et al. Brush cytology for pancreatic carcinoma: an analysis of factors influencing results. *Gastrointest Endosc*. 1996;44(3):300–304.
92. Vandervoort J, Soetikno RM, Montes H, et al. Accuracy and complication rate of brush cytology from bile duct versus pancreatic duct. *Gastrointest Endosc*. 1999;49(3 Pt 1):322–327.
93. Kochman ML. EUS in pancreatic cancer. *Gastrointest Endosc*. 2002;56: S6–S12.
94. Mallery JS, Centeno BA, Hahn PF, et al. Pancreatic tissue sampling guided by EUS, CT/US, and surgery: a comparison of sensitivity and specificity. *Gastrointest Endosc*. 2002;56:218–224.

95. Barthet M, Portal I, Boujaoude J, et al. Endoscopic ultrasonographic diagnosis of pancreatic cancer complicating chronic pancreatitis. *Endoscopy*. 1996;28(6):487–491.
96. Sackett DL, Haynes RB, Guyatt GH, Tugwell P. *Clinical Epidemiology: A Basic Science for Clinical Medicine*. 2nd ed. Boston: Little, Brown; 1991.
97. Kaufman AR, Sivak Jr MV. Endoscopic ultrasonography in the differential diagnosis of pancreatic disease. *Gastrointest Endosc*. 1989;35:214–219.
98. Nattermann C, Goldschmidt AJ, Dancygier H. [Endosonography in the assessment of pancreatic tumors: a comparison of the endosonographic findings of carcinomas and segmental inflammatory changes]. *Dtsch Med Wochenschr*. 1995;120:1571–1576 [in German].
99. Glasbrenner B, Schwartz M, Pauls S, et al. Prospective comparison of endoscopic ultrasound and endoscopic retrograde cholangiopancreatography in the preoperative assessment of masses in the pancreatic head. *Dig Surg*. 2000;17:468–474.
100. Varadarajulu S, Tamhane A, Eloubeidi MA. Yield of EUS-guided FNA of pancreatic masses in the presence or the absence of chronic pancreatitis. *Gastrointest Endosc*. 2005;62(5):728–736; quiz 751, 753.
101. Yu XJ, Long J, Fu DL, et al. Analysis of gene expression profiles in pancreatic carcinoma by using cDNA microarray. *Hepatobiliary Pancreat Dis Int*. 2003;2(3):467–470.
102. Chhieng DC, Benson E, Eltoum I, et al. MUC1 and MUC2 expression in pancreatic ductal carcinoma obtained by fine-needle aspiration. *Cancer*. 2003;99(6):365–371.
103. Crnogorac-Jurcevic T, Missiaglia E, Blaveri E, et al. Molecular alterations in pancreatic carcinoma: expression profiling shows that dysregulated expression of S100 genes is highly prevalent. *J Pathol*. 2003;201(1): 63–74.
104. Iacobuzio-Donahue CA, Ashfaq R, Maitra A, et al. Highly expressed genes in pancreatic ductal adenocarcinomas: a comprehensive characterization and comparison of the transcription profiles obtained from three major technologies. *Cancer Res*. 2003;63(24):8614–8622.
105. Jonckheere N, Perrais M, Mariette C, et al. A role for human MUC4 mucin gene, the ErbB2 ligand, as a target of TGF-beta in pancreatic carcinogenesis. *Oncogene*. 2004;23(34):5729–5738.
106. Juuti A, Nordling S, Louhimo J, et al. Loss of p27 expression is associated with poor prognosis in stage I-II pancreatic cancer. *Oncology*. 2003;65(4): 371–377.
107. Missiaglia E, Blaveri E, Terris B, et al. Analysis of gene expression in cancer cell lines identifies candidate markers for pancreatic tumorigenesis and metastasis. *Int J Cancer*. 2004;112(1):100–112.
108. Su SB, Motoo Y, Iovanna JL, et al. Expression of p8 in human pancreatic cancer. *Clin Cancer Res*. 2001;7(2):309–313.
109. Maacke H, Jost K, Opitz S, et al. DNA repair and recombination factor Rad51 is over-expressed in human pancreatic adenocarcinoma. *Oncogene*. 2000;19(23):2791–2795.
110. Biankin AV, Morey AL, Lee CS, et al. DPC4/Smad4 expression and outcome in pancreatic ductal adenocarcinoma. *J Clin Oncol*. 2002;20(23): 4531–4542.
111. Boltze C, Schneider-Stock R, Aust G, et al. CD97, CD95 and Fas-L clearly discriminate between chronic pancreatitis and pancreatic ductal adenocarcinoma in perioperative evaluation of cryocut sections. *Pathol Int*. 2002;52(2):83–88.
112. Casey G, Yamanaka Y, Friess H, et al. p53 mutations are common in pancreatic cancer and are absent in chronic pancreatitis. *Cancer Lett*. 1993; 69(3):151–160.
113. Di Sebastiano P, di Mola FF, Di Febbo C, et al. Expression of interleukin 8 (IL-8) and substance P in human chronic pancreatitis. *Gut*. 2000;47(3): 423–448.
114. Liao Q, Kleeff J, Xiao Y, et al. Preferential expression of cystein-rich secretory protein-3 (CRISP-3) in chronic pancreatitis. *Histol Histopathol*. 2003; 18(2):425–433.
115. Logsdon CD, Simeone DM, Binkley C, et al. Molecular profiling of pancreatic adenocarcinoma and chronic pancreatitis identifies multiple genes differentially regulated in pancreatic cancer. [erratum appears in *Cancer Res*. 2003;63(12):3445]. *Cancer Res*. 2003;63(10):2649–2657.
116. Mitas M, Cole DJ, Hoover L, et al. Real-time reverse transcription-PCR detects KS1/4 mRNA in mediastinal lymph nodes from patients with non-small cell lung cancer. *Clin Chem*. 2003;49:312–315.
117. Yamaguchi Y, Watanabe H, Yrdiran S, et al. Detection of mutations of p53 tumor suppressor gene in pancreatic juice and its application to diagnosis of patients with pancreatic cancer: comparison with K-ras mutation. *Clin Cancer Res*. 1999;5(5):1147–1153.
118. Sturm PD, Rauws EA, Hruban RH, et al. Clinical value of K-ras codon 12 analysis and endobiliary brush cytology for the diagnosis of malignant extrahepatic bile duct stenosis. *Clin Cancer Res*. 1999;5(3): 629–635.
119. Stewart CJ, Burke GM. Value of p53 immunostaining in pancreaticobiliary brush cytology specimens. *Diagn Cytopathol*. 2000;23(5):308–313.
120. Levy MJ, Clain JE, Clayton A, et al. Preliminary experience comparing routine cytology results with the composite results of digital image analysis and fluorescence in situ hybridization in patients undergoing EUS-guided FNA. *Gastrointest Endosc*. 2007;66(3):483–490.
121. Chari ST, Takahashi N, Levy MJ, et al. A diagnostic strategy to distinguish autoimmune pancreatitis from pancreatic cancer. *Clin Gastroenterol Hepatol*. 2009;7(10):1097–1103.
122. Keogan MT, Tyler D, Clark L, et al. Diagnosis of pancreatic carcinoma: role of FDG PET. *AJR. Am J Roentgenol*. 1998;171(6):1565–1570.
123. Rajput A, Stellato TA, Faulhaber PF, et al. The role of fluorodeoxyglucose and positron emission tomography in the evaluation of pancreatic disease. *Surgery*. 1998;124(4):793–797.
124. Bares R, Klever P, Hauptmann S, et al. F-18 fluorodeoxyglucose PET in vivo evaluation of pancreatic glucose metabolism for detection of pancreatic cancer. *Radiology*. 1994;192(1):79–86.
125. Higashi T, Saga T, Nakamoto Y, et al. Diagnosis of pancreatic cancer using fluorine-18 fluorodeoxyglucose positron emission tomography (FDG PET): usefulness and limitations in "clinical reality." *Ann Nucl Med*. 2003;17:261–279.
126. Nakamoto Y, Higashi T, Sakahara H, et al. Delayed (18)F-fluoro-2-deoxy-D-glucose positron emission tomography scan for differentiation between malignant and benign lesions in the pancreas. *Cancer*. 2000;89:2547–2554.
127. van Kouwen MC, Jansen JB, van Goor H, et al. FDG-PET is able to detect pancreatic carcinoma in chronic pancreatitis. *Eur J Nucl Med Mol Imaging*. 2005;32(4):399–404.
128. Kajiwara M, Kojima M, Konishi M, et al. Autoimmune pancreatitis with multifocal lesions. *J Hepatobiliary Pancreat Surg*. 2008;15(4):449–452.
129. Sah RP, Pannala R, Chari ST, et al. Prevalence, diagnosis, and profile of autoimmune pancreatitis presenting with features of acute or chronic pancreatitis. *Clin Gastroenterol Hepatol*. 2010;8(1):91–96.
130. Chari ST, Smyrk TC, Levy MJ, et al. Diagnosis of autoimmune pancreatitis: the Mayo Clinic experience. *Clin Gastroenterol Hepatol*. 2006;4(8): 1010–1016; quiz 934.
131. Ghazale A, Chari ST, Smyrk TC, et al. Value of serum IgG4 in the diagnosis of autoimmune pancreatitis and in distinguishing it from pancreatic cancer. *Am J Gastroenterol*. 2007;102(8):1646–1653.
132. Choi EK, Kim MH, Lee TY, et al. The sensitivity and specificity of serum immunoglobulin G and immunoglobulin G4 levels in the diagnosis of autoimmune chronic pancreatitis: Korean experience. *Pancreas*. 2007; 35(2):156–161.
133. Frulloni L, Lunardi C, Simone R, et al. Identification of a novel antibody associate with autoimmune pancreatitis. *N Engl J Med*. 2009;361(22): 2135–2142.
134. Kubota K, Kato S, Akiyama T, et al. Differentiating sclerosing cholangitis caused by autoimmune pancreatitis and primary sclerosing cholangitis according to endoscopic duodenal papillary features. *Gastrointest Endosc*. 2008;68(6):1204–1208.
135. Kamisawa T, Tu Y, Egawa N, et al. A new diagnostic endoscopic tool for autoimmune pancreatitis. *Gastrointest Endosc*. 2008;68(2):358–361.
136. Deshpande V, Mino-Kenudson M, Brugge WR, et al. Endoscopic ultrasound guided fine needle aspiration biopsy of autoimmune pancreatitis: diagnostic criteria and pitfalls. *Am J Surg Pathol*. 2005; 29(11):1464–1471.
137. Farrell JJ, Garber J, Sahani D, Brugge WR. EUS findings in patients with autoimmune pancreatitis. *Gastrointest Endosc*. 2004;60(6):927–936.
138. Levy MJ, Reddy RP, Wiersema MJ, et al. EUS-guided trucut biopsy in establishing autoimmune pancreatitis as the cause of obstructive jaundice. *Gastrointest Endosc*. 2005;61(3):467–472.
139. Mizuno N, Bhatia V, Hosoda W, et al. Histological diagnosis of autoimmune pancreatitis using EUS-guided trucut biopsy: a comparison study with EUS-FNA. *J Gastroenterol*. 2009;44(7):742–750.
140. Bang SJ, Kim MH, Kim do H, et al. Is pancreatic core biopsy sufficient to diagnose autoimmune chronic pancreatitis? *Pancreas*. 2008;36(1):84–89.
141. Sugumar A, Levy MJ, Kamisawa T, et al. Utility of endoscopic retrograde pancreatogram (ERP) to diagnose autoimmune pancreatitis (AIP): an international, double blind randomized, multicenter study [abstract]. *Gastrointest Endosc*. 2009;69:AB124.
142. Hoki N, Mizuno N, Sawaki A, et al. Diagnosis of autoimmune pancreatitis using endoscopic ultrasonography. *J Gastroenterol*. 2009;44(2):154–159.
143. Kamisawa T, Shimosegawa T, Okazaki K, et al. Standard steroid treatment for autoimmune pancreatitis. *Gut*. 2009;58(11):1504–1507.
144. Pannala R, Chari ST. Corticosteroid treatment for autoimmune pancreatitis. *Gut*. 2009;58(11):1438–1439.
145. Ghazale A, Chari ST, Zhang L, et al. Immunoglobulin G4-associated cholangitis: clinical profile and response to therapy. *Gastroenterology*. 2008; 134(3):706–715.
146. Carter JE, Nelson JJ, Eves M, Boudreaux C. *Giardia lamblia* infection diagnosed by endoscopic ultrasound-guided fine-needle aspiration. *Diagn Cytopathol*. 2007;35(6):363–365.

147. Cherian JV, Somasundaram A, Ponnusamy RP, Venkataraman J. Peripancreatic tuberculous lymphadenopathy: an impostor posing diagnostic difficulty. *JOP*. 2007;8(3):326–329.
148. Boujaoude JD, Honein K, Yaghi C, et al. Diagnosis by endoscopic ultrasound guided fine needle aspiration of tuberculous lymphadenitis involving the peripancreatic lymph nodes: a case report. *World J Gastroenterol*. 2007;13(3):474–477.
149. Canto MI, Goggins M, Yeo CJ, et al. Screening for pancreatic neoplasia in high-risk individuals: an EUS-based approach. *Clin Gastroenterol Hepatol*. 2004;2:606–621.
150. Brune K, Abe T, Canto M, et al. Multifocal neoplastic precursor lesions associated with lobular atrophy of the pancreas in patients having a strong family history of pancreatic cancer. *Am J Surg Pathol*. 2006; 30(9):1067–1076.
151. Brentnall TA, Bronner MP, Byrd DR, et al. Early diagnosis and treatment of pancreatic dysplasia in patients with a family history of pancreatic cancer. *Ann Intern Med*. 1999;131:247–255.
152. Lecesne R, Taourel P, Bret PM, et al. Acute pancreatitis: interobserver agreement and correlation of CT and MR cholangiopancreatography with outcome. *Radiology*. 1999;211:727–735.
153. Arvanitakis M, Delhaye M, De Maertelaere V, et al. Computed tomography and magnetic resonance imaging in the assessment of acute pancreatitis. *Gastroenterology*. 2004;126:715–723.
154. Ballinger AB, Barnes E, Alstead EM, Fairclough PD. Is intervention necessary after a first episode of acute idiopathic pancreatitis? *Gut*. 1996;38: 293–295.
155. Yusoff IF, Raymond G, Sahai AV. A prospective comparison of the yield of EUS in primary vs. recurrent idiopathic acute pancreatitis. *Gastrointest Endosc*. 2004;60:673–678.
156. Tandon M, Topazian M. Endoscopic ultrasound in idiopathic acute pancreatitis. *Am J Gastroenterol*. 2001;96(3):705–709.
157. Norton SA, Alderson D. Endoscopic ultrasonography in the evaluation of idiopathic acute pancreatitis. *Br J Surg*. 2000;87(12):1650–1655.
158. Coyle WJ, Pineau BC, Tarnasky PR, et al. Evaluation of unexplained acute and acute recurrent pancreatitis using endoscopic retrograde cholangiopancreatography, sphincter of Oddi manometry and endoscopic ultrasound. *Endoscopy*. 2002;34(8):617–623.
159. Liu CL, Lo CM, Chan JK, et al. EUS for detection of occult cholelithiasis in patients with idiopathic pancreatitis. *Gastrointest Endosc*. 2000;51(1):28–32.
160. Morris-Stiff G, Al-Allak A, Frost B, et al. Does endoscopic ultrasound have anything to offer in the diagnosis of idiopathic acute pancreatitis? *JOP*. 2009;10(2):143–146.
161. Lee SP, Nicholls JF, Park HZ. Biliary sludge as a cause of acute pancreatitis. *N Engl J Med*. 1992;326:589–593.
162. Ros E, Navarro S, Bru C, et al. Occult microlithiasis in "idiopathic" acute pancreatitis: prevention of relapses by cholecystectomy or ursodeoxycholic acid therapy. *Gastroenterology*. 1991;101:1701–1709.
163. Dahan P, Andant C, Levy P, et al. Prospective evaluation of endoscopic ultrasonography and microscopic examination of duodenal bile in the diagnosis of cholecystolithiasis in 45 patients with normal conventional ultrasonography. *Gut*. 1996;38:277–281.
164. Wilcox CM, Kilgore M. Cost minimization analysis comparing diagnostic strategies in unexplained pancreatitis. *Pancreas*. 2009;38(2):117–121.
165. Bret PM, Reinhold C, Taourel P, et al. Pancreas divisum: evaluation with MR cholangiopancreatography. *Radiology*. 1996;199(1):99–103.
166. Bhutani MS, Hoffman B, Hawes RH. Diagnosis of pancreas divisum by endoscopic ultrasonography. *Endoscopy*. 1999;31:167–169.
167. Chen RYM, Hawes RH, Wallace MB, Hoffman BJ. Diagnosing pancreas divisum in patients with abdominal pain and pancreatitis: is endoscopic ultrasound (EUS) accurate enough? [abstract]. *Gastrointest Endosc*. 2002; 55:AB96.
168. Lai R, Freeman ML, Cass OW, Mallery S. Accurate diagnosis of pancreas divisum by linear-array endosonography. *Endoscopy*. 2004;36:705–709.
169. Vaughan R, Mainie I, Hawes RH, et al. Accuracy endoscopic ultrasound in the diagnosis of pancreas divisum in a busy clinical setting [abstract]. *Gastrointest Endosc*. 2006;63:AB263.
170. Carnes ML, Romagnuolo J, Cotton PB. Miss rate of pancreas divisum by magnetic resonance cholangiopancreatography in clinical practice. *Pancreas*. 2008;37(2):151–153.
171. Catalano MF, Lahoti S, Alcocer E, et al. Dynamic imaging of the pancreas using real-time endoscopic ultrasonography with secretin stimulation. *Gastrointest Endosc*. 1998;48:580–587.
172. Irisawa A, Mishra G, Hernandez LV, Bhutani MS. Quantitative analysis of endosonographic parenchymal echogenicity in patients with chronic pancreatitis. *J Gastroenterol Hepatol*. 2004;19(10):1199–1205.
173. Das A, Nguyen CC, Li F, Li B. Digital image analysis of EUS images accurately differentiates pancreatic cancer from chronic pancreatitis and normal tissue. *Gastrointest Endosc*. 2008;67(6):861–867.
174. Norton ID, Zheng Y, Wiersema MS, et al. Neural network analysis of EUS images to differentiate between pancreatic malignancy and pancreatitis. *Gastrointest Endosc*. 2001;54(5):625–629.
175. Kumon RE, Pollack MJ, Faulx AL, et al. In vivo characterization of pancreatic and lymph node tissue by using EUS spectrum analysis: a validation study. *Gastrointest Endosc*. 2009;71(1):53–63.
176. Romagnuolo J, Vela S, Hoffman B, et al. Accuracy of contrast-enhanced harmonic endoscopic ultrasound (CEH-EUS) using Definity® [abstract]. *Gastrointest Endosc*. 2009;69:AB324–AB325.
177. Kitano M, Sakamoto H, Matsui U, et al. A novel perfusion imaging technique of the pancreas: contrast-enhanced harmonic EUS (with video). *Gastrointest Endosc*. 2008;67(1):141–150.
178. Wilson SR, Jang HJ, Kim TK, Burns PN. Diagnosis of focal liver masses on ultrasonography: comparison of unenhanced and contrast-enhanced scans. *J Ultrasound Med*. 2007;26(6):775–787. quiz 788–790.
179. Trillaud H, Bruel JM, Valette PJ, et al. Characterization of focal liver lesions with SonoVue-enhanced sonography: international multicenter-study in comparison to CT and MRI. *World J Gastroenterol*. 2009; 15(30):3748–3756.
180. Hocke M, Schulze E, Gottschalk P, et al. Contrast-enhanced endoscopic ultrasound in discrimination between focal pancreatitis and pancreatic cancer. *World J Gastroenterol*. 2006;12(2):246–250.
181. Janssen J, Schlorer E, Greiner L. EUS elastography of the pancreas: feasibility and pattern description of the normal pancreas, chronic pancreatitis, and focal pancreatic lesions. *Gastrointest Endosc*. 2007;65(7):971–978.
182. Giovannini M, Thomas B, Erwan B, et al. Endoscopic ultrasound elastography for evaluation of lymph nodes and pancreatic masses: a multicenter study. *World J Gastroenterol*. 2009;15(13):1587–1593.

CHAPTER 14

EUS IN PANCREATIC TUMORS

Mohammad Al-Haddad | John DeWitt

Key Points

EUS is the most sensitive imaging modality for the detection of pancreatic masses. It is particularly useful for identification of tumors undetected by other methods, such as computed tomography (CT).

A normal-appearing pancreas without a mass essentially rules out the possibility of pancreatic cancer. If cancer is expected but EUS demonstrates chronic pancreatitis with or without a focal mass, follow-up EUS, CT, or referral for possible surgery should be considered.

More recent studies have failed to confirm early studies suggesting that EUS was superior to CT for staging pancreatic neoplasms. The differences may result from improved CT technology, changing criteria for surgical exploration, or different staging classifications used in the various studies.

Because of anatomic and equipment limitations, CT and magnetic resonance imaging (MRI) are superior to EUS for detection of metastatic cancer. EUS-guided fine-needle aspiration (FNA) of liver metastases, ascites, or celiac adenopathy may avoid the need for surgical exploration.

EUS is superior to CT and angiography for detection of tumor invasion of the portal vein or confluence. CT appears to be superior to EUS for invasion of the superior mesenteric vessels and major arteries of the upper abdomen.

Among proposed criteria for vascular invasion, the identification of an irregular vessel wall, visible tumor within the vessel lumen, or the presence of venous collateral vessels may maximize the specificity for detection of true involvement by pancreatic cancer.

EUS FNA of pancreatic tumors has a sensitivity of 85% and a specificity approaching 100%. Diagnostic yield appears to be maximized by the presence of on-site cytopathology interpretation. EUS-guided Tru-Cut biopsy of pancreatic tumors is currently best reserved for transgastric biopsy following negative or nondiagnostic EUS FNA.

Most studies comparing EUS, CT, and MRI have demonstrated no significant differences among these modalities for determination of resectability of pancreatic cancer. However, EUS is usually used before surgery in combination with CT or MRI to evaluate vascular invasion or previously undetected metastases. Optimal preoperative evaluation of these patients depends on referral patterns and availability of EUS, but it should be individualized on a case-by-case basis.

EUS is the most accurate modality for detection of pancreatic neuroendocrine tumors (PNETs), particularly tumors smaller than 2.0 cm in diameter. Optimal workup of patients with suspected PNETs should incorporate EUS, EUS FNA, and somatostatin receptor scintigraphy.

EUS FNA may rarely identify pancreatic metastases in patients with a simultaneous or remote history of malignant disease. These tumors are more likely to have well-defined margins compared with primary pancreatic cancer.

INTRODUCTION

Examination of the pancreas and other upper abdominal retroperitoneal structures by endoscopic ultrasonography (EUS) is considered the most technically challenging to master, and this region is the most difficult to visualize reproducibly with EUS. However, once these skills are learned, EUS permits the most detailed nonoperative view of the pancreas that is available. This chapter summarizes the role of EUS for the evaluation of solid pancreatic neoplasms.

DETECTION OF PANCREATIC TUMORS

EUS is the most sensitive nonoperative imaging test for the detection of benign or malignant pancreatic lesions (Figs. 14.1 and 14.2). A summary of the results of 23 studies containing 1096 patients over a 21-year period found the sensitivity of EUS for detection of a pancreatic mass to be 95%, with a range of 85% to 100%.[1–23] Some of these studies, however, included benign pancreatic disease and ampullary tumors,[1–4,11,12,17–19] which may bias the analysis of tumor detection in favor of EUS. Therefore, caution must be exercised when extrapolating these data to pancreatic malignancy. In 16 studies that compared EUS with computed tomography (CT) over the same time period,[3,4,6–13,16–19,21,22] the sensitivity of EUS (98%) for mass detection was superior to that of CT (77%; Table 14.1). EUS is clearly superior to conventional CT[3,4,6,16] and transabdominal ultrasound[2–4,6,12] for pancreatic tumor detection. Compared with single-detector helical CT, however, EUS has been reported to be either equivalent[13] or superior.[11,17–19]

Currently available CT scanners use a 32- or 64-row detector that enables acquisition of multiple images with very thin collimation and three-dimensional reconstruction of ductal and parenchymal anatomy.[24,25] A few studies comparing EUS with multidetector-row CT (MDCT) for pancreatic tumors demonstrated the superiority of EUS for tumor detection compared with 4-row CT. Agarwal et al[21] reported an EUS sensitivity of 100% for the diagnosis of cancer compared with 86% for MDCT. Similarly, DeWitt et al[22] reported that the sensitivity of EUS (98%) was statistically superior to that of MDCT (86%) for a cohort of 80 patients with pancreatic cancer. There are relatively sparse

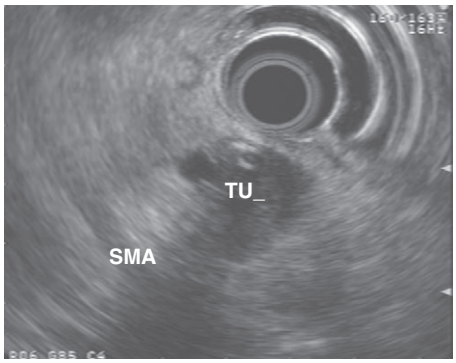


FIGURE 14.1 Linear EUS image (5 MHz) of a poorly defined, hypoechoic 22 × 21 mm ductal adenocarcinoma (TU) in the head of the pancreas adjacent to but not involving the superior mesenteric artery (SMA). A plastic biliary stent is present. Multidetector computed tomography with dual-phase imaging did not visualize this tumor.

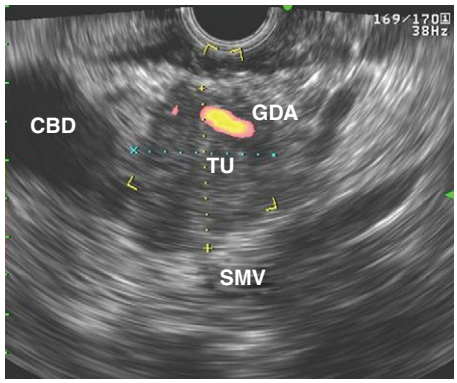


FIGURE 14.2 Linear EUS image (6 MHz) of a 2.5-cm mass (TU) in the head of the pancreas occluding the gastroduodenal artery (GDA). Doppler imaging demonstrates preserved blood flow within the vessel. The mass does not invade the duodenal wall or the superior mesenteric vein (SMV) on this image. The common bile duct (CBD) is obstructed and dilated above the mass.

TABLE 14.1

Sensitivity of EUS Compared with Other Imaging Tests for Detection of Pancreatic Masses

Authors (yr)	Patients (*n*)	Sensitivity (%)					
		EUS	CT	MRI	US	PET	ERCP
Lin et al[2] (1989)	33	94	—	—	91	—	—
Rosch et al[3] (1991)	102	99	77	—	67	—	90
Rosch et al[4] (1992)	60	98	85	—	78	—	—
Palazzo et al[6] (1993)	49	91	66	—	64	—	—
Muller et al[7] (1994)	33	94	69	83	—	—	—
Marty et al[8] (1995)	37	92	63	—	—	—	—
Melzer et al[9] (1996)	12	100	83	—	—	—	—
Dufour et al[10] (1997)	24	92	88	—	—	—	—
Howard et al[11] (1997)	21	100	67	—	—	—	—
Sugiyama et al[12] (1997)	73	96	86	—	81	—	—
Legmann et al[13] (1998)	30	100	92	—	—	—	—
Gress et al[16] (1999)	81	100	74	—	—	—	—
Midwinter et al[17] (1999)	34	97	76	—	—	—	—
Mertz et al[18] (2000)	31	93	53	—	—	87	—
Rivadeneira et al[19] (2003)	44	100	68	—	—	—	—
Ainsworth et al[20] (2003)	22	87	—	96	—	—	—
Agarwal et al[21] (2004)	71	100	86	—	—	—	—
Dewitt et al[22] (2004)	80	98	86	—	—	—	—
Total Subjects	837	837	782	55	317	31	102
Overall Sensitivity	—	98	77	88	76	87	90

comparative data comparing EUS with magnetic resonance imaging (MRI) for tumor detection. EUS has been reported to be either superior[7] or inferior[20] to MRI. Future studies comparing EUS with 3.0 or higher Tesla MRI will be needed to define the roles of each modality in the diagnosis of pancreatic masses.

EUS is particularly useful for identification of small tumors that have gone undetected by other imaging modalities.[1,3,7,13,17,21,22] For tumors up to 20 mm in diameter, EUS was found to have a sensitivity of 90% to 100% compared with 40% to 67% for CT and 33% for MRI.[7,13] With thinner slice imaging and precisely timed contrast administration coupled with multiplanar reconstruction,[24,26] CT may now be able to identify small pancreatic masses that previously went undetected by conventional or even single-detector dual-phase imaging.[22] In all patients with obstructive jaundice in whom CT or MRI results do not definitively identify a pancreatic lesion, EUS should be performed both to detect any tumor and to exclude non-neoplastic diseases.

EUS may fail to identify true pancreatic masses in patients with chronic pancreatitis, diffusely infiltrating carcinoma, a prominent ventral-dorsal split, or a recent episode (<4 weeks) of acute pancreatitis. In a study of 80 patients with clinical suspicion of pancreatic cancer and a normal EUS result, Catanzaro et al[27] found that no patient with a normal pancreatic EUS result developed cancer during a follow-up period of 24 months. Therefore, a normal pancreas by EUS examination essentially rules out pancreatic cancer, but follow-up EUS or other study should be undertaken when EUS demonstrates chronic pancreatitis without a definite mass. Acoustic shadowing caused by an indwelling biliary or pancreatic stent may impede visualization of a small pancreatic mass.

Owing to the ability of EUS to provide high-resolution images, there has been interest in using this technique to screen asymptomatic high-risk cohorts for early cancer detection. Brentnall et al[28] first reported the use of endoscopic retrograde cholangiopancreatography (ERCP), EUS, spiral CT, serum carcinoembryonic antigen (CEA), and serum CA 19-9 testing in 14 patients from three kindreds with a history of familial pancreatic cancer. Seven of the 14 patients were believed to have dysplasia on the basis of clinical history and abnormalities on EUS and ERCP, all of whom had confirmed dysplastic changes at surgery. Using a decision-analysis model, the same investigators[29] concluded that endoscopic screening for pancreatic cancer in high-risk individuals was cost effective, with an incremental cost-effectiveness ratio of $16,885 per life-year saved. Screening remained cost effective if the prevalence of dysplasia was greater than 16% or if the sensitivity of EUS was greater than 84%.

Canto et al[30] evaluated an EUS-based screening approach in a prospective cohort of 38 asymptomatic individuals with Peutz-Jeghers syndrome or in kindreds with three or more or two affected relatives with pancreatic cancer. Six pancreatic benign and malignant masses were found by EUS. The diagnostic yield for detecting clinically significant pancreatic neoplasms was 5.3% (2 of 38). A more recent study[31] found that EUS was superior to MRI among high-risk asymptomatic patients and that EUS could disclose adenocarcinoma and side branch intraductal papillary mucinous neoplasm during first-time screening in individuals with family history of pancreatic cancer or other familial cancer syndromes.[32] These studies suggest that EUS-based screening of asymptomatic high-risk individuals for pancreatic cancer is feasible and cost effective. However, current data are insufficient to recommend endoscopic screening for these patients.

Both autoimmune pancreatitis (AIP) and primary pancreatic lymphoma (PPL) may mimic primary pancreatic cancer, and accurate preoperative detection may prevent unnecessary surgery. AIP most commonly manifests with obstructive jaundice, abdominal pain, and weight loss.[33,34] The EUS morphology of AIP may include diffuse pancreatic enlargement, a focal mass, focal hypoechoic areas, bile duct wall thickening, or peripancreatic lymphadenopathy.[33–36] EUS fine-needle aspiration (FNA) may demonstrate a nonspecific plasmacytic predominant chronic inflammatory infiltrate but overall has variable sensitivity and poor specificity. Diagnosis may also be obtained by EUS-guided Tru-Cut biopsy (EUS TCB).[36] PPL may result in a mass lesion indistinguishable from adenocarcinoma. Although EUS and radiographic imaging alone may not help to confirm the diagnosis of PPL, EUS FNA with flow cytometry is very accurate for this diagnosis.[37] PPL should be suspected based on clinical appearance, lack of definite malignancy, and abundance of abnormal lymphocytes on rapid cytologic review.

Imaging-based technologies such as contrast-enhanced (CE) EUS may be used to differentiate pancreatic tumors from other nonmalignant conditions. Dietrich et al[38] reported that CE EUS with Levovist demonstrated tumor hypovascularity in 57 of 62 patients (92%) with pancreatic ductal adenocarcinoma, whereas all other nonmalignant pancreatic lesions revealed an isovascular or hypervascular pattern. Nevertheless, the most promising application of CE EUS is to aid in differentiating chronic pancreatitis from ductal adenocarcinoma. Using Optison to assess pancreatic tumors and focal chronic pancreatitis in 23 patients, Becker et al[39] reported an overall sensitivity and specificity of CE EUS for the diagnosis of pancreatic carcinoma of 94% and 100%, respectively. Hocke et al[40] found that CE EUS with SonoVue increased the sensitivity and specificity for discrimination of benign and malignant pancreatic lesions from 73.2% to 91.1% and from 83.3% to 93.3%, respectively. Several limitations to the routine use of CE EUS include cost and the lack of both agent availability and expertise with this technique.

EXAMINATION CHECKLIST

1. **Lymph nodes:** Examination of the following stations for possible metastatic disease: celiac axis, peripancreatic (including head, body, and tail), porta hepatis, gastrohepatic ligament, aortocaval, and possibly posterior mediastinal stations. Metastatic lymph nodes are usually round, well defined, hypoechoic, and at least 5 mm in diameter. However, not all malignant lymph nodes have all these features. If a suspected lymph node is identified, its characteristics and distance from the tumor should be noted. EUS fine-needle aspiration (FNA) should be performed in suspected distant metastatic lymph nodes.
2. **Liver:** Transgastric and limited transduodenal examination of the liver for metastatic lesions. Liver metastases from primary pancreatic cancer are usually hypoechoic and well defined. One or more than one lesion may be identified. EUS FNA of any suspected lesion should be performed when accessible.
3. **Ascites:** Examininination for a triangular or irregularly shaped anechoic region just outside the duodenal or gastric wall. This may be secondary to peritoneal metastases or chronic venous occlusion. EUS-guided fluid aspiration should be performed when possible.
4. **Vascular invasion:** For tumors in the pancreatic head, the relationship of the tumor with the portal vein, portosplenic confluence, superior mesenteric vessels, hepatic artery and gastroduodenal artery should be noted. For tumors in the body of the pancreas, the relationship of the tumor with the celiac artery, superior mesenteric artery, portal confluence, hepatic artery, and splenic vessels should be defined. For tumors in the pancreatic tail, the splenic vessels and celiac artery should be interrogated. The interrelationship of the vessel and the tumor should be carefully examined. Notation may be stated as follows: intact hyperechoic tumor/vessel interface, adherent to vessel wall without irregular interface, irregular tumor/vessel

EXAMINATION CHECKLIST—cont'd

interface, tumor invasion or occlusion of the vessel. For occlusion of the portal or superior mesenteric vein, venous collateral vessels in the liver hilum or periduodenal region should be noted. For splenic vein occlusion, collateral vessels in the splenic hilum or gastric fundus should be observed.

5. **Tumor:** The following characteristics of all visualized masses should be noted: maximal dimensions, irregular or well-defined borders, isoechoic or hypoechoic or hyperechoic characteristics, and any solid or cystic structures.
6. **EUS FNA:** Tissue sampling should be performed from the most distant metastatic site first. If ascites, a distant metastatic lymph node, or a suspicious liver lesion is noted, these should be sampled for biopsy first. If biopsy results are negative for malignancy, then either the suspected tumor or a regional lymph node may be sampled. The following information should be noted from each biopsy site: numbers of passes required, whether suction is used, and whether preliminary interpretation of any specimen obtained is available.
7. **Staging:** All suspected malignant tumors of the pancreas should be assigned a TNM stage based on the most current American Joint Committee on Cancer (AJCC) staging classification.

STAGING OF PANCREATIC TUMORS

Staging of pancreatic malignancy is done according to the American Joint Committee for Cancer (AJCC) staging TNM classification, which describes the tumor extension (T), lymph node involvement (N), and distant metastases (M) of tumors, respectively. Reported accuracies of T staging by EUS range from 63% to 94% (Table 14.2).[4,6,7,13,14,16,17,19,22,41–51] This wide variation may stem from improved detection of distant metastasis or vascular invasion by MDCT, resulting in less operative management for suspected locally advanced or metastatic disease. The exclusion of such patients may have resulted in the decreased T-staging accuracy of some more recent studies compared with earlier ones. Some tertiary referral centers attempt to achieve negative surgical margins by surgical reconstruction of the portal or superior mesenteric vein in patients with venous invasion but without thrombosis or occlusion (Figs. 14.3 to 14.5).[52,53] To

TABLE 14.2

Accuracy of EUS for Tumor and Nodal Staging of Pancreatic Cancer

Authors (yr)	Patients Enrolled (*n*)	Patients to Surgery with Pancreatic Cancer (*n*)	Accuracy (%)	
			T Stage	N Stage
Ahmad et al[41] (2000)	NA	89	69	54
Akahoshi et al[14] (1998)	96	37	64	50
Buscail et al[42] (1999)	73	26	73	69
DeWitt et al[22] (2004)	104	53	67	41
Gress et al[16] (1999)	151	75	85	72
Grimm et al[44] (1990)	NA	26	85	72
Giovannini et al[43] (1994)	90	26	NR	80
Legmann et al[13] (1998)	30	22	90	86
Midwinter et al[17] (1999)	48	23	NR	74
Mukai et al[45] (1991)	26	26	NR	65
Muller et al[7] (1994)	49	16	82	50
Palazzo et al[6] (1993)	64	49	82	64
Ramsay et al[46] (2004)	27	22	63	69
Rivadeneira et al[19] (2003)	NA	44	NR	84
Rosch et al[4] (1992)	60	40	NR	72
Rosch et al[47] (1992)	46	35	94	80
Soriano et al[48] (2004)	127	62	62	65
Tio et al[50] (1990)	43	36	92	74
Tio et al[49] (1996)	70	52	84	69
Yasuda et al[51] (1993)	NA	29	NR	66

N, nodal stage; NA, not applicable; NR, not reported; T, tumor stage.

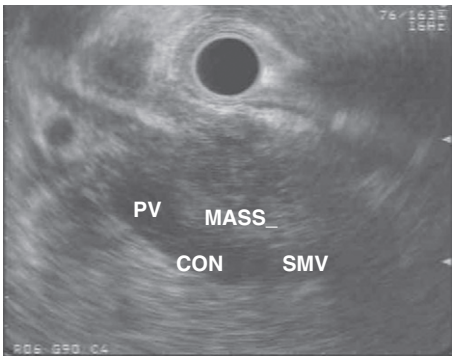


FIGURE 14.3 Radial image (7.5 MHz) of a large pancreatic head mass with adherence and invasion into the superior mesenteric vein (SMV). The mass extends proximally to involve the portal vein confluence (CON) and the portal vein (PV).

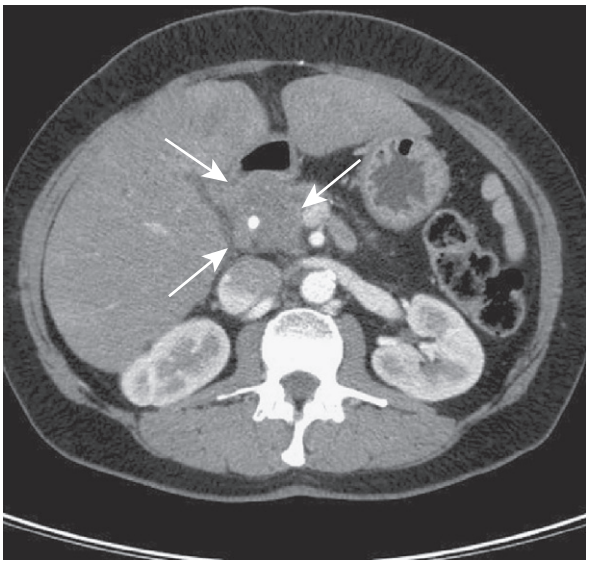


FIGURE 14.4 Computed tomography image of the same patient as in Figure 14.3 demonstrating probable invasion into the superior mesenteric vein by the pancreatic head mass *(arrows).*

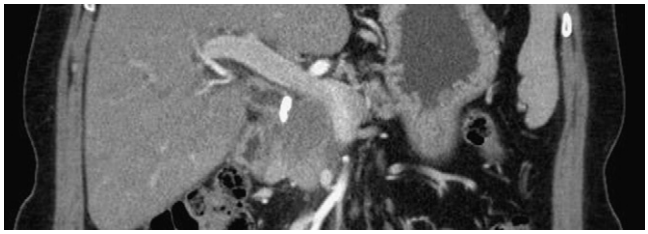


FIGURE 14.5 Multiplanar reconstruction of the axial computed tomography image in the same patient as in Figure 14.3 along the portal vein and superior mesenteric vein (SMV). Invasion of the SMV is seen on this image.

reflect such surgical trends more accurately, the 1997 staging criteria were updated in the 2003 AJCC manual (sixth edition), to distinguish potentially resectable (T3) from unresectable (T4) tumors. The current AJCC 2003 staging criteria classify vascular invasion of only the celiac artery or the superior mesenteric artery as T4 cancer (Table 14.3).

Despite the variations of T-staging criteria described for pancreatic cancer, nodal (N) metastases have uniformly been classified as absent (N0) or present (N1) across all AJCC editions, including the latest sixth edition. The accuracy of EUS for N staging of pancreatic tumors ranges from 41% to 86%.[4,6,7,13,14,16,17,19,22,42–51,54] Various criteria have been proposed for endosonographic detection of metastatic lymph nodes, including size greater than 1 cm, hypoechoic echogenicity, distinct margins, and round shape. When all four features are present within a lymph node, there is an 80% to 100% chance of malignant invasion.[55,56] The sensitivity of EUS alone for the diagnosis of metastatic adenopathy in pancreatic cancer is 28% to 92%.[6,7,14,17,19,46,48,49] However, most investigators report sensitivities of less than 65%. This low sensitivity presumably occurs for two reasons. First, most metastatic lymph nodes do not have all four of the endosonographic features described earlier[55] and may therefore be incorrectly assumed to be benign. Second, peritumoral inflammation and large tumor size may contribute to poor detection of adenopathy.[57]

The specificity of EUS alone for the diagnosis of metastatic adenopathy in pancreatic cancer is 26% to 100%.[6,7,14,17,19,46,48,49] However, most investigators report specificities greater than 70%. It is presumed that the addition of EUS FNA of suspicious lymph nodes may increase the specificity; however, few data have described the impact of the addition of EUS FNA to EUS alone. Cahn et al[58] reported that EUS FNA diagnosed lymph node metastasis in 7 of 13 patients (62%) with pancreatic cancer in whom sampling was performed. For tumors involving the head of the pancreas, malignant lymph nodes are removed en bloc with the surgical specimen. Therefore, accurate detection of these lymph nodes is not essential,[22] and routine EUS FNA of peritumoral lymph nodes with pancreatic head cancers may not be necessary. Because preoperative identification and EUS FNA of celiac nodes may preclude surgery, meticulous survey of this region is critical during staging of all pancreatic tumors. In one series, mediastinal lymph node metastases were reported to occur in 7% of patients undergoing EUS evaluation of pancreatic masses.[59] Therefore, a brief survey of this region may be helpful during staging of pancreatic lesions.

Early studies found that EUS was superior to conventional CT for tumor[6,7] and nodal[4,6,7,45] staging of pancreatic cancer (Table 14.4). Although a more recent study reported that EUS was superior to CT for T staging,[22] most studies found that the two modalities are equivalent for both T[17,46,48] and N staging.[13,17,19,22,46,48] Soriano et al,[48] conversely, found that helical CT was superior to EUS in the assessment of locoregional extension among 62 patients with pancreatic cancer. Similar to CT, early studies showed that EUS was superior to MRI for staging of pancreatic tumors.[6,7] However, two more recent studies[46,48] found no difference between EUS and MRI for both T and N staging. Clearly, the initial advantage demonstrated by EUS over other imaging modalities for the staging of pancreatic tumors has narrowed considerably. Future studies that compare EUS with

TABLE 14.3

American Joint Committee on Cancer 2003 TNM Staging Classification for Pancreatic Cancer*

Stage	Description
Primary Tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor limited to the pancreas, ≤2 cm in greatest dimension
T2	Tumor limited to the pancreas, >2 cm in greatest dimension
T3	Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery
T4	Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)
Regional Lymph Nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
Distant Metastasis (M)	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
Ajcc Stage Groupings	
Stage 0	TisN0M0
Stage IA	T1N0M0
Stage IB	T2N0M0
Stage IIA	T3N0M0
Stage IIB	T1, N1, M0 T1N1M or T2N1M0 or T3N1M0
Stage III	T4anyNM0
Stage IV	AnyTanyNM1

*Exocrine pancreas.

From Greene FL, Page DL, Fleming ID, et al., eds. *American Joint Committee on Cancer: AJCC Cancer Staging Manual.* 6th ed. Philadelphia: Lippincott-Raven; 2003;179-188.

TABLE 14.4

Comparison of the Accuracy of EUS with Computed Tomography, Magnetic Resonance Imaging, and Ultrasound for Tumor and Nodal Staging of Pancreatic Cancer

		Accuracy of EUS (%)		Accuracy of CT (%)		Accuracy of MRI (%)		Accuracy of US (%)	
Authors (yr)	Patients (*n*)	T	N	T	N	T	N	T	N
Mukai et al[45] (1991)	26	—	65	—	38	—	—	—	58
Rosch et al[4] (1992)	40	—	72	—	38	—	—	—	53
Palazzo et al[6] (1993)	64	82	64	45	50	50	56	—	37
Muller et al[7] (1994)	16	82	50	56	38	57	50	—	—
Legmann et al[13] (1998)	22	90	86	86	77	—	—	—	—
Midwinter et al[17] (1999)	23	—	74	—	65	—	—	—	—
Rivadeneira et al[19] (2003)	44	—	84	—	68	—	—	—	—
Soriano et al[48] (2004)	62	63	67	73	56	62	60	—	—
Ramsay et al[46] (2004)	27	63	69	76	63	83	56	—	—
DeWitt et al[22] (2004)	53	67	44	41	47	—	—	—	—

CT, computed tomography; MRI, magnetic resonance imaging; N, nodal stage; T, tumor stage; US, ultrasound.

MDCT and higher-Tesla MRI are needed to confirm these findings and further define the role of EUS for the locoregional staging of pancreatic tumors.

For detection of non-nodal metastatic cancer, CT and MRI are superior to EUS because of both the anatomic limitations of normal upper gastrointestinal anatomy and the limited range of EUS imaging. Although the entire left and caudate lobes of the liver may be seen by transgastric imaging in most patients, a portion of the right lobe may not be visualized by EUS. Therefore, EUS clearly cannot replace but may supplement other modalities for staging of hepatic metastases. The principal advantages of EUS for evaluation of the liver metastases are detection of small lesions missed by other imaging modalities[60,61] and the ability to sample visualized accessible masses by EUS FNA (Figs. 14.6 and 14.7).[60–62] The sensitivity of EUS FNA for benign and malignant liver masses reportedly ranges from 82% to 94%,[62,63] and the diagnosis of liver metastases from pancreatic cancer generally precludes surgical resection.[63] EUS may also identify and aspirate ascites either previously detected or undetected by other imaging studies (Figs. 14.8 to 14.10).[64,65] Identification of malignant ascites and liver metastases by EUS FNA is associated with poor survival following diagnosis.[66]

VASCULAR INVASION BY PANCREATIC TUMORS

Interpretation of data regarding the accuracy of EUS for vascular invasion is difficult for several reasons. First, little histologic correlation exists with intraoperative findings regarding vascular invasion in most studies. True vascular invasion may be overestimated or underestimated by intraoperative findings[67,68] and may therefore give false information regarding the accuracy of EUS staging. Second, no established consensus exists among endosonographers on the optimal criteria that should be used for EUS

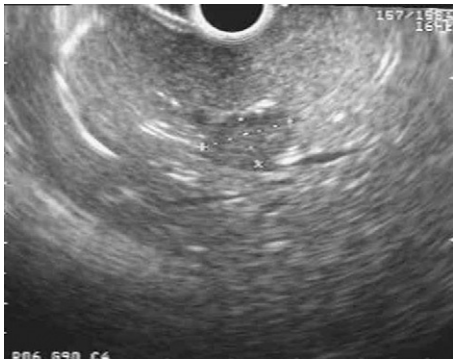


FIGURE 14.6 Linear EUS image (6 MHz) of a 6-mm hypoechoic mass in the left lobe of the liver in a patient with a 2.5-cm mass in the head of the pancreas. The liver lesion was not seen on computed tomography scan.

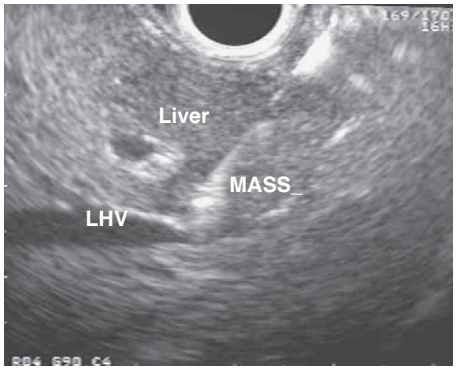


FIGURE 14.7 EUS fine-needle aspiration of the liver mass in the same patient as in Figure 14.6. Cytologic examination confirmed metastatic adenocarcinoma, thus making the tumor unresectable. LHV, left hepatic vein.

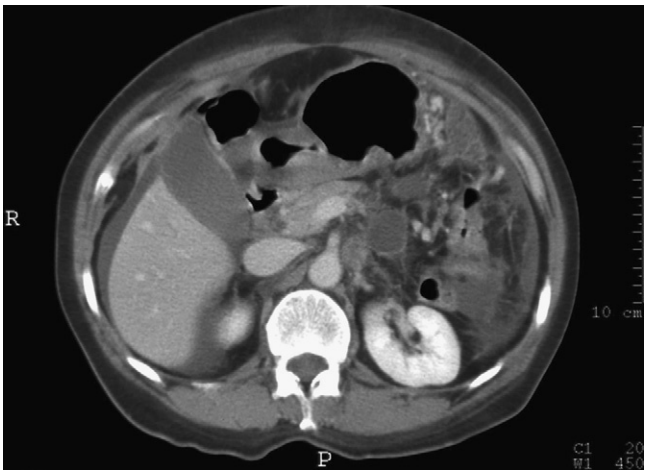


FIGURE 14.8 Axial computed tomography image demonstrating a 3-cm cystic pancreatic body mass and perihepatic ascites.

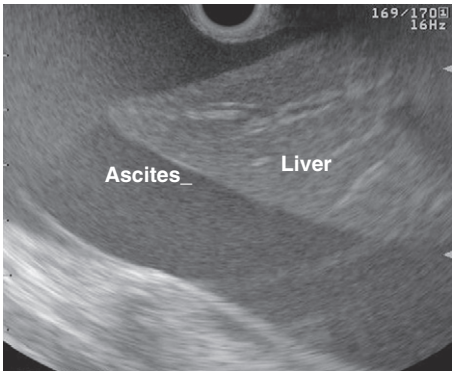


FIGURE 14.9 Linear EUS image (6.0 MHz) of perihepatic ascites.

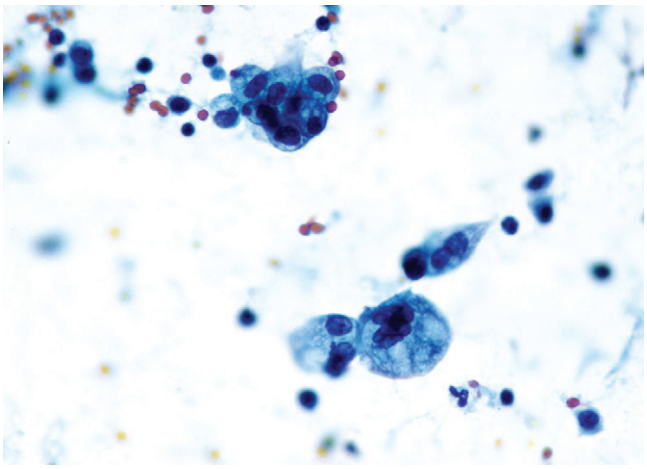


FIGURE 14.10 Cytology specimen from ascites fluid demonstrating metastatic adenocarcinoma (Diff-Quik stain; 100×).

assessment of vascular invasion by pancreatic or other tumors. Consequently, multiple criteria have been proposed by various authors for this indication.

For overall vascular invasion, the accuracy of EUS ranges from 40% to 100% (Table 14.5).[9,10,16,18,19,42,45,46,48] The sensitivity and specificity of EUS for malignant vascular invasion range from 42% to 91% and 89% to 100%, respectively.[16,42,46,48,69] Although some studies demonstrated that EUS was more accurate[9,16,18,19,45] than CT for vascular invasion, some investigators reported that the accuracy of CT was superior[10,46,48] to that of EUS. Overall accuracy of MRI is reportedly equivalent[48] or superior[46] to that of EUS. For overall venous invasion, EUS is reportedly superior[6] or equivalent to CT.[8] Overall sensitivity and accuracy of EUS for arterial invasion are 56%[8] and 50%,[6] respectively. Angiography is consistently inferior to EUS and CT for assessment of vascular infiltration by tumor and therefore has no current role in the staging of pancreatic tumors.[4,45,48]

The sensitivity of EUS for tumor invasion of the portal vein or portal vein confluence is 60% to 100%,[1,4,12,17,47,70,71] with most studies demonstrating sensitivities greater than 80%. The sensitivity of EUS for portal vein invasion is also consistently superior to that of CT[4,12,17,47] and angiography.[4,12,47,70] For the superior mesenteric vein, superior mesenteric artery, and celiac artery, the sensitivity of EUS is only 17% to 83%,[42] 17%,[18] and approximately 50%,[4,47] respectively. The sensitivity of CT for staging of the superior mesenteric artery[17,18] and celiac artery[4,47] appears to be better than that of EUS. EUS staging of the superior mesenteric vessels may be difficult because of the inability to visualize the entire course of the vessel or the obscuring of these vessels by a large tumor in the uncinate or inferior portion of the pancreatic head.[71] This situation is in contrast to the splenic artery and vein, which are generally easily seen and staged well by EUS (Fig. 14.11).[1,47,70,71] Until further conclusive data become available, assessment of tumor resectability should be done by both EUS and CT (or MRI) rather than by EUS alone.

Several investigators have attempted to describe the accuracy of various endosonographic findings to assess vascular invasion by malignant pancreatic tumors. Using the criterion of "rough edged vessel with compression," Yasuda et al[1] found sensitivity, specificity, and accuracy of 79%, 87%, and 81%, respectively, for malignant invasion of the portal venous system. Rosch et al[4] found sensitivity, specificity, and accuracy of 91%, 96%, and 94%, respectively, for invasion of the portal vein by using the criterion of "abnormal contour, loss of hyperechoic interface, and close contact." In a further blinded videotape review,[71] these same investigators found that no single criterion was able to predict venous invasion with sensitivity and specificity exceeding 80% each. However, these investigators found that both complete vascular obstruction and the presence of collateral vessels demonstrated specificity of 94% for vascular invasion. Similarly, Snady et al[72] reported 100% specificity for presence of venous collateral

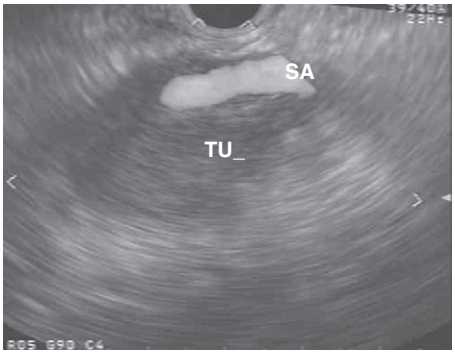


FIGURE 14.11 Linear EUS image (6 MHz) of a 3-cm pancreatic body mass (TU) invading the splenic artery (SA). Doppler imaging demonstrates preserved blood flow within the vessel.

TABLE 14.5

Comparison of the Overall Accuracy of EUS with Computed Tomography, Ultrasound, Angiography, and Magnetic Resonance Imaging for Vascular Invasion by Pancreatic Cancer

Authors (yr)	Patients (*n*)	Test	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Mukai et al[45]* (1991)	26	EUS	—	—	—	—	77
		CT	—	—	—	—	38
		US	—	—	—	—	50
		Angiography	—	—	—	—	56
Melzer et al[9] (1996)	13	EUS	—	—	—	—	92
		CT	—	—	—	—	61
Dufour et al[10] (1997)	24	EUS	—	—	—	—	40
		CT	—	—	—	—	90
Buscail et al[42†] (1999)	32	EUS	67	100	100	83	88
Gress et al[16] (1999)	75	EUS	91	96	94	93	93
		CT	15	100	100	60	62
Mertz et al[18] (2000)	6	EUS	—	—	—	—	100
		CT	—	—	—	—	50
Tierney et al[69] (2001)	45	EUS	87	—	—	—	—
		CT	33	—	—	—	—
Rivadeneira et al[19] (2003)	9	EUS	—	—	—	—	100
		CT	—	—	—	—	45
Ramsay et al[46] (2004)	19	EUS	56	89	—	—	68
		CT	80	78	—	—	89
		MRI	56	100	—	—	78
Soriano et al[48] (2004)	62	EUS	42	97	89	74	76
		CT	67	94	89	80	83
		MRI	59	84	72	74	74
		Angiography	21	100	100	64	67

*Retroperitoneal vasculature.
†Includes some patients with ampullary cancer.
CT, computed tomography; MRI, magnetic resonance imaging; NPV, negative predictive value; PPV, positive predictive value; US, ultrasound.

vessels, tumor in the lumen, and loss of hyperechoic interface. Depending on the EUS criteria chosen, Brugge et al[70] found sensitivity and specificity ranging from 40% to 80% and 23% to 100%, respectively, for malignant invasion of the portal vein. A tradeoff exists among various criteria for sensitivity and specificity for vascular invasion. However, criteria with the highest specificity are needed to optimize selection of those patients most likely to benefit from surgical exploration. Therefore, the findings of an irregular vascular wall, venous collateral vessels, and visible tumor within the vessel are the preferred criteria for assessment of vascular invasion.

RESECTABILITY OF PANCREATIC TUMORS

Complete surgical removal of pancreatic cancer with negative histopathologic margins (R0 resection) is the only potential curative treatment and is an independent predictor of postoperative survival.[73,74] Therefore, the principal role of preoperative evaluation is to identify patients with resectable disease who may benefit from surgery accurately while avoiding surgery in patients with suspected unresectable disease.

In a pooled analysis of nine studies involving 377 patients (Table 14.6), the sensitivity and specificity of EUS for resectability of pancreatic cancer was 69% and 82%, respectively.[11,13,16,22,41,42,46,48,69] Ranges of reported sensitivities and specificities were 23% to 91% and 63% to 100%, respectively. Overall EUS accuracy for tumor resectability is 77%. Eight of these nine studies also compared the accuracy of EUS with that of one or more imaging modalities.

Because most studies reported that EUS is similar to both CT and MRI for assessment of resectability, some investigators proposed that optimal preoperative imaging of pancreatic cancer requires the use of multiple modalities. Using a decision analysis, Soriano et al[48] found that accuracy for tumor resectability was maximized and costs were minimized when CT or EUS was performed initially, followed by the other test, in patients with potentially resectable neoplasms. Ahmad et al[41] proposed that although individually EUS and MRI are not sensitive for tumor resectability, the use of these studies may increase the positive predictive value (PPV) of resectability compared with either test alone. Tierney et al[69] suggested that CT should be performed initially but EUS should also be used in most patients because of its improved detection of vascular invasion. When surgery was performed only when MDCT and EUS results agreed on tumor resectability, DeWitt et al[22] reported a nonsignificant trend toward improved accuracy of resectability compared with either study alone. Other studies suggested that EUS should be incorporated into preoperative imaging to prevent unnecessary surgery[42] and to aid in the detection and staging of tumors missed by CT.[13,22] Clearly, no consensus exists on the best test or tests necessary for preoperative staging of suspected pancreatic tumors (Table 14.7). An EUS-based management algorithm for suspected pancreatic cancer is proposed (Fig. 14.12). In reality, however, the role of EUS in these patients depends on its availability, referral patterns, and local expertise. Further cost and decision analysis and comparative studies of EUS with the most current CT and MRI techniques will be required to optimize surgical exploration in appropriate patients.

EUS FINE-NEEDLE ASPIRATION OF PANCREATIC CANCER

Before the advent of EUS, FNA or core biopsy of pancreatic masses was performed either intraoperatively[75,76] or percutaneously under CT or ultrasound guidance.[77–80] Intraoperative FNA of pancreatic tumors is an accurate, safe technique,[78] but it may increase intraoperative time considerably, especially with on-site interpretation of specimens. Previous enthusiasm over the use of percutaneous FNA, however, has decreased as a result of reports of needle-tract seeding,[81–84] and the development of EUS FNA.

EUS FNA is performed using a linear array echoendoscope while the patient is under conscious sedation and is undergoing appropriate cardiorespiratory monitoring. Placement of a transducer on the distal tip of the echoendoscope permits visualization of needle advancement into the target lesion under real-time ultrasound guidance. Various commercially available FNA needles are available, ranging in size from 19 to 25 gauge. Doppler techniques should be used to examine the projected path of the needle, to avoid puncturing intervening blood vessels while trying to minimize the amount of normal pancreatic tissue that has to be traversed. Once the target lesion is accessed through the gastric or duodenal wall, the stylet is withdrawn, and suction is applied. A to-and-fro rapid jabbing movement within the pancreatic tumor is performed for 30 to 45 seconds. The echogenic tip of the needle should be kept in view at all times to avoid deeper tissue penetration. The needle is then withdrawn back into the sheath, and the entire system is removed all together. The material within the needle lumen is then expressed onto two glass slides; one is air dried for rapid staining and on-site review (if possible), and the other is alcohol fixed for future review. The use of suction in subsequent passes depends on the cellularity of the initial few passes: suction should be applied if the specimens are too scant and avoided if the specimens are too bloody.

Advancement of the EUS FNA needle through the biopsy channel can be challenging for lesions in the uncinate process. A short scope position (similar to that used for ERCP) may be helpful and is obtained by slow withdrawal of the scope from the second or third portion while the lesion is kept in view

TABLE 14.6

Test Characteristics of EUS for Resectability of Pancreatic Cancer

Authors (yr)	Patients (n)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Howard et al[11]* (1997)	21	75	77	67	83	76
Legmann et al[13] (1998)	27	90	83	95	75	92
Buscail et al[42] (1999)	26	47	100	100	50	65
Gress et al[16] (1999)	75	95	92	93	94	93
Ahmad et al[41] (2000)	63	61	63	69	55	62
Tierney et al[69] (2001)	24	93	67	82	83	83
Soriano et al[48] (2004)	62	23	100	100	64	67
Ramsay et al[46] (2004)	26	56	83	91	38	63
DeWitt et al[22] (2004)	53	88	68	71	86	77
Totals	377	69	82	86	72	77

*Includes six patients with ampullary cancer.
NPV, negative predictive value; PPV, positive predictive value.

TABLE 14.7

Comparison of EUS with Computed Tomography, Magnetic Resonance Imaging, and Angiography for Resectability of Pancreatic Cancer

Authors (yr)	Patients (*n*)	Modality	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Howard et al[11]* (1997)	22	EUS	75	77	67	83	76
		CT	63	100	100	80	86
		Angiography	38	92	75	71	71
Legmann et al[13] (1998)	27	EUS	90	83	95	75	92
		CT	90	100	100	77	93
Gress et al[16] (1999)	75	EUS	95	92	93	94	93
	58	CT	97	19	58	83	60
Ahmad et al[41] (2000)	63	EUS	61	63	69	55	62
		MRI	73	72	77	68	73
Tierney et al[69] (2001)	24	EUS	93	67	82	83	83
		CT	100	33	71	100	75
Ramsay et al[46] (2004)	26	EUS	56	83	91	38	63
		CT	79	67	88	50	76
		MRI	81	83	93	67	83
Soriano et al[48] (2004)	62	EUS	23	100	100	64	67
		CT	67	97	95	77	83
		MRI	57	90	81	73	75
		Angiography	37	100	65	71	
DeWitt et al[22] (2004)	53	EUS	88	68	71	86	77
		CT	92	64	70	90	77

*Includes six patients with ampullary cancer.
CT, computed tomography; MRI, magnetic resonance imaging; NPV, negative predictive value; PPV, positive predictive value.

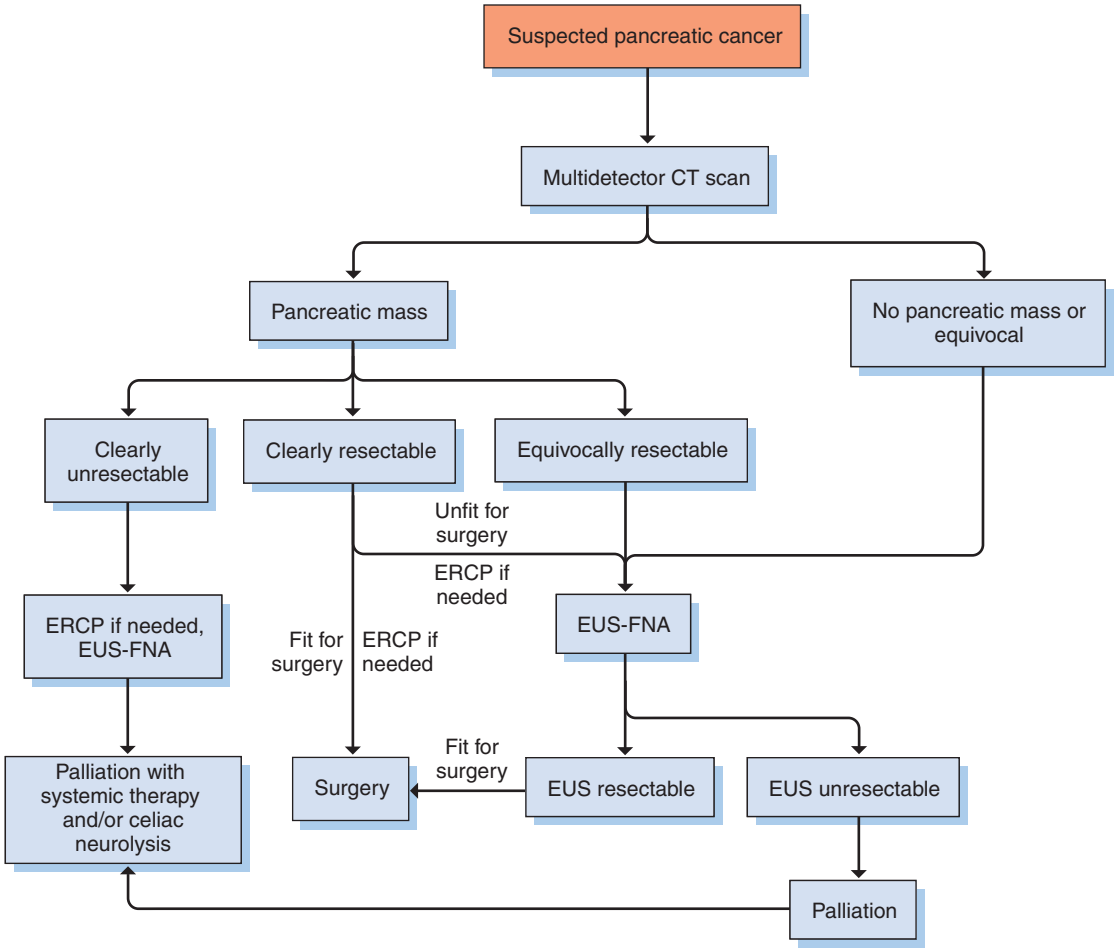


FIGURE 14.12 A proposed EUS-based management algorithm for suspected pancreatic cancer. CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; FNA, fine-needle aspiration.

endosonographically. However, this position is generally unstable, and the scope occasionally slips back into the stomach. Fine movements of the endoscope, maximal elevation of the distal tip, and insufflation of the balloon may help to keep this position.

Biopsy of uncinate lesions may also be accomplished by advancement of endoscope into a long position, which is obtained by pushing the scope into the apex of the duodenal bulb or proximal second portion. This position is more stable compared with the short position; however, needle advancement can be difficult. Once the lesion is visualized in either position, the scope tip is deflected upward against the lesion, and air is aspirated from the lumen to minimize the distance between the lesion and the scope tip. The shortest distance between the scope and the target lesion is always sought, to minimize the amount of normal tissue that the needle is required to traverse. Once in this position, it is still not uncommon to face difficulty passing the needle out of the channel because of the angulation. In this situation, the endosonographer may be required to reorient the endoscope within the stomach or duodenum and to deflect the tip of the scope downward. This reorientation may then permit gentle advancement of the needle out of the biopsy channel. Once the needle is outside the channel, the distal tip of the scope may then be deflected upward again to bring the lesion back into view. Finally, a 25-gauge needle may be helpful for biopsy of these lesions.

For biopsy of pancreatic tail lesions, the scope is typically in a short position with maximal upward deflection. If vascular structures are found between the transducer and the target lesion, slight reorientation of the scope tip position usually permits location of a safe site for biopsy without intervening vessels.

Since the first reported use of EUS FNA of a pancreatic mass was described by Vilmann et al[84] in 1992, multiple investigators have documented their experience of EUS FNA of pancreatic tumors[21,55,58,85–101] in more than 1700 patients (Table 14.8). The overall sensitivity and specificity of EUS FNA for the diagnosis of pancreatic tumors are 85% and 98%, respectively (Fig. 14.13). Some investigators have even reported a sensitivity of EUS FNA for pancreatic cancer exceeding 90% in patients following negative or nondiagnostic sampling from previous ERCP or a percutaneous approach.[92,94] Despite excellent sensitivity, the negative predictive value (NPV) of EUS FNA for pancreatic tumors is 55%.[21,85,87,90,91,94,97,100,101] Therefore, a negative or nondiagnostic biopsy result does not completely exclude the possibility of malignancy. Fritscher-Ravens et al[102] found that in a series of 207 consecutive patients with focal pancreatic lesions, the sensitivity of EUS FNA for the diagnosis of malignancy in patients with normal parenchyma (89%) was superior to that in patients with parenchymal evidence of chronic pancreatitis (54%). The presence of chronic pancreatitis may also hinder cytologic interpretation of pancreatic biopsy, thus decreasing sensitivity of EUS FNA of pancreatic masses.[103]

Because most studies document an overall sensitivity of EUS FNA for pancreatic tumors greater than 80%, most endosonographers should expect to eventually achieve this level of competency. At least 40 EUS FNA procedures are required for a novice endosonographer to achieve at least 80% sensitivity for the diagnosis of pancreatic cancer.[104] Short mentored training of EUS FNA appears to permit significant improvements in EUS FNA

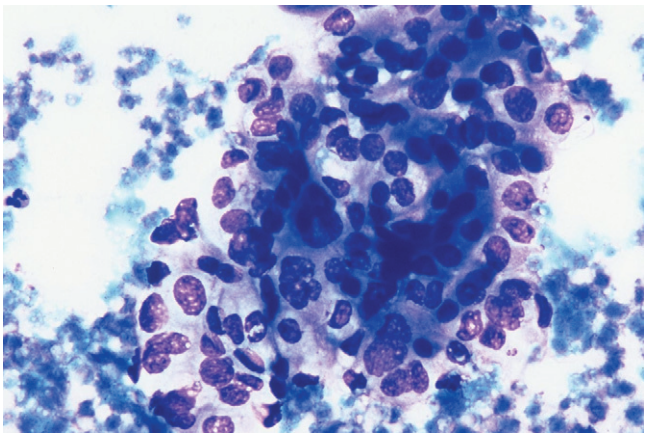


FIGURE 14.13 Cytology from EUS fine-needle aspiration in the same patient as in Figure 14.12. Pleomorphic, overlapping cells with an increased nuclear-to-cytoplasmic ratio are present consistent with adenocarcinoma (hematoxylin and eosin; 20×).

TABLE 14.8

Summary of Articles Summarizing the Test Characteristics of EUS Fine-Needle Aspiration of Pancreatic Cancer

Authors (yr)	Patients (*n*)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Giovannini et al[86] (1995)	43	75	—	—	—	—
Wegener et al[87] (1995)	11	44	100	100	29	55
Cahn et al[58] (1996)	50	85	100	—	—	—
Faigel et al[85] (1997)	45	94	100	—	82	—
Chang et al[89] (1997)	47	83	80	—	—	88
Bhutani et al[101] (1997)	47	64	100	100	16	—
Wiersema et al[98] (1997)	124	86	100	—	—	88
Gress et al[93] (1997)	121	80	100	—	—	85
Binmoeller et al[88] (1998)	45	76	100	—	—	—
Hunerbein et al[95] (1998)	26	88	100	—	—	—
Fritscher-Ravens et al[91] (1999)	45	80	100	100	80	—
Williams et al[99] (1999)	144	82	100	—	—	85
Voss et al[97] (2000)	90	75	88	98	26	—
Gress et al[92] (2001)	102	93	100	—	—	—
Harewood et al[94] (2002)	185	94	—	96	63	92
Ylagan et al[100] (2002)	80	78	100	100	78	—
Raut et al[96] (2003)	233	91	100	—	—	92
Eloubeidi et al[90] (2003)	158	84	97	99	64	84
Agarwal et al[21] (2004)	81	89	100	100	56	90
Totals	1,677	85	98	98	55	88

NPV, negative predictive value; PPV, positive predictive value.

accuracy, principally by decreasing the number of inadequate specimens.[105] Current American Society of Gastrointestinal Endoscopy guidelines recommend that at least 25 supervised EUS FNA procedures be performed during monitored training to maximize proficiency. Training for EUS FNA is best accomplished by expert formal instruction in a high-volume referral practice.

At most tertiary referral centers, on-site cytopathology assistance is provided to offer immediate feedback to the endosonographer about the quality of EUS FNA specimens obtained. On-site review correlates highly with the final diagnosis[106] and can both improve diagnostic certainty and minimize diagnostic uncertainty.[107] Two studies[108,109] reported that at least five to seven EUS FNA passes for pancreatic masses should be performed to maximize diagnostic yield. This information may prove helpful to endosonographers performing EUS FNA when rapid pathology interpretation is not available. We recommend that hospital and personnel resources be used when feasible to provide on-site pathology interpretation. Occasionally, on-site cytology review of a suspected pancreatic cancer demonstrates insufficient tissue to confirm malignancy. Possible reasons are tumor necrosis (particularly seen with larger tumors), fibrosis, or hypervascularity. Yield may be increased by "fanning the lesion," by using different angles of scope deflection to sample the peripheral parts of the lesion. Increasing the number of passes may also overcome this problem, but it may increase the amount of blood in the sample. In this situation, avoiding suction and switching to a smaller-gauge needle may help to limit the amount of blood in the specimen. Finally, EUS TCB may be considered in these cases.

The most commonly used commercially available EUS FNA needle sizes are 19, 22, and 25 gauge. Two studies evaluated the use of 22-gauge compared with 25-gauge needles. Lee et al[110] reported no difference in cellular yield or the ability of the blinded cytopathologists to render a diagnosis in the two groups. In a prospective randomized trial, Siddiqui et al[111] found similar diagnostic yield using the same number of passes with 67 patients in each group.

Major complications following EUS FNA of solid pancreatic masses occur in 0.5% to 2.5% of patients.[90,93,98,112–114] Because of this exceedingly small risk, antibiotics are not usually required following EUS FNA of solid lesions. Gress et al[93] reported a 1.2% (2 out of 121) risk of pancreatitis and a 1% (1 out of 121) risk of severe bleeding following EUS FNA of solid pancreatic masses. Another prospective trial[113] reported that 2 out of 100 (2%) of patients developed acute pancreatitis following EUS FNA of a pancreatic mass; both these patients had a history of recent pancreatitis. Therefore, caution should be exercised when EUS FNA is performed in these patients. Following EUS FNA of the pancreas, Eloubeidi et al[90] reported self-limited immediate postprocedure complications in 10 out of 158 (6.3%) patients including hypoxia, abdominal pain, excessive but inconsequential bleeding at the biopsy site, and sore throat. During the first 3 days after the procedure, 20 out of 78 patients contacted reported at least one minor symptom. One patient had mild acute pancreatitis. Two patients had emergency room visits, and one of them was admitted with dehydration.

In another prospective study, Al-Haddad et al[112] reported no delayed complications following EUS FNA of 127 patients with solid pancreatic masses who were followed up for 30 days. In a series of 248 patients, including 134 patients who underwent EUS FNA of solid lesions, O'Toole et al[114] reported a rate of complications of 0 out of 134 (0%). The risk of peritoneal seeding of tumor cells following EUS FNA (2.2%) appears to be less than with CT-guided FNA (16.3%).[115]

To date, no large prospective trials have compared the accuracy of EUS FNA with that of percutaneous FNA of pancreatic masses. Qian and Hecht[116] reported that CT FNA was superior to EUS FNA of pancreatic masses. However, Mallery et al[117] found no significant difference in accuracy between surgically directed CT FNA and EUS FNA of pancreatic masses. Nevertheless, the results of those two studies are difficult to generalize because of selection bias, in that tumors sampled by EUS FNA were more difficult compared with those imaged by CT or other imaging studies. It appears that percutaneous FNA is an acceptable option for sampling of pancreatic tumors that are visible, accessible, and clearly inoperable based on imaging findings. For all other lesions, EUS FNA is preferable to percutaneous FNA. Furthermore, the initial use of EUS and of EUS FNA appears to be a more cost-effective strategy for the initial workup of patients with suspected pancreatic malignancy.[118,119]

Despite excellent accuracy and a low incidence of major complications, EUS FNA of pancreatic masses has several limitations. First, an on-site cytopathologist during EUS FNA is recommended for assessment of specimen adequacy. Second, PPLs and well-differentiated ductal adenocarcinomas are often difficult to diagnose by use of cytologic features alone. Finally, the low NPV of EUS FNA does not permit exclusion of malignancy in negative specimens. To overcome these limitations, a spring-loaded 19-gauge Tru-Cut core biopsy needle (QuickCore; Wilson-Cook, Winston-Salem, NC) was developed to obtain histologic tissue samples using a standard linear array echoendoscope.[120] Larghi et al[121] reported an overall success rate of 74% in obtaining pancreatic tissue using EUS TCB in 23 consecutive patients with solid pancreatic masses. When a transduodenal was used, the success rate decreased from 100% to 41% compared with the transgastric approach. These investigators reported that transduodenal biopsy was difficult when the required upward deflection of the echoendoscope to bring the target lesion into appropriate position precluded extension of the needle from the accessory channel.

Another study, by Varadarajulu et al,[122] compared EUS TCB with EUS FNA for multiple sites and found no difference in diagnostic accuracy between the two devices. A more recent large series of 113 patients undergoing pancreatic EUS TCB included lesions in the pancreatic head, neck, body, and tail.[123] Overall, 90 of 113 (80%) patients were eventually diagnosed as having malignant lesions. The sensitivity and diagnostic accuracy of EUS TCB were 62% and 68%, respectively. No significant difference was found in diagnostic yield for lesions in the pancreatic head or uncinate process compared with the neck, body, or tail.

The use of TCB is recommended in certain situations in which studies have demonstrated better diagnostic yield, including AIP[36] and lymphoma.[124] In addition, TCB could be used as a rescue technique when on-site FNA results are inconclusive or when this service is not available.

Some investigators evaluated whether analysis of abnormal genes increased the diagnostic yield of EUS FNA of pancreatic masses (Table 14.9).[125–131] Tada et al[131] quantitatively analyzed mutant K-*ras* gene expression from EUS FNA specimens in 34 patients with adenocarcinoma ($n = 26$) and chronic pancreatitis ($n = 8$). Mutant gene was detected at high amounts (>2% of total *ras* genes) in 20 of 26 (77%) specimens. In contrast, mutant gene was absent or present at low levels despite suspicious cytologic findings in patients with benign pancreatic lesions. A larger series, by Maluf-Filho et al,[128] described a nonsignificant increase in the overall diagnostic accuracy from 59% to 89% when K-*ras* analysis was added to cytopathology in 74 patients with pancreatic cancer. The addition of other somatic mutations such as p53 and p16 to K-*ras* was shown to increase the sensitivity of cancer detection to 100% when FNA results were inconclusive.[130] Because of the relative high diagnostic accuracy of standard EUS FNA, as well as the relatively high cost and limited availability of these genetic tests, it appears that use of genetic testing of EUS FNA samples should be limited to research protocols and diagnostically inconclusive specimens.

TABLE 14.9

Summary of Studies Describing the Role of Genetic Markers in the Diagnosis of Pancreatic Cancer

Authors (yr)	Patients (*n*)	Lesion	Technique	Target
Tada et al[131] (2002)	34	PDC, CP	PCR	K-*ras*
Itoi et al[125] (2005)	62	PDC, CP	IHC	P53 protein
Kitoh et al[126] (2005)	17	PDC	PCR	PDC-associated genes
Mishra et al[129] (2006)	70	PDC, cysts	PCR	Telomerase
Laurell et al[127] (2006)	12	PDC, normal pancreas	RT-PCR	PDC-associated genes
Maluf-Filho et al[128] (2007)	74	PDC, CP, NET	PCR	K-*ras*
Salek et al[130] (2007)	101	PDC, CP	CGCE, SSCP	K-*ras*, p53, and p16 proteins

CGCE, cycling-gradient capillary electrophoresis; CP, chronic pancreatitis; IHC, immunohistochemical analysis; NET, neuroendocrine tumor; PCR, polymerase chain reaction; PDC, pancreatic ductal carcinoma; RT-PCR, real-time polymerase chain reaction; SSCP, single-strand conformation polymorphism.

PANCREATIC NEUROENDOCRINE TUMORS

Pancreatic neuroendocrine tumors (PNETs) represent less than 10% of pancreatic tumors. These rare neoplasms have an overall prevalence of 10 per 1 million.[132] Approximately one third of these tumors are classified as functional PNETs (FPNETs) in which excessive tumor hormone production produces a distinct clinical syndrome. The two most clinically important FPNETs are gastrinomas and insulinomas. When a distinct series of symptoms is present (i.e., refractory hypoglycemia for insulinoma or abdominal pain, diarrhea, and peptic ulcer disease for gastrinoma) and imaging reveals a pancreatic mass, the clinical suspicion of PNET is relatively straightforward. Excessive secretory products are then measured to confirm the suspected diagnosis. When PNETs do not produce a clinical syndrome, they are classified as nonfunctional (NFPNETs).[133] Because of a lack of characteristic symptoms related to hormone excess, NFPNETs are usually recognized later, with larger tumors, and they produce nonspecific symptoms such as jaundice, weight loss, abdominal pain, or pancreatitis.[134,135]

Differentiation between benign and malignant PNETs is difficult based on surgical pathology alone.[136] Therefore, malignancy is usually confirmed by the presence of distant metastases, and benign disease is confirmed by clinical follow-up.[137] As with primary ductal adenocarcinoma, surgical resection is the only cure for these tumors.[138,139] Therefore, a high index of suspicion coupled with a stepwise preoperative evaluation for localization may optimize patient selection for potentially curative surgery.

In a series of studies that compared EUS with other imaging modalities (Table 14.10), the sensitivity of EUS for detection of PNETs was 77% to 94% (Fig. 14.14).[140–147] EUS appears especially useful for detection of small PNETs (<2.5 cm) missed by other imaging studies (Fig. 14.15). The sensitivity of transabdominal ultrasound detection of PNETs is between 7% and 29%.[141,144,147] Similarly, early studies with CT demonstrated poor detection, with reported sensitivities of 14% to 30%.[141,144,147] Gouya et al[145] studied a cohort of 30 patients with 32 insulinomas over 13 years. The sensitivity of EUS was 94% compared with 29% for nonhelical CT and 57% for dual-phase MDCT. Early studies that compared EUS with MRI[144,147] demonstrated a sensitivity of 25% to 29% for MRI. More recent studies, however, demonstrated a sensitivity of 85% to 100%[148,149] and a PPV of 96%[150] for PNET detection. Because PNETs are hypervascular tumors, angiography sometimes demonstrates a "blushing" pattern in the pancreas in suspected PNET. The sensitivity of diagnostic angiography for tumor detection is less than 30%.[140,144]

The clinical utility of somatostatin receptor scintigraphy (SRS) for identification of insulinomas is limited, with sensitivities ranging from 14% to 60%.[144,146,147] For other PNETs, SRS has a reported sensitivity of up to 58% to 86% for tumor detection.[147,151,152] Proye et al[146] found that for a series of patients with histologically proven insulinoma ($n = 20$) or gastrinoma ($n = 21$), the sensitivity and PPV of EUS were 77% and 94%, respectively, for pancreatic tumors. For the same patients, the sensitivity and PPV of SRS for insulinoma and gastrinoma were 60% and 100% and 25% and 100%, respectively. When both tests were combined for patients with insulinoma ($n = 9$) and for those with gastrinoma ($n = 14$), the overall sensitivity of combined EUS and SRS was 89% and 93%, respectively. It appears that the combination of EUS and SRS may optimize preoperative identification of PNETs and limit the need for more invasive tests such as angiography. As with pancreatic adenocarcinoma,[118,119] the early incorporation of EUS into the preoperative localization of PNETs appears to be cost effective, principally by decreasing the need for more invasive tests and their associated morbidity.[153]

The use of EUS FNA permits tissue confirmation of suspected primary or metastatic PNETs (Figs. 14.16 to 14.18). In a retrospective study of 30 patients, Ardengh et al[154] reported sensitivity, specificity, PPV, NPV, and accuracy of EUS-guided FNA of 82.6%, 85.7%, 95%, 60%, and 83.3%, respectively, for tumor diagnosis. Ginès et al[155] demonstrated a sensitivity of 90% for EUS FNA of 10 patients with FPNETs with a mean tumor size of 12 mm. These studies showed that EUS may not only identify but also accurately sample PNETs. The advent of immunohistochemistry facilitated the diagnosis of neuroendocrine tumors.[156–159] For example, neuron-specific enolase, synaptophysin, and chromogranin A were found to have sensitivity and specificity exceeding 90%. Such high accuracy makes immunohistochemistry invaluable if adequate tissue is available.

Preoperative EUS-guided injection of India ink has been demonstrated to aid in intraoperative localization of insulinoma.[160] This information may confirm clinically suspected tumors and help in appropriate planning of medical or surgical management. Commercial assays allow genetic markers to be reliably assessed on FNA specimens. A study of 29 patients with PNETs who were followed up for an average of 33 months showed that the presence of allelic microsatellite loss was associated with increased PNET recurrence, progression, and mortality.[161]

PANCREATIC METASTASES

Isolated pancreatic masses usually represent either focal chronic pancreatitis or benign or malignant primary pancreatic tumors. Rarely, secondary involvement of the pancreas by systemic malignant disease may occur and has been reported in 2% to 3% of pancreatic resections.[162–164] Accurate identification of isolated pancreatic metastases is clinically important because aggressive surgical resection in selected patients may permit long-term survival.[165–167] In other patients, however, proper diagnosis may avoid unnecessary surgery and may permit triage to more appropriate nonoperative therapy.

TABLE 14.10

Comparison of EUS with Computed Tomography, Ultrasound, Magnetic Resonance Imaging, Somatostatin Receptor Scintigraphy, and Angiography for Evaluation of Pancreatic Neuroendocrine Tumors

Authors (yr)	Patients (*n*)	Tumor (*n*)	Test	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Rosch et al[140] (1992)	37	Insulinoma (31)	EUS	82	95	—	—	—
		Gastrinoma (7)	CT	0				
		Glucagonoma (1)	US	0				
			Angiography	27				
Palazzo et al[141] (1993)	30	Insulinoma (13)	EUS	79	—	—	—	—
			CT	14				
			US	7				
		Gastrinoma (17)	EUS	79				
Zimmer et al[147] (1996)	20	Gastrinoma (10)	EUS	79	—	—	—	—
			CT	29				
			MRI	29				
			US	29				
			SRS	86				
		Insulinoma (10)	EUS	93				
			CT	21				
			MRI	7				
			US	7				
			SRS	14				
Proye et al[146]* (1998)	41	All PNETs	EUS	77	—	94	—	—
		Insulinoma (20)	SRS	60		100		
		Gastrinoma (21)	SRS	25		100		
		Insulinoma (9)	EUS+S	89				
		Gastrinoma (14)	RS	93				
De Angelis et al[144] (1999)	23	Insulinoma (12)	EUS	87	—	—	—	—
			CT	30				
			MRI	25				
			US	17				
			SRS	15				
			Angiography	27				
Ardengh et al[143] (2000)	12	Insulinoma (12)	EUS	83	—	—	—	—
			CT	17				
Anderson et al[142] (2000)	75	Gastrinoma (36)	EUS	100	94	95	100	97
	14	Insulinoma (36)	EUS	88	100	100	43	89
			Angiography	44				
Gouya et al[145†] (2003)	38	Insulinoma (38)	EUS	94	—	—	—	—
			CT	29-94				

*Overall sensitivity of combined EUS and SRS was 89% for insulinoma (n = 9) and 93% for gastrinoma (n = 14).
†Sensitivity of CT for nonhelical CT, thick section MDCT, and thin section MDCT were 29%, 57% and 94%, respectively.
CT, computed tomography; MRI, magnetic resonance imaging; PNET, pancreatic neuroendocrine tumor; SRS, somatostatin receptor scintigraphy; US, ultrasound.

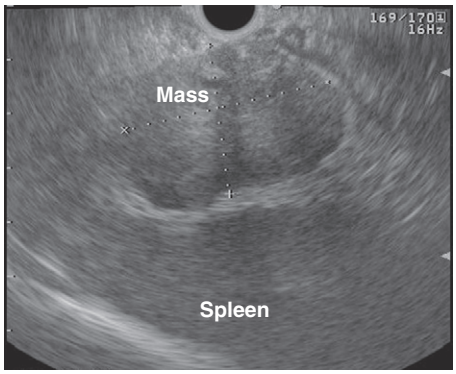


FIGURE 14.14 Linear EUS image (6.0 MHz) of a 4.5-cm well-defined hypoechoic mass in the tail of the pancreas. This patient was asymptomatic.

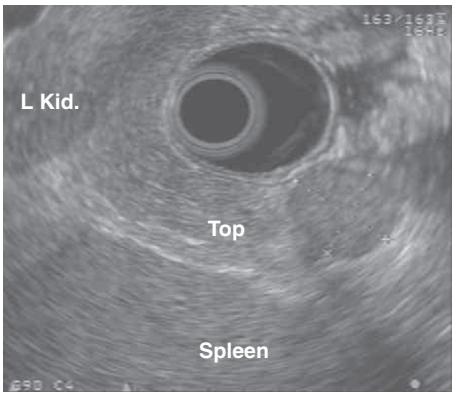


FIGURE 14.15 One subcentimeter hypoechoic pancreatic tail mass in a patient with multiple endocrine neoplasia type 1 (MEN-1). Computed tomography of the pancreas demonstrated no masses in the pancreas. L Kid., left kidney.

EUS features of pancreatic metastases appear to be different from features observed in primary pancreatic cancer. In seven patients with metastatic pancreatic lesions, Palazzo et al[168] described homogeneous, round, well-circumscribed lesions in 15 out of 16 masses observed. Compared with patients with primary cancer (n = 80), DeWitt et al[169] found that pancreatic metastases (n = 24) were more likely to have well-defined rather than irregular margins. In a report of 11 patients with renal cell carcinoma (RCC) metastatic to the pancreas, Bechade et al[170] found that 10 patients' tumors had well-defined borders.

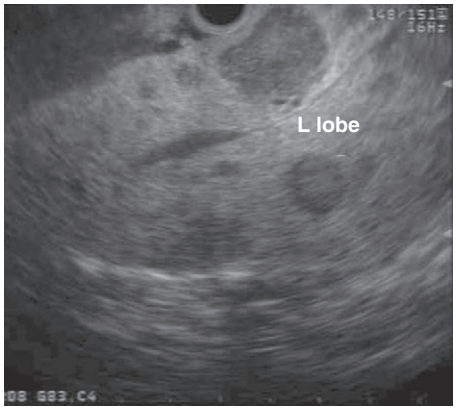


FIGURE 14.16 Examination of the liver in the patient in Figure 14.14 demonstrated multiple hypoechoic masses in the left lobe (L lobe) of the liver that suggested metastases.

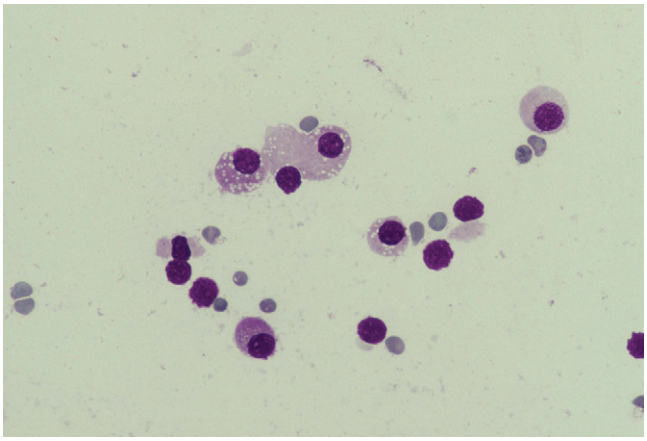


FIGURE 14.18 Cytology from the EUS fine-needle aspiration demonstrating plasmacytoid cells with eccentric nuclei consistent with a metastatic neuroendocrine tumor. Because the patient was without symptoms, this tumor was classified as a nonfunctional pancreatic neuroendocrine tumor with liver metastases.

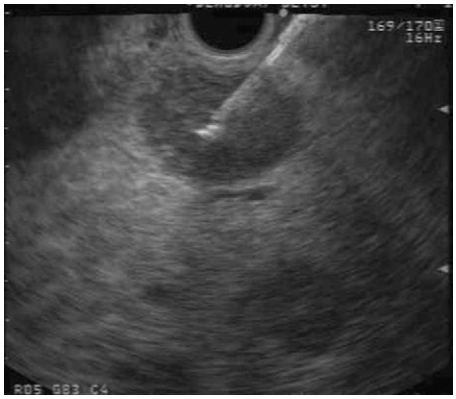


FIGURE 14.17 EUS fine-needle aspiration of one of the hypoechoic masses seen in the left lobe of liver in the patient in Figure 14.14.

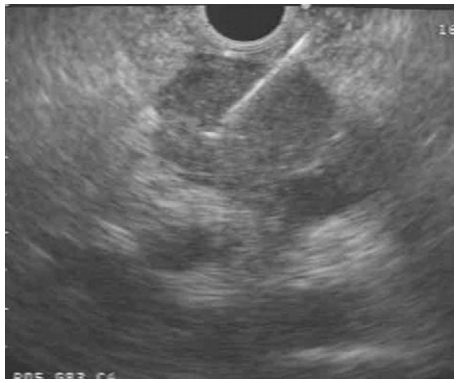


FIGURE 14.19 EUS fine-needle aspiration of a well-defined, hypoechoic 1.5-cm mass in the head of the pancreas. This patient had a remote history of renal cell carcinoma removed 12 years earlier.

Therefore, it appears that EUS visualization of a well-defined pancreatic mass in a patient with a history of malignancy should raise suspicion of a metastatic lesion.

EUS FNA permits an accurate cytologic diagnosis of metastatic lesions to the pancreas (Figs. 14.19 and 14.20; Video 14.1). In a series of 12 patients, Fritscher-Ravens et al[171] reported metastatic lesions from primary RCC ($n = 3$), breast cancer ($n = 2$), esophageal cancer ($n = 2$), colon cancer ($n = 2$), non–small cell lung cancer ($n = 1$), non-Hodgkin lymphoma ($n = 1$), and ovarian cancer ($n = 1$). DeWitt et al[169] reported the use of EUS FNA for the diagnosis of metastasis from primary kidney ($n = 10$), skin ($n = 6$), lung ($n = 4$), colon ($n = 2$), liver ($n = 1$), and stomach ($n = 1$) cancer in 24 patients. Metastasis to the pancreas may occur many years (especially for RCC) after diagnosis of the primary tumor. Obtaining a detailed medical history of previous malignancy may raise the suspicion of this diagnosis. In patients with a remote history of malignant disease, obtaining of additional cytologic material for cell block and the use of immunocytochemistry may be helpful to confirm the diagnosis of pancreatic metastases and recurrent malignancy.[169]

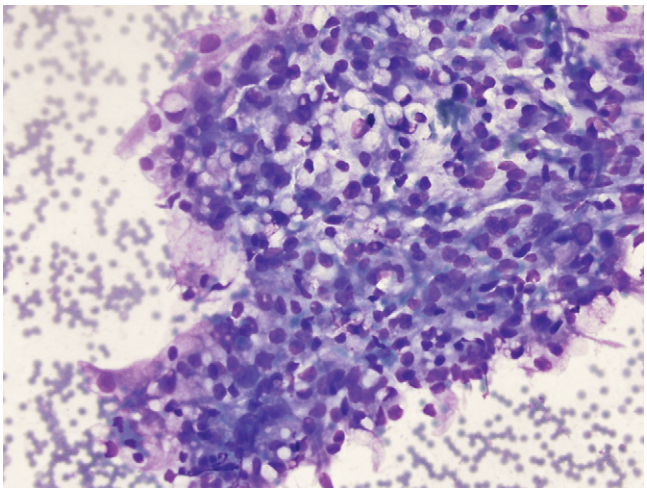


FIGURE 14.20 Cytology from EUS fine-needle aspiration in the same patient as in Figure 14.19 demonstrating clear cells consistent with metastatic, recurrent renal cell carcinoma. These findings were confirmed by surgical resection.

REFERENCES

1. Yasuda K, Mukai H, Fujimoto S, et al. The diagnosis of pancreatic cancer by endoscopic ultrasonography. *Gastrointest Endosc*. 1988;34:1–8.
2. Lin JT, Wang JT, Wang TH. The diagnostic value of endoscopic ultrasonography in pancreatic disorders. *Taiwan Yi Xue Hui Za Zhi*. 1989;88: 483–487.
3. Rosch T, Lorenz R, Braig C, et al. Endoscopic ultrasound in pancreatic tumor diagnosis. *Gastrointest Endosc*. 1991;37:347–352.
4. Rosch T, Braig C, Gain T, et al. Staging of pancreatic and ampullary carcinoma by endoscopic ultrasonography: comparison with conventional sonography, computed tomography, and angiography. *Gastroenterology*. 1992;102:188–199.
5. Snady H, Cooperman A, Siegel J. Endoscopic ultrasonography compared with computed tomography with ERCP in patients with obstructive jaundice or small peri-pancreatic mass. *Gastrointest Endosc*. 1992;38: 27–34.
6. Palazzo L, Roseau G, Gayet B, et al. Endoscopic ultrasonography in the diagnosis and staging of pancreatic adenocarcinoma: results of a prospective study with comparison to ultrasonography and CT scan. *Endoscopy*. 1993;25:143–150.
7. Muller MF, Meyenberger C, Bertschinger P, et al. Pancreatic tumors: evaluation with endoscopic US, CT, and MR imaging. *Radiology*. 1994;190: 745–751.
8. Marty O, Aubertin JM, Bouillot JL, et al. [Prospective comparison of ultrasound endoscopy and computed tomography in the assessment of locoregional invasiveness of malignant ampullar and pancreatic tumors verified surgically]. *Gastroenterol Clin Biol*. 1995;19:197–203.
9. Melzer E, Avidan B, Heyman Z, et al. Preoperative assessment of blood vessel involvement in patients with pancreatic cancer. *Isr J Med Sci*. 1996;32:1086–1088.
10. Dufour B, Zins M, Vilgrain V, et al. [Comparison between spiral x-ray computed tomography and endosonography in the diagnosis and staging of adenocarcinoma of the pancreas: clinical preliminary study]. *Gastroenterol Clin Biol*. 1997;21:124–130.
11. Howard TJ, Chin AC, Streib EW, et al. Value of helical computed tomography, angiography, and endoscopic ultrasound in determining resectability of periampullary carcinoma. *Am J Surg*. 1997;174:237–241.
12. Sugiyama M, Hagi H, Atomi Y, Saito M. Diagnosis of portal venous invasion by pancreatobiliary carcinoma: value of endoscopic ultrasonography. *Abdom Imaging*. 1997;22:434–438.
13. Legmann P, Vignaux O, Dousset B, et al. Pancreatic tumors: comparison of dual-phase helical CT and endoscopic sonography. *AJR Am J Roentgenol*. 1998;170:1315–1322.
14. Akahoshi K, Chijiiwa Y, Nakano I, et al. Diagnosis and staging of pancreatic cancer by endoscopic ultrasound. *Br J Radiol*. 1998;71:492–496.
15. Harrison JL, Millikan KW, Prinz RA, Zaidi S. Endoscopic ultrasound for diagnosis and staging of pancreatic tumors. *Am Surg*. 1999;65:659–664; discussion 664–655.
16. Gress FG, Hawes RH, Savides TJ, et al. Role of EUS in the preoperative staging of pancreatic cancer: a large single-center experience. *Gastrointest Endosc*. 1999;50:786–791.
17. Midwinter MJ, Beveridge CJ, Wilsdon JB, et al. Correlation between spiral computed tomography, endoscopic ultrasonography and findings at operation in pancreatic and ampullary tumours. *Br J Surg*. 1999;86: 189–193.
18. Mertz HR, Sechopoulos P, Delbeke D, Leach SD. EUS, PET, and CT scanning for evaluation of pancreatic adenocarcinoma. *Gastrointest Endosc*. 2000;52:367–371.
19. Rivadeneira DE, Pochapin M, Grobmyer SR, et al. Comparison of linear array endoscopic ultrasound and helical computed tomography for the staging of periampullary malignancies. *Ann Surg Oncol*. 2003;10: 890–897.
20. Ainsworth AP, Rafaelsen SR, Wamberg PA, et al. Is there a difference in diagnostic accuracy and clinical impact between endoscopic ultrasonography and magnetic resonance cholangiopancreatography? *Endoscopy*. 2003;35:1029–1032.
21. Agarwal B, Abu-Hamda E, Molke KL, et al. Endoscopic ultrasound-guided fine needle aspiration and multidetector spiral CT in the diagnosis of pancreatic cancer. *Am J Gastroenterol*. 2004;99:844–850.
22. DeWitt J, Devereaux B, Chriswell M, et al. Comparison of endoscopic ultrasonography and multidetector computed tomography for detecting and staging pancreatic cancer. *Ann Intern Med*. 2004;141:753–763.
23. Fisher L, Segarajasingam DS, Stewart C, et al. Endoscopic ultrasound guided fine needle aspiration of solid pancreatic lesions: performance and outcomes. *J Gastroenterol Hepatol*. 2009;24:90–96.
24. Rafique A, Freeman S, Carroll N. A clinical algorithm for the assessment of pancreatic lesions: utilization of 16- and 64-section multidetector CT and endoscopic ultrasound. *Clin Radiol*. 2007;62:1142–1153.
25. Prokesch RW, Schima W, Chow LC, Jeffrey RB. Multidetector CT of pancreatic adenocarcinoma: diagnostic advances and therapeutic relevance. *Eur Radiol*. 2003;13:2147–2154.
26. Bronstein YL, Loyer EM, Kaur H, et al. Detection of small pancreatic tumors with multiphasic helical CT. *AJR Am J Roentgenol*. 2004;182:619–623.
27. Catanzaro A, Richardson S, Veloso H, et al. Long-term follow-up of patients with clinically indeterminate suspicion of pancreatic cancer and normal EUS. *Gastrointest Endosc*. 2003;58:836–840.
28. Brentnall TA, Bronner MP, Byrd DR, et al. Early diagnosis and treatment of pancreatic dysplasia in patients with a family history of pancreatic cancer. *Ann Intern Med*. 1999;131:247–255.
29. Rulyak SJ, Kimmey MB, Veenstra DL, Brentnall TA. Cost-effectiveness of pancreatic cancer screening in familial pancreatic cancer kindreds. *Gastrointest Endosc*. 2003;57:23–29.
30. Canto MI, Goggins M, Yeo CJ, et al. Screening for pancreatic neoplasia in high-risk individuals: an EUS-based approach. *Clin Gastroenterol Hepatol*. 2004;2:606–621.
31. Langer P, Kann PH, Fendrich V, et al. Five years of prospective screening of high-risk individuals from families with familial pancreatic cancer. *Gut*. 2009;58:1410–1418.
32. Poley JW, Kluijt I, Gouma DJ, et al. The yield of first-time endoscopic ultrasonography in screening individuals at a high risk of developing pancreatic cancer. *Am J Gastroenterol*. 2009;104:2175–2181.
33. Farrell JJ, Garber J, Sahani D, Brugge WR. EUS findings in patients with autoimmune pancreatitis. *Gastrointest Endosc*. 2004;60:927–936.
34. Raina A, Yadav D, Krasinskas AM, et al. Evaluation and management of autoimmune pancreatitis: experience at a large US center. *Am J Gastroenterol*. 2009;104:2295–2306.
35. Hoki N, Mizuno N, Sawaki A, et al. Diagnosis of autoimmune pancreatitis using endoscopic ultrasonography. *J Gastroenterol*. 2009;44:154–159.
36. Levy MJ, Reddy RP, Wiersema MJ, et al. EUS-guided Trucut biopsy in establishing autoimmune pancreatitis as the cause of obstructive jaundice. *Gastrointest Endosc*. 2005;61:467–472.
37. Khashab M, Mokadem M, DeWitt J, et al. Endoscopic ultrasound-guided fine-needle aspiration with or without flow cytometry for the diagnosis of primary pancreatic lymphoma: a case series. *Endoscopy*. 2010;42: 228–231.
38. Dietrich CF, Ignee A, Braden B, et al. Improved differentiation of pancreatic tumors using contrast-enhanced endoscopic ultrasound. *Clin Gastroenterol Hepatol*. 2008;6:590–597.
39. Becker D, Strobel D, Bernatik T, Hahn EG. Echo-enhanced color- and power-Doppler EUS for the discrimination between focal pancreatitis and pancreatic carcinoma. *Gastrointest Endosc*. 2001;53:784–789.
40. Hocke M, Schulze E, Gottschalk P, et al. Contrast-enhanced endoscopic ultrasound in discrimination between focal pancreatitis and pancreatic cancer. *World J Gastroenterol*. 2006;12:246–250.
41. Ahmad NA, Lewis JD, Siegelman ES, et al. Role of endoscopic ultrasound and magnetic resonance imaging in the preoperative staging of pancreatic adenocarcinoma. *Am J Gastroenterol*. 2000;95:1926–1931.
42. Buscail L, Pages P, Berthelemy P, et al. Role of EUS in the management of pancreatic and ampullary carcinoma: a prospective study assessing resectability and prognosis. *Gastrointest Endosc*. 1999;50:34–40.
43. Giovannini M, Seitz JF. Endoscopic ultrasonography with a linear-type echoendoscope in the evaluation of 94 patients with pancreatobiliary disease. *Endoscopy*. 1994;26:579–585.
44. Grimm H, Maydeo A, Soehendra N. Endoluminal ultrasound for the diagnosis and staging of pancreatic cancer. *Baillieres Clin Gastroenterol*. 1990;4:869–888.
45. Mukai H, Nakajima M, Yasuda K, et al. [Preoperative diagnosis and staging of pancreatic cancer by endoscopic ultrasonography (EUS): a comparative study with other diagnostic tools]. *Nippon Shokakibyo Gakkai Zasshi*. 1991;88:2132–2142.
46. Ramsay D, Marshall M, Song S, et al. Identification and staging of pancreatic tumours using computed tomography, endoscopic ultrasound and mangafodipir trisodium-enhanced magnetic resonance imaging. *Australas Radiol*. 2004;48:154–161.
47. Rosch T, Dittler HJ, Lorenz R, et al. [The endosonographic staging of pancreatic carcinoma]. *Dtsch Med Wochenschr*. 1992;117:563–569.
48. Soriano A, Castells A, Ayuso C, et al. Preoperative staging and tumor resectability assessment of pancreatic cancer: prospective study comparing endoscopic ultrasonography, helical computed tomography, magnetic resonance imaging, and angiography. *Am J Gastroenterol*. 2004;99:492–501.
49. Tio TL, Sie LH, Kallimanis G, et al. Staging of ampullary and pancreatic carcinoma: comparison between endosonography and surgery. *Gastrointest Endosc*. 1996;44:706–713.
50. Tio TL, Tytgat GN, Cikot RJ, et al. Ampullopancreatic carcinoma: preoperative TNM classification with endosonography. *Radiology*. 1990;175: 455–461.

51. Yasuda K, Mukai H, Nakajima M, Kawai K. Staging of pancreatic carcinoma by endoscopic ultrasonography. *Endoscopy*. 1993;25:151–155.
52. Howard TJ, Villanustre N, Moore SA, et al. Efficacy of venous reconstruction in patients with adenocarcinoma of the pancreatic head. *J Gastrointest Surg*. 2003;7:1089–1095.
53. Al-Haddad M, Martin JK, Nguyen J, et al. Vascular resection and reconstruction for pancreatic malignancy: a single center survival study. *J Gastrointest Surg*. 2007;11:1168–1174.
54. Ahmad NA, Lewis JD, Ginsberg GG, et al. EUS in preoperative staging of pancreatic cancer. *Gastrointest Endosc*. 2000;52:463–468.
55. Bhutani MS, Hawes RH, Hoffman BJ. A comparison of the accuracy of echo features during endoscopic ultrasound (EUS) and EUS-guided fine-needle aspiration for diagnosis of malignant lymph node invasion. *Gastrointest Endosc*. 1997;45:474–479.
56. Catalano MF, Sivak Jr MV, Rice T, et al. Endosonographic features predictive of lymph node metastasis. *Gastrointest Endosc*. 1994;40:442–446.
57. Nakaizumi A, Uehara H, Iishi H, et al. Endoscopic ultrasonography in diagnosis and staging of pancreatic cancer. *Dig Dis Sci*. 1995;40:696–700.
58. Cahn M, Chang K, Nguyen P, Butler J. Impact of endoscopic ultrasound with fine-needle aspiration on the surgical management of pancreatic cancer. *Am J Surg*. 1996;172:470–472.
59. Hahn M, Faigel DO. Frequency of mediastinal lymph node metastases in patients undergoing EUS evaluation of pancreaticobiliary masses. *Gastrointest Endosc*. 2001;54:331–335.
60. Nguyen P, Feng JC, Chang KJ. Endoscopic ultrasound (EUS) and EUS-guided fine-needle aspiration (FNA) of liver lesions. *Gastrointest Endosc*. 1999;50:357–361.
61. tenBerge J, Hoffman BJ, Hawes RH, et al. EUS-guided fine needle aspiration of the liver: indications, yield, and safety based on an international survey of 167 cases. *Gastrointest Endosc*. 2002;55:859–862.
62. Hollerbach S, Willert J, Topalidis T, et al. Endoscopic ultrasound-guided fine-needle aspiration biopsy of liver lesions: histological and cytological assessment. *Endoscopy*. 2003;35:743–749.
63. DeWitt J, LeBlanc J, McHenry L, et al. Endoscopic ultrasound-guided fine needle aspiration cytology of solid liver lesions: a large single-center experience. *Am J Gastroenterol*. 2003;98:1976–1981.
64. Chang KJ, Albers CG, Nguyen P. Endoscopic ultrasound-guided fine needle aspiration of pleural and ascitic fluid. *Am J Gastroenterol*. 1995;90: 148–150.
65. Nguyen PT, Chang KJ. EUS in the detection of ascites and EUS-guided paracentesis. *Gastrointest Endosc*. 2001;54:336–339.
66. DeWitt J, Yu M, Al-Haddad M, et al. Survival in patients with pancreatic cancer following the diagnosis of malignant ascites or liver metastases by EUS-FNA. *Gastrointest Endosc*. 2010;71:260–265.
67. Furukawa H, Kosuge T, Mukai K, et al. Helical computed tomography in the diagnosis of portal vein invasion by pancreatic head carcinoma: usefulness for selecting surgical procedures and predicting the outcome. *Arch Surg*. 1998;133:61–65.
68. Ishikawa O, Ohigashi H, Sasaki Y, et al. Intraoperative cytodiagnosis for detecting a minute invasion of the portal vein during pancreatoduodenectomy for adenocarcinoma of the pancreatic head. *Am J Surg*. 1998; 175:477–481.
69. Tierney WM, Francis IR, Eckhauser F, et al. The accuracy of EUS and helical CT in the assessment of vascular invasion by peripapillary malignancy. *Gastrointest Endosc*. 2001;53:182–188.
70. Brugge WR, Lee MJ, Kelsey PB, et al. The use of EUS to diagnose malignant portal venous system invasion by pancreatic cancer. *Gastrointest Endosc*. 1996;43:561–567.
71. Rosch T, Dittler HJ, Strobel K, et al. Endoscopic ultrasound criteria for vascular invasion in the staging of cancer of the head of the pancreas: a blind reevaluation of videotapes. *Gastrointest Endosc*. 2000;52:469–477.
72. Snady H, Bruckner H, Siegel J, et al. Endoscopic ultrasonographic criteria of vascular invasion by potentially resectable pancreatic tumors. *Gastrointest Endosc*. 1994;40:326–333.
73. Benassai G, Mastrorilli M, Quarto G, et al. Factors influencing survival after resection for ductal adenocarcinoma of the head of the pancreas. *J Surg Oncol*. 2000;73:212–218.
74. Richter A, Niedergethmann M, Sturm JW, et al. Long-term results of partial pancreaticoduodenectomy for ductal adenocarcinoma of the pancreatic head: 25-year experience. *World J Surg*. 2003;27:324–329.
75. Saez A, Catala I, Brossa R, et al. Intraoperative fine needle aspiration cytology of pancreatic lesions: a study of 90 cases. *Acta Cytol*. 1995;39: 485–488.
76. Schadt ME, Kline TS, Neal HS, et al. Intraoperative pancreatic fine needle aspiration biopsy: results in 166 patients. *Am Surg*. 1991;57:73–75.
77. Brandt KR, Charboneau JW, Stephens DH, et al. CT- and US-guided biopsy of the pancreas. *Radiology*. 1993;187:99–104.
78. Bret PM, Nicolet V, Labadie M. Percutaneous fine-needle aspiration biopsy of the pancreas. *Diagn Cytopathol*. 1986;2:221–227.
79. Di Stasi M, Lencioni R, Solmi L, et al. Ultrasound-guided fine needle biopsy of pancreatic masses: results of a multicenter study. *Am J Gastroenterol*. 1998;93:1329–1333.
80. Sperti C, Pasquali C, Di Prima F, et al. Percutaneous CT-guided fine needle aspiration cytology in the differential diagnosis of pancreatic lesions. *Ital J Gastroenterol*. 1994;26:126–131.
81. Caturelli E, Rapaccini GL, Anti M, Fabiano A, Fedeli G. Malignant seeding after fine-needle aspiration biopsy of the pancreas. *Diagn Imaging Clin Med*. 1985;54:88–91.
82. Ferrucci JT, Wittenberg J, Margolies MN, Carey RW. Malignant seeding of the tract after thin-needle aspiration biopsy. *Radiology*. 1979;130: 345–346.
83. Smith FP, Macdonald JS, Schein PS, Ornitz RD. Cutaneous seeding of pancreatic cancer by skinny-needle aspiration biopsy. *Arch Intern Med*. 1980;140:855.
84. Vilmann P, Jacobsen GK, Henriksen FW, Hancke S. Endoscopic ultrasonography with guided fine needle aspiration biopsy in pancreatic disease. *Gastrointest Endosc*. 1992;38:172–173.
85. Faigel DO, Ginsberg GG, Bentz JS, et al. Endoscopic ultrasound-guided real-time fine-needle aspiration biopsy of the pancreas in cancer patients with pancreatic lesions. *J Clin Oncol*. 1997;15:1439–1443.
86. Giovannini M, Seitz JF, Monges G, et al. Fine-needle aspiration cytology guided by endoscopic ultrasonography: results in 141 patients. *Endoscopy*. 1995;27:171–177.
87. Wegener M, Pfaffenbach B, Adamek RJ. Endosonographically guided transduodenal and transgastral fine-needle aspiration puncture of focal pancreatic lesions. *Bildgebung*. 1995;62:110–115.
88. Binmoeller KF, Thul R, Rathod V, et al. Endoscopic ultrasound-guided, 18-gauge, fine needle aspiration biopsy of the pancreas using a 2.8 mm channel convex array echoendoscope. *Gastrointest Endosc*. 1998;47: 121–127.
89. Chang KJ, Nguyen P, Erickson RA, et al. The clinical utility of endoscopic ultrasound-guided fine-needle aspiration in the diagnosis and staging of pancreatic carcinoma. *Gastrointest Endosc*. 1997;45:387–393.
90. Eloubeidi MA, Chen VK, Eltoum IA, et al. Endoscopic ultrasound-guided fine needle aspiration biopsy of patients with suspected pancreatic cancer: diagnostic accuracy and acute and 30-day complications. *Am J Gastroenterol*. 2003;98:2663–2668.
91. Fritscher-Ravens A, Schirrow L, Atay Z, et al. [Endosonographically controlled fine needle aspiration cytology: indications and results in routine diagnosis]. *Z Gastroenterol*. 1999;37:343–351.
92. Gress F, Gottlieb K, Sherman S, Lehman G. Endoscopic ultrasonography-guided fine-needle aspiration biopsy of suspected pancreatic cancer. *Ann Intern Med*. 2001;134:459–464.
93. Gress FG, Hawes RH, Savides TJ, et al. Endoscopic ultrasound-guided fine-needle aspiration biopsy using linear array and radial scanning endosonography. *Gastrointest Endosc*. 1997;45:243–250.
94. Harewood GC, Wiersema MJ. Endosonography-guided fine needle aspiration biopsy in the evaluation of pancreatic masses. *Am J Gastroenterol*. 2002;97:1386–1391.
95. Hunerbein M, Dohmoto M, Haensch W, Schlag PM. Endosonography-guided biopsy of mediastinal and pancreatic tumors. *Endoscopy*. 1998; 30:32–36.
96. Raut CP, Grau AM, Staerkel GA, et al. Diagnostic accuracy of endoscopic ultrasound-guided fine-needle aspiration in patients with presumed pancreatic cancer. *J Gastrointest Surg*. 2003;7:118–126; discussion 127–118.
97. Voss M, Hammel P, Molas G, et al. Value of endoscopic ultrasound guided fine needle aspiration biopsy in the diagnosis of solid pancreatic masses. *Gut*. 2000;46:244–249.
98. Wiersema MJ, Vilmann P, Giovannini M, et al. Endosonography-guided fine-needle aspiration biopsy: diagnostic accuracy and complication assessment. *Gastroenterology*. 1997;112:1087–1095.
99. Williams DB, Sahai AV, Aabakken L, et al. Endoscopic ultrasound guided fine needle aspiration biopsy: a large single centre experience. *Gut*. 1999; 44:720–726.
100. Ylagan LR, Edmundowicz S, Kasal K, et al. Endoscopic ultrasound guided fine-needle aspiration cytology of pancreatic carcinoma: a 3-year experience and review of the literature. *Cancer*. 2002;96:362–369.
101. Bhutani MS, Hawes RH, Baron PL, et al. Endoscopic ultrasound guided fine needle aspiration of malignant pancreatic lesions. *Endoscopy*. 1997; 29:854–858.
102. Fritscher-Ravens A, Brand L, Knofel WT, et al. Comparison of endoscopic ultrasound-guided fine needle aspiration for focal pancreatic lesions in patients with normal parenchyma and chronic pancreatitis. *Am J Gastroenterol*. 2002;97:2768–2775.
103. Schwartz DA, Unni KK, Levy MJ, et al. The rate of false-positive results with EUS-guided fine-needle aspiration. *Gastrointest Endosc*. 2002;56: 868–872.

104. Mertz H, Gautam S. The learning curve for EUS-guided FNA of pancreatic cancer. *Gastrointest Endosc*. 2004;59:33–37.
105. Harewood GC, Wiersema LM, Halling AC, et al. Influence of EUS training and pathology interpretation on accuracy of EUS-guided fine needle aspiration of pancreatic masses. *Gastrointest Endosc*. 2002;55:669–673.
106. Eloubeidi MA, Tamhane A, Jhala N, et al. Agreement between rapid onsite and final cytologic interpretations of EUS-guided FNA specimens: implications for the endosonographer and patient management. *Am J Gastroenterol*. 2006;101:2841–2847.
107. Klapman JB, Logrono R, Dye CE, Waxman I. Clinical impact of on-site cytopathology interpretation on endoscopic ultrasound-guided fine needle aspiration. *Am J Gastroenterol*. 2003;98:1289–1294.
108. Erickson RA, Sayage-Rabie L, Beissner RS. Factors predicting the number of EUS-guided fine-needle passes for diagnosis of pancreatic malignancies. *Gastrointest Endosc*. 2000;51:184–190.
109. LeBlanc JK, Ciaccia D, Al-Assi MT, et al. Optimal number of EUS-guided fine needle passes needed to obtain a correct diagnosis. *Gastrointest Endosc*. 2004;59:475–481.
110. Lee JH, Stewart J, Ross WA, et al. Blinded prospective comparison of the performance of 22-gauge and 25-gauge needles in endoscopic ultrasound-guided fine needle aspiration of the pancreas and peri-pancreatic lesions. *Dig Dis Sci*. 2009;54:2274–2281.
111. Siddiqui UD, Rossi F, Rosenthal LS, et al. Aslanian HR. EUS-guided FNA of solid pancreatic masses: a prospective, randomized trial comparing 22-gauge and 25-gauge needles. *Gastrointest Endosc*. 2009;70:1093–1097.
112. Al-Haddad M, Wallace MB, Woodward TA, et al. The safety of fine-needle aspiration guided by endoscopic ultrasound: a prospective study. *Endoscopy*. 2008;40:204–208.
113. Gress F, Michael H, Gelrud D, et al. EUS-guided fine-needle aspiration of the pancreas: evaluation of pancreatitis as a complication. *Gastrointest Endosc*. 2002;56:864–867.
114. O'Toole D, Palazzo L, Arotcarena R, et al. Assessment of complications of EUS-guided fine-needle aspiration. *Gastrointest Endosc*. 2001;53:470–474.
115. Micames C, Jowell PS, White R, et al. Lower frequency of peritoneal carcinomatosis in patients with pancreatic cancer diagnosed by EUS-guided FNA vs. percutaneous FNA. *Gastrointest Endosc*. 2003;58:690–695.
116. Qian X, Hecht JL. Pancreatic fine needle aspiration: a comparison of computed tomographic and endoscopic ultrasonographic guidance. *Acta Cytol*. 2003;47:723–726.
117. Mallery JS, Centeno BA, Hahn PF, et al. Pancreatic tissue sampling guided by EUS, CT/US, and surgery: a comparison of sensitivity and specificity. *Gastrointest Endosc*. 2002;56:218–224.
118. Harewood GC, Wiersema MJ. A cost analysis of endoscopic ultrasound in the evaluation of pancreatic head adenocarcinoma. *Am J Gastroenterol*. 2001;96:2651–2656.
119. Chen VK, Arguedas MR, Kilgore ML, Eloubeidi MA. A cost-minimization analysis of alternative strategies in diagnosing pancreatic cancer. *Am J Gastroenterol*. 2004;99:2223–2234.
120. Levy MJ, Jondal ML, Clain J, Wiersema MJ. Preliminary experience with an EUS-guided Trucut biopsy needle compared with EUS-guided FNA. *Gastrointest Endosc*. 2003;57:101–106.
121. Larghi A, Verna EC, Stavropoulos SN, et al. EUS-guided Trucut needle biopsies in patients with solid pancreatic masses: a prospective study. *Gastrointest Endosc*. 2004;59:185–190.
122. Varadarajulu S, Fraig M, Schmulewitz N, et al. Comparison of EUS-guided 19-gauge Trucut needle biopsy with EUS-guided fine-needle aspiration. *Endoscopy*. 2004;36:397–401.
123. Thomas T, Kaye PV, Ragunath K, Aithal G. Efficacy, safety, and predictive factors for a positive yield of EUS-guided Trucut biopsy: a large tertiary referral center experience. *Am J Gastroenterol*. 2009;104:584–591.
124. Eloubeidi MA, Mehra M, Bean SM. EUS-guided 19-gauge Trucut needle biopsy for diagnosis of lymphoma missed by EUS-guided FNA. *Gastrointest Endosc*. 2007;65:937–939.
125. Itoi T, Takei K, Sofuni A, et al. Immunohistochemical analysis of p53 and MIB-1 in tissue specimens obtained from endoscopic ultrasonography-guided fine needle aspiration biopsy for the diagnosis of solid pancreatic masses. *Oncol Rep*. 2005;13:229–234.
126. Kitoh H, Ryozawa S, Harada T, et al. Comparative genomic hybridization analysis for pancreatic cancer specimens obtained by endoscopic ultrasonography-guided fine-needle aspiration. *J Gastroenterol*. 2005;40:511–517.
127. Laurell H, Bouisson M, Berthelemy P, et al. Identification of biomarkers of human pancreatic adenocarcinomas by expression profiling and validation with gene expression analysis in endoscopic ultrasound-guided fine needle aspiration samples. *World J Gastroenterol*. 2006;12:3344–3351.
128. Maluf-Filho F, Kumar A, Gerhardt R, et al. Kras mutation analysis of fine needle aspirate under EUS guidance facilitates risk stratification of patients with pancreatic mass. *J Clin Gastroenterol*. 2007;41:906–910.
129. Mishra G, Zhao Y, Sweeney J, et al. Determination of qualitative telomerase activity as an adjunct to the diagnosis of pancreatic adenocarcinoma by EUS-guided fine-needle aspiration. *Gastrointest Endosc*. 2006;63:648–654.
130. Salek C, Benesova L, Zavoral M, et al. Evaluation of clinical relevance of examining K-*ras*, p16 and p53 mutations along with allelic losses at 9p and 18q in EUS-guided fine needle aspiration samples of patients with chronic pancreatitis and pancreatic cancer. *World J Gastroenterol*. 2007;13:3714–3720.
131. Tada M, Komatsu Y, Kawabe T, et al. Quantitative analysis of K-*ras* gene mutation in pancreatic tissue obtained by endoscopic ultrasonography-guided fine needle aspiration: clinical utility for diagnosis of pancreatic tumor. *Am J Gastroenterol*. 2002;97:2263–2270.
132. Jensen RT, Norton JA. Pancreatic endocrine tumors. In: Feldman M, Scharschmidt BF, Sleisenger MH, eds. *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*. 7th ed, Philadelphia: WB Saunders; 2002:988–1016.
133. Modlin IM, Tang LH. Approaches to the diagnosis of gut neuroendocrine tumors: the last word (today). *Gastroenterology*. 1997;112:583–590.
134. Madura JA, Cummings OW, Wiebke EA, et al. Nonfunctioning islet cell tumors of the pancreas: a difficult diagnosis but one worth the effort. *Am Surg*. 1997;63:573–577; discussion 577–578.
135. Lam KY, Lo CY. Pancreatic endocrine tumour: a 22-year clinico-pathological experience with morphological, immunohistochemical observation and a review of the literature. *Eur J Surg Oncol*. 1997;23:36–42.
136. Kloppel G, Heitz PU. Pancreatic endocrine tumors. *Pathol Res Pract*. 1988;183:155–168.
137. Schindl M, Kaczirek K, Kaserer K, Niederle B. Is the new classification of neuroendocrine pancreatic tumors of clinical help? *World J Surg*. 2000;24:1312–1318.
138. Akerstrom G, Hellman P, Hessman O, Osmak L. Surgical treatment of endocrine pancreatic tumours. *Neuroendocrinology*. 2004;80(suppl 1):62–66.
139. Azimuddin K, Chamberlain RS. The surgical management of pancreatic neuroendocrine tumors. *Surg Clin North Am*. 2001;81:511–525.
140. Rosch T, Lightdale CJ, Botet JF, et al. Localization of pancreatic endocrine tumors by endoscopic ultrasonography. *N Engl J Med*. 1992;326:1721–1726.
141. Palazzo L, Roseau G, Chaussade S, et al. [Pancreatic endocrine tumors: contribution of ultrasound endoscopy in the diagnosis of localization]. *Ann Chir*. 1993;47:419–424.
142. Anderson MA, Carpenter S, Thompson NW, et al. Endoscopic ultrasound is highly accurate and directs management in patients with neuroendocrine tumors of the pancreas. *Am J Gastroenterol*. 2000;95:2271–2277.
143. Ardengh JC, Rosenbaum P, Ganc AJ, et al. Role of EUS in the preoperative localization of insulinomas compared with spiral CT. *Gastrointest Endosc*. 2000;51:552–555.
144. De Angelis C, Carucci P, Repici A, Rizzetto M. Endosonography in decision making and management of gastrointestinal endocrine tumors. *Eur J Ultrasound*. 1999;10:139–150.
145. Gouya H, Vignaux O, Augui J, et al. CT, endoscopic sonography, and a combined protocol for preoperative evaluation of pancreatic insulinomas. *AJR Am J Roentgenol*. 2003;181:987–992.
146. Proye C, Malvaux P, Pattou F, et al. Noninvasive imaging of insulinomas and gastrinomas with endoscopic ultrasonography and somatostatin receptor scintigraphy. *Surgery*. 1998;124:1134–1143; discussion 1143–1134.
147. Zimmer T, Stolzel U, Bader M, et al. Endoscopic ultrasonography and somatostatin receptor scintigraphy in the preoperative localisation of insulinomas and gastrinomas. *Gut*. 1996;39:562–568.
148. Semelka RC, Custodio CM, Cem Balci N, Woosley JT. Neuroendocrine tumors of the pancreas: spectrum of appearances on MRI. *J Magn Reson Imaging*. 2000;11:141–148.
149. Van Nieuwenhove Y, Vandaele S, Op de Beeck B, Delvaux G. Neuroendocrine tumors of the pancreas. *Surg Endosc*. 2003;17:1658–1662.
150. Thoeni RF, Mueller-Lisse UG, Chan R, et al. Detection of small, functional islet cell tumors in the pancreas: selection of MR imaging sequences for optimal sensitivity. *Radiology*. 2000;214:483–490.
151. Gibril F, Reynolds JC, Doppman JL, et al. Somatostatin receptor scintigraphy: its sensitivity compared with that of other imaging methods in detecting primary and metastatic gastrinomas. A prospective study. *Ann Intern Med*. 1996;125:26–34.
152. van Eijck CH, Lamberts SW, Lemaire LC, et al. The use of somatostatin receptor scintigraphy in the differential diagnosis of pancreatic duct cancers and islet cell tumors. *Ann Surg*. 1996;224:119–124.
153. Bansal R, Tierney W, Carpenter S, et al. Cost effectiveness of EUS for preoperative localization of pancreatic endocrine tumors. *Gastrointest Endosc*. 1999;49:19–25.

154. Ardengh JC, de Paulo GA, Ferrari AP. EUS-guided FNA in the diagnosis of pancreatic neuroendocrine tumors before surgery. *Gastrointest Endosc*. 2004;60:378–384.
155. Ginès A, Vazquez-Sequeiros E, Soria MT, et al. Usefulness of EUS-guided fine needle aspiration (EUS-FNA) in the diagnosis of functioning neuroendocrine tumors. *Gastrointest Endosc*. 2002;56:291–296.
156. Baker MS, Knuth JL, DeWitt J, et al. Pancreatic cystic neuroendocrine tumors: preoperative diagnosis with endoscopic ultrasound and fine-needle immunocytology. *J Gastrointest Surg*. 2008;12:450–456.
157. Chang F, Vu C, Chandra A, et al. Endoscopic ultrasound-guided fine needle aspiration cytology of pancreatic neuroendocrine tumours: cytomorphological and immunocytochemical evaluation. *Cytopathology*. 2006;17:10–17.
158. Collins BT, Cramer HM. Fine-needle aspiration cytology of islet cell tumors. *Diagn Cytopathol*. 1996;15:37–45.
159. Kidd M, Modlin IM, Mane SM, et al. Q RT-PCR detection of chromogranin A: a new standard in the identification of neuroendocrine tumor disease. *Ann Surg*. 2006;243:273–280.
160. Zografos GN, Stathopoulou A, Mitropapas G, et al. Preoperative imaging and localization of small sized insulinoma with EUS-guided fine needle tattooing: a case report. *Hormones (Athens)*. 2005;4:111–116.
161. Fasanella KE, McGrath KM, Sanders M, et al. Pancreatic endocrine tumor EUS-guided FNA DNA microsatellite loss and mortality. *Gastrointest Endosc*. 2009;69:1074–1080.
162. Roland CF, van Heerden JA. Nonpancreatic primary tumors with metastasis to the pancreas. *Surg Gynecol Obstet*. 1989;168:345–347.
163. Nakeeb A, Lillemoe KD, Cameron JL. The role of pancreaticoduodenectomy for locally recurrent or metastatic carcinoma to the periampullary region. *J Am Coll Surg*. 1995;180:188–192.
164. Sperti C, Pasquali C, Liessi G, et al. Pancreatic resection for metastatic tumors to the pancreas. *J Surg Oncol*. 2003;83:161–166; discussion 166.
165. Z'Graggen K, Fernandez-del Castillo C, Rattner DW, et al. Metastases to the pancreas and their surgical extirpation. *Arch Surg*. 1998;133:413–417; discussion 418–419.
166. Ghavamian R, Klein KA, Stephens DH, et al. Renal cell carcinoma metastatic to the pancreas: clinical and radiological features. *Mayo Clin Proc*. 2000;75:581–585.
167. Faure JP, Tuech JJ, Richer JP, et al. Pancreatic metastasis of renal cell carcinoma: presentation, treatment and survival. *J Urol*. 2001;165:20–22.
168. Palazzo L, Borotto E, Cellier C, et al. Endosonographic features of pancreatic metastases. *Gastrointest Endosc*. 1996;44:433–436.
169. DeWitt J, Jowell P, Leblanc J, et al. EUS-guided FNA of pancreatic metastases: a multicenter experience. *Gastrointest Endosc*. 2005;61:689–696.
170. Bechade D, Palazzo L, Fabre M, Algayres JP. EUS-guided FNA of pancreatic metastasis from renal cell carcinoma. *Gastrointest Endosc*. 2003;58:784–788.
171. Fritscher-Ravens A, Sriram PV, Krause C, et al. Detection of pancreatic metastases by EUS-guided fine-needle aspiration. *Gastrointest Endosc*. 2001;53:65–70.

CHAPTER 15

EUS IN THE EVALUATION OF PANCREATIC CYSTS

Ian D. Penman | Anne Marie Lennon

Key Points

The differential diagnosis of pancreatic cystic lesions is wide: most of these lesions are pseudocysts, but detection of mucinous neoplasms is most important because these may be malignant or may have malignant potential.

The diagnostic accuracy of EUS morphologic features is limited, as is the value of fluid cytology and measurement of tumor markers.

A combination of EUS features, fluid cytology, and carcinoembryonic or amylase levels may improve accuracy in detecting (potentially) malignant lesions.

Fine-needle aspiration of cystic lesions under antibiotic cover is safe, with low rates of bleeding, infection, and pancreatitis.

Accurate diagnosis and management of pancreatic cystic lesions require careful evaluation of the clinical setting, other imaging modalities, and multidisciplinary collaboration.

INTRODUCTION

Pancreatic cystic lesions (PCLs), once thought to be rare, are now detected more frequently as a result of the increased use of high-resolution computed tomography (CT) and magnetic resonance imaging (MRI). As many as 20% of patients undergoing imaging for nonpancreatic reasons are found to have at least one pancreatic cyst, and a prospective autopsy series reported a prevalence of PCLs of 24%.[1,2] These lesions represent a broad spectrum of pathologic changes from simple cysts to hyperplasia to neoplasia. Most (80% to 90%) lesions in patients being investigated for pancreaticobiliary problems are pseudocysts; congenital or simple cysts and other rarities account for approximately 10%. Cystic neoplasms, mainly serous cystadenoma, mucinous cystadenoma, mucinous cystadenocarcinoma, and intraductal papillary mucinous neoplasia (IPMN), comprise the remaining 10%. PCLs thus represent an important and increasing disease burden and pose a difficult diagnostic and management problem: how to predict accurately which lesions are mucinous and require resection and, conversely, those that can be ignored or followed safely by interval imaging.

Despite advances in CT and MRI, the ability of cross-sectional modalities to characterize these lesions correctly, and to differentiate between benign and malignant lesions, remains limited. Endoscopic ultrasonagraphy (EUS) is ideally suited to imaging pancreatic lesions because of its high resolution and ability to sample cystic lesions or adjacent lymph nodes. This chapter discusses the different types of PCLs, their endosonographic features, and the role of fine-needle aspiration (FNA) for cytologic and tumor marker analysis. A diagnostic approach to patients with PCLs is also described. The EUS features of pseudocysts are described, but therapy of these lesions is discussed further in Chapter 22, and solid pancreatic tumors are discussed in Chapter 14.

EUS AND OTHER IMAGING MODALITIES

The differential diagnosis of PCL is wide (Table 15.1). Management and outcome depend on accurate characterization of these lesions because mucinous lesions have malignant potential and should be considered for resection in fit patients. Conversely, serous cystadenomas are benign and rarely become malignant, and surgery is reserved for those lesions that are enlarging or causing symptoms. Herein lies the problem, however, in that accurate preoperative diagnosis of different PCLs is often difficult.

Most studies of the diagnostic accuracy of noninvasive imaging using ultrasonography, CT, and MRI have been small retrospective case series containing different lesion types. Only a few well-designed prospective studies have been reported. Not surprisingly, therefore, reported accuracies vary widely, from 20% to 88%,[3,4] and it is difficult to draw meaningful conclusions. In a prospective study of 100 serous cystadenomas (with histologic confirmation in 68), however, the accuracy of ultrasonography, CT, and MRI was 53%, 54%, and 74%, respectively.[5] This finding highlights the limitations of cross-sectional imaging, even in this homogeneous and well-characterized study population. Published studies of the diagnostic accuracy of CT[3,4,6–11] were summarized by Oh et al[12] (Table 15.2).

Although numerous case series of the performance of EUS in evaluating these lesions have been reported, these studies also suffer from the same limitations of small size, retrospective design, lack of blinding, and often lack of histologic confirmation (Table 15.3). Furthermore, few studies directly comparing EUS and CT/MRI have been published so far. Of the two large prospective series reported to date, Brugge et al[13] conducted a multicenter collaborative study to determine the most accurate combination of EUS features, cytologic findings, and cyst fluid tumor markers for differentiating mucinous lesions from other types. A total of

TABLE 15.1

Classification of Pancreatic Cystic Lesions

Type of Lesion	Percentage of Cases (%)
Pseudocysts	80-90
Neoplastic	5-10
Serous cystadenoma	
Mucinous cystadenoma	
Mucinous cystadenocarcinoma	
Intraductal papillary mucinous neoplasm	
Cystic endocrine tumor	
Solid and pseudopapillary neoplasm	
Acinar cell cystadenocarcinoma	
Congenital	5-10
"Simple" cyst	
Polycystic disease	
Cystic fibrosis	
Von Hippel–Lindau–associated cysts	
Other	
Lymphoepithelial cyst	Rare
Parasitic infection (e.g., amebiasis, *Ascaris* infection)	

TABLE 15.2

Studies of Diagnostic Accuracy of Computed Tomography Scanning in Pancreatic Cystic Lesions

Authors (yr)	Patients (*n*)	Comparisons	Accuracy (%)
Johnson et al[4] (1988)	35	SCA, MCN	93-95 for SCA and MCN
Procacci et al[6] (1997)	26	SCA	61
Procacci et al[7] (1999)	100	SCA, MCN	60
Le Borgne et al[3] (1999)	349	SCA, MCA, MCAC	20-30
Curry et al[8] (2000)	50	SCA, MCN	23-41 for SCA
Walsh et al[9]* (2002)	34	SCA, MCN, PC	38-78
Cohen-Scali et al[10] (2003)	33	Macrocystic SCA, PC/MCA	83 for SCA
Bassi et al[5]* (2003)	100	SCA	54
Gerke et al[11] (2006)	41	Benign vs M/PM	71

*Prospective studies.

MCA, mucinous cystic neoplasm; MCAC, mucinous cystadenocarcinoma; MCN, mucinous cystic neoplasm; M/PM, malignant/potentially malignant; PC, pseudocyst; SCA, serous cystadenoma.

Adapted from Oh HC, Kim MH, Hwang CY, et al. Cystic lesions of the pancreas: challenging issues in clinical practice. *Am J Gastroenterol.* 2008;103:229-239.

TABLE 15.3

Studies of Diagnostic Accuracy of EUS in Pancreatic Cystic Lesions

Authors (yr)	Technique	Patients (*n*)	Histologic Confirmation	Accuracy of EUS (%)	Accuracy of Cytology (%)
Brugge et al[13]* (2004)	EUS FNA	341	112	51	59
Frossard et al[14]* (2003)	EUS FNA	127	67	77	97
Sedlack et al[39] (2002)	EUS FNA	34	34	82	55
Hernandez et al[40] (2002)	EUS FNA	43	9	Predicted malignancy in 8/9	Sensitivity for malignancy 2/9
Gress et al[21] (2000)	EUS	35	35	Not stated	—
Koito et al[41] (1997)	EUS	52	52	92-96 (for neoplastic lesions)	—
Ahmad et al[42] (2001)	EUS	98	48	No features predictive of malignancy	—
Ahmad et al[43] (2003)	EUS	31	31	40-93 Interobserver variation ++	—
Chatelain et al[44] (2002)	EUS	8	8	Not stated	—
Gerke et al[45] (2006)	EUS	66	43	65	—

*Prospective studies.

FNA, fine-needle aspiration.

341 patients underwent EUS and FNA with measurement of carcinoembryonic antigen (CEA), CA72-4, CA125, CA19-9, and CA15-3 concentrations. Some 112 of these patients subsequently underwent surgical resection, and the accuracy of EUS morphology was only 51%, with cytology faring little better at 59%. A CEA concentration greater than 192 ng/mL was 79% accurate for distinguishing mucinous lesions, and no combination of tests performed better than cyst fluid CEA concentration alone. The role of tumor markers is discussed in more detail later.

A similar single-center French study of 67 patients found that the overall accuracy of EUS morphology for all types of cystic lesion was 73%,[14] with significant variations according to lesion type. Sensitivity for serous lesions was only 43%, whereas that for mucinous cystadenomas was 65% and for cystadenocarcinomas 88%. In contrast to the U.S. study, the sensitivities of cytology for mucinous lesions, malignant mucinous lesions, serous lesions, and pseudocysts, respectively, were 94%, 100%, 100%, and 100%. The specificity for all these lesions was, as expected, 98% to 100%. A broad panel of tumor markers was analyzed, and although a low CEA level (<5 ng/mL) was predictive of serous lesions and a high amylase or lipase concentration was associated with pseudocysts, tumor marker analysis contributed little to the results of cytology.

CONGENITAL OR "SIMPLE" CYSTS

Congenital or "simple" cysts are usually seen as a coincidental finding during CT imaging of the abdomen (Fig. 15.1). They can occur as part of the spectrum of adult polycystic kidney disease and also in von Hippel–Lindau syndrome (Fig. 15.2), although serous cystadenomas also occur in the latter. The clinical importance of small, simple-looking cysts discovered incidentally is unknown, and few, if any, observational follow-up studies have been performed to date. A study of 86 small cysts that were resected found that 75 of these cysts were benign, and most of the rest had, at worst, borderline or "in situ" malignancy.[15] At EUS, these cysts are usually small, thin walled, and uniformly anechoic, with no mural nodularity or papillary elements. The surrounding pancreas shows no features of chronic pancreatitis, and, if aspirated, the fluid looks bland and contains only small numbers of inflammatory cells and low concentrations of CEA and amylase.

PSEUDOCYSTS

Accounting for approximately 80% of PCLs, pseudocysts usually occur in the setting of an episode of acute pancreatitis or insidiously in patients with chronic pancreatitis, mostly in middle-aged men.

Knowledge of the clinical presentation is therefore essential in aiding accurate differentiation of pseudocysts from cystic neoplasms. Pseudocysts lack a true epithelial lining; the wall consists of inflammatory and fibrous tissue. This wall is thin in early pseudocysts but may become thick as they mature. Pseudocysts are often extremely large, although they are usually unilocular and anechoic (Video 15.1; Fig. 15.3). The fluid density may increase if necrotic debris or infection is present, however, and occasionally this finding may lead to suspicion of a cystic neoplasm (Figs. 15.4 and 15.5). Septations are rare but do occur (Fig. 15.6); there may be features of acute or chronic pancreatitis elsewhere in the gland, and it may be possible to demonstrate direct communication with the pancreatic duct, features that support a diagnosis of pseudocyst over neoplasm.

Other features that should be noted are the distance between the intestinal wall and the cyst lumen and the presence of interposed (by Doppler examination) or collateral vessels as evidence of segmental portal hypertension secondary to portal or splenic vein thrombosis. Reactive, inflammatory-looking lymph nodes may also be seen adjacent to the pseudocyst.

Because pseudocysts lack an epithelial lining, no epithelial cells should be present in FNA samples, unless there is contamination of the needle with gastric or duodenal epithelium during puncture. Aspirated fluid is of low viscosity, often dark, turbid, or even bloody, and contains inflammatory cells such as macrophages and histiocytes. Raised amylase (>5000 U/mL) and lipase (>2000 U/mL) concentrations are present, but levels of other tumor markers should be low, although increased CEA levels have been reported when infection is present.

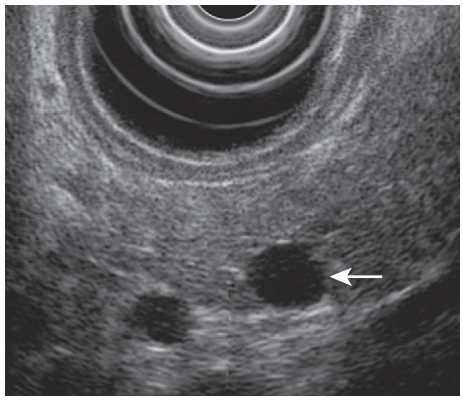


FIGURE 15.1 Simple pancreatic cyst. A thin-walled and simple-looking 5-mm cyst *(arrow)* is seen in the pancreatic body. There is no solid mural component, no debris within the cyst, and no mass lesion, and the surrounding pancreatic parenchyma is normal.

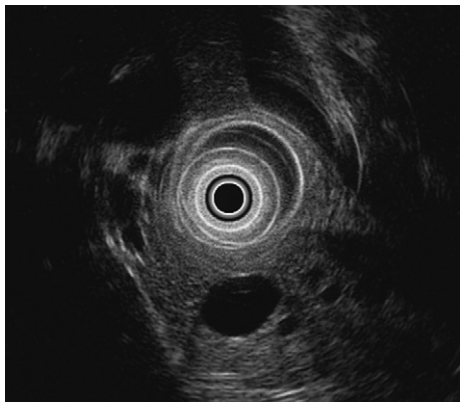


FIGURE 15.2 Von Hippel–Lindau syndrome (VHL). A simple 1-cm cyst is seen in the pancreatic body in a patient with VHL. Cysts may be numerous, but they are either simple or benign serous cystadenomas in the pancreas, despite the high risk of malignancy elsewhere in this condition.

SEROUS CYSTADENOMA

Serous cystadenomas, the most common form of cystadenoma, account for 10% to 45% of cases. Serous cystadenomas are much more common in women and classically occur (>80%) in the body or tail of the pancreas,[16] although some investigators have reported a greater preponderance in the pancreatic head and neck. These lesions classically consist of numerous (more than six) well-demarcated microcystic (<2 cm) lesions (Figs. 15.7 and 15.8) with thin septa.[6] In fewer than 20% of cases, the cysts are associated with central fibrosis or calcification. Solid and macrocystic variant forms of serous cystadenomas have also been described, with the solid appearance resulting from coalescence of multiple tiny (1- to 2-mm) cysts.[17–19] The appearance of focal cyst wall nodularity or thickening, intracystic mucin or floating debris, echogenic ductal wall thickening, or pancreatic duct dilatation is unusual and suggests that the lesion is actually a mucinous tumor.[20–22]

The morphologic characteristics of serous cystadenomas are often diagnostic of the lesion (Video 15.2).[19] Nevertheless, cytologic examination may improve the diagnostic accuracy of EUS. FNA can be difficult owing to the small size of the cysts coupled with the vascular nature of these lesions. The cytologic appearance is of serous fluid containing small cuboidal cells that stain for glycogen but not mucin. Sometimes the aspirate is bloody or contains hemosiderin-laden macrophages because of the

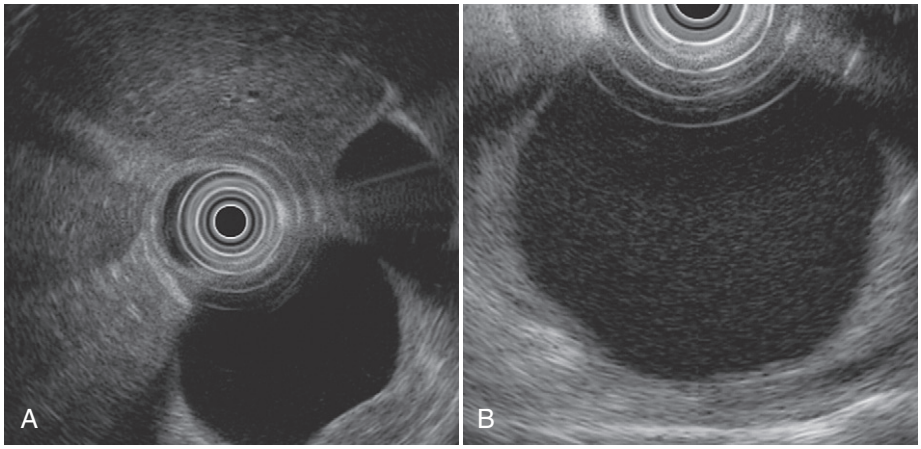


FIGURE 15.3 Pseudocysts. A, Radial EUS in a patient with a recent episode of pancreatitis reveals a 3-cm, thin-walled, anechoic cystic lesion in close contact with the gastric wall. **B,** Similar findings in another patient with chronic abdominal pain, who presented with chronic pancreatitis and a pseudocyst.

vascular nature of this lesion.[23] The fluid classically contains low amylase, CA15-3, CA72-4, and CEA concentrations. A CEA concentration of less than 5 ng/mL virtually excludes a mucinous lesion and lends support to the diagnosis of a serous cystadenoma.[23,24] The prognosis is usually excellent, although a 3% risk of malignancy was reported in one study.[25] Within this study, few pathologic features differentiated benign from malignant lesions, and malignancy became apparent only when metachronous metastases appeared.[25]

MUCINOUS CYSTADENOMA AND ADENOCARCINOMA

Mucinous cystic lesions are rarer than serous cystadenomas and account for approximately 10% of cystic neoplasms. Unlike serous cystadenomas, mucinous cystic lesions are classified as benign, borderline, or malignant; benign and borderline forms have the potential for malignant transformation. They occur most often in young or middle-aged women (90%), with solitary cysts found in the body and tail of the pancreas, on a background

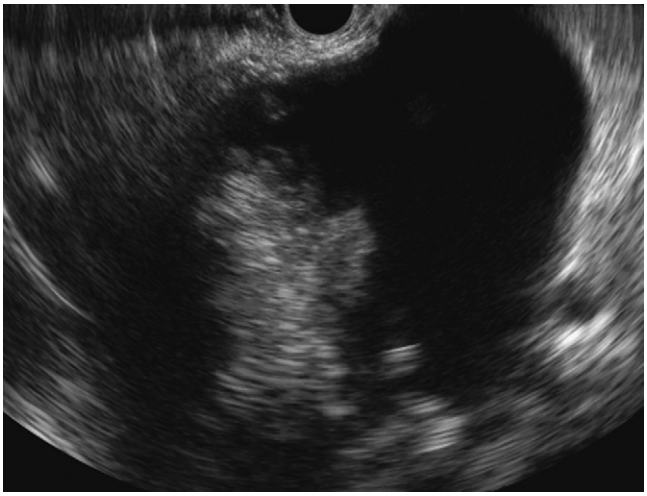


FIGURE 15.4 Infected pseudocyst in patient with severe acute pancreatitis and fever. The irregular hyperechoic material seen within the cyst raises the suspicion of a cystic neoplasm but it is not murally based. Fine-needle aspiration cytology revealed only macrophages and debris; the amylase concentration was greater than 6000 U/mL.

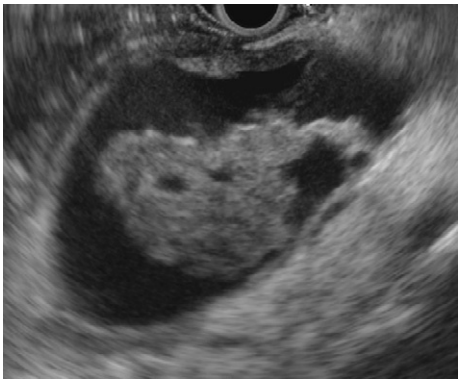


FIGURE 15.5 Atypical appearance of pseudocyst. The patient presented with chronic abdominal pain and weight loss. The EUS appearances are suspicious for a mucinous neoplasm, but fine-needle aspiration revealed old blood-stained fluid with inflammatory cells, low carcinoembryonic antigen levels, and an amylase concentration greater than 66,000 U/mL. Because of ongoing concerns, the lesion was resected, and a pseudocyst was confirmed.

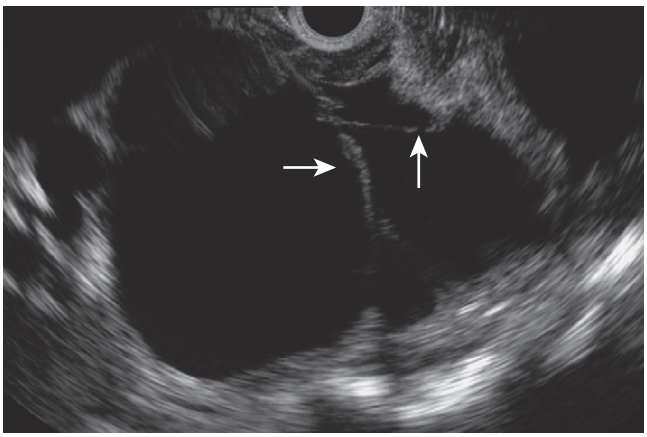


FIGURE 15.6 Thin-walled internal septations *(arrows)* in a patient with a long-standing pseudocyst.

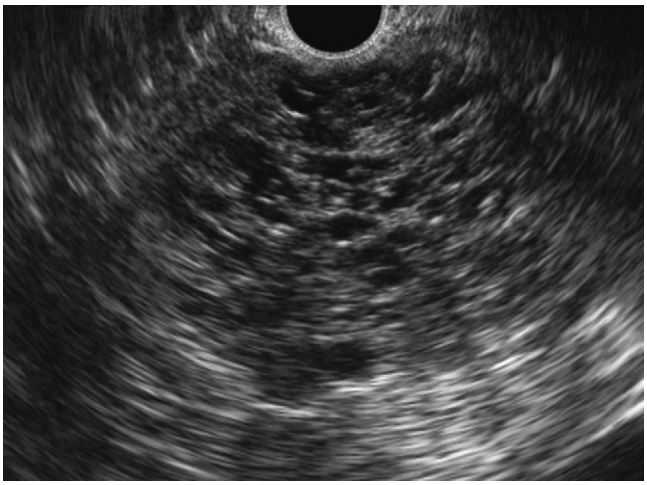


FIGURE 15.7 Serous cystadenoma. Typical appearance of a 2.5-cm microcystic serous cystadenoma. It has multiple small, anechoic cystic areas and a "honeycomb" appearance. This lesion does not show the central area of fibrosis or calcification that is sometimes present.

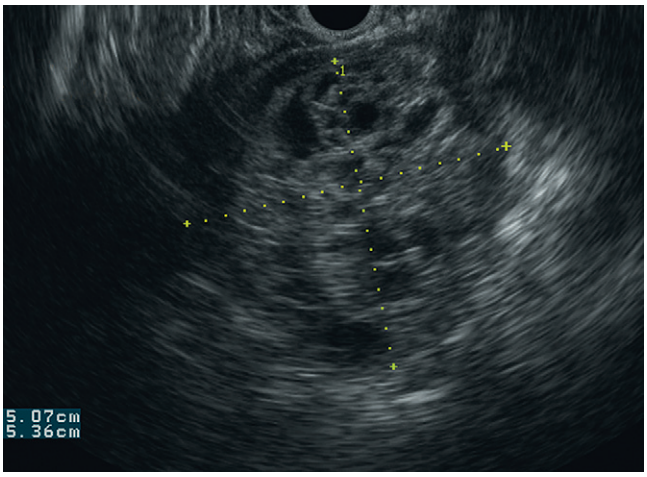


FIGURE 15.8 A 5-cm solid variant serous cystadenoma in the pancreatic body. Note the numerous small cysts with thin septations.

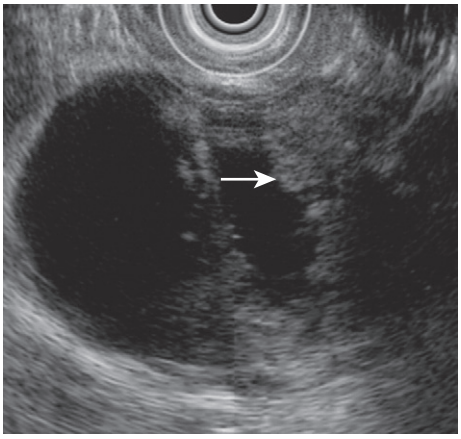


FIGURE 15.9 Mucinous cystadenoma. Numerous solid, papillary projections from the cyst wall are seen *(arrow)*. Fine-needle aspiration revealed mucin-positive cuboidal cells, and resection confirmed a benign mucinous cystadenoma.

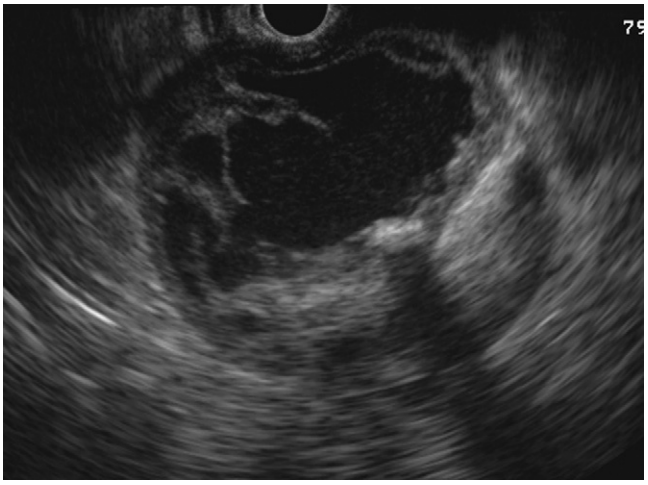


FIGURE 15.10 Mucinous cystadenoma. This macrocystic, unilocular lesion has a thick wall, focal peripheral calcification, and echogenic contents.

ovarian stroma that contains both estrogen and progesterone receptors. The morphologic appearance is of a macrocystic (>2 cm) lesion with few septations (Fig. 15.9).[21,22] Peripheral calcification, which is found in 15% of patients, is highly suggestive but may also be seen in solid and pseudopapillary neoplasms.[4,26] The presence of other cystic lesions elsewhere in the pancreas or a dilated pancreatic duct is unusual, and, if present, a diagnosis of IPMN should be considered.

The risk of malignancy increases with larger lesions (>3 cm).[27] The presence of an irregular or thickened cyst wall, solid regions within the cysts, an adjacent solid mass (Figs. 15.10 and 15.11), or a strictured, obstructed, or displaced pancreatic duct suggests malignant transformation (Video 15.3).[21,28] FNA can be useful in confirming the diagnosis. The cyst wall and septa should be sampled, in addition to aspirating the fluid. Aspiration can be difficult because of the viscous nature of the fluid, but it is easier when a 19-G needle is used. Cytology demonstrates viscous fluid containing mucin and columnar epithelial cells. The presence of columnar cells is not pathognomonic because these cells are also found in IPMN.[23] The presence of columnar epithelial cells from the stomach or duodenum can further complicate the cytologic interpretation, and care should be taken to avoid contamination of the cyst fluid by using a stylet during initial cyst puncture.

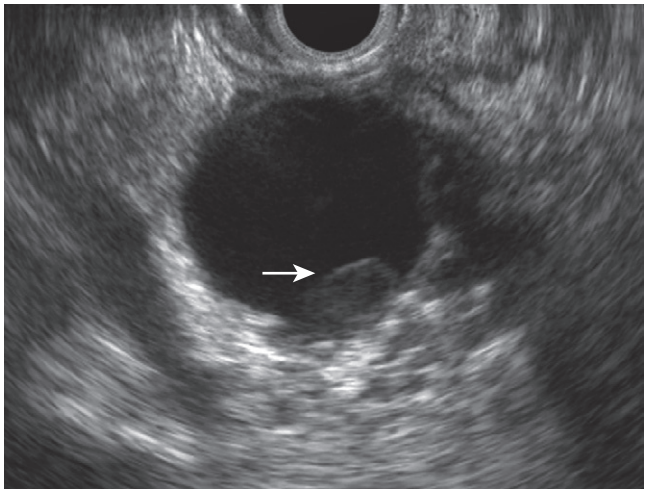


FIGURE 15.11 Mucinous cystadenoma. A small mural nodule is seen *(arrow)* in this 15-mm lesion. Mucin stain of aspirated fluid was positive, but carcinoembryonic antigen and amylase concentrations were not raised.

INTRADUCTAL PAPILLARY MUCINOUS NEOPLASIA

IPMN is relatively rare, accounting for 1% to 3% of pancreatic exocrine tumors.[29,30] It has a slight male preponderance (62%), with a peak in the sixth decade, and occurs most frequently in the head of the pancreas. IPMN may be classified as arising from the main duct or the branch ducts, or it may be of mixed type. Endoscopic appearances include the presence of a dilated main pancreatic duct or side branch, depending on the site of the tumor.[18,21,31] A gaping papilla extruding mucus is found in 25% to 50% of patients.[32] A communication between side and main duct branches is a feature, although this is not always present because it can be obstructed by mucin. Filling defects in the pancreatic duct at magnetic resonance cholangiopancreatography (MRCP) or endoscopic retrograde cholangiopancreatography (ERCP) can result from tumor nodules or mucus plugs (Video 15.4). IPMN can sometimes manifest as a solid mass, although this is rare. IPMN can also be associated with parenchymal changes resulting from obstruction of the duct, and this finding can make it difficult to differentiate IPMN from chronic pancreatitis.

The presence of features such as a focal hypoechoic mass, mural nodules (Fig. 15.12), or a large unilocular cystic component is suggestive of malignancy. Higher-frequency intraductal ultrasound (IDUS) catheter probes have been used in some studies to characterize IPMN, and they may be able to provide extra information about the longitudinal extent of duct involvement, the presence of mural nodules, and invasion of the pancreatic parenchyma. In combination with MRCP, IDUS may aid in planning the extent of surgical resection by defining disease extent along the main pancreatic duct.[33,34] However, pancreatoscopy and IDUS are difficult, labor-intensive techniques requiring expensive equipment and expertise. IDUS cannot visualize structures more than a few millimeters from the duct, and this may limit the usefulness of this modality. The use of pancreatoscopy and IDUS has been restricted to a few major referral centers and is likely to remain so.

IPMN is clinically and pathologically heterogeneous. The degree of cytologic atypia can vary from minimal to severe or frankly malignant, with features resembling mucinous cystic neoplasms or even ductal adenocarcinoma. Psammomatous

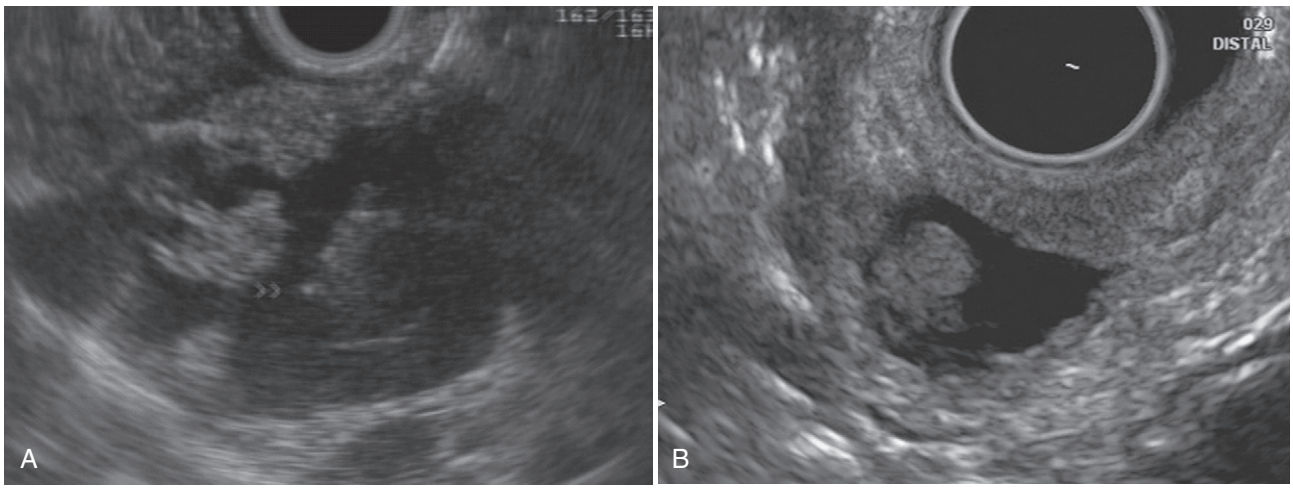


FIGURE 15.12 Main duct intraductal papillary mucinous neoplasia (IPMN). A, The main pancreatic duct is markedly dilated, and hyperechoic nodules can be seen arising from the duct wall. **B,** Mural nodule arising from the pancreatic duct wall in a patient with a main duct IPMN.

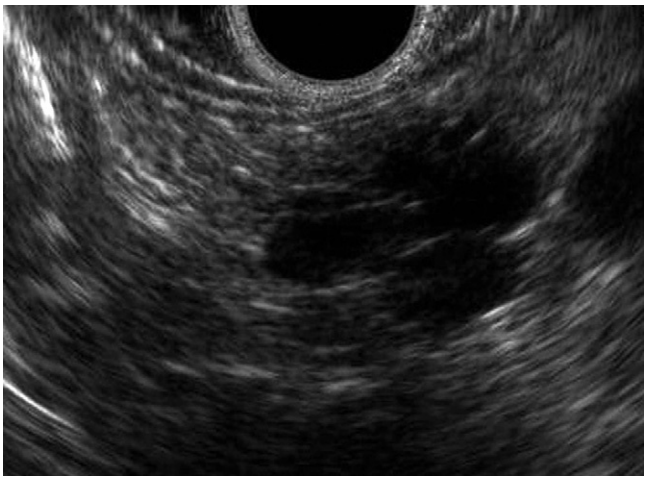


FIGURE 15.13 Side branch intraductal papillary mucinous neoplasia in the pancreatic body, seen as a small cluster of grape-like dilatations of pancreatic branch ducts. No nodule or mass lesion is evident.

calcification is uncommon but highly suggestive of IPMN. Different patterns of mucin immunohistochemistry have been observed,[29,35] but whether these are prognostically important is unknown. These patterns also demonstrate molecular heterogeneity. Little is known about tumor markers in these lesions; the patterns reported are generally similar to those of mucinous neoplasms, although CEA levels can be highly variable. A high amylase concentration may be noted, in keeping with an origin from, or communication with, the pancreatic duct.

How best to manage IPMN is controversial: some experts advocate resection of all lesions and cite the limited ability of preoperative evaluations to predict the presence of malignancy. Other experts prefer a watchful waiting policy for lesions without high-risk features (branch duct origin, size <3 cm, absence of solid lesion or mural nodules, absence of high-grade dysplasia on FNA), given the low risk of malignancy (Fig. 15.13). The decision also depends on the location in the pancreas (e.g., head versus tail) and the patient's age and fitness status, all of which determine surgical risk as well as patient preference. IPMN and its management have been comprehensively reviewed.[29]

SOLID CYSTIC PSEUDOPAPILLARY NEOPLASM

Although the solid cystic pseudopapillary neoplasm was once thought to be rare, this distinctive lesion is now better recognized and increasingly reported. It accounts for 10% of cystic pancreatic tumors. It is usually discovered incidentally in young women, can occur anywhere in the pancreas, and may be very large. In some patients, symptoms related to the size of the tumor or pain from bleeding into it can be the presenting features. The hallmarks of this lesion are central hemorrhagic cystic degeneration and a pseudocapsule that may calcify. Thus, solid, cystic, and "pseudopapillary" areas may all be seen (Fig. 15.14). The cell of origin is unknown, but this lesion has eosinophilic cytoplasm and mixed immunohistochemical features of endocrine, epithelial, and mesenchymal differentiation. These are slow-growing tumors, and when they are resected, the prognosis is excellent.

Only a few case reports and small case series of either abdominal ultrasonography or EUS have been reported.[36,37] Lesions are usually well demarcated, and they may appear solid or mixed solid and cystic, with or without septations. Peripheral calcification may limit examination of the internal echo structure. The hemorrhagic degeneration often results in a bloody, necrotic FNA sample, which can provide a clue to the diagnosis, although the histologic features are usually characteristic.

CYSTIC ENDOCRINE TUMORS

Most neuroendocrine tumors of the pancreas are solid, but uncommonly they may be cystic, either primarily or secondary to cystic degeneration (Fig. 15.15). The EUS features are variable, and cytologic examination reveals a homogeneous population of small cells with scant cytoplasm. Little information exists about tumor marker levels in these lesions.

OTHER CYSTIC LESIONS

Ductal adenocarcinoma of the pancreas may occasionally show cystic degeneration, which can confuse the clinical picture. Lymphoepithelial cysts are rare, occur in middle-aged men, and may appear solid on EUS.[38] These cysts are lined by keratinizing squamous epithelium, and cyst CEA levels may be high. Many other cystic lesions of the pancreas have been reported as rarities, including dermoid cysts, metastases to the pancreas, and parasitic

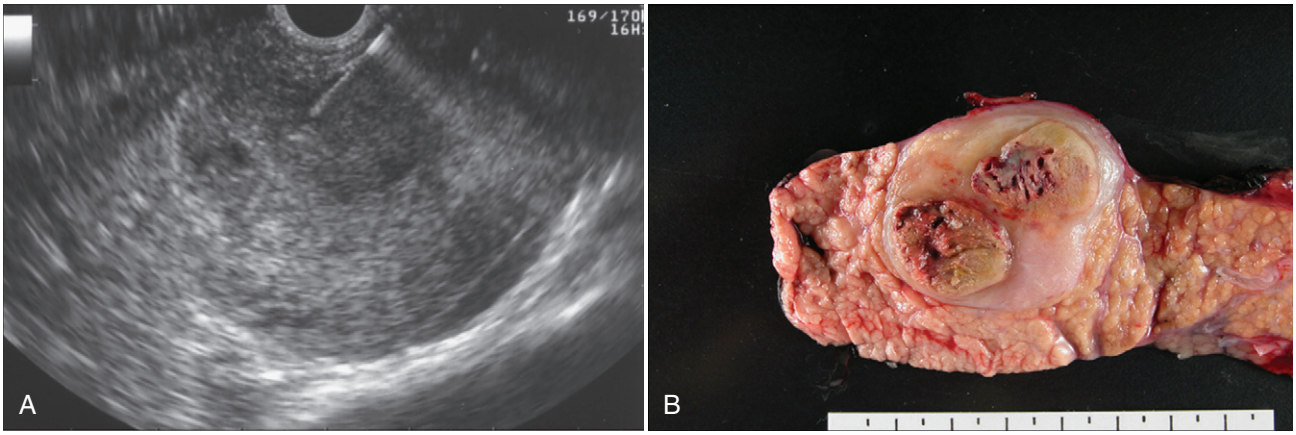


FIGURE 15.14 Pancreatic cyst lesion. A, EUS image of a pancreatic cyst lesion in the body of the gland that reveals both solid and cystic components. Fine-needle aspiration proved this to be a solid cystic pseudopapillary neoplasm. **B,** The corresponding surgical specimen from distal pancreatectomy is shown here.

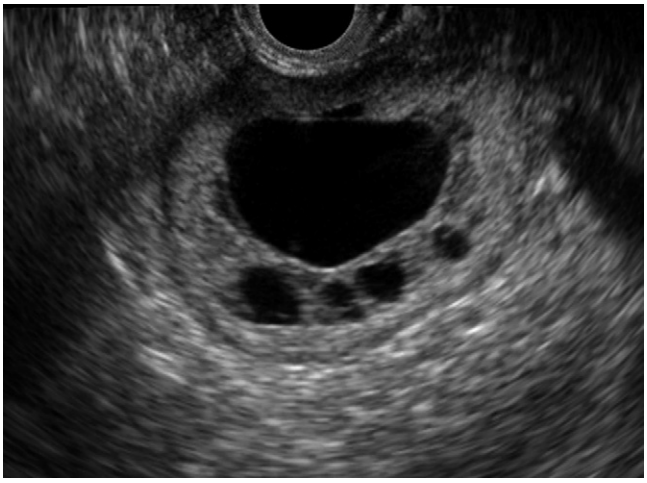


FIGURE 15.15 Cystic endocrine tumor. Note the thick wall. A 19-G core biopsy of the cyst wall was undertaken, and immunohistochemistry confirmed a cystic neuroendocrine tumor.

infections (e.g., amebiasis, *Ascaris* infection). These possibilities should always be borne in mind, especially when the clinical and imaging features are not typical of the more common cystic lesions.

ENDOSONOGRAPHIC APPEARANCES OF CYSTIC LESIONS

The EUS approach to examining the pancreas is described in detail in Chapter 12, and FNA techniques are described in Chapter 20. The general EUS approach to PCLs is described in this section, and the appearances of specific PCLs are described in earlier sections.

When a cystic lesion has been identified, the size, exact location, relation to adjacent vessels and organs, and presence of locoregional or distant metastases should be noted because this information may influence management. The cyst itself should be examined to determine the wall thickness, the presence of focal irregularity, any papillary projections, or an associated mass. The cyst size, the thickness of any septations, and the presence of echo-dense mucus or debris should also be assessed because these features are more often reported in malignant cystic tumors.

Several investigators have tried to determine EUS features that are predictive of malignancy.[13,14,21,39–45] Koito et al[41] found that a thick wall or septum, a protruding tumor, and microcystic type were associated with malignancy, whereas thin septa and simple-looking cysts were benign. These investigators found this system to have an accuracy of 96% and 92% for malignant and benign lesions, respectively. Gress et al[21] reported that mucinous cystadenocarcinomas were more likely to be characterized by a hypoechoic cystic-solid mass or a complex cyst and were frequently associated with a dilated main pancreatic duct. Benign IPMN was characterized by a dilated main pancreatic duct in conjunction with hyperechoic thickening of the duct wall. Intraductal papillary carcinoma had similar features but additionally revealed a hypoechoic mass. Sedlack et al[39] found that a wall thickness of 3 mm or more, macrosepation (cyst compartment >10 mm), a mass or intramural growth, or cystic dilation of the main pancreatic duct predicted a malignant or potentially malignant cystic lesion with an overall accuracy of 82%. Song et al[20] examined endoscopic appearances that could differentiate cystic tumors from pseudocysts and found that parenchymal changes, septa, and mural nodules were independent predictors of cystic tumors. Studies of EUS accuracy in PCLs are summarized in Table 15.3.

Not all studies, however, confirmed that EUS appearances alone can reliably differentiate benign from malignant PCLs.[42] Interobserver agreement in examining different endoscopic features and in differentiating neoplastic from non-neoplastic PCL has been shown to be moderately good in detecting a solid component, fair for the presence of an abnormal pancreatic duct, debris, or septations, and also only fair for the diagnosis of neoplastic versus non-neoplastic lesions.[43] As discussed earlier, a large prospective multicenter U.S. study[13] found that the accuracy of EUS imaging features for diagnosing mucinous lesions was only 51%, and so, despite its high resolution, EUS appearances clearly have limitations. EUS may also be technically challenging in certain situations when the patient's anatomy is altered by previous surgery or compression by a large lesion. EUS imaging is also sometimes limited by attenuation of the ultrasound beam in lesions greater than 6 cm in diameter.

EUS-GUIDED FINE-NEEDLE ASPIRATION

FNA cytology has been safely performed for many years under ultrasound, CT, or EUS guidance. The ultrasound or CT approach may be hampered when the lesion is small or, in the case of ultrasonography, where there is intervening gas. Technical difficulties in acquiring specimens can also limit the usefulness of these

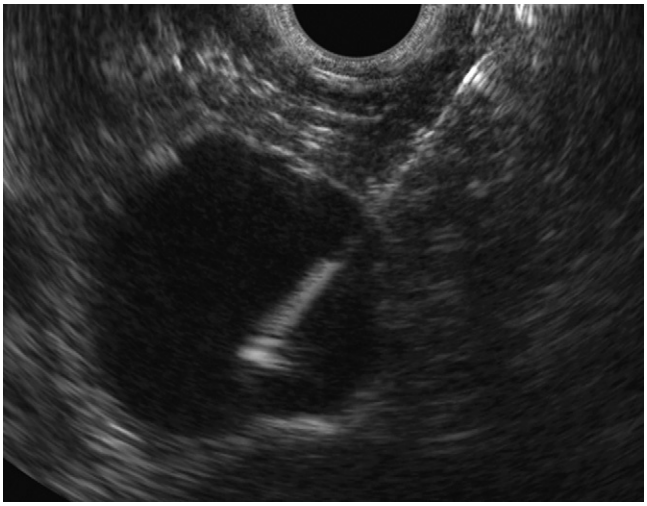


FIGURE 15.16 EUS fine-needle aspiration (FNA). Either a 22-G or a 19-G needle can be used. In this case, a 22-G needle was sufficient to aspirate the lesion completely. Aspiration should continue until the lesion collapses or no further fluid is obtained. This technique may reduce the risk of infection and also facilitates FNA of the cyst walls.

imaging modalities. CT-guided FNA is associated with a risk, albeit low, of peritoneal dissemination of cancer cells.[45,46] EUS overcomes many of these limitations. Its high definition means that it can visualize lesions as small as 2 to 3 mm, as well as defining surrounding structures. The proximity of the echoendoscope tip to the lesion reduces the distance a needle has to travel and minimizes the risk of needle tract seeding (Video 15.5).

EUS-guided FNA is a safe procedure, with reported complication rates of less than 1%.[47,48] The yield of fluid is usually low in serous cystadenomas because of their microcystic nature, and aspiration of fluid in mucinous lesions may be difficult because of the fluid's viscosity. In this case, or when the lesion is large, aspiration to dryness is easier with a 19-G needle (Fig. 15.16). To minimize the risks of subsequent infection, it is recommended that the number of cyst punctures be kept to a minimum (ideally one) and that the cyst be aspirated completely when possible (see Video 15.4). Antibiotic prophylaxis, usually with intravenous ciprofloxacin before the procedure, followed by 2 days of oral ciprofloxacin, is also recommended, although the evidence base to support these recommendations is not strong.[49]

EUS-GUIDED CORE BIOPSIES AND BRUSH CYTOLOGY

The use of core biopsy needles may be appropriate when a mass lesion is present, and this technique may assist in accurate diagnosis of the nature of PCLs.[50] Levy et al[50] undertook EUS-guided core biopsy in 10 patients with PCLs, and the procedure was technically successful in 7. In the other 3 patients, a nondiagnostic sample was obtained. These investigators performed biopsies of the cyst wall and overlapping pancreatic parenchyma, and the findings altered management in the majority. Unfortunately, none of the patients had a mucinous lesion, and so it is not possible to say whether this technique can allow demonstration of an ovarian stroma. It is also feasible only for lesions in the body or tail of pancreas. Finally, this approach does not obviate the need for FNA sampling of cyst fluid for cytology and measurement of tumor markers.

A 25-G through-the-needle cytologic brush was developed for EUS-guided assessment of PCLs. After puncture of the cyst with a 19-G needle, the brush is inserted through the needle and into the cyst cavity. The wall can be sampled in addition to standard fluid cytology and tumor marker analysis. A prospective blinded study of 41 lesions in 39 patients found that the EchoBrush (Cook Endoscopy, Winston-Salem, NC) detected intracellular mucin more frequently (56% versus 22%).[51] The EchoBrush also detected three cases of high-grade dysplasia not found with standard cytologic examination. These preliminary results will need to be corroborated by further studies but are promising. Concerns regarding case reports of severe intracystic bleeding have been raised, especially in patients taking anticoagulants or antiplatelet agents, and more data are needed before this device can be routinely recommended for use in patients with PCLs.

COMPLICATIONS OF EUS FINE-NEEDLE ASPIRATION OF CYSTIC LESIONS

Complications of FNA of PCLs are uncommon. Intracystic hemorrhage and infection each occur in less than 1% of cases, and the reported rate of procedure-related pancreatitis is 1% to 2% Thus, the overall complication rate is variously reported as 2% to 5%. In a French study,[52] three cases of acute pancreatitis occurred in 114 patients undergoing aspiration of PCLs, whereas Lee et al[53] reported acute pancreatitis in 1%, with an overall complication rate of 2.2%.

CYTOLOGY AND CYST FLUID ANALYSIS

The specificity of cytology in most studies is excellent and approaches 100%, but the sensitivity varies considerably in reported series. This finding reflects the difficulty of interpreting these lesions, especially when the cellularity of samples is low. Brandwein et al[54] and Brugge et al[13] reported sensitivities of 55% and 59%, respectively, for differentiating benign from malignant or potentially malignant PCLs. This finding contrasts with studies by Hernandez et al[40] and Frossard et al,[14] who demonstrated sensitivities of 89% and 97%, respectively. Reasons for these widely varying results are not clear but may relate to the presence of an experienced cytopathologist in the procedure room. The sensitivity of cytologic aspiration of pancreatic duct fluid has also been examined, again with greatly varying sensitivity, ranging from 21%[55] to 75%.[56]

The sensitivity of cytology can be affected by several factors. Operator experience affects performance, and the presence of a cytopathologist during the EUS examination can help to confirm the adequate cellularity of the sample. Sampling error may occur in both microcystic and mucinous lesions in which cellular atypia is patchy and may lead to false-negative results. Moreover, the presence of blood or benign epithelial cells from the gastric or duodenal mucosa can make interpretation difficult or can lead to false-positive results.

Analysis of Cyst Fluid Tumor Markers and Biochemistry

Given the limited sensitivity of cytology, the value of tumor markers in aspirated cyst fluid was examined. Tumor markers studied include CEA, CA19-9, CA72-4, CA125, and CA15-3. CEA is found in high levels in mucinous tumors, whereas levels are low in pseudocysts (unless infected) and serous cystadenomas.[40,24,57] The sensitivity and specificity of CEA vary depending on the study and the CEA threshold used. A CEA level of less than 5 ng/mL is associated with a sensitivity of 57% to 100% and a specificity of 77% to 86% for serous cystadenomas.[24,57] A low level does effectively exclude a mucinous lesion, however. A cutoff of more than 400 ng/mL was associated with 100% specificity in differentiating mucinous cystic neoplasms from pseudocysts in one study,[58] but not in another, in which the sensitivity (13%) and specificity (75%) were poor.[14] In the largest prospective study to date,

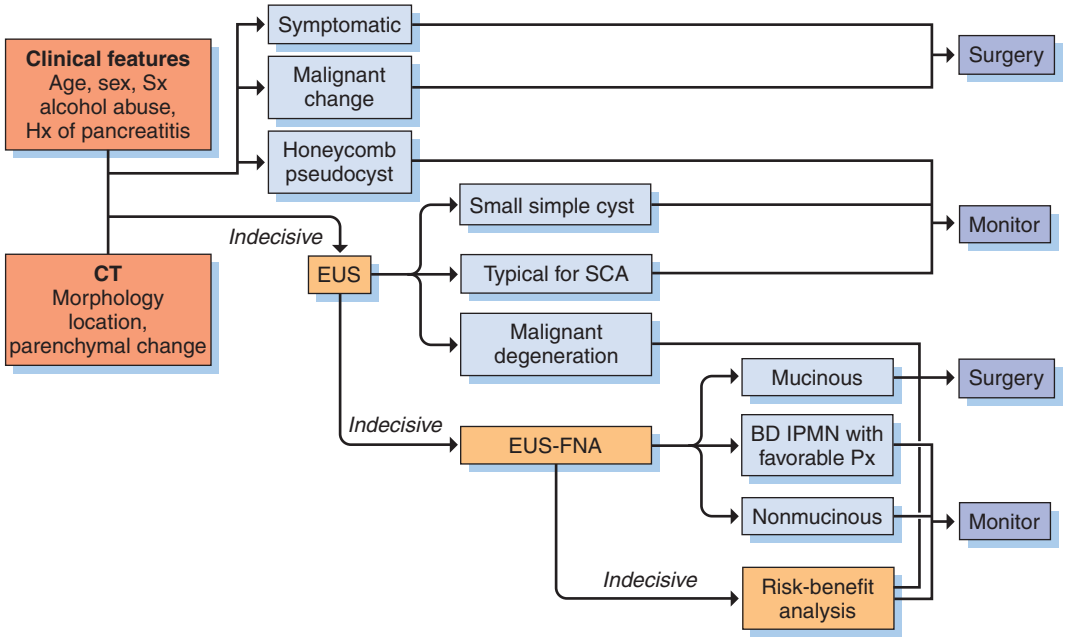


FIGURE 15.17 EUS-based algorithmic approach to the management of pancreatic cystic lesions. BD, branch duct; CT, computed tomography; FNA, fine-needle aspiration; Hx, history; IPMN, intraductal papillary mucinous neoplasia; Px, prognosis; SCA, serous cystadenoma; Sx, symptoms. *(From Oh HC, Kim MH, Hwang CY, et al. Cystic lesions of the pancreas: challenging issues in clinical practice.* Am J Gastroenterol. *2008;103:229-239.)*

Brugge et al[13] used receiver-operator characteristic curves to determine the optimum cutoff value of CEA and found this to be 192 ng/mL. This value was associated with an accuracy of 79% for differentiating mucinous from other cyst types, significantly better than the accuracy of EUS morphology alone (51%) or cytology (59%). In this study, no combination of morphologic features, cytology, and tumor markers was better than CEA alone. CEA assays are standardized for serum and not cyst fluid, and different assays exist, thus making comparisons of different studies difficult.

A pooled analysis of 12 studies[24] confirmed the limited sensitivity of fluid cytology (48% for malignant lesions) and concluded the flowing regarding tumor markers and biochemistry:

- Amylase concentrations lower than 250 U/mL virtually exclude a pseudocyst (sensitivity, 44%; specificity, 98%).
- CEA concentrations lower than 5 mg/mL strongly suggest a serous cystadenoma (sensitivity, 50%; specificity, 95%).
- CEA concentrations higher than 800 mg/mL strongly suggest a mucinous lesion (sensitivity, 48%; specificity, 98%).

CA19-9 is another tumor marker that has been used to identify PCLs. Frossard et al[14] found that a CA19-9 level greater than 50,000 U/mL had 15% sensitivity and 81% specificity in differentiating mucinous cysts from other cystic lesions, whereas it had 86% sensitivity and 85% specificity in distinguishing cystadenocarcinoma from other cystic lesions. Pooled analysis found that values of less than 37 U/mL had a sensitivity of 19% and specificity of 98% for a serous cystadenoma or pseudocyst.[24] The usefulness of CA19-9 may be limited, however, because concentrations are often raised in inflammatory conditions or when biliary obstruction is present.[40,59]

Two other tumor markers, CA72-4 and CA15-3, were also examined. CA72-4 was able to distinguish mucinous cystadenomas from serous cystadenomas and pseudocysts with 63% sensitivity and 98% specificity,[58] whereas other investigators suggested that CA72-4 is more useful than CEA or CA15-3 estimation, with a sensitivity and specificity of 87.5% and 94%, respectively.[58] CA15-3 was also used to distinguish mucinous cystadenomas from mucinous cystadenocarcinomas. Rubin et al[60] reported that a threshold of 30 U/mL was associated with 100% sensitivity and 100% specificity. At present, however, the performance of tumor markers other than CEA is inadequate for diagnostic purposes, and measurement of these other markers, outside of research studies, is not justified.

Although they are not tumor markers, amylase and lipase concentrations are often measured. Amylase is found in high concentration in pseudocysts and IPMN,[61] with levels greater than 5000 U/L having quoted sensitivities and specificities of 61% to 94% and 58% to 74%, respectively, for differentiating pseudocysts from other PCLs.[14,49]

Other studies have examined the role of molecular markers in the prediction of malignancy in PCLs.[62] K-*ras* mutations are present more frequently in malignant lesions.[63] Khalid et al[64] reported a multicenter U.S. study of cytology, CEA levels, and detailed DNA analysis incorporating DNA quantification, K-*ras* mutation and multiple allelic loss analysis in 113 patients with a variety of PCLs. K-*ras* mutations were highly predictive of a mucinous lesion (odds ratio, 20.9; specificity, 96%). All malignant cysts with negative cytologic evaluation (10 of 40) could be diagnosed as malignant by using DNA analysis. If this approach is verified by other studies, it will offer an exciting step forward in the preoperative identification of patients with malignant PCLs.

DIAGNOSTIC APPROACH

Most patients have already undergone CT before they are referred for EUS. If not, however, a multidetector CT scan of the pancreas, surrounding areas, and liver is recommended. From this scan and the clinical features, a clear diagnosis or at least the decision to resect may be made (e.g., a large macrocystic lesion in the pancreatic tail in a middle-aged woman). When the diagnosis is not clear or surgery is believed to pose a high risk (e.g., a lesion in the pancreatic head in an older patient of borderline fitness status), EUS is indicated. A pragmatic algorithm for the differential diagnosis and management of PCLs is shown in Figure 15.17.

A standard radial or linear EUS examination of the entire pancreas and surrounding structures is performed, and the cystic lesion is then carefully assessed, by noting the features listed in Table 15.4 and in the examination checklist at the end of the chapter (see Video 15.1). If the lesion is clearly a pseudocyst, it is assessed for suitability for endoscopic drainage, either under EUS or endoscopically. When drainage will not be performed in the same procedure, the optimum site for drainage is marked by diathermy, clipping, or submucosal dye injection. If a cystic neoplasm is suspected, or if the diagnosis is unclear, EUS FNA is

TABLE 15.4

Features of Cystic Pancreatic Lesions

	Serous Cystadenoma	Mucinous Cystadenoma/ Carcinoma	IPMN	Solid and Pseudopapillary Neoplasm	Pseudocyst	Simple Cyst
Location	Body/tail > head	Body/tail > head	Arise from main duct or side branch; head > body/tail	Anywhere	Anywhere	Anywhere
Malignant potential	Very low	High	Variable; high	Low (5%-10%)	Nil	Nil
EUS features	Multiple small cysts; often microcystic "honeycomb"; central fibrosis or calcification	Macrocystic (1-3+); can be large; septations; nodularity or papillary projections	Mural nodule or mass arising in dilated main or side branch of PD	Mixed solid-cystic; hemorrhagic center	Unilocular, variable size and wall thickness; echogenic material; features of acute/chronic pancreatitis	Usually small, thin-walled, uniformly echo-poor/ anechoic
Communication with PD	Rare	Rare	Yes, often dilated ++	Rare	Sometimes	No
Vascularity	++	++	+/−	+/−	+/− (variable)	−
Cytology	Bland glycogen-positive cuboidal cells	Columnar/cuboidal, mucin-positive cells; may show atypia, dysplasia, or malignant features	Columnar/cuboidal mucin-positive cells; may show atypia, dysplasia, or malignant features	Heterogeneous; eosinophilic, papillary cells, PAS-positive deposits, vimentin positivity	Macrophages, inflammatory cells, debris	Hypocellular, mainly inflammatory cells
Cyst fluid	Small volume, low viscosity	Often large volume, high viscosity	Small volume, high viscosity	Low viscosity, bloody and necrotic	Large volume, low viscosity, may be blood-stained or turbid	Variable volume, low viscosity, pale fluid
Amylase	Low	Low	Variable, often high	Low	High	Low
CEA	Low	Variable, usually high	Variable	Unknown	Low	Low
Other markers	Low	Variable	Variable	Unknown	Variable	Low

CEA, carcinoembryonic antigen; IPMN, intraductal papillary mucinous neoplasia; PAS, periodic acid–Schiff stain; PD, pancreatic duct.

performed, using a 19- or 22-G needle and with antibiotic coverage (see Video 15.2). The cyst is completely aspirated if at all possible, and the fluid is sent for cytologic examination and measurement of amylase and CEA concentrations. The wall of the cyst or any associated mass or lymph nodes must also be sampled. The patient is observed for 2 to 4 hours after the procedure and is allowed home if well, with written advice about complications and a 3-day supply of oral ciprofloxacin.

FUTURE DEVELOPMENTS

EUS is not without limitations in the evaluation of PCLs (Table 15.5), and these restrictions need to be addressed. Contrast-enhanced EUS and sonoelastography showed promising results in initial studies.[65,66] The ability of tumor markers and amylase estimation to identify PCLs is limited, and further studies of molecular markers are therefore eagerly awaited.

At present, surgical resection is the only curative treatment for pancreatic cystic neoplasms, yet it carries appreciable morbidity and even mortality, especially in patients who may be of borderline fitness status. Carefully conducted long-term EUS follow-up studies of nonresected cysts would be important for understanding the natural history of cystic lesions better. Sahani et al,[15] for example, found that 75 of 86 resected cysts less than 3 cm in size were benign and could have been followed up or managed nonsurgically.

An extensive literature is available on ethanol ablation of nonpancreatic cysts, and extrapolating from this, the possibility of EUS-guided therapy was explored. In a preliminary study, Gan et al[67] reported the feasibility and safety of EUS-guided alcohol injection into pancreatic cystic tumors, with short-term resolution in 62% of patients. A multicenter randomized trial found that one or two ablations resulted in a greater reduction in cyst size compared with saline instillation, with a similar safety profile.[68] Overall, complete pancreatic cyst ablation, as defined

TABLE 15.5

Important Limitations of EUS in the Evaluation of Pancreatic Cystic Lesions

Procedure Aspect	Limitation
Technical	Attenuation of imaging in large (>6 cm) lesions
EUS imaging	Considerable overlap of morphologic features of lesions
FNA	Aspiration of viscous fluid with 22-G needles Small volumes obtained in microcystic lesions Limited accuracy of cytology: contamination with columnar gastroduodenal epithelium; sampling error: dysplasia and malignant change are patchy in mucinous lesions
Amylase concentration	May be raised in lesions that communicate with the pancreatic duct
CEA level	May be raised in infected pseudocysts and lymphoepithelial cysts
Other tumor markers (e.g., CA19-9, CA72-4)	Unproven value; investigational role

CEA, carcinoembryonic antigen; FNA, fine-needle aspiration.

by CT, occurred in one third of patients. Two cases of pancreatitis occurred in the ethanol-treated group (5%), and self-limiting abdominal pain was also noted in 12% to 16%. The combination of ethanol and paclitaxel injection was also reported in one small case series.[69] These newer EUS-guided ablative therapies are discussed in more detail in Chapter 24.

EXAMINATION CHECKLIST

Localize and describe cyst
- Site and size
- Wall thickness
- Distance from lumen; interposed vessels
- Focal irregularity, papillary projections, or mural nodules
- Associated mass lesion
- Central or peripheral calcification
- Septation(s)
- Debris or echogenic material in cyst
- Communication with pancreatic duct

Examine rest of pancreas

Perform EUS-guided fine-needle aspiration (FNA) of all solid lesions

Perform EUS-guided FNA of cyst fluid under antibiotic cover, preferably one pass

Evacuate cyst contents if possible

Determine carcinoembryonic antigen and amylase levels, as well as cytologic features

REFERENCES

1. Zhang XM, Mitchell DG, Dohke M, et al. Pancreatic cysts: depiction on single-shot fast spin-echo MR images. *Radiology*. 2002;223:547–553.
2. Kimura W, Nagai H, Kuroda A, et al. Analysis of small cystic lesions of the pancreas. *Int J Pancreatol*. 1995;18:197–206.
3. Le Borgne J, de Calan L, Partensky C. Cystadenomas and cystadenocarcinomas of the pancreas: a multi-institutional retrospective study of 398 cases. French Surgical Association. *Ann Surg*. 1999;230:152–161.
4. Johnson CD, Stephens DH, Charboneau JW, et al. Cystic pancreatic tumors: CT and sonographic assessment. *AJR Am J Roentgenol*. 1988;151:1133–1138.
5. Bassi C, Salvia R, Molinari E, et al. Management of 100 consecutive cases of pancreatic serous cystadenoma: wait for symptoms and see at imaging or vice versa? *World J Surg*. 2003;27:319–323.
6. Procacci C, Graziani R, Bicego E, et al. Serous cystadenoma of the pancreas: report of 30 cases with emphasis on the imaging findings. *J Comput Assist Tomogr*. 1997;21:373–382.
7. Procacci C, Biasiutti C, Carbognin G, et al. Characterization of cystic tumors of the pancreas: CT accuracy. *J Comput Assist Tomogr*. 1999;23:906–912.
8. Curry CA, Eng J, Horton KM, et al. CT of primary cystic pancreatic neoplasms: can CT be used for patient triage and treatment? *AJR Am J Roentgenol*. 2000; 175:99–103.
9. Walsh RM, Henderson JM, Vogt DP, et al. Prospective preoperative determination of mucinous pancreatic cystic neoplasms. *Surgery*. 2002;132: 628–633; discussion 633–634.
10. Cohen-Scali F, Vilgrain V, Brancatelli G, et al. Discrimination of unilocular macrocystic serous cystadenoma from pancreatic pseudocyst and mucinous cystadenoma with CT: initial observations. *Radiology*. 2003;228: 727–733.
11. Gerke H, Jaffe TA, Mitchell RM, et al. Endoscopic ultrasound and computer tomography are inaccurate methods of classifying cystic pancreatic lesions. *Dig Liver Dis*. 2006;38:39–44.
12. Oh HC, Kim MH, Hwang CY, et al. Cystic lesions of the pancreas: challenging issues in clinical practice. *Am J Gastroenterol*. 2008;103:229–239.
13. Brugge WR, Lewandrowski K, Lee-Lewandrowski E, et al. Diagnosis of pancreatic cystic neoplasms: a report of the Cooperative Pancreatic Cyst Study. *Gastoenterology*. 2004;126:1330–1336.
14. Frossard JL, Amouyal P, Amouyal G, et al. Performance of endosonography-guided fine needle aspiration and biopsy in the diagnosis of pancreatic cystic lesions. *Am J Gastroenterol*. 2003;98:1516–1524.
15. Sahani DV, Saokar A, Hahn PF, Fernandez-Del Castillo C. Pancreatic cysts 3 cm or smaller: how aggressive should treatment be? *Radiology*. 2006;238: 912–919.
16. Pyke CM, van Heerden JA, Colby TV, et al. The spectrum of serous cystadenoma of the pancreas: clinical, pathologic, and surgical aspects. *Ann Surg*. 1992;215:132–139.
17. Lewandrowski K, Warshaw A, Compton C. Macrocystic serous cystadenoma of the pancreas: a morphologic variant differing from microcystic adenoma. *Hum Pathol*. 1992;23:871–875.
18. Ariyama J, Suyama M, Satoh K, Wakabayashi K. Endoscopic ultrasound and intraductal ultrasound in the diagnosis of small pancreatic tumours. *Abdom Imaging*. 1998;23:380–386.
19. Gouhiri M, Soyer P, Barbagelatta M, Rymer R. Macrocystic serous cystadenoma of the pancreas: CT and endosonographic features. *Abdom Imaging*. 1999;24:72–74.
20. Song MH, Lee SK, Kim MH, et al. EUS in the evaluation of pancreatic cystic lesions. *Gastrointest Endosc*. 2003;57:891–896.
21. Gress F, Gottlieb K, Cummings O, et al. Endoscopic ultrasound characteristics of mucinous cystic neoplasms of the pancreas. *Am J Gastroenterol*. 2000;95:961–965.
22. Levy MJ. Pancreatic cysts. *Gastrointest Endosc*. 2009;69(suppl):S110–S116.
23. Centeno BA, Lewandrowski KB, Warshaw AL, et al. Cyst fluid cytologic analysis in the differential diagnosis of pancreatic cystic lesions. *Am J Clin Pathol*. 1994;101:483–487.
24. van der Waaij L, van Dullemen HM, Porte RJ. Cyst fluid analysis in the differential diagnosis of pancreatic cystic lesions: a pooled analysis. *Gastrointest Endosc*. 2005;62:383–389.
25. Strobel O, Z'graggen K, Schmitz-Winnenthal FH, et al. Risk of malignancy in serous cystic neoplasms of the pancreas. *Digestion*. 2003;68:24–33.
26. Sarr MG, Carpenter HA, Prabhakar LP, et al. Clinical and pathologic correlation of 84 mucinous cystic neoplasms of the pancreas: can one reliably differentiate benign from malignant (or premalignant) neoplasms? *Ann Surg*. 2000;231:205–212.
27. Thompson LD, Becker RC, Przygodzki RM, et al. Mucinous cystic neoplasm (mucinous cystadenocarcinoma of low-grade malignant potential) of the pancreas: a clinicopathologic study of 130 cases. *Am J Surg Pathol*. 1999;23:1–16.
28. Zamboni G, Scarpa A, Bogina G, et al. Mucinous cystic tumors of the pancreas: clinicopathological features, prognosis, and relationship to other mucinous cystic tumors. *Am J Surg Pathol*. 1999;23:410–422.
29. Belyaev O, Seelig MH, Muller CA, et al. Intraductal papillary mucinous neoplasms of the pancreas. *J Clin Gastroenterol*. 2008;42:284–294.
30. Sugiyama M, Atomi Y. Extrapancreatic neoplasms occur with unusual frequency in patients with intraductal papillary mucinous tumours of the pancreas. *Am J Gastroenterol*. 1999;94:470–473.
31. Inui K, Nakazawa S, Yoshino J, et al. Mucin-producing tumor of the pancreas: intraluminal ultrasonography. *Hepatogastroenterology*. 1998;45: 1996–2000.
32. Seo DW, Kang GH. Twenty-six cases of mucinous ductal ectasia of the pancreas. *Gastrointest Endosc*. 1999;50:592–594.
33. Hara T, Yamaguchi T, Ishihara T, et al. Diagnosis and patient management of intraductal papillary-mucinous tumor of the pancreas by using peroral pancreatoscopy and intraductal ultrasonography. *Gastroenterology*. 2002; 122:34–43.
34. Telford JJ, Carr-Locke DL. The role of ERCP and pancreatoscopy in cystic and intraductal tumours. *Gastrointest Endosc Clin N Am*. 2002; 96:1429–1434.
35. Luttges J, Zamboni G, Longnecker D, Kloppel G. The immunohistochemical mucin expression pattern distinguishes different types of intraductal papillary mucinous neoplasms of the pancreas and determines their relationship to mucinous noncystic carcinoma and ductal adenocarcinoma. *Am J Surg Pathol*. 2001;25:942–948.
36. Lee DH, Yi BH, Lim JW, Ko YT. Sonographic findings of solid and papillary epithelial neoplasm of the pancreas. *J Ultrasound Med*. 2001;20: 1229–1232.
37. Nadler EP, Novikov A, Landzberg BR, et al. The use of endoscopic ultrasound in the diagnosis of solid pseudopapillary tumors of the pancreas in children. *J Pediatr Surg*. 2002;37:1370–1373.
38. Anagnostopoulos PV, Pipinos II, Rose WW, Elkus R. Lymphoepithelial cyst in the pancreas: a case report and review of the literature. *Dig Surg*. 2000;17:309–314.
39. Sedlack R, Affi A, Vazquez-Sequeiros E, Norton ID, et al. Utility of EUS in the evaluation of cystic pancreatic lesions. *Gastrointest Endosc*. 2002;56: 543–547.
40. Hernandez LV, Mishra G, Forsmark C, et al. Role of endoscopic ultrasound (EUS) and EUS-guided fine needle aspiration in the diagnosis and treatment of cystic lesions of the pancreas. *Pancreas*. 2002;25: 222–228.
41. Koito K, Namieno T, Nagakawa T, et al. Solitary cystic tumor of the pancreas: EUS-pathologic correlation. *Gastrointest Endosc*. 1997;45:268–276.

42. Ahmad NA, Kochman ML, Lewis JD, Ginsberg GG. Can EUS alone differentiate between malignant and benign cystic lesions of the pancreas? *Am J Gastroenterol*. 2001;96:3295–3300.
43. Ahmad NA, Kochman ML, Brensinger C, et al. Interobserver agreement among endosonographers for the diagnosis of neoplastic versus non-neoplastic pancreatic cystic lesions. *Gastrointest Endosc*. 2003;58:59–64.
44. Chatelain D, Hammel P, O'Toole D, et al. Macrocystic form of serous cystadenoma. *Am J Gastroenterol*. 2002;97:2566–2571.
45. Gerke H, Jaffe TA, Mitchell RM, et al. Endoscopic ultrasound and computer tomography are inaccurate methods of classifying cystic pancreatic lesions. *Dig Liver Dis*. 2006;38:39–44.
46. Caturelli E, Rapaccini GL, Anti M, et al. Malignant seeding after fine-needle aspiration biopsy of the pancreas. *Diagn Imaging Clin Med*. 1985;54: 88–91.
47. Giovannini M, Seitz JF, Monges G, et al. Fine needle aspiration cytology guided by endoscopic ultrasonography: results in 141 patients. *Endoscopy*. 1995;27:171–177.
48. Williams DB, Sahai AV, Aabakken L, et al. Endoscopic ultrasound guided fine needle aspiration biopsy: a large single centre experience. *Gut*. 1999; 44:720–726.
49. American Society for Gastrointestinal Endoscopy Standards of Practice Committee. ASGE guideline: the role of endoscopy in the diagnosis and the management of cystic lesions and inflammatory fluid collections of the pancreas. *Gastrointest Endosc*. 2005;61:363–370.
50. Levy MJ, Smyrk TC, Reddy RP, et al. Endoscopic ultrasound-guided trucut biopsy of the cyst wall for diagnosing cystic pancreatic tumors. *Clin Gastroenterol Hepatol*. 2005;3:974–979.
51. Gill KR, Al-Haddad MA, Krishna M, et al. EchoBrush vs. standard endoscopic ultrasound-fine needle aspiration (EUS-FNA) techniques for cytologic evaluation of cystic pancreatic lesions (CPLs): final results of blinded prospective comparison study [abstract]. *Gastrointest Endosc*. 2009;69:AB234–AB235.
52. O'Toole D, Palazzo L, Arotcarena R, et al. Assessment of complications of EUS-guided fine-needle aspiration. *Gastrointest Endosc*. 2001;53:470–474.
53. Lee LS, Saltzman JR, Bounds BC, et al. EUS-guided fine needle aspiration of pancreatic cysts: a retrospective analysis of complications and their predictors. *Clin Gastroenterol Hepatol*. 2005;3:231–236.
54. Brandwein SL, Farrell JJ, Centeno BA, Brugge WR. Detection and tumor staging of malignancy in cystic, intraductal, and solid tumors of the pancreas by EUS. *Gastrointest Endosc*. 2001;53:722–727.
55. Maire F, Couvelard A, Hammel P, et al. Intraductal papillary mucin tumours of the pancreas: the preoperative value of cytologic and histopathologic diagnosis. *Gastrointest Endosc*. 2003;58:701–706.
56. Lai R, Stanley MW, Bardales R, et al. Endoscopic ultrasound-guided pancreatic duct aspiration: diagnostic yield and safety. *Endoscopy*. 2002;34: 715–720.
57. Hammel P, Levy P, Voitot H, et al. Preoperative cyst fluid analysis is useful for the differential diagnosis of cystic lesions of the pancreas. *Gastroenterology*. 1995;108:1230–1235.
58. Hammel P, Voitot H, Vilgrain V, et al. Diagnostic value of CA 72-4 and carcinoembryonic antigen determination in the fluid of pancreatic cystic lesions. *Eur J Gastroenterol Hepatol*. 1998;10:345–348.
59. Sperti C, Pasquali C, Pedrazzoli S, et al. Expression of mucin-like carcinoma-associated antigen in the cyst fluid differentiates mucinous from nonmucinous pancreatic cysts. *Am J Gastroenterol*. 1997;92:672–675.
60. Rubin D, Warshaw AL, Southern JF, Lewandrowski KB, et al. Expression of CA 15.3 protein in the cyst contents distinguishes benign from malignant pancreatic mucinous cystic neoplasms. *Surgery*. 1994;115:52–55.
61. Sand JA, Hyoty MK, Mattila J, et al. Clinical assessment compared with cyst fluid analysis in the differential diagnosis of cystic lesions in the pancreas. *Surgery*. 1996;119:275–280.
62. Khalid A. Differentiating neoplastic from benign lesions of the pancreas: translational techniques. *Clin Gastroenterol Hepatol*. 2009;7(suppl 11): S55–S58.
63. Schoedel KE, Finkelstein SD, Ohori NP. K-Ras and microsatellite marker analysis of fine-needle aspirates from intraductal papillary mucinous neoplasms of the pancreas. *Diagn Cytopathol*. 2006;34:605–608.
64. Khalid A, Zahid M, Finkelstein SD, et al. Pancreatic cyst fluid DNA analysis in evaluating pancreatic cysts: a report of the PANDA study. *Gastrointest Endosc*. 2009;69:1095–1102.
65. Iglesias-Garcia J, Larino-Noia J, Abdulkader A, et al. EUS elastography for the characterization of solid pancreatic masses. *Gastrointest Endosc*. 2009; 70:1101–1108.
66. Giovannini M. Contrast-enhanced endoscopic ultrasound and elastosonoendoscopy. *Best Pract Res Clin Gastroenterol*. 2009;23:767–779.
67. Gan I, Bounds B, Brugge WR. EUS-guided ethanol lavage of cystic lesions of the pancreas is feasible and safe [abstract]. *Gastrointest Endosc*. 2004;59: AB94.
68. DeWitt J, McGreevy K, Schmidt CM, Brugge WR. EUS-guided ethanol versus saline solution lavage for pancreatic cysts: a randomized, double-blind study. *Gastrointest Endosc*. 2009;70:710–723.
69. Oh HC, Seo DW, Lee TY, et al. New treatment for cystic tumors of the pancreas: EUS guided ethanol lavage with paclitaxel injection. *Gastrointest Endosc*. 2008;67:636–642.

CHAPTER 16 EUS IN BILE DUCT, GALLBLADDER, AND AMPULLARY LESIONS

Bertrand Napoléon | M. Victoria Alvarez-Sánchez | Costas Markoglou | Christine Lefort

Key Points

In patients with low or moderate risk of common bile duct (CBD) stones, EUS is recommended before endoscopic retrograde cholangiopancreatography (ERCP) is performed.

In patients with acute pancreatitis of unknown origin or right hypochondrial pain with normal transabdominal ultrasonographic findings, EUS should be considered.

In patients with a CBD stricture of unknown origin, EUS should be performed and, if inconclusive, followed by ERCP with tissue sampling with or without intraductal ultrasonography (IDUS).

Gallbladder polyps larger than 5 mm in diameter may be investigated with EUS to determine the risk of malignancy and the therapeutic approach.

Ampullary tumors can be staged with EUS and IDUS. EUS is best to differentiate between early (adenoma, T1) and advanced (T2 to T4) tumors. IDUS may help to stage early tumors.

BILE DUCT STONES

Endoscopic retrograde cholangiopancreatography (ERCP) has long been considered the best diagnostic method for common bile duct (CBD) stones. Moreover, ERCP allows stone removal during the same endoscopic session when it is combined with endoscopic sphincterotomy (EST). Nevertheless, ERCP remains an invasive method with substantial complications,[1–3] although when the procedure is performed by experienced endoscopists, the complications and mortality rates can decrease to less than 5% and 0.1% respectively.[4] Furthermore, because it can be difficult to differentiate small stones from aerobilia, many ERCP procedures are completed with EST, to confirm the diagnosis of choledocholithiasis. EST has a complication rate of 5% to 10%,[5–8] with a current mortality rate lower than 1%.[5–10] Long-term sequelae, such as stenosis and nonobstructive cholangitis, occur in 10% of patients overall,[11–13] because of the permanent loss of biliary sphincter function.[14]

An accurate diagnostic tool associated with lower morbidity and mortality rates was awaited, to replace ERCP and to reserve EST for patients with CBD stones. ERCP remained the first-line examination until the appearance of transcutaneous abdominal ultrasonography (US). Nowadays, in patients presenting with clinical or laboratory suspicion of CBD stones, US is always used for the initial diagnostic evaluation. However, although US is very specific for the diagnosis of choledocholithiasis, it is not particularly sensitive,[15,16] even though the calcium present within CBD stones is a strong reflector of ultrasound waves. Adjacent duodenal air interferes with imaging of the distal bile duct, and the ultrasound beam is often attenuated in obese patients. Computed tomography (CT) also has an unacceptably low sensitivity.

Helical CT, multidetector CT, endoscopic ultrasonography (EUS), and magnetic resonance cholangiopancreatography (MRCP) have improved the diagnosis of CBD stones and preclude the need for cholangiography (ERCP or perioperative opacification). The sensitivity, specificity, and accuracy of helical CT range from 85% to 88%, 88% to 97%, and 86% to 94%, respectively.[17,18] In one comparative study with MRCP and EUS, helical CT remained inferior,[19] although multiplanar reconstructions with multidetector CT improved specificity.[20,21] Therefore, EUS and MRCP are the most accurate minimally invasive methods for diagnosing CBD stones. Some questions remain, however. What are the respective performances of EUS, and MRCP? What is the best endosonographic approach (radial, linear, or intraductal)? What is the respective place of EUS, MRCP, and ERCP in the evaluation of bile duct stones? In this chapter, an attempt is made to answer these questions by objective evaluation of the literature.

What Are the Respective Performances of EUS and MRCP?

EUS provides excellent sonographic visualization of the extrahepatic biliary tree. Bile duct stones are shown as echo-rich structures (Fig. 16.1) within the ampulla or CBD, possibly moving within the bile duct, with or without acoustic shadowing or inflammatory thickening of the bile duct (Fig. 16.2). The accuracy of EUS is better than that of ERCP for the detection of small CBD stones[22] (Fig. 16.3), with minimal or no invasiveness[23–25] and a lower technical failure rate.[25,26] The specificity of EUS in ruling out the presence of CBD stones was 98%[27] in some series. EUS detects bile duct sludge as well as microlithiasis (Fig. 16.4), often missed by the other imaging techniques.[28]

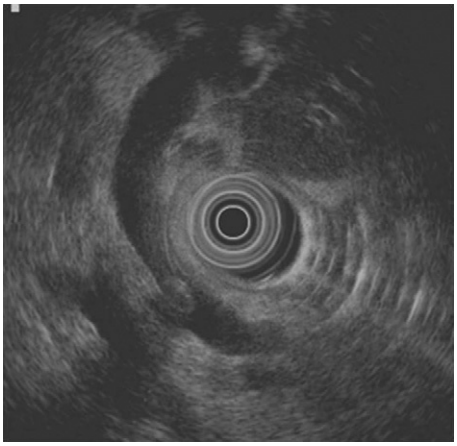


FIGURE 16.1 Common bile duct stone as imaged using a radial echoendoscope

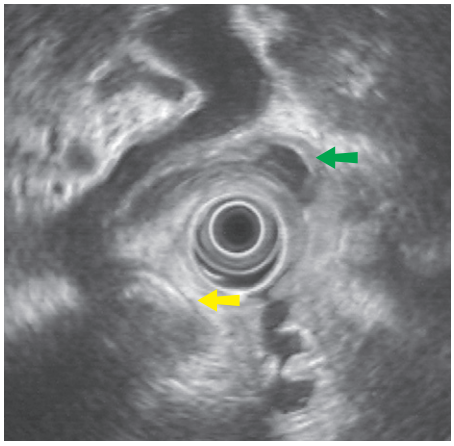


FIGURE 16.2 Common bile duct stone (*yellow arrow*) with cystic wall thickening (*green arrow*).

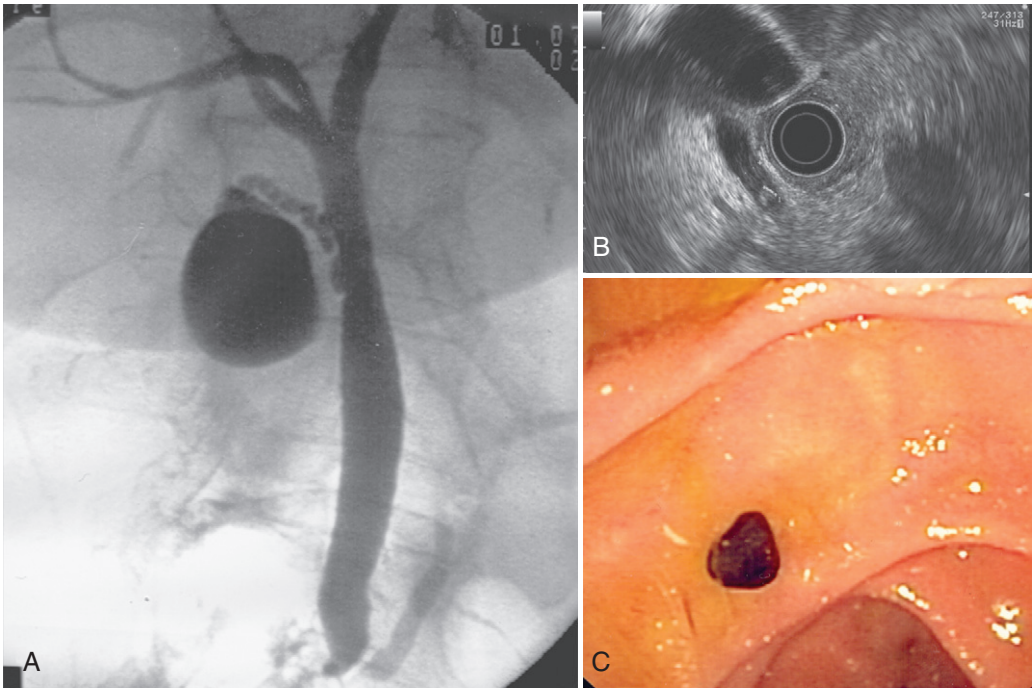


FIGURE 16.3 Common bile duct (CBD) stone. Small CBD stone not seen at endoscopic retrograde cholangiopancreatography (**A**) but identified at EUS (**B**) and confirmed by biliary sphincterotomy (**C**).

MRCP is a completely noninvasive procedure regarded as more accurate than CT for the diagnosis of choledocholithiasis.[19,29] The two main disadvantages of this technique are the limited spatial resolution and the difficulty of diagnosing CBD stones in the peripapillary region. Moreover, MRCP is absolutely contraindicated in patients with a permanent pacemaker or cerebral aneurysm clips, and claustrophobic patients (estimated to represent 4% of the population[30]) cannot undergo the examination. EUS offers higher resolution than MRCP (0.1 versus 1 to 1.5 mm), and its detection rate of choledocholithiasis does not vary with stone size, unlike in MRCP.[31,32] Thus, it was not surprising when investigators reported that stones not diagnosed with MRCP were always smaller than 10 mm[33–35] and that the sensitivity of MRCP decreased to approximately 65% for diagnosing stones smaller than 5 mm.[19,32,34] Nevertheless, future improvements in imaging may permit the detection of smaller calculi, as shown in one series.[36]

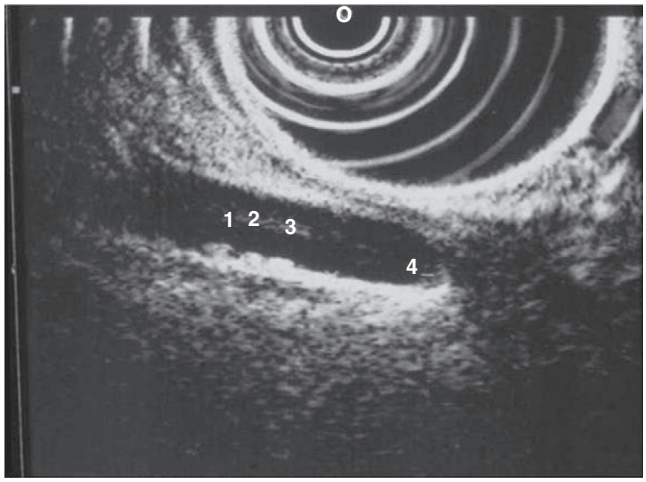


FIGURE 16.4 Common bile duct microlithiasis (n = 4). *(Courtesy of Mohamad Eloubeidi, MD.)*

TABLE 16.1

Performance of EUS in the Diagnosis of Common Bile Duct Stones

Authors (yr)	Level of Proof*	Patients (*n*)	Frequency of CBD stones (%)	EUS				
				Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Prat et al[39] (1996)	1	119	66	93	97	98	88	95
Kohut et al[40] (2002)	1	134	68	93	93	98	87	94
Meroni et al[41] (2004)	1	47	15	71	90	55	95	—
Aubertin et al[42] (1996)	1	50	24	96	96	92	100	98
Canto et al[23] (1998)	2	64	30	84	98	94	93	94
Napoléon et al[22] (2003)	2	334	22	81	96	85	94	93
Buscarini et al[43] (2003)	2	463	52	98	99	99	98	97
Aubé et al[36] (2005)	2	45	34	94	97	94	97	96
Berdah et al[38] (2001)	2	68	20	96	97	93	100	98
Burtin et al[45] (1997)	2	68	49	97	98	100	96	98
Chak et al[109] (1999)	2	31	36	88	98	100	95	97
Dancygier et al[46] (1994)	2	31	39	96	50	100	—	98
Kohut et al[47] (2003)	2	55	9	75	99	100	98	98
Ney et al[48] (2005)	2	68	32	96	99	100	97	98
Norton et al[49] (1997)	2	50	48	86	94	95	89	92
Liu et al[110] (2001)	2	139	35	98	98	100	96	99
Prat et al[50] (2001)	2	123	27	100	100	100	100	100
Shim et al[55] (1995)	3	132	21	89	100	100	97	98
Palazzo et al[26] (1995)	3	422	36	95	98	—	—	96
Amouyal et al[56] (1994)	3	62	36	97	100	94	97	96
Sugiyama and Atomi[54] (1997)	3	142	36	97	99	100	95	98
Materne et al[53] (2000)	3	50	26	97	88	94	93	94
De Ledinghen et al[52] (1999)	3	32	31	100	95	91	100	97
Kondo et al[19] (2005)	3	30	86	98	50	92	100	93
Dittrick et al[62] (2005)	3	30	37	100	84	56	100	—
Latcher et al[63] (2000)	3	50	66	96	75	89	93	94
Ainsworth et al[64] (2004)	3	163	33	90	99	98	94	93
Scheiman et al[51] (2001)	3	28	18	80	95	80	96	—
Montariol et al[65] (1998)	3	215	19	85	93	75	96	92

*Level 1, technique compared with endoscopic retrograde cholangiopancreatography (ERCP) + systematic endoscopic sphincterotomy (EST) with a very short interval between the technique and ERCP; level 2, technique compared with ERCP + EST if positive, and clinical and biologic follow-up of at least 6 months if negative; level 3, technique compared with ERCP or with perioperative cholangiography.

CBD, common bile duct; NPV, negative predictive value; PPV, positive predictive value.

To compare the performance of each technique, some parameters must be considered. The first consideration is the delay between the performance of the technique being evaluated and the "gold standard" examination. In fact, spontaneous stone migration between the two examinations can lead to false-positive results. In a study of discrepancies between EUS and ERCP in relation to the time elapsed between the two procedures, stone migration was found to have occurred in 21% of patients within 1 month.[37] Ideally, in comparative studies, the gold standard examination should be performed immediately after the evaluated technique, or at least during the subsequent 48 hours. Second, the perfect,"gold standard" is a matter of debate. ERCP and perioperative cholangiography are the reference techniques most commonly chosen. Nevertheless, it is well known that opacification alone is not sufficient to exclude CBD stones, because its sensitivity is approximately 90% (89% in a study comparing EUS and ERCP). The best gold standard is the association of ERCP, EST, and instrumental exploration of the CBD (with a Dormia basket or balloon). However, because of associated morbidity and mortality, it is difficult ethically to propose this approach in patients at low or moderate risk of CBD stones. Another approach in these patients would be to perform ERCP, EST, and bile duct exploration when a stone is evidenced, and to follow up the patient when the diagnosis of a stone has been excluded. Because some patients with CBD stones missed by the investigation remain symptom free for a long time, follow-up must be sufficiently long for adequate conclusions to be drawn. In series in which patients were followed for up to 1 year, no stone was evidenced after 6 months of follow-up.[22,38] Six months should therefore be the standard follow-up period.

Publications evaluating the respective performances of EUS and MRCP can therefore be classified into three groups (Tables 16.1 and 16.2), according to the level of proof, from the more significant to the less significant:

1. The technique is compared with the gold standard (ERCP, EST, and CBD instrumental exploration) with a very short interval between the two examinations.[39–42]
2. The technique is compared with ERCP and EST if a stone is evidenced, and with clinical and biologic follow-up of at least 6 months if not.[22,23,36,38,43–50]
3. The technique is compared with cholangiography (ERCP or perioperative cholangiography).[19,26,51–65]

Since the 1990s, studies have investigated the issue of EUS and MRCP for the diagnosis of choledocholithiasis. The diagnostic performance of EUS was evaluated in two meta-analyses covering 2673 and 3532 patients.[66,67] The pooled sensitivity and specificity of EUS were 89% to 94% and 94% to 95%, respectively. Evidence for the use of MRCP for the diagnosis of CBD stones was examined in a systematic review of 10 studies; MRCP achieved a high sensitivity (range, 80% to 100%) and specificity (range, 83% to 98%).[68] Depending on comparative studies, EUS was found to be superior[36,37] or equivalent[1,36,53,64,65] to MRCP (Table 16.3).[69–76] Two meta-analyses[77,78] comparing EUS and MRCP for depicting CBD stones showed high diagnostic performance for both modalities. Although no statistically significant

TABLE 16.2

Performance of Magnetic Resonance Cholangiopancreatography in the Diagnosis of Common Bile Duct Stones

			Magnetic Resonance Cholangiopancreatography				
Authors (yr)	Level of Proof*	Patients (*n*)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Gautier et al[44] (2004)	2	99	96	99	—	—	—
Aubé et al[36] (2005)	2	45	88	97	93	93	—
Modifi et al[69] (2008)	2	49	100	96	—	—	—
Topal et al[70] (2003)	2	315	95	100	100	98	—
Cervi et al[57] (2000)	3	60	100	94	—	—	—
Demartines[58] (2000)	3	70	100	96	93	100	—
Kim et al[59] (2002)	3	121	95	95	—	—	95
Stiris et al[60] (2000)	3	50	88	94	97	81	—
Taylor et al[61] (2002)	3	146	98	89	84	99	—
Materne et al[53] (2000)	3	50	91	94	88	95	92
De Ledinghen et al[52] (1999)	3	32	100	73	62	100	82
Kondo et al[19] (2005)	3	30	88	75	96	50	86
Ainsworth et al[64] (2004)	3	163	87	97	95	93	—
Scheiman et al[51] (2001)	3	28	40	96	66	88	—
Ausch et al[71] (2005)	3	773	94	98	80	99	—
Griffin et al[72] (2003)	3	115	84	96	91	93	92
De Waele et al[73] (2007)	3	104	83	98	91	95	94
Hallal et al[74] (2005)	3	29	100	91	50	100	92
Makary et al[75] (2005)	3	64	94	98	94	98	—
Moon et al[76] (2005)	3	32	80	83	89	71	81

*Level 1, technique compared with endoscopic retrograde cholangiopancreatography (ERCP) + systematic endoscopic sphincterotomy (EST) with a very short interval between the technique and ERCP; level 2, technique compared with ERCP + EST if positive, and clinical and biologic follow-up of at least 6 months if negative; level 3, technique compared with ERCP or with perioperative cholangiography.

NPV, negative predictive value; PPV, positive predictive value.

TABLE 16.3

Comparative Performance of EUS and Magnetic Resonance Cholangiopancreatography in the Diagnosis of Bile Duct Stones (Mean and Variance of Diagnostic Variables as Proportions)

Aggregated Variables	EUS (95% CI)	MRCP (95% CI)
Sensitivity	0.93 (0.87-0.98)	0.85 (0.77-0.93)
Specificity	0.96 (0.91-1.0)	0.93 (0.88-0.98)
Positive predictive value	0.93 (0.87-0.99)	0.92 (0.87-0.96)
Negative predictive value	0.96 (0.94-0.98)	0.92 (0.87-0.96)

CI, confidence interval; MRCP, magnetic resonance cholangiopancreatography.
Adapted from Verma D, Kapadia A, Eisen GM, et al. EUS vs MRCP for detection of choledocholithiasis. *Gastrointest Endosc.* 2006;64:248-254.

differences were evidenced, EUS had trend a toward higher sensitivity and specificity (93% and 88% to 96%, respectively) than MRCP (83% to 85% and 89% to 93%, respectively). Therefore, EUS should be preferred to MRCP. This is especially obvious when small stones are possible, as in acute biliary pancreatitis. Nevertheless, depending on countries and local resources, the choice between these two techniques should also take into consideration other factors such as procedure availability, physician experience, and cost.

What Is the Best Endosonographic Approach (Radial, Linear, or Intraductal)?

In all the foregoing series, radial echoendoscopes were used. Nevertheless, the accuracy seems comparable to that of linear echoendoscopes, as indicated in three series[40,63,79] that compared linear EUS with ERCP plus EST or choledochotomy with choledochoscopy (see Table 16.1).

The use of extraductal catheter probe EUS (EDUS) was also evaluated in two studies.[42,80] In the earlier published prospective study, EDUS with a radial scanning catheter probe was performed before ERCP and EST in patients with suspected CBD stones or other bile flow obstruction of the distal CBD.[80] EDUS detected 33 of 34 bile duct stones. In eight patients, the stones were missed on ERCP and were seen with EST. More recently, the same group conducted another prospective trial to compare the diagnostic potential of EDUS with that of conventional EUS.[79] In this study, EDUS was nearly as accurate as linear array EUS.

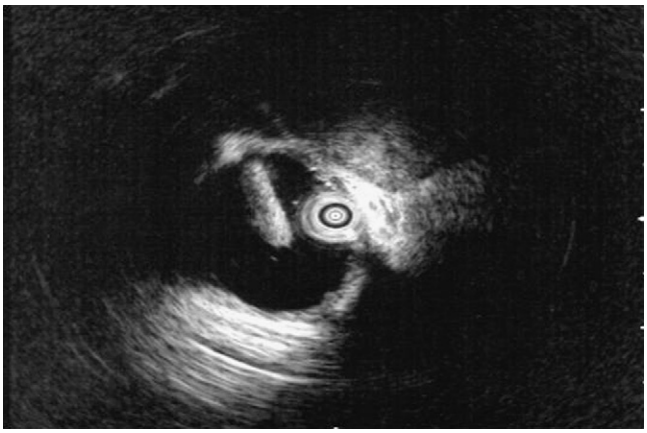


FIGURE 16.5 Common bile duct stone seen at intraductal ultrasonography.

Intraductal ultrasonography (IDUS) has also been proposed for this indication (Fig. 16.5). In a prospective study of patients with suspected CBD stones who underwent ERCP, IDUS was performed in those with equivocal cholangiograms or cholangiographic evidence of stones. IDUS revealed false-positive as well as false-negative results. No lithiasis was found in 36% of patients with a positive finding on ERCP. This result, according to the investigators, was partly caused by the existence of aerobilia. In 35% of patients with a negative ERCP result, sludge or stones were found on IDUS and confirmed following EST. IDUS led to a change in management in 37% of patients.[81] Another study demonstrated that additional IDUS to confirm complete stone clearance after EST decreased the recurrence rate of CBD stones

(13.2% in the non-IDUS group and 3.4% in the IDUS group).[82] The comparative sensitivity for the diagnosis of choledocholithiasis of MRCP, ERCP, and IDUS was 80%, 90%, and 95%, respectively, in a prospective trial showing that accuracy of IDUS plus ERCP was superior to that of ERCP alone.[83] However, IDUS cannot be proposed as a routine procedure because of the morbidity associated with ERCP. It may be proposed, before EST, in patients in whom CBD stones have been found at EUS or MRCP, but not at ERCP, or in addition to EST to confirm complete stone clearance.

What Is the Respective Place of EUS, MRCP, and ERCP?

The performance of alternative imaging procedures results in a considerable reduction in the numbers of inappropriate invasive investigations of the bile duct.[22,25,43,84–86] One meta-analysis comparing an EUS-guided ERCP strategy with an ERCP-only strategy found that the use of EUS significantly reduced the risk of overall complications (relative risk, 0.35) by safely avoiding ERCP in 67.1% of patients.[86]

A question remains about performing unnecessary EUS or MRCP before ERCP in patients suspected of harboring a CBD stone. Patients suspected of having CBD stones on clinical and laboratory criteria or ultrasound findings can be grouped into risk classes, ranging from low to high.[87,88] The definition of risk classes is not uniform in the literature.[88–91] The criteria used are variable and do not allow a true comparison of the series. Nevertheless, when one considers the main series, the proportion of high-risk patients who actually have CBD stones is less than 80% (66% to 78%),[23,38,39,43,92] whereas fewer than 40% of patients classified as being at intermediate (also called moderate) risk have choledocholithiasis (19% to 44%).[23,26,38,39,54–56,77] Most investigators consider that ERCP could be performed as a first-line approach in patients at high risk of CBD stones,[22–23,26,89] although it may be impossible to avoid unnecessary ERCP completely.[93] EUS as a first-line approach, in patients at high risk, has already found some support either to exclude a stone or to demonstrate another cause of biliary symptoms.[29,43] Moreover, EUS should enhance the efficiency of EST by encouraging the use of aggressive techniques, such as precut papillotomy, when appropriate. However, no general agreement has been reached with regard to the clinical applicability of EUS, particularly when compared with ERCP.[94] The best approach is probably to perform EUS with or without EST (when a stone is evidenced) during the same endoscopic procedure (Video 16.1).

For intermediate-risk patients, the general consensus is to consider EUS (or MRCP) as the first-line diagnostic approach (after US).[25,84–86] This approach was evaluated in the context of laparoscopic cholecystectomy.[38] First-line ERCP was performed in patients considered to be at high risk according to preoperative criteria, and EUS was carried out before laparoscopic cholecystectomy in intermediate-risk patients. EUS followed by EST, if needed, was performed in 35% of the patients. Choledocholithiasis was found in 19% of patients at intermediate risk and in 78% of those at high risk. This endoscopic approach for choledocholithiasis and laparoscopic approach for gallstones proved to be an efficient option, optimized by the use of EUS. After a mean follow-up of 32 months, no retained stones were found in this series of 300 patients. For low-risk patients, the approach will differ depending on the definition. When low-risk patients are defined as patients with some symptoms compatible with CBD stones, some liver test abnormalities, or enlarged CBD at US, they should be treated as intermediate-risk patients. Conversely, when low-risk patients are defined as patients with no symptoms of CBD stones, no liver test abnormalities, and no CBD dilatation at US, no further examination is warranted. Figure 16.6 is an algorithm for investigation of patients with suspected CBD stones according to risk stratification.

With regard to cost effectiveness, the trend is toward a financial advantage of a first-line EUS strategy. In a prospective study of 485 patients suspected of having CBD stones, EUS was always performed, whether the patient had been classified as high risk or not. Positive EUS results were confirmed by ERCP and EST. The mean cost for patients managed by the EUS-based strategy was significantly lower than that for patients who had ERCP.[43] The EUS-guided ERCP strategy resulted in a 14% reduction in ERCP procedures, and it was also cost saving in another retrospective study of a similar group of patients.[95] Other investigators found that EUS was the most cost-effective strategy in the intermediate-risk group, whereas in patients with a probability of CBD stones greater than 50% (high-risk group), the most

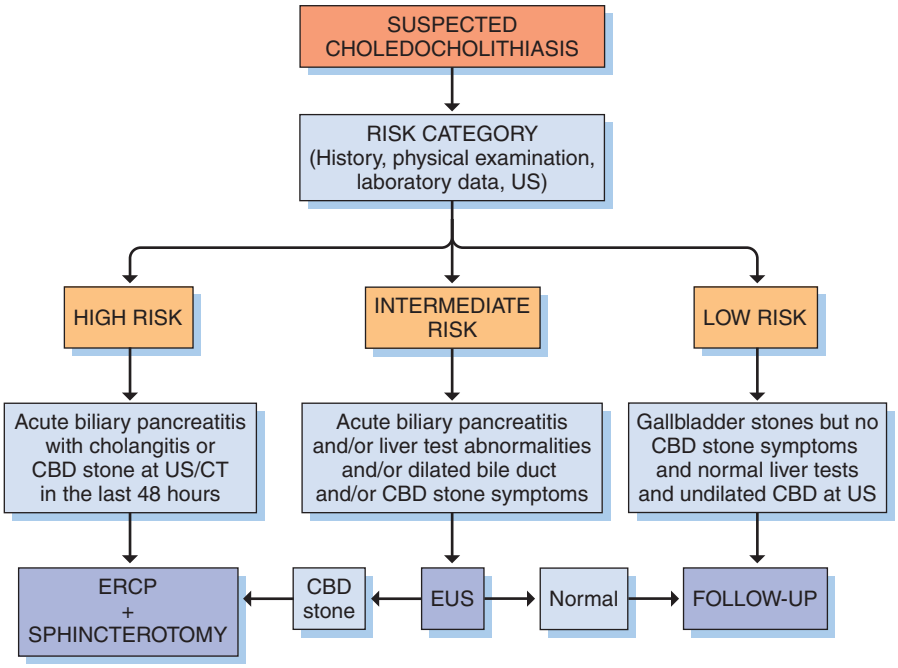


FIGURE 16.6 Algorithm in patients with suspected choledocholithiasis. CBD, common bile duct; CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; US, ultrasonography.

cost-effective approach was to perform ERCP first.[23,64,93,96] In patients with acute pancreatitis, an economic evaluation highlighted that EUS was the dominant strategy with lower costs, fewer procedures, and fewer complications. This was especially obvious in patients with severe acute pancreatitis.[97] Finally, a randomized study comparing EUS plus ERCP during the same endoscopic session and EUS plus ERCP in two separate sessions for the management of choledocholithiasis showed that the average procedure time and days of hospitalization were significantly reduced ($P > .001$) in the first group. This resulted in significant differences in terms of hospitalization rate and total costs.[98] As always, the estimation of cost will differ depending on countries and health care systems. It is also influenced by local operator expertise. The skill of the operator is crucial, not only for the accuracy of EUS, but also for the performance and complication rate of ERCP and the subsequent need for repeated explorations.

Finally, EUS is the ideal alternative to cholangiography. Only those patients with CBD stones would be selected for ERCP and EST. MRCP should be reserved for patients who have contraindications to EUS or when the availability of EUS is limited. The need for ERCP could be obviated, if biliary EUS proved normal,[22,25,85,86] unless symptoms persisted or recurred during follow-up. The best approach, when there is clinical, biochemical, or ultrasound suspicion of a CBD stone, is to perform EUS and then ERCP as indicated (by EUS findings) on the same day by experienced physicians in specialized centers. When this approach is impossible, high-risk patients may be managed with ERCP initially.

EUS and Gallstones

The performance of abdominal US in diagnosing gallstones is excellent. A meta-analysis showed a sensitivity and specificity of 97% and 95%, respectively.[99] After adjustment, the sensitivity decreased to 88%. Sensitivity is lower for small stones with a diameter of less than 3 mm, for cystic stones, and in "difficult" patients, for example, those with obesity or meteorism. The use of bile crystal analysis is justified when discordance is noted between negative US findings and symptoms.[100] Because of the value of EUS in diagnosing small CBD stones, this procedure has also been evaluated in the gallbladder (Fig. 16.7). The first series of Dill et al[101] in 1995 showed that EUS was as accurate as crystal bile analysis for the diagnosis of microlithiasis (Fig. 16.8), and EUS failed on only one occasion to demonstrate microlithiasis in a group of 58 patients with biliary-type pain and negative US findings. Subsequently, the utility of EUS in the detection of cholecystolithiasis in patients with biliary pain and normal results of US was also supported by three other studies showing EUS to be a promising modality that could influence the management plan of these patients.[102–104] In one of these studies,[103] the sensitivity of EUS for the diagnosis of gallstones was 96%, and the specificity was 86%.

Some patients with acute idiopathic pancreatitis have biliary sludge or microlithiasis undetected by other imaging techniques. Although the reported incidence of occult gallstones is widely variable, ranging from 10% to 73%,[105–108] gallstones remain the most common cause of pancreatitis in patients with an intact gallbladder. Gallstones were found by EUS in 14 of 18 patients with negative findings on US by Liu et al[27] in 2000. In a 1999 study performed by Chak et al[109] that compared EUS and US, the sensitivity was 91% versus 50%, and the accuracy was 97% versus 83%, respectively. In a larger series,[28] 168 patients referred with a diagnosis of idiopathic pancreatitis were evaluated. EUS identified gallbladder lithiasis (sludge or very small stones) in 40% of patients, whether or not it was associated with CBD stones, that had been missed by other examinations. Overall, EUS was able to find a cause of the acute pancreatitis in 80% of patients (Video 16.2). In addition, EUS established a presumptive diagnosis in 31% of 201 patients with a single episode of unexplained attack in another study, by Yusoff et al.[111] The most frequent causes of these attacks in patients with a gallbladder were chronic pancreatitis and biliary sludge.

A systematic review evaluating the role of EUS in idiopathic pancreatitis showed a high diagnostic yield, especially in patients with a single idiopathic episode, and in patients with recurrent idiopathic attacks and gallbladder in situ.[112] Moreover, a cost minimization analysis identified EUS as the most cost-effective initial test in the evaluation of idiopathic pancreatitis when EUS was compared with other strategies (ERCP with manometry and bile aspiration, and laparoscopic cholecystectomy).[113] Therefore, an EUS-based strategy seems to be the best approach to evaluate patients with idiopathic pancreatitis because of the high diagnostic accuracy of EUS, not only for gallbladder sludge and stones, but also for pancreatic diseases and because of the minimally invasive nature of this technique. In patients with multiple unexplained attacks, particularly after cholecystectomy, ERCP and sphincter of Oddi manometry should be considered if results of EUS are negative.

Summary

EUS is the most effective method for confirming the presence or absence of CBD stones. Its use in avoiding unnecessary ERCP or EST has been validated in patients at low or moderate risk of CBD stones. MRCP can probably be used as an alternative but with two limitations: (1) older-generation equipment should be avoided if possible; and (2) EUS is still preferred in the setting of acute pancreatitis, in which symptomatic stones can be very small. For patients at high risk of CBD stones, two approaches can be considered: (1) ERCP with or without EST (when CBD stones are seen during cholangiography) or EUS with or without

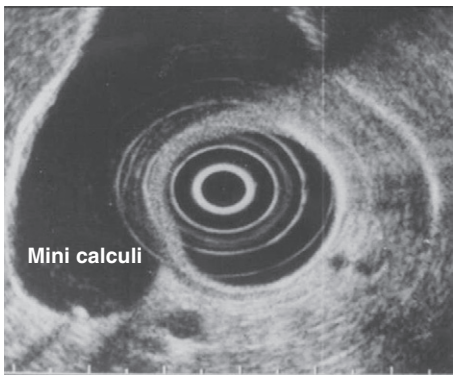


FIGURE 16.7 Gallstones.

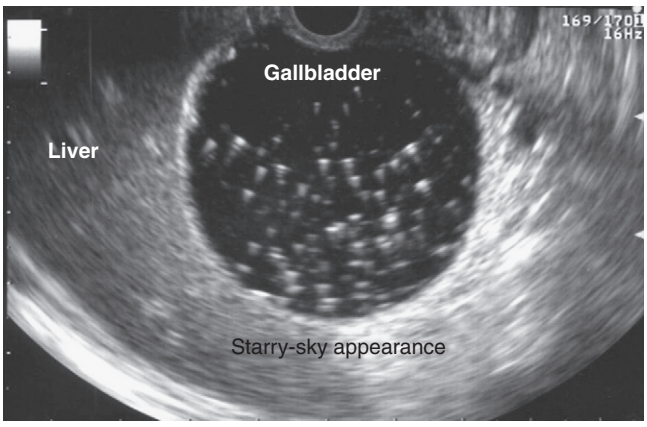


FIGURE 16.8 Gallbladder microlithiasis (appears as "stary-sky").

EST carried out during the same session (when CBD stones are noted by EUS). EUS is now the second-line examination after US for the diagnosis of gallbladder lithiasis in patients with unexplained right hypochondrial pain and in patients with acute pancreatitis of unknown origin.

DIAGNOSTIC CHECKLIST: BILE DUCT STONES

Common bile duct stone or gallstone
- Hyperechoic mobile image with or without acoustic shadowing

Associated signs
- Dilation of extrahepatic ducts and/or cystic duct
- Thickening of the gallbladder and/or ductal walls
- Thickening of the ampulla
- Perigallbladder fluid

BILE DUCT TUMORS

Diagnosis of the nature of bile duct strictures and staging of cholangiocarcinomas remain challenges for the gastroenterologist. Although transcutaneous US and helical CT can reliably demonstrate dilated bile ducts, they allow assessment of the cause in only two thirds of cases.[16,114] Apart from contiguous tumor invasion or metastasis, MRCP appears to be no better than ERCP in the diagnosis of malignancy.[115] ERCP has high diagnostic accuracy in the confirmation of obstructive jaundice, but the diagnostic information obtained for tumor-associated obstruction is limited because only indirect tumor signs such as stenosis, prestenotic dilation, or both are visualized, and the tumor itself is generally not seen. Intraductal tissue samplings are commonly used at the time of ERCP.

Brushing has poor results in the diagnosis of bile duct tumors, owing to the desmoplastic nature of these tumors, and results are frequently negative for extrinsic tumors (pancreatic cancer, gallbladder cancer, metastatic lymph nodes).[116] Forceps biopsy during ERCP has a higher sensitivity than does ERCP brush cytology,[117,118] but it is also limited, except in malignant polypoid lesions. This situation led to the development of techniques that abrade the tumor surface to improve cytologic yield. The combination of stricture dilation to 10-Fr, endoscopic needle aspiration and biliary brush cytology was shown to improve the diagnostic yield in malignant strictures significantly compared with brushings alone.[119] Nevertheless, these results have not been confirmed.[120]

Bile duct biopsy during cholangioscopy[121,122] is the most effective method, with a sensitivity of 93% to 96%. However, cholangioscopy remains an invasive procedure rarely performed in Western countries. Moreover, the problem of identifying the cause and characteristics of a biliary stricture remains, even when both invasive and noninvasive imaging procedures are available.[123,124]

How Can EUS and IDUS Overcome These Difficulties?

EUS has proved to be a useful tool in biliary obstruction because it readily visualizes the CBD. Therefore, it can be helpful in the differential diagnosis of bile duct strictures and neoplasias, as well as in local tumor staging (Fig. 16.9).[125–128] In a meta-analysis of nine studies with a total of 555 patients, EUS had an estimated sensitivity of 78% and a specificity of 84% in detecting malignant biliary strictures.[66]

The ability to yield tissue by EUS-guided fine-needle aspiration (FNA) significantly improves the diagnostic yield when evaluating biliary strictures, with minimal risk of complications. Because the distal CBD is located immediately under the echoendoscope transducer when it is examined from the duodenal bulb, EUS performs extremely well for evaluating distal biliary strictures. Thus, EUS FNA is highly accurate in diagnosing malignancy in distal biliary strictures, particularly in patients with pancreatic head masses.[129–136] In this setting, the overall EUS FNA sensitivity and specificity rates range from 84% to 91% and from 71% to 100%, respectively.[133–138] Nevertheless, reported accuracies are lower for cholangiocarcinomas, mainly because of the difficult approach to the hilar cholangiocarcinomas (Klatskin tumors). Most proximal biliary strictures are cholangiocarcinomas, but as many as 20% have benign causes, and imaging features are not sufficient to differentiate between benign and malignant strictures.

Cytologic diagnosis is helpful for planning appropriate management and to avoid unnecessary surgery. However, the evaluation of hilar biliary strictures is challenging. Imaging the hepatic hilum is more difficult because it frequently is too far from the probe. Proximal biliary lesions tend to be small and diffusely infiltrating, unlike distal biliary lesions, which frequently manifest as solid masses. The diagnostic sensitivity of EUS FNA is reported to be 45% to 86% for all biliary strictures, whereas the sensitivity and negative predictive value (NPV) for proximal biliary strictures are 25% to 89% and 29% to 67%, respectively (Table 16.4).[138–145] These percentages may overestimate the real performance of EUS FNA in hilar strictures because most of the studies included a mixture of proximal and distal strictures.

Technologic advances seem promising. Limited experience with a forward-viewing linear echoendoscope (GF-UCT160J-AL5, Olympus Medical System Europe, Hamburg) suggests improved imaging of hilar strictures and an easier EUS FNA technique.[146]

With the advent of high-frequency (20-MHz) mini-probes over a guidewire, IDUS has emerged as a feasible and potentially useful imaging technique in the diagnosis of biliary stricture. Mini-probes can now be easily inserted through the papilla without prior papillotomy. In a minority of patients (11%), sphincterotomy is necessary to introduce the guidewire.[147] IDUS provides an accurate image of the bile duct wall and surrounding tissue. Even when the penetration depth is limited (2 cm), this is sufficient to provide a precise image of an intraductal lesion (Fig. 16.10) and possible invasion or compression of adjacent structures. IDUS is faster and easier to learn than conventional EUS. It should be performed before drainage, to avoid inflammatory artifacts, and therefore should be better performed by ERCP experts during the same procedure.[148] Complete examination of bile duct strictures is possible in the majority of patients. The literature indicates that IDUS could be used to pass through biliary strictures in 86% to 100% of cases,[119,147,149–154] which are mostly patients who did not have previous dilation. Most failures resulted from tight strictures of the hilum or intrahepatic ducts that the guidewire could not cross.[147,149,150]

In Klatskin tumors, the examination is generally possible from the opposite side when the right or left hepatic duct stenosis cannot be crossed by the probe. The presence of the guidewire in the bile duct throughout the procedure does not often interfere with US imaging (in case of artifact, the guidewire could be removed before IDUS). The most recent generation of IDUS (three-dimensional IDUS imaging system; Olympus Medical Systems, Tokyo, Japan) consists of an ultrasonic probe that is automatically moved for scanning within an external tube. It carries out linear and radial scanning simultaneously in real time with one scanning operation. Three-dimensional images can be generated automatically, and the time required for the examination is reduced compared with two-dimensional IDUS. Some investigators[155] suggested that three-dimensional IDUS could be more useful for evaluating the extent of cholangiocarcinoma, but comparative studies between two- and three-dimensional systems are necessary to assess other possible advantages of this technology.

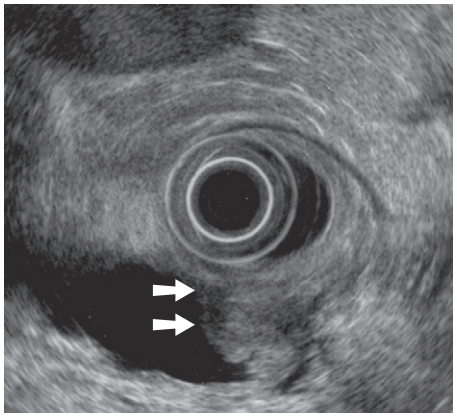


FIGURE 16.9 Common bile duct infiltrative cholangiocarcinoma (*arrows*).

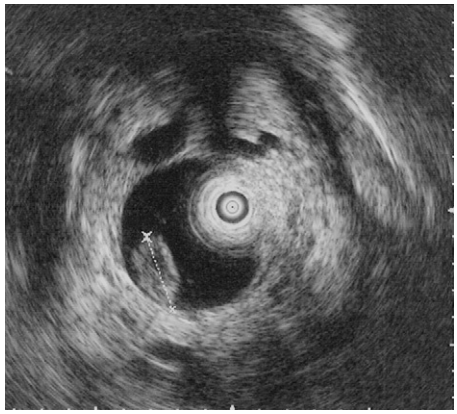


FIGURE 16.10 Early biopsy-proven common bile duct cholangiocarcinoma as noted on intraductal ultrasonography.

TABLE 16.4

Operating Characteristics of EUS Fine-Needle Aspiration in Biliary Strictures

Authors (yr)	Strictures (n)	Hilar Biliary Strictures (n)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)	Sensitivity in Hilar Strictures (%)
Fritscher-Ravens et al[140] (2000)	10	10	89	—	—	—	—	89
Rösch et al[166] (2002)	43	3	62	79	76	66	—	—
Lee et al[138] (2004)	42	1	47	100	100	50	—	—
Eloubeidi et al[141] (2004)	28	15	86	100	100	57	88	67
Fritscher-Ravens et al[142] (2003)	44	44	89	100	100	67	91	89
Rösch et al[143] (2004)	28	11	43	100	100	58	70	25
Byrne et al[139] (2004)	35	3	45	—	—	—	—	—
Meara et al[144] (2006)	46	—	87	100	—	—	—	—
DeWitt et al[145] (2006)	24	24	77	100	100	29	79	77

NPV, negative predictive value; PPV, positive predictive value.

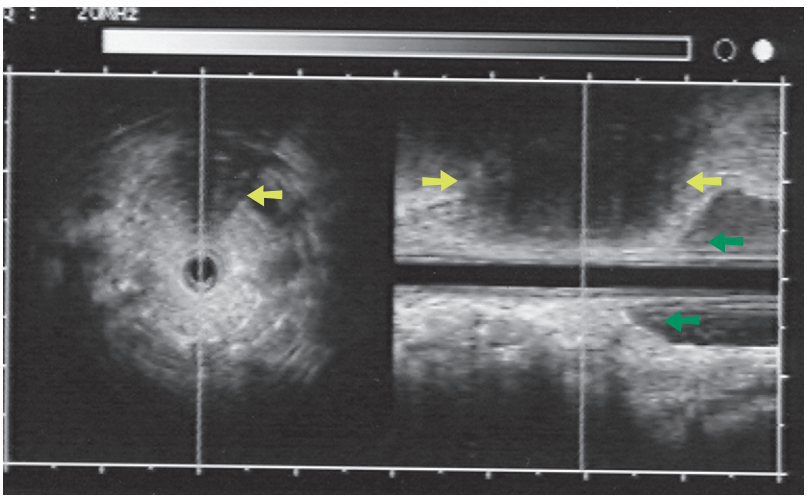


FIGURE 16.11 Three-dimensional intraductal ultrasonography showing biliary duct stenosis (*green arrows*) and pancreatic adenocarcinoma (*yellow arrows*).

As with EUS, three layers are seen in the bile duct wall. The first hyperechoic layer corresponds to the mucosa, in addition to a border echo; the second hypoechoic layer consists of the smooth muscle fibers with fibroelastic tissue; and the third hyperechoic layer is the thin and loose connective tissue with a border echo.[156,157] The criteria for malignancy of a stricture are disruption of the normal three-layer sonographic pattern of the bile duct wall (outer echogenic, middle hypoechoic, inner echogenic) (Fig. 16.11), a hypoechoic infiltrating lesion with irregular margins, heterogeneous echo-poor areas invading surrounding tissue, and continuation of the main hypoechoic mass into adjacent structures. Findings considered diagnostic of a benign stricture (Fig. 16.12) include preservation of the normal three-layer sonographic wall pattern, homogeneous echo patterns, smooth margins, hyperechogenic lesions, and the absence of a mass lesion. For lesions with intermediate echogenicity, asymmetrical lesions are considered malignant, whereas symmetrical lesions are classified as benign; however, asymmetry has not been considered by all investigators as a criterion for malignancy.[121,129,149,158]

The accuracy of IDUS in differentiating benign from malignant strictures ranged from 76% to 92% in series of patients with various causes of biliary stricture.[119,121,149,151,152,154,159] In 2002, Tamada et al[159] proposed other IDUS criteria. Interruption of the bile duct wall is considered specific for tumor-related stricture.

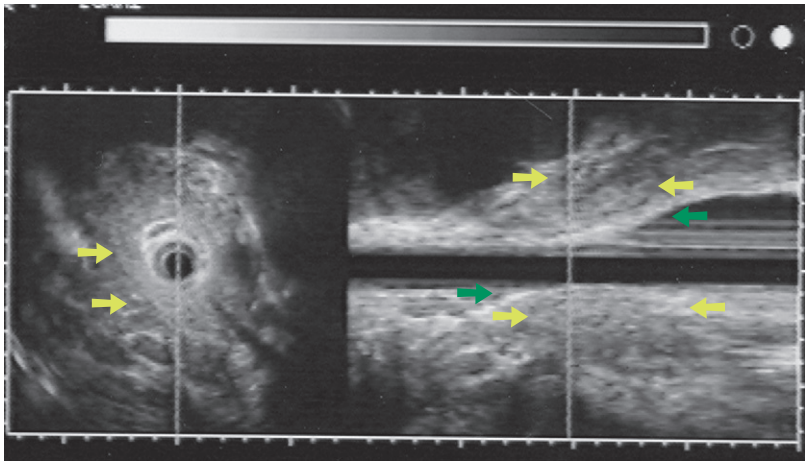


FIGURE 16.12 Three-dimensional intraductal ultrasonography showing biliary duct stenosis (*green arrows*) and inflammatory extrinsic compression following acute pancreatitis (*yellow arrows*).

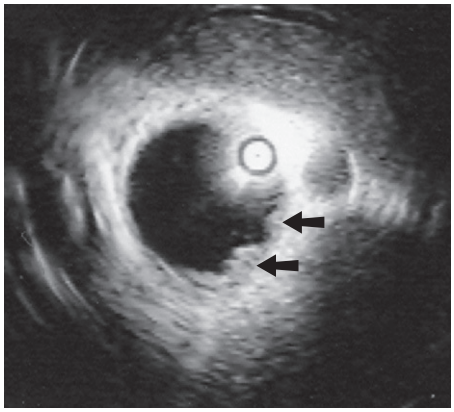


FIGURE 16.13 Two-dimensional intraductal ultrasonography showing biliary papillomatosis with intrahepatic polypoid spread.

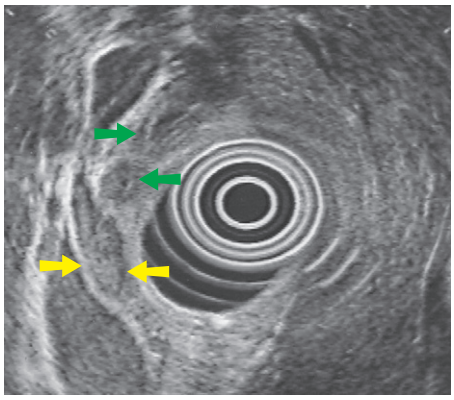


FIGURE 16.14 Sclerosing cholangitis with thickened, irregular common bile duct (*green arrows*) and cystic wall (*yellow arrows*).

Sessile tumors–even when they remain intraductal or extend outside the CBD wall—and tumor size greater than 10 mm are the other major positive criteria indicating malignancy. Echogenicity of the stricture, which is probably highly operator dependent, is no longer considered a factor predictive of malignancy.

Most patients without the previously mentioned criteria and with negative sampling results do not have a malignant lesion. The presence of two of the criteria, even with negative biopsy results, is highly suggestive of malignancy. The absence of IDUS criteria of malignancy and the negativity of biopsy results indicate a benign lesion with 95% accuracy and 100% NPV.[159] A previous history of choledocholithiasis or surgery of the biliary tract has been found to predict a benign lesion. More recently, another study evaluated IDUS in 45 patients with biliary strictures with no mass lesion seen with CT or MRI. The main finding was that wall thickness of up to 8 mm can be a powerful parameter for excluding malignancy with 100% NPV in the absence of extrinsic compression.[153] IDUS is very effective in confirming extrinsic compression by a vascular structure or by a stone impacted in the cystic duct and compressing the CBD (Mirizzi's syndrome).[119,147,159,160]

Biliary papillomatosis is also detected accurately by IDUS. In contrast, this disorder is frequently misdiagnosed with usual imaging techniques such as ERCP, EUS, and MRI. Biliary ducts with normal appearance alternating with areas covered by polypoid lesions protruding into the lumen establish the diagnosis.[161,162] In 30 patients with cholangiocarcinoma studied by IDUS, biliary papillomatosis was shown in 3 (10%) and was confirmed by biopsy or surgery.[160] When ERCP identified a polypoid lesion inside the CBD, IDUS was the only test able to detect combined biliary papillomatosis inside the intrahepatic ducts (Fig. 16.13). The clinical impact of this diagnosis can be important because young patients with biliary papillomatosis without advanced cholangiocarcinoma should be treated with a Whipple resection in combination with partial hepatectomy or liver transplantation.[162]

In the diagnostically difficult group of patients with underlying primary sclerosing cholangitis and dominant stenoses, IDUS was traditionally considered no more accurate than other imaging modalities in the diagnosis of cholangiocarcinoma (Fig. 16.14).[163] However, more recent studies have shown encouraging results.[164,165] In a prospective study,[164] 40 patients with primary sclerosing cholangitis underwent ERCP with IDUS. The sensitivity, specificity, accuracy, positive predictive value (PPV), and NPV of IDUS for predicting malignancy were 87.5%, 91%, 90%, 70%, and 97%, respectively. In one false-negative and three false-positive results, IDUS showed the same morphology with interrupted wall structure and symmetrical wall thickness. Therefore, some limitations of IDUS still remain in this clinical setting.

How to Approach a Bile Duct Stricture

Because the performance of different diagnostic tests continues to be disappointing, the decision concerning the optimal use of the various imaging modalities is critical. In a prospective comparative study of ERCP or percutaneous transhepatic cholangiography (PTC), MRCP, CT, and EUS, 40 patients with biliary stricture underwent all four imaging tests.[166] The specificity was improved when MRCP was combined with EUS. In addition, a prospective study on 142 patients with nonicteric cholestasis and common hepatic duct dilatation of unclear origin showed that a diagnostic

algorithm with MRCP followed by EUS was highly sensitive and specific (90% and 98%, respectively) for the early diagnosis of extrahepatic bile duct carcinoma.[167] Considering the respective limits and risks of EUS (with and without FNA) and ERCP plus IDUS, the following choice should be proposed. If the stricture is localized at the level of the CBD, EUS should be proposed after noninvasive imaging modalities, based on its good performance in distal biliary lesions and its ability to sample tissue (Videos 16.3 and 16.4). In the difficult group of patients with proximal strictures, EUS and EUS FNA have several limitations, and ERCP-based tissue acquisition may be better,[145] in addition to the possibility of performing IDUS.[119,129,159] In view of its low NPV, EUS FNA should be reserved for negative or nondiagnostic ERCP brush cytology results only if a high probability of malignancy exists. Nevertheless, some investigators proposed the systematic addition of EUS FNA to ERCP brushings to optimize the diagnostic yield.[168]

Although peroral cholangioscopy is not widely used because of the fragility and complicated use of the older cholangioscopes, it allows direct visualization and targeted biopsy of bile duct lesions. When compared with ERCP brush cytology in a Japanese study, cholangioscopy was 100% sensitive and 89% specific for biliary strictures and increased the diagnostic accuracy to more than 90%.[169] A multicenter study reported on the preliminary experience of ERCP followed by peroral cholangioscopy on patients with indeterminate biliary strictures.[170] The sensitivity and specificity of peroral cholangioscopy for detection of malignancy were 78% and 100%, respectively. As progressive improvements in design, maneuverability, and optical resolution of cholangioscopes develop, peroral cholangioscopy will likely become a helpful adjunct to ERCP in the assessment of biliary strictures.

It may therefore be reasonable to propose the following algorithm for the management of the bile duct strictures[171]:

- For CBD strictures: EUS plus FNA followed by ERCP with IDUS and brush cytology/forceps biopsy if needed.
- For common hepatic duct and hilar strictures: MRI plus ERCP with IDUS and brush cytology/forceps biopsy under fluoroscopy or cholangioscopy. EUS FNA when a strong clinical suspicion of malignancy persists after negative results of an ERCP-based workup.

How to Stage Cholangiocarcinoma

When bile duct carcinoma is diagnosed, the aim of the investigation is to determine whether the patient can be treated surgically or not. The first important criterion is the tumor (T) and node (N) staging. Histologically, early cancer manifests with the deepest invasion limited to the mucosa or fibromuscular layer of the extrahepatic bile duct, regardless of lymph node metastasis. Serosa is found in part of the anterior and right posterior wall of the hilar, superior, and middle bile duct. Bile duct carcinomas are staged according to the following classification, modified from the TNM staging system: T1, limited to the CBD wall; T2, invasion beyond the CBD wall; and T3, invasion of adjacent structures such as the pancreas, duodenum, and portal vein.

In a prospective study comparing EUS and IDUS in biliary strictures, the accuracy of IDUS in T staging (77.7%) was higher than that of EUS (54.1%).[129] EUS accuracy was inferior mainly in hilar or common hepatic duct strictures because of the limited field of examination. N staging was comparable, but other investigators found that the depth of penetration of the standard 20-MHz catheter probe was not adequate for the evaluation of lymph nodes associated with advanced malignant strictures.[119] EUS and IDUS were not able to differentiate T1 from T2 bile duct cancers. In fact, the main question for the staging of biliary tumors is resectability, which relies on vascular, longitudinal, and pancreatic spread. The available imaging modalities are used to try to select patients who are eligible for this very high-risk and difficult surgical procedure. Conventional investigations (MRI, helical CT) can be useful to contraindicate surgery in some patients, such as those with a Bismuth type IV Klatskin tumor. Nevertheless, the exact longitudinal spread of bile duct carcinoma is not easily detected.

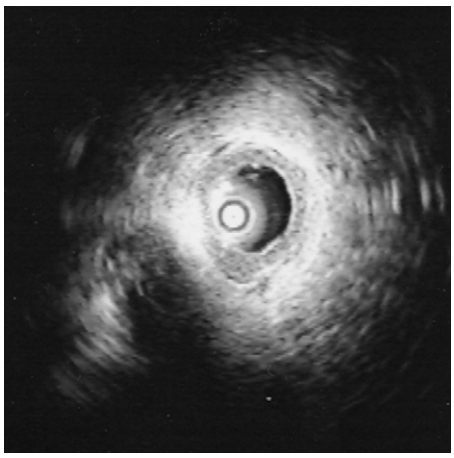


FIGURE 16.15 Intraductal ultrasonography showing inflammatory wall thickening (*arrow*) after stenting.

The diagnostic problem of microscopic involvement of the bile duct wall has not been overcome, with resulting understaging in terms of the resectional margins. Cholangiography and peroral choledochoscopy with biopsy also have limitations in determining the extent of longitudinal and in-depth spread.[172,173] Although EUS is limited in its ability to assess disease extent along the walls of the hepatic ducts, IDUS seems promising. In an initial series, Tamada et al[174] concluded that IDUS accuracy in the assessment of longitudinal cancer extension to the hepatic side of the stricture was 72% with selected criteria (notching of the outer margins).[150] This accuracy was increased when asymmetric wall thickening was considered as a criterion of longitudinal tumor spread on both hepatic and duodenal sides, with an accuracy of 84% and 86%, respectively, compared with ERCP (47% and 43%).[150] In a later series by Inui and Miyoshi,[155] longitudinal spread was also diagnosed when irregular thickening of the bile duct was observed continuously and away from the main lesion. Overall accuracy of IDUS for assessing intraductal spreading was 84.6%. The only limitation is the inflammatory thickening induced when prior drainage of the biliary tract has been performed (Fig. 16.15).[148] Consequently, IDUS must be carried out at the same time as index ERCP or transhepatic drainage.

IDUS is also very accurate (100%) in defining involvement of the portal vein and right hepatic artery (Fig. 16.16), which are the two most frequently affected vessels. The left and common hepatic arteries are more rarely involved and are not easily seen because IDUS cannot visualize the area outside the hepatoduodenal ligament.[175,176] In the two most recent preoperative studies of Tamada et al,[175,176] the accuracy of IDUS in detecting vascular involvement was significantly higher than the accuracy of angiography for both the portal vein (100% versus 50%) and the right hepatic artery (100% versus 33%). Invasion of the adjacent pancreatic parenchyma by a bile duct tumor should be determined, to propose duodenopancreatectomy in combination with bile duct resection. IDUS was also superior to EUS in identifying slight invasion of the pancreatic parenchyma (accuracy, 100% versus 78%),[148] but the therapeutic impact is probably small because IDUS may understage intraductal infiltration.

Control series comparing the performance of each imaging modality (CT, MRCP, EUS, and IDUS) are lacking. A clinical

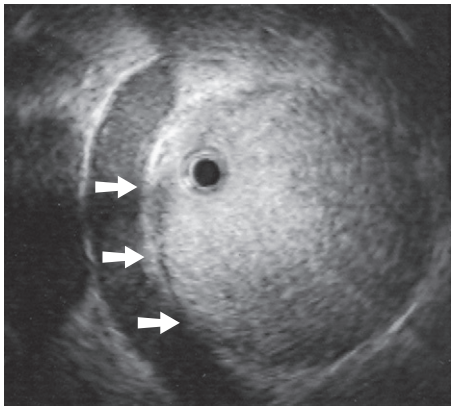


FIGURE 16.16 Intraductal ultrasonography showing vascular staging of cholangiocarcinoma with no infiltration of the right hepatic artery (*arrows*).

approach in patients with Klatskin tumors should be to start with MRI and magnetic resonance angiography. In patients with resectable tumors, ERCP plus IDUS should be the second step, carried out preoperatively. For bile duct tumors, EUS remains the most effective approach. ERCP plus IDUS should be proposed only when the upper part of the tumor cannot be seen with EUS or when doubt remains concerning spread to the portal vein. Finally, EUS and IDUS are useful tools in determining the nature of a biliary stenosis and for staging of cholangiocarcinoma. As a result of their respective limitations (hilum for EUS, and the need for biliary drainage with IDUS), the use of these techniques depends on the clinical presentation and results of conventional imaging.

DIAGNOSTIC CHECKLIST: BILE DUCT TUMORS

Cholangiocarcinoma
- Hypoechoic thickening of the wall with or without a mass
- Polypoid intraluminal tumor
- Involvement of vessels, pancreas, liver, ampulla, or duodenum
- Bile duct dilation

Papillomatosis
- Polypoid intraluminal tumor with alternation of normal bile duct wall

Mirizzi's syndrome
- Compression of the common bile duct by an intracystic stone
- Regular thickening of bile duct wall

Other benign stenosis
- Regular thickening without wall disruption

GALLBLADDER DISEASE (EXCLUDING STONES)

Polyps

The widespread use of US led to the identification of an increasing number of polypoid lesions of the gallbladder. Indeed, 4% to 7% of the healthy population has been reported to have polyps in the gallbladder.[177–179] Cholesterol, inflammatory, and fibrous polyps have no malignant potential, and surgical intervention is not required as long as the patient is asymptomatic. In contrast, adenomatous polyps must be resected because the adenoma-carcinoma sequence is well characterized in the biliary epithelium and gallbladder.[161,180] In a histologic review of a large series of 1605 sequential cholecystectomy specimens, histologic transition from adenoma to carcinoma was revealed. All in situ carcinomas were associated with adenomatous components.[181] The same association was found in 19% of invasive carcinomas. Moreover, gallbladder carcinoma has one of the most dismal prognoses among malignancies of the digestive system, except at an early stage.

With regard to treatment, laparoscopic surgery is a minimally invasive method for removal of the gallbladder. However, the rate of procedure-related complications has been reported to be as high as 4.3%,[182,183] and postcholecystectomy syndrome develops in up to 20% of patients.[184,185] It is therefore important to establish criteria to select candidates for surgery among patients with gallbladder polyps. However, it is difficult to make differential diagnoses of such lesions by US, CT, or MRI, and the incidental finding of a gallbladder polyp in an asymptomatic patient often leads to a clinical dilemma. Solitary lesions, greater than 10 mm in diameter, of sessile appearance and hypoechogenicity are findings suggestive of a neoplastic polyp,[181,186] and in these patients surgical treatment should be performed.[187,188] However, polyps smaller than 10 mm in diameter and appearing as echogenic pedunculated masses on US images are generally cholesterol and inflammatory polyps, and only follow-up should be recommended. This approach can be debated, however. In a study of 70 patients with polypoid lesions that were smaller than 2 cm, 34.6% of non-neoplastic polyps were more than 10 mm in diameter.[189] Moreover, investigators reported that 30% of polyps measuring 11 to 20 mm in diameter are cholesterol polyps.[190] The indication of cholecystectomy for gallbladder polyps larger than 10 mm should be re-evaluated. However, 19% to 29% of polyps between 5 and 10 mm in diameter correspond to adenomas.[186,191] A precise diagnosis of the origin of the polyp is necessary to determine the best therapeutic approach. Considering its higher-resolution performance, EUS should be more accurate than US for imaging gallbladder lesions.[186,191,192]

The gallbladder wall can readily be seen with EUS as a two-layered structure. The inner hypoechoic layer represents the mucosa, muscular layer, and subserosal fibrous layer. The outer hyperechoic layer represents the subserosal fat layer and serosa.[193–196] In some cases, a hyperechoic layer is demonstrated on the inner hypoechoic layer. This is considered to be mainly an interface echo. Gallbladder polyp is defined as a fixed echo structure protruding into the gallbladder lumen without acoustic shadowing on EUS. For Azuma et al,[192] EUS was better than US in diagnosing the nature of gallbladder polyps: of 89 polyps smaller than 2 cm, 86.5% were correctly diagnosed by EUS, compared with only 51.7% by US. The sensitivity, specificity, PPV, and NPV value of EUS in the diagnosis of carcinoma were 91.7%, 87.7%, 75.9%, and 96.6%, respectively.

Two series proposed a scoring system that relied on EUS findings to ascertain the risk of neoplasia.[189,191] In a retrospective analysis of EUS findings in 70 patients operated on for polypoid gallbladder lesions smaller than 20 mm, Sadamoto et al[189] analyzed the morphologic characteristics of gallbladder polyps by multivariate stepwise logistic regression. The polypoid lesions confirmed by cholecystectomy were classified into two groups: neoplastic (adenomas and adenocarcinomas) and non-neoplastic (fibrous, inflammatory, and cholesterol polyps). The EUS variables studied were the maximum diameter and height/width ratio of the largest polyps, echo level, internal echo pattern, surface patterns, number and shape of polyps, presence of hyperechoic spots, and presence of gallstones. The variables of internal echo pattern and hyperechoic spots were statistically significant, in addition to tumor size. All neoplastic polyps, including the smaller ones, were shown on EUS with a relatively heterogeneous internal echo pattern. In contrast, large cholesterol polyps (>10 mm in diameter) had a homogeneous internal echo pattern.

Investigators have proposed that the heterogeneous internal echo pattern of neoplastic lesions corresponds to their irregular internal structure, seen in the resected specimens, resulting from cancerous tubular structures and mixed cellularity. The hyperechoic spotting has been reported to represent a mass of foamy histiocytes containing cholesterol.[179,190] Hyperechoic spotting is highly significant for cholesterol polyps.[189,190] However, investigators have reported that, in two cases of polypoid adenocarcinomas, hyperechoic spotting represented the accumulation of foamy cells underneath cancerous epithelium.[189] The overall EUS score for the risk of neoplastic polyps was calculated as follows: maximum diameter in millimeters plus internal echo pattern score plus hyperechoic spots score (heterogeneous, +4; homogeneous, 0; presence of hyperechoic spots, −5; absence of hyperechoic spots, 0). The sensitivity, specificity, and accuracy with scores of 12 or higher were 77.8%, 82.7%, and 82.9%, respectively.[189] According to these results, polypoid lesions with a score of at least 12 have a high likelihood of being neoplastic. The sensitivity, specificity, and accuracy of a score lower than 12 for the diagnosis of non-neoplastic polyp were not evaluated.

Another scoring system based on five EUS variables was proposed to predict the malignancy of gallbladder polyps.[191] It was based on layer structure, echo pattern, margin, stalk, and number of polyps. The EUS scoring system was developed retrospectively using data obtained from a reference group of 79 patients and applied to a validation group of 53 patients (26 patients with polyps 5 to 15 mm in diameter). According to the results of this study, size was the most significant predictor of neoplastic polyps. All polyps with a diameter of 5 mm or less were non-neoplastic, whereas 94% of polyps larger than 15 mm were neoplastic. When the size of a gallbladder polyp exceeded 15 mm, the risk of neoplasia increased significantly compared with that of polyps measuring 5 to 10 or 10 to 15 mm in diameter. However, polyps that were 5 to 10 and 10 to 15 mm in diameter showed no significant difference in terms of risk of malignancy. For polyps measuring between 5 and 15 mm, the risk of neoplasia was significantly greater, with a score of at least 6, than for polyps with a score of less than 6, with a sensitivity, specificity, and accuracy of 81%, 86%, and 84%, respectively. The investigators concluded that use of the scoring system in patients with 5- to 15-mm gallbladder polyps could identify those patients at risk of neoplasia, and that echo pattern was more important than size in the differential diagnosis of gallbladder polyps in this group of patients.

Ten years after these first series, few improvements have been developed. Polyp size remains a strong factor, influencing EUS accuracy, and a critical issue to predict the neoplastic nature of the gallbladder polyps. Although the presence of hypoechoic foci was the best individual predictive factor for neoplastic polyps in one recent series, polyps larger than 15 mm in diameter had also significantly increased risk of malignancy.[197] In another study, although EUS was always superior to US for all polyp sizes, EUS accuracy was only 44% among polyps smaller than 10 mm, in comparison with 89% for those larger than 10 mm.[198]

Considering the results of these series, it would appear that gallbladder polyps may be differentiated more accurately with EUS than with US. Nevertheless, the results are insufficient and not accurate enough to make the choice between surgery and clinical follow-up. Findings at EUS only complement other relevant clinical information and are more useful in the management of high-risk surgical patients. A systematic surgical approach for gallbladder polyps larger than 1 cm in diameter remains the safest choice. EUS could be used to image polyps that measure between 5 and 10 mm. In cases of suspicious EUS findings, surgery would be performed earlier to avoid the risk of losing patients during follow-up. In other cases, EUS would be a reference examination for polyps that exhibit growth or changes in echo patterns and shape on US follow-up.[199,200] Nevertheless, the role of EUS in this setting must be confirmed in further series.

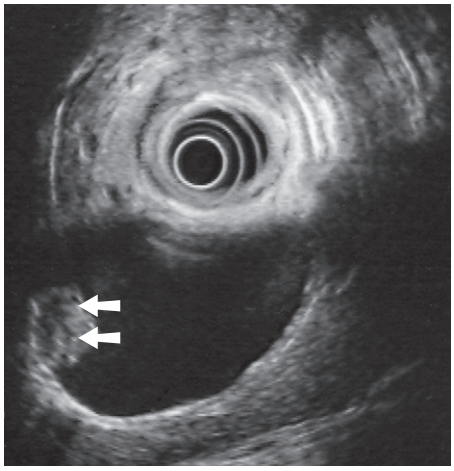


FIGURE 16.17 Adenomatous gallbladder polyp 15 mm in diameter (*arrows*).

Gallbladder Tumors

Preoperative differentiation of adenomas from adenocarcinomas is unnecessary because adenomas have malignant potential,[181] and both lesions should be treated surgically. However, with the replacement of open cholecystectomy by the laparoscopic approach, the preoperative diagnosis of gallbladder cancer is very important, given that recurrence of cancer in the abdominal wall[36] has occasionally been reported after laparoscopic cholecystectomy in patients with advanced carcinomas. Advances in abdominal US and CT have made it possible to diagnose gallbladder carcinoma at an earlier stage. However, these modalities can stage only advanced lesions. Because EUS is helpful in differentiating benign from malignant polyps, it can help to determine the optimal surgical approach: laparoscopy for benign polyps or early cancer, and open surgery for advanced cancer.[201]

The accuracy of EUS in gallbladder cancer staging depends on the criteria chosen. The integrity of the wall layers at the base of a gallbladder polyp is the determinant (Fig. 16.17). Fujita et al[194] retrospectively divided the tumors into four groups, with good interobserver correlation. Type A was a pedunculated mass including a solid echo pattern with a fine nodular surface. Type B was a broad-based mass with an irregular surface and an intact outer hyperechoic layer. In type C, the outer hyperechoic layer of the wall was irregular because of a mass echo, whereas in type D, the entire layer structure was disrupted. The definition of T staging of gallbladder carcinoma according to the American Joint Commission on Cancer (AJCC)[202] is as follows: Tis, carcinoma in situ; T1a, invasion of lamina propria; T1b, invasion of muscle layer; T2, tumor invades the perimuscular connective tissue without extension beyond the serosa; T3, tumor penetrates the serosa and/or directly invades the liver and/or one other adjacent organ (the stomach, duodenum, colon, pancreas, omentum, or extrahepatic bile ducts); and T4, tumor invades portal vein or hepatic artery or invades two or more extrahepatic organs. adjacent organs. After correlation of EUS aspect and pathologic features, the investigators proposed that type A cancer on EUS should be classified before surgery as Tis, because cancer invasion is confined to the mucosa with no invasion of the surrounding epithelium. Type C cancer invades the adipose layer of the subserosa; therefore, its preoperative T staging should be T2. Type B carcinomas can be T1 or T2, because their depth of invasion varies from mucosa to the fibrous layer of the subserosa. This is the most difficult type to classify correctly because diagnosing the depth of invasion is complicated when the outer hyperechoic layer is preserved.

In another retrospective study, of 41 patients with gallbladder cancer,[203] a strong correlation between EUS images and

histopathologic tumor stage was found. EUS and histopathologic findings were compared, especially the depth of invasion of the lesion in the resected specimens. EUS images were classified according to the shape of the tumor and the adjacent gallbladder wall structure, as follows: type A, pedunculated mass with preserved adjacent wall structure; type B, sessile and/or broad-based mass with a preserved outer hyperechoic layer of the gallbladder wall; type C, sessile and/or broad-based mass with a narrowed outer hyperechoic layer; and type D, sessile and/or broad-based mass with a disrupted outer hyperechoic layer. The four types of EUS image correlated with the histologic depth of invasion and T stage. Type A corresponded to Tis, type B to T1, type C to T2, and type D to T3 to T4. The corresponding accuracies of EUS classification were 100%, 75.6%, 85.3%, and 92.7% for types 1, 2, 3, and 4, respectively. The best results were found for Tis or T3 to T4 tumors. Extended cholecystectomy with systematic lymph node dissection and resection of the liver bed could be applied in type D tumors, and a celioscopic cholecystectomy could be performed for Tis tumors. The difference between T1 and T2 tumors was more difficult to establish. The differential diagnosis between T1 and T2 polypoid gallbladder tumors was easier when a hypoechoic area within the deeper part of the tumor was found by EUS. This finding indicates subserosal invasion,[204] but it is valuable only for polypoid gallbladder tumors.

The value of EUS FNA in the diagnosis and staging of gallbladder tumors remains questionable. EUS FNA appears to be a safe procedure for obtaining samples from gallbladder masses for cytologic examination.[205–207] It may also be used for confirming lymph node involvement because the existence of malignant lymph nodes indicates stage III disease irrespective of T staging.[208] Nevertheless, the real impact of the FNA result depends on each clinical case. Considering the limited morbidity of surgery, it is certainly not reasonable to take the risk of a false-negative FNA result in operable patients. The place of EUS in the staging of gallbladder cancer remains questionable because the series are scarce and retrospective. Nevertheless, EUS appears to be effective in confirmation of early tumors. In these cases, surgery should begin with a laparoscopic approach. EUS also allows the diagnosis of more advanced cases (≥T3), in which open cholecystectomy with extensive resection should be considered. In other cases, open cholecystectomy with adaptation of the procedure during surgery remains the more prudent approach.

Other Etiologies of Wall Thickening

A large number of diseases can induce a localized or diffuse thickening of the gallbladder wall (Table 16.5). Faced with a diffuse thickening with perivesicular fluid, the main issue is to differentiate acute cholecystitis from other diagnoses. In acute cholecystitis, thickening of the gallbladder wall (>3 mm) is generally combined with an intravesicular thick component, including stones, pus, or fibrin residues.[209] A comparable thickening possibly associated with perivesicular fluid can be seen in ascites, portal hypertension, viral hepatitis, and hypoalbuminemia.[209,210] The internal component of the gallbladder and the clinical symptoms are helpful in the differential diagnosis.

Other conditions with diffuse or localized thickening can be difficult to differentiate from neoplastic disease. Chronic cholecystitis is a common disease combining gallstones and a hyperechoic wall with a preserved layer structure. The wall is usually uniformly involved, but localized thickening is possible.[211] Adenomyomatosis of the gallbladder is usually considered a benign condition. Thickening of the wall is combined with the presence of small cysts, which usually represent intramural diverticula (dilated Rokitansky-Aschoff sinuses). Ultrasonographically, preservation of the layers is visible in a thickened wall with anechoic areas and sometimes associated with hyperechoic echoes (comet-tail artifact, V-shaped reverberation ultrasound artifact).[186] According to the extent and site of involvement, adenomyomatosis was conventionally classified into three types: localized, generalized, and segmental.

The diagnosis is generally easy with conventional US because cancer does not usually mimic adenomyomatosis.[212] Nevertheless, some cases can be difficult to diagnose, especially the localized type, and the relationship between segmental adenomyomatosis and gallbladder carcinoma is questionable. Segmental adenomyomatosis appears to be a high-risk condition for gallbladder carcinoma, especially in elderly patients.[213] The other types of adenomyomatosis do not show any association with a significant increase in the incidence of gallbladder carcinoma. Xanthogranulomatous cholecystitis (XGC) is an uncommon form of chronic inflammation of the gallbladder, the clinical presentation of which is similar to that of cholecystitis. In a large 15-year series of cholecystectomy, XGC was present in 1.46% of patients.[214] It was associated with lithiasis in 85%. XGC may simulate gallbladder cancer. EUS can sometimes visualize hyperechoic nodules in the gallbladder wall, probably representing xanthogranulomas.[215]

The role of EUS in the diagnosis of gallbladder wall thickening remains poorly analyzed. Mizuguchi et al[201] compared EUS, conventional US, CT, and MRI in the differential diagnosis of gallbladder wall thickening (seven cases of gallbladder cancer, nine cases of chronic cholecystitis, five cases of XGC, and four cases

TABLE 16.5

Characteristics and Etiologies of Gallbladder Wall Thickening

	EUS	
Diseases	**Thickening**	**Other Signs**
Acute cholecystitis	Localized or diffuse, layers preserved	Perigallbladder fluid
Chronic cholecystitis	High echogenicity	
Gallbladder carcinoma	Localized, layers inconsistently preserved	Polyp or mass
Adenomyomatosis	Localized or diffuse, layers preserved	Anechoic areas (cysts), hyperechoic echoes, comet-tail artifact
Xanthogranulomatous cholecystitis	Localized or diffuse, layers inconsistently preserved	Hyperechoic nodules in the gallbladder wall
Portal hypertension, viral hepatitis, ascites, or hypoalbuminemia	Diffuse, layers preserved	
Extrahepatic portal venous obstruction	Localized, layers preserved	Varices inside the gallbladder wall
Primary cholangitis	Diffuse, layers preserved	Irregular thickening
Diffuse papillomatosis	Localized or diffuse, layers inconsistently preserved	
Anomalous arrangement of the pancreatobiliary duct	Diffuse, layers preserved	Predominant thickening of the hypoechoic layer

of adenomyomatosis). The multiple-layer pattern was demonstrated by EUS more efficiently than by other imaging modalities. Loss of multiple-layer patterns of the gallbladder wall demonstrated by EUS was the most specific finding in diagnosing gallbladder cancer. It is nevertheless not pathognomonic because this finding can also be seen in XGC.[215]

In other diseases, the presence of complementary abnormalities is helpful in making the diagnosis. In sclerosing cholangitis, the gallbladder is involved in 15% of cases.[209] Irregular thickening also involves the extrahepatic ducts with alternating stenosis and dilation.[209,216] In extrahepatic portal venous obstruction, varices are observed inside the gallbladder wall in 43% of cases,[217] and they can induce localized thickening. Perivesicular varices or ascites can also be seen. Diffuse regular thickening can also be observed in patients with anatomic variants of the pancreatobiliary duct.[217,218] Generally, this thickening is greater than 4 mm and predominantly involves the hypoechoic layer.[218] It has been confirmed pathologically in as many as 91% of patients when biliary ducts are not dilated.[219] Finally, the diffuse papillomatosis of the biliary tract may also involve the gallbladder and may manifest as a thickening with a protruding mass[220] combined with biliary duct polyps.

Summary

The place of EUS in gallbladder disease remains questionable. US is generally sufficient to determine diagnosis and treatment. In some patients with gallbladder polyps (5 to 10 mm in diameter, or >10 mm in patients with poor operative status), EUS should be proposed to help define the therapeutic choice. EUS may also be helpful before surgery in patients with suspected gallbladder cancer or in those with large polyps (>15 mm), to highlight criteria that can guide the surgical choice: a laparoscopic approach in tumors without modification of the structural layer of the wall, extensive resection for tumors causing entire disruption of the layer structure, and open cholecystectomy with adaptation perioperatively for other cases. Finally, in cases of doubtful diagnosis on abdominal US, EUS can be useful in differentiating benign from malignant lesions in the presence of diffuse wall thickening.

AMPULLARY TUMORS

Tumors of the ampulla of Vater originate from the pancreaticobiliary-duodenal junction, limited by the sphincter of Oddi. The pancreatic duct and the CBD join in the ampulla of Vater and form a distal common channel in about 85% of individuals. The normal ampulla starts approximately 2 mm outside the duodenal wall and penetrates the muscularis propria somewhat more distally, to form an intraduodenal segment 9 to 25 mm in length.[221] Many different tumors arise from the ampulla of Vater, including benign tubular and villous adenoma, carcinoma, and several rare other pathologic types, such as lipoma, fibroma, neurofibroma, leiomyoma, lymphangioma, hemangioma, and various neuroendocrine tumors.

Adenomas occur sporadically and in the setting of polyposis syndromes. They are considered premalignant, and the adenoma-carcinoma sequence has been assumed to be the main explanation for the pathogenesis of periampullary cancer.[222] Benign adenomas are being detected more frequently during gastroscopy, and they now represent an important proportion of endoscopically treated ampullary tumors.[223] Moreover, endoscopic surveillance programs are recommended for patients with familial adenomatosis polyposis (FAP) syndrome because the abnormal findings of the major duodenal papilla, a common site of extracolonic adenoma or malignancy in these patients, show progression of endoscopic and histologic features during follow-up.[224] Tumors can also be discovered in symptomatic patients who present with jaundice, abdominal pain, weight loss, pancreatitis, or anemia.

Carcinoma of the ampulla (papillary carcinoma) spreads by extension to contiguous organs and by invasion of lymphatic or venous vessels. Most ampullary cancers develop from the mucosa of the ampulla and infiltrate the Oddi muscle going through it. These tumors gradually invade the muscularis propria and the serosa of the duodenum and grow beyond the serosa toward the pancreas. Nevertheless, compared with pancreatic cancer, ampullary neoplasia has a much better prognosis because of onset of symptoms at an earlier tumor stage. EUS should be useful in two situations: to confirm the diagnosis of an ampullary tumor and to stage adenocarcinoma (Video 16.5).

Diagnosis of an ampullary tumor is not always easy endoscopically. The tumors are macroscopically polypoid or ulcerative. The polypoid form can be visible or unexposed (intramural). Bile stasis may also contribute to gallstone formation. In fact, between 6% and 38% of patients with ampullary neoplasm also have coexistent choledocholithiasis.[225–229] Limitations stem from false-positive results following stone migration, false-negative findings as a result of endoampullary growth, or the coexistence of stones leading to diagnostic errors because of similar clinical manifestations. These limitations also exist for pathologic features. First, biopsy results can be falsely negative owing to endoampullary growth in 5% to 38% of cases.[228–232] In these cases, EST is necessary to expose the endoampullary growth and to allow secondary positive biopsy results. Second, the differential diagnosis between an inflammatory tissue adenoma and a low-grade dysplasia adenoma can be difficult for the pathologist, and repeated biopsies may be necessary. Finally, standard forceps biopsies are not representative of the overall status of the tumor: benign adenomas may harbor foci of carcinoma that may be either superficial or invasive, just as benign tissue elements may be found in ampullary carcinomas.[233] In fact, biopsy samples underestimate the presence of adenocarcinoma in 19% to 30% of cases.[228–232]

Considering these drawbacks, the differential diagnosis of a normal ampulla, odditis, or a real tumor can be difficult. Whether EUS should be used to diagnose an ampulloma in a patient with a protruding ampulla without mucosal abnormalities is questionable. Few series have addressed this problem. Will et al[234] reported a series of 133 patients with unclear biliary problems, cholestasis, or tumors of the papilla that were found by duodenoscopy in which EUS sensitivity and specificity in the detection of malignant lesions of the papilla and the peripapillary region were 92.3% and 75.3%, respectively. This low specificity was confirmed by other series.

In 1993, Keriven et al[235] showed that the only specific signs to confirm the presence of an ampulloma were criteria in favor of an invasive tumor (at least with infiltration of the duodenal muscularis propria) or the presence of endoluminal growth in the CBD (Fig. 16.18) or the Wirsung duct. The other criteria—echogenicity (Fig. 16.19), enlargement of the ampulla, and CBD or Wirsung duct dilation (Fig. 16.20)—were not specific and were possibly seen in sclerosing odditis or even in the normal ampulla. These results were confirmed by Rösch et al.[236] EUS sensitivity in the detection of an ampullary tumor is high in symptomatic patients, and it is certainly lower in asymptomatic ones. A diagnosis of ampullary tumor without EUS abnormalities is common in patients with FAP. This situation emphasizes the truth that, if EUS is a useful tool in the diagnosis of ampulloma in some patients, only biopsy can reliably confirm the diagnosis.

Finally, two different situations can be encountered (Fig. 16.21): (1) in patients with a suspicion of ampullary obstruction (clinically, biochemically, or by morphologic examination) but with inconclusive biopsy findings and no specific criteria of ampullary tumor at EUS, EST with repeated biopsy is needed to differentiate odditis from an early ampullary tumor; and (2) in asymptomatic patients with a suspicion of early

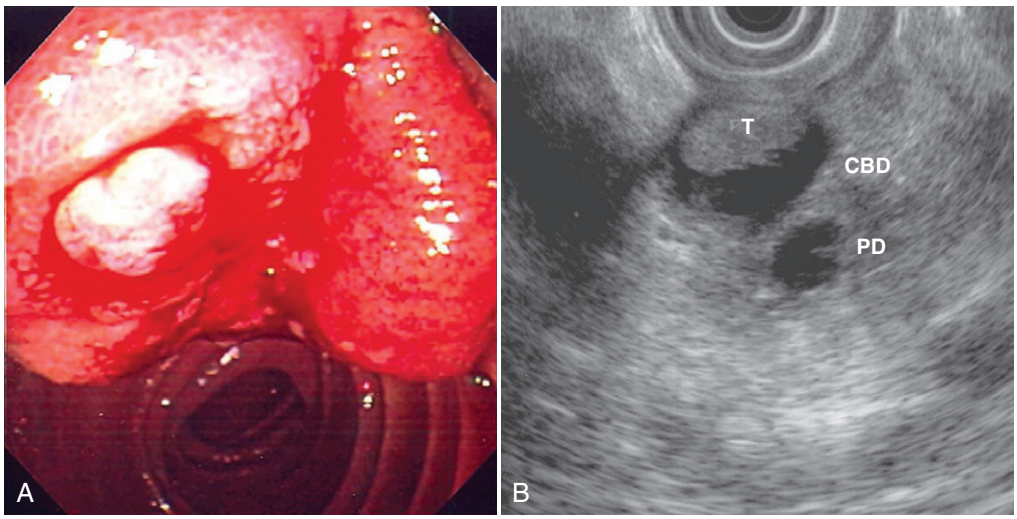


FIGURE 16.18 Ampullary cancer. **A,** Endoscopic view of an ampullary cancer. **B,** On examination using the radial echoendoscope, the tumor (T) is seen to invade the common bile duct (CBD), pancreatic duct (PD) and duodenal wall layers.

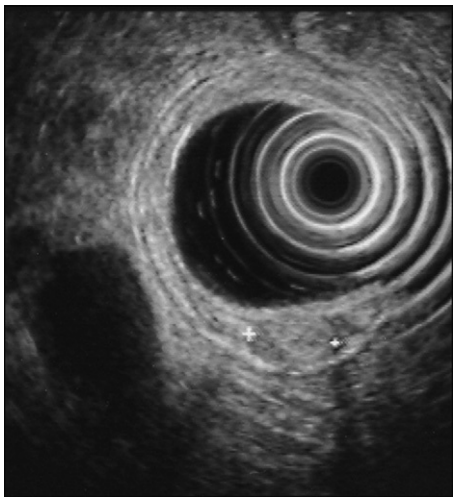


FIGURE 16.19 uT1 ampulloma.

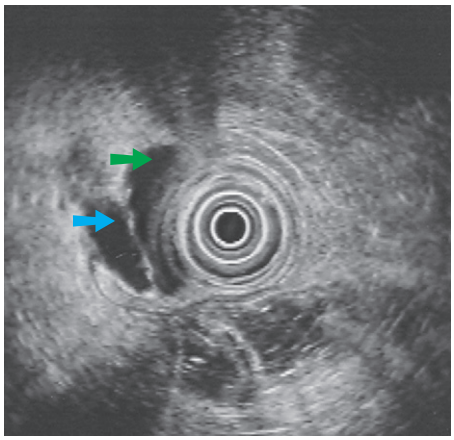


FIGURE 16.20 Sclerosing odditis with dilation of the ducts. *Green arrow,* common bile duct; *blue arrow,* pancreatic duct.

tumor at endoscopy but inconclusive biopsy findings and normal EUS results, only follow-up with repeated biopsy can be recommended.

As for other digestive cancers, the aim of staging is to choose the best therapeutic approach and to determine the prognosis. For a long time, the Whipple operation was the only potentially

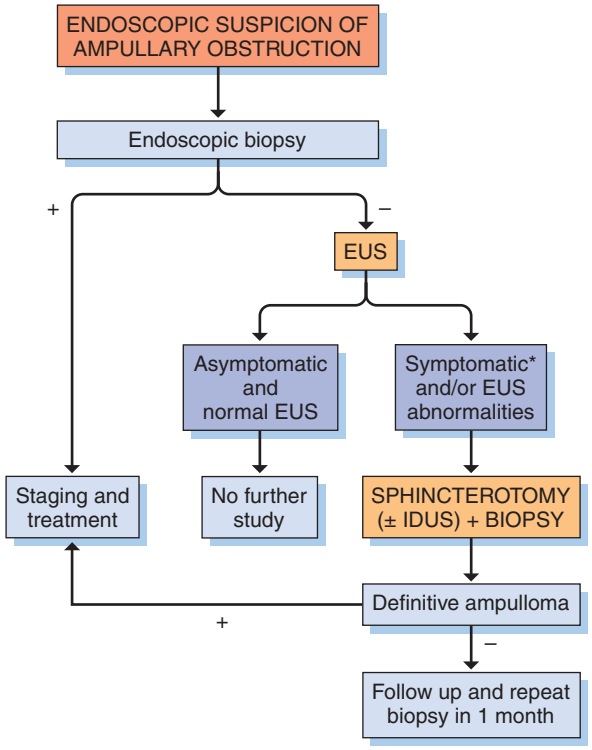


FIGURE 16.21 Diagnostic algorithm for patients with endoscopic suspicion of ampullary tumor. IDUS, intraductal ultrasonography.

curative treatment. In patients with benign tumors or early cancer, the same treatment was generally undertaken. Surgical ampullectomy was rarely done, owing to its morbidity and the impossibility of ascertaining before the pathologic analysis that there was no likelihood of metastatic lymph nodes. Since the 1990s, progressive developments in endoscopic ampullectomy have allowed for the curative treatment of benign adenomas or early cancers in 70% to 80% of patients.[237–240] Snare ampullectomy has a lower morbidity rate (6% to 36%[223,228,241–243]) than local surgical excision,[230] and essentially no mortality (0% to 1%). Nevertheless, morbidity remains significant, and careful patient selection is required to avoid an unnecessary endoscopic approach that would need to be completed by a Whipple operation. Two limitations of the endoscopic curative approach must be considered: tumors with a risk of lymph node metastasis and intraductal invasion inside the pancreatic duct or CBD (technical limitation).

TABLE 16.6

Performances of Ultrasonographic Modalities in the Staging of the Ampulloma as a Higher-Stage Tumor than uT1

Authors (yr)	Patients (n)	Techniques	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Tio et al[246] (1996)	32	EUS	100	60	93	100	94
Menzel et al[259] (1999)	15	IDUS	100	80	91	100	93
Mukai et al[128] (1992)	23	EUS	93	78	87	88	87
Itoh et al[260] (1997)	32	IDUS	85	100	100	91	94
Cannon et al[245] (1999)	50	EUS	88	100	100	80	90
Artifon et al[254] (2009)	27	EUS	100	—	93	—	93
Chen et al[255] (2009)	31	EUS	96	57	89	80	88
Ito et al[257] (2007)	40	EUS	95	62	69	93	78
Ito et al[257] (2007)	40	IDUS	89	85	85	90	88

IDUS, intraductal ultrasonography; NPV, negative predictive value; PPV, positive predictive value.

This evolution explains the role of pretherapeutic staging, not only to assess the resectability of the tumor, but also to determine which tumors may be resected endoscopically (benign adenomas and early cancer without intraductal infiltration).

According to the TNM classification[244] used to stage ampullary tumors, T1 corresponds to tumors not extending beyond the sphincter of Oddi, T2 tumors are those invading the muscularis propria of the duodenal wall, T3 corresponds to tumors invading the adjacent pancreas by less than 2 cm, and T4 tumors invade the pancreas deeply or involve adjacent organs or blood vessels. Nevertheless, this classification is not perfect, because stage T1 includes early cancers invading the mucosa or limited to the sphincter of Oddi as well as tumors invading the duodenal submucosa. The Japanese staging system developed by biliary surgeons is more selective. T1 tumors are divided into d0 tumors limited to the sphincter of Oddi and d1 tumors that invade the duodenal submucosa; stage d2 is equivalent to T2. The difference is marked in terms of the risk of lymph node metastasis. Although the risk for T1 tumors ranges from 0% to 20%,[245–247] it is very different for d0 (0%) and d1 (30%) tumors.[248–250] The presence of metastatic lymph nodes is of course greater in more advanced tumors: 55% in T2 and 78% in T3 to T4 lesions.[248] Logically, Japanese surgeons consider d0 cancer as an early cancer. In these patients, endoscopic ampullectomy should be performed with curative intent.

Various imaging modalities, such as US, CT, angiography, ERCP, MRCP, and EUS, have been used to stage the lesion and evaluate its resectability. These tumors often grow around the ampulla, far from the mesenteric and portal vessels, with rapid symptomatic signs such as jaundice and pancreatitis. It is therefore rare to see a large tumor originating from the ampulla and invading the vessels. The likelihood of the tumor's resectability is then easier to determine than for pancreatic adenocarcinomas. More important is the T staging, which allows the prognosis to be determined and the choice between surgical and endoscopic resection to be made.

EUS is the most reliable modality for local preoperative staging of these lesions. In the earliest series, EUS was shown to be superior to CT, US, and angiography[128,236] for evaluation of T and N staging and for determining resectability (95% accuracy in assessing portal venous system involvement[236]). These results were confirmed in more recent studies comparing EUS (radial or linear) with conventional or helical CT for staging as well as for resectability.[251–257] In the largest series of 50 consecutive patients with ampullary neoplasms, EUS was compared with CT, MRI, and angiography and was found to be more accurate than CT (78% versus 24%, respectively) and MRI (46%) in the overall assessment of T stage.[245] EUS understaging of true T3 lesions or overstaging of true T2 carcinomas accounted for most of the errors in the EUS T-stage assessment, probably as a result of desmoplastic peritumoral pancreatitis, which cannot easily be differentiated from foci of invasive carcinoma.[246]

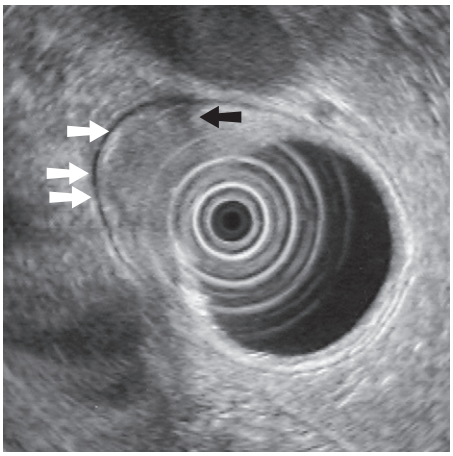


FIGURE 16.22 U1Tsm ampulloma (*black arrow*) with disruption of the submucosa (*white arrows* indicate muscularis propria).

Nevertheless, this differentiation is not mandatory, given that the same surgical treatment is used for T2 and T3 tumors.

More important is the accuracy of EUS in determining whether endoscopic resection can be used with curative intent. The accuracy of EUS in confirming that the T stage is higher than T1 is very good, with an overall success rate of 90% (ranging from 78% to 94%) (Table 16.6). Its ability to show intraductal infiltration also seems to be good, although this has not yet been clearly evaluated in the literature. However, EUS is limited in its ability to show infiltration of the duodenal submucosa, because the sphincter of Oddi is not seen with 7.5 or 12 MHz, even though the infiltration of the third hyperechoic layer of the duodenum sometimes permits the diagnosis of a d1 tumor (Fig. 16.22).[258] EUS also has low accuracy in the detection of lymph node metastases (53% to 87%), with an NPV of less than 75%, which is insufficient to consider that a T1 tumor is N0.[128,236,245–246,254–256,259,260] MRI was found not to be statistically superior to EUS for nodal staging,[207] whereas CT was less sensitive and specific.[254,255] Because EUS-guided FNA is highly accurate in sampling tissue from extraluminal lesions,[261] use of this technique may increase the diagnostic accuracy of preoperative EUS; however, no specific studies have yet been published. In any case, the accuracy would certainly not be 100%.

EUS can therefore be considered a highly accurate modality for predicting the unresectability of ampullary carcinoma and determining the T stage. Nevertheless, in view of the difficulty of selecting patients correctly for endoscopic ampullectomy, EUS is not sufficient because it does not demarcate the sphincter of Oddi and its NPV for the presence of metastatic lymph nodes is very low. Two complementary examinations, duodenoscopy and

IDUS, may be useful. On duodenoscopy, ulceration above the roof of the ampulla, separated from the papilla by normal mucosa, indicates a lesion invading the duodenal submucosa and should be considered invasive.[241] For other tumors, IDUS should be proposed. Intraductal catheter probes (Fig. 16.23) employ a higher frequency (20 MHz) and show a marked improvement in resolution compared with the 7.5 or 12 MHz used for conventional EUS. However, these probes have some restrictions: the ultrasonic probe should be inserted into the tumor by ERCP, and the scanning area is smaller than that for EUS, so N staging is more difficult.[259] However, IDUS is the only imaging modality that can provide an image of the sphincter of Oddi muscle layer as a distinct layer.[260] The possibility of delineating the sphincter of Oddi and the duodenal submucosa allows the staging of tumors as in the Japanese classification, especially in the differentiation of d0 from d1 tumors (Fig. 16.24).

In the first series of 32 patients with cancer of the papilla of Vater, the accuracy of IDUS was 87.5%, and its sensitivity and specificity in assessing lymph node metastases were 66.7% and 91.3%, respectively.[260] The diagnostic accuracy of tumor dissemination was greatest for early tumors, with a rate of 100%, 92.3%, and 100% for d0, d1, and d2 lesions, respectively. In the experience of Napoleón et al,[262] in 31 patients with uT1N0 disease without intraductal involvement at EUS, IDUS had an accuracy of 89% for parietal staging (d0 versus >d0) (d0 versus d1 or d2); in 19% of patients, true infiltration of the submucosa was diagnosed. IDUS was also very accurate in showing intraductal involvement, with 100% accuracy (Fig. 16.25).[260,262]

Considering the respective performances of these investigations, a three-step algorithm (Fig. 16.26) can be applied to ascertain whether an ampullary tumor may be treated curatively by endoscopic ampullectomy:

1. Duodenoscopy: If ulceration is seen above the roof of the ampulla, this indicates submucosal infiltration; a Whipple resection should be considered.
2. EUS: Patients with tumors staged above uT1 and tumors with intraductal infiltration can be selected for a Whipple resection with no further exploration.
3. IDUS (uT1 tumors without intraductal infiltration at EUS and without duodenal ulceration at duodenoscopy): Patients with tumors without submucosal infiltration and intraductal spread should be considered for endoscopic ampullectomy with curative intent.

In the experience of Napoleón et al,[262] this algorithm is very effective in the selection of patients for endoscopic ampullectomy. In 81% of 24 patients selected using this sequence, the pathologic specimen confirmed that the resection was complete, with no tumor infiltration of the duodenal submucosa or extension into the ducts. As for local surgical excision, the overall recurrence rate after snare ampullectomy is 13% (ranging from 0% to 30%).[237–240,242,243,263–275] EUS is needed, in combination with endoscopy and biopsy, in the follow-up of patients with ampullary adenomas treated endoscopically, especially to detect intraductal recurrence.

EUS and IDUS staging of ampullary tumors must be performed before any invasive treatment of the ampulla of Vater is performed, particularly before diathermic biopsy, EST, or biliary stent insertion. These procedures may compromise EUS interpretation by introducing air and creating artifacts, as was observed in some series. In the presence of a transpapillary endobiliary stent, EUS T-stage accuracy was reduced from 84% to 72%.[245] This was most common in the understaging of T2 and T3 carcinomas. Moreover, the bile duct wall thickness, measured by an IDUS probe, was more than doubled in patients with an endobiliary drainage catheter in place for as little as 14 days,[148] and it could be interpreted as intraductal spread.

Economic studies concerning the value of pretherapeutic staging are rare. Only one series showed that use of EUS in the selection of patients for local resection may be a cost-effective approach in the management of ampullary tumors.[276]

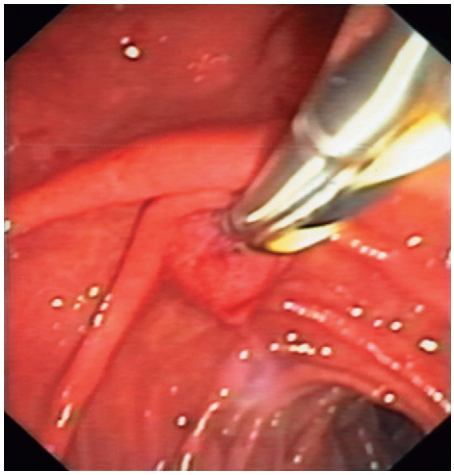
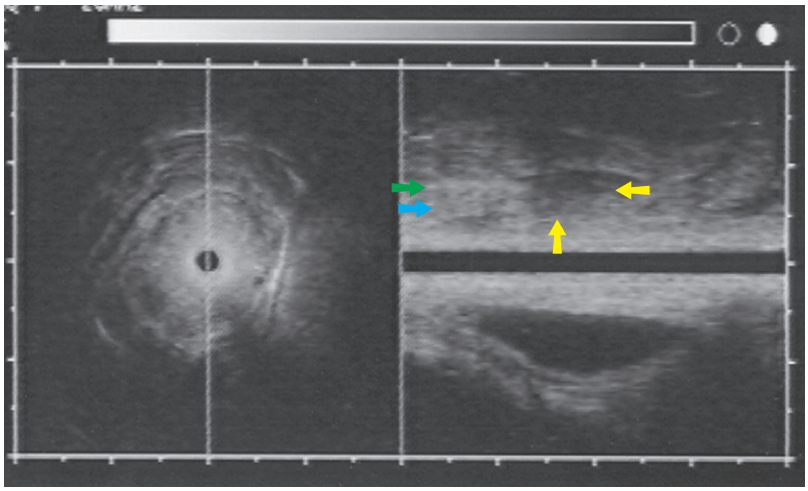


FIGURE 16.23 Intraductal ultrasonography over a guidewire for staging of ampulloma.

FIGURE 16.24 Three-dimensional intraductal ultrasonography showing a d1 ampulloma. *Yellow arrows*, tumor with disruption of the submucosa; *green arrow*,normal submucosa; *blue arrow*, sphincter of Oddi.



Summary

EUS can be helpful in the diagnosis of ampullary tumors, especially advanced lesions with no endoscopic abnormalities. EUS is also useful in the management of ampullary cancer because it is fairly accurate in the assessment of resectability and prognosis. With the development of curative endoscopic treatment for benign tumors and early cancers of the ampulla, accurate staging is needed for patient selection. A three-step algorithm combining duodenoscopy, EUS, and IDUS is promising.

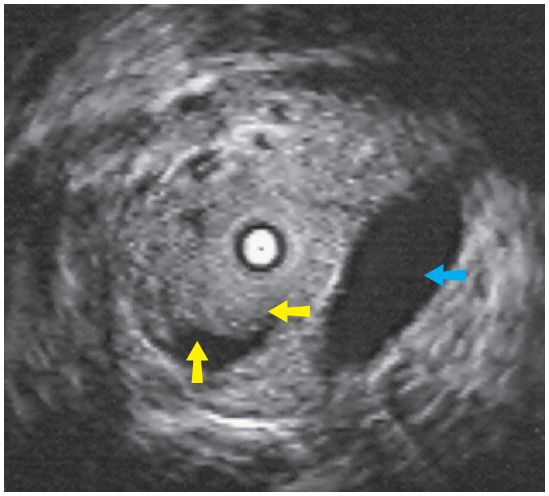
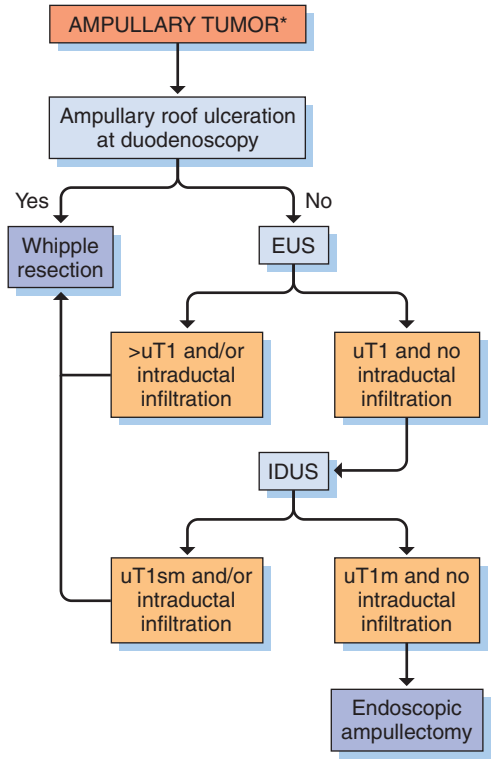


FIGURE 16.25 Intraductal ultrasonography showing an ampulloma. *Yellow arrows*, intrabiliary spread; *blue arrow*, normal pancreatic duct.



** After CT scan or MRI excluding N+ or M+ stages.*
uT1sm, tumor involved submucosal layer; uT1m, tumor limited to mucosal layer.

FIGURE 16.26 EUS-based algorithm for treating patients with ampullary tumors. CT, computed tomography; IDUS; intraductal ultrasonography; MRT, magnetic resonance imaging.

DIAGNOSTIC CHECKLIST: AMPULLARY DISEASE

Ampullary tumors
- Hypoechoic or hyperechoic thickening of the ampulla
- Polypoid intraductal tumor
- Involvement of vessels, pancreas, or duodenum
- Bile or pancreatic duct dilation

Odditis
- Hypoechoic or hyperechoic thickening of the ampulla
- Duodenal wall layers preserved
- No intraductal polypoid infiltration
- Bile or pancreatic duct dilation

EXAMINATION CHECKLIST

Extrahepatic ducts (dilatation, stones)
Intrahepatic ducts (dilation)
Left and right liver lobe
Gallbladder
Ampulla (including intraductal ultrasonography in the case of T1 ampullary lesions)
Pancreas and Wirsung duct
Lymph nodes
Ascites
Portal hypertension

REFERENCES

1. Davis WZ, Cotton PB, Arias A. ERCP and sphincterotomy in the context of laparoscopic cholecystectomy: academic and community practice patterns and results. *Am J Gastroenterol*. 1997;92:597–601.
2. Loperfido S, Angelini G, Benedetti G. Major early complications from diagnostic and therapeutic ERCP: a prospective multicenter study. *Endoscopy*. 1999;31:125–130.
3. Andriulli A, Loperfido S, Napolitano G, et al. Incidence rates of post-ERCP complications: a systematic survey of prospective studies. *Am J Gastroenterol*. 2007;102:1781–1788.
4. Cotton PB, Garrow DA, Gallagher J, et al. Risk factors for complications after ERCP: a multivariate analysis of 11,497 procedures over 12 years. *Gastrointest Endosc*. 2009;70:80–88.
5. Freeman ML, Nelson DB, Sherman S, et al. Complications of endoscopic biliary sphincterotomy. *N Engl J Med*. 1996;335:908–918.
6. Sherman S, Ruffolo TA, Hawes RH, et al. Complications of endoscopic sphincterotomy. *Gastroenterology*. 1991;101:1068–1072.
7. Cotton PB, Geenen JE, Sherman S, et al. Endoscopic sphincterotomy for stones by experts is safe, even in younger patients with normal ducts. *Ann Surg*. 1998;227:201–204.
8. Barthet M, Lesavre N, Desjeux A, et al. Complications of endoscopic sphincterotomy: results from a single tertiary referral center. *Endoscopy*. 2002;34:991–997.
9. Lambert ME, Betts CD, Hill J, et al. Endoscopic sphincterotomy: the whole truth. *Br J Surg*. 1991;78:473–476.
10. Rabenstein T, Schneider HT, Nicklas M, et al. Impact of skill and experience of the endoscopist on the outcome of endoscopic sphincterotomy techniques. *Gastrointest Endosc*. 1999;50:628–636.
11. Hawes RH, Cotton PB, Vallon AG. Follow up 6–11 years after duodenoscopic sphincterotomy for stones in patients with prior cholecystectomy. *Gastroenterology*. 1990;98:1008–1012.
12. Sugiyama M, Atomi Y. Risk factors of late complications after endoscopic sphincterotomy for bile duct stones: long-term (more than 10 years) follow-up study. *Am J Gastroenterol*. 2002;97:2763–2770.
13. Folkers MT, Disario JA, Adler DG. Long-term complications of endoscopic biliary sphincterotomy for choledocholithiasis: a North-American perspective. *Am J Gastroenterol*. 2009;104:2868–2869.
14. Bergman JG, van Berkel AM, Groen AK, et al. Biliary manometry, bacterial characteristics, bile composition, and histologic changes fifteen to seventeen years after endoscopic sphincterotomy. *Gastrointest Endosc*. 1997;45:400–405.
15. Dong B, Chen M. Improved sonographic visualization of choledocholithiasis. *J Clin Ultrasound*. 1987;15:185–190.

16. Stott MA, Farrands PA, Guyer PB, et al. Ultrasound of the common bile duct in patients undergoing cholecystectomy. *J Clin Ultrasound*. 1991; 19:73–76.
17. Neitlich JD, Topazian M, Smith RC, et al. Detection of choledocholithiasis: comparison of unenhanced helical CT and endoscopic retrograde cholangiopancreatography. *Radiology*. 1997;203:753–757.
18. Polkowski M, Palucki J, Regula J, et al. Helical computed tomographic cholangiography versus endosonography for suspected bile duct stones: a prospective blinded study in non-jaundiced patients. *Gut*. 1999;45: 744–749.
19. Kondo S, Isayama H, Akahane M, et al. Detection of common bile duct stones: comparison between endoscopic ultrasonography, magnetic resonance cholangiography, and helical-computed tomography cholangiography. *Eur J Radiol*. 2005;54:271–275.
20. Anderson SW, Rho E, Soto JA. Detection of biliary duct narrowing and choledocholithiasis: accuracy of portal venous phase multidetector CT. *Radiology*. 2008;247:418–427.
21. Okada M, Fukada J, Toya K, et al. The value of drip infusion cholangiography using multidetector-row helical CT in patients with choledocholithiasis. *Eur Radiol*. 2005;15:2140–2145.
22. Napoléon B, Dumortier J, Keriven-Souquet O, et al. Do normal findings at biliary endoscopic ultrasonography obviate the need for endoscopic retrograde cholangiography in patients with suspicion of common bile duct stone? A prospective follow-up of 238 patients. *Endoscopy*. 2003; 35:411–415.
23. Canto MIF, Chak A, Stellato T, et al. Endoscopic ultrasonography versus cholangiography for the diagnosis of choledocholithiasis. *Gastrointest Endosc*. 1998;47:439–448.
24. Lightdale CJ. Indications, contraindications and complications of endoscopic ultrasonography. *Gastrointest Endosc*. 1996;43:15–19.
25. Lee YT, Chan FK, Leung WK, et al. Comparison of EUS and ERCP in the investigation with suspected biliary obstruction caused by choledocholithiasis: a randomized study. *Gastrointest Endosc*. 2008;67:660–668.
26. Palazzo L, Girollet PP, Salmeron M, et al. Value of endoscopic ultrasonography in the diagnosis of common bile duct stones: comparison with surgical exploration and ERCP. *Gastrointest Endosc*. 1995;42: 225–231.
27. Liu CL, Lo CM, Chan JK, et al. EUS for detection of occult cholelithiasis in patients with idiopathic pancreatitis. *Gastrointest Endosc*. 2000;51:28–32.
28. Frossard JL, Sosa-Valencia L, Amouyal G, et al. Usefulness of endoscopic ultrasonography in patients with "idiopathic" acute pancreatitis. *Am J Med*. 2000;109:196–200.
29. Bret PM, Reinhold C. Magnetic resonance cholangiopancreatography. *Endoscopy*. 1997;29:472–486.
30. Kay CL. Which test to replace diagnostic ERCP-MRCP or EUS? *Endoscopy*. 2003;35:426–428.
31. Lambert R. Clinical outcome of EUS in biliary diseases. *Endoscopy*. 2000; 32:558–561.
32. Savides TJ. EUS-guided ERCP for patients with intermediate probability for choledocholithiasis: is it time for all us to start doing this? *Gastrointest Endosc*. 2008;67:669–672.
33. Chan WL, Chan AC, Lam WW, et al. Choledocholithiasis: comparison of MR cholangiography and endoscopic retrograde cholangiography. *Radiology*. 1996;200:85–89.
34. Mendler MH, Bouillet P, Sautereau P, et al. Value of MR cholangiography in the diagnosis of obstructive diseases of the biliary tree: a study of 58 cases. *Am J Gastroenterol*. 1998;93:2482–2490.
35. Zidi SH, Prat F, Le Guen O, et al. Use of magnetic resonance cholangiography in the diagnosis of choledocholithiasis: prospective comparison with the reference imaging method. *Gut*. 1999;44:118–122.
36. Aubé C, Delorme B, Yzet T, et al. MR cholangiopancreatography versus endoscopic sonography in suspected common bile duct lithiasis: a prospective, comparative study. *AJR Am J Roentgenol*. 2005;184:55–62.
37. Frossard JL, Hadengue A, Amouyal G, et al. Choledocholithiasis: a prospective study of spontaneous common bile duct stone migration. *Gastrointest Endosc*. 2000;51:175–179.
38. Berdah SV, Orsoni P, Berge T, et al. Follow-up of selective endoscopic ultrasonography and/or endoscopic retrograde cholangiography prior to laparoscopic cholecystectomy: a prospective study of 300 patients. *Endoscopy*. 2001;33:216–220.
39. Prat F, Amouyal G, Amouyal P, et al. Prospective controlled study of endoscopic ultrasonography and endoscopic retrograde cholangiography in patients with suspected bile duct lithiasis. *Lancet*. 1996;347:75–79.
40. Kohut M, Nowakowska-Dulawa E, Marek T, et al. Accuracy of linear endoscopic ultrasonography in the evaluation of patients with suspected common bile duct stones. *Endoscopy*. 2002;34:299–303.
41. Meroni E, Bisagni P, Bona S, et al. Pre-operative endoscopic ultrasonography can optimise the management of patients undergoing laparoscopic cholecystectomy with a normal liver function tests as the sole risk factor for choledocholithiasis: a prospective study. *Dig Liver Dis*. 2004;36: 73–77.
42. Aubertin JM, Levoir D, Bouillot JL, et al. Endoscopic ultrasonography immediately prior to laparoscopic cholecystectomy: a prospective evaluation. *Endoscopy*. 1996;28:667–673.
43. Buscarini E, Tansini P, Vallisa D, et al. EUS for suspected choledocholithiasis: do benefits outweigh costs? A prospective, controlled study. *Gastrointest Endosc*. 2003;57:510–518.
44. Gautier G, Pilleul F, Crombe-Ternamian A, et al. Contribution of magnetic resonance cholangiopancreatography to the management of patients with suspected common bile duct stones. *Gastroenterol Clin Biol*. 2004;28:129–134.
45. Burtin P, Palazzo L, Canard JM, et al. Diagnostic strategies for extrahepatic cholestasis of indefinite origin: endoscopic ultrasonography or retrograde cholangiography? Results of a prospective study. *Endoscopy*. 1997;29:349–355.
46. Dancygier H, Natterman C. The role of endoscopic ultrasonography in biliary tract disease: obstructive jaundice. *Endoscopy*. 1994;26:800–802.
47. Kohut S, Nowak A, Nowakowska-Dulawa E, et al. Endosonography with linear array instead endoscopic retrograde cholangiography in patients with moderate suspicion of common bile duct stones. *World J Gastroenterol*. 2003;9:612–614.
48. Ney MV, Maluf-Filho F, Sakai P, et al. Echo-endoscopy versus endoscopic retrograde cholangiography for the diagnosis of choledocholithiasis: the influence of the size of the stone and diameter of the common bile duct. *Arq Gastroenterol*. 2005;42:239–243.
49. Norton SA, Alderson D. Prospective comparison of endoscopic endosonography and endoscopic retrograde cholangiopancreatography in the detection of bile duct stones. *Br J Surg*. 1997;84:1366–1369.
50. Prat F, Edery J, Meduri B, et al. Early EUS of the bile duct before endoscopic sphincterotomy for acute biliary pancreatitis. *Gastrointest Endosc*. 2001;54:724–729.
51. Scheiman JM, Carlos RC, Barnett JL, et al. Can endoscopic ultrasound or magnetic resonance cholangiopancreatography replace ERCP in patients with suspected biliary disease? A prospective trial and cost analysis. *Am J Gastroenterol*. 2001;96:2900–2904.
52. De Ledinghen V, Lecesne R, Raymond JM, et al. Diagnosis of choledocholithiasis: EUS or magnetic resonance cholangiography? A prospective controlled study. *Gastrointest Endosc*. 1999;49:26–31.
53. Materne R, Van Beers BE, Gigot JF, et al. Extrahepatic biliary obstruction: magnetic resonance imaging compared with endoscopic ultrasonography. *Endoscopy*. 2000;32:3–9.
54. Sugiyama M, Atomi Y. Endoscopic ultrasonography for diagnosing choledocholithiasis: a prospective comparative study with ultrasonography and computed tomography. *Gastrointest Endosc*. 1997;45:143–146.
55. Shim CS, Joo JH, Park CW, et al. Effectiveness of endoscopic ultrasonography in the diagnosis of choledocholithiasis prior to laparoscopic cholecystectomy. *Endoscopy*. 1995;27:428–432.
56. Amouyal P, Amouyal G, Levy P, et al. Diagnosis of choledocholithiasis by endoscopic ultrasonography. *Gastroenterology*. 1994;106:1062–1067.
57. Cervi C, Aube C, Tuech JJ, et al. Nuclear magnetic resonance cholangiography in biliary disease. Prospective study in 60 patients. *Ann Chir*. 2000; 125:428–434.
58. Demartines N, Eisner L, Schnabel K, et al. Evaluation of magnetic resonance cholangiography in the management of bile duct stones. *Arch Surg*. 2000;135:148–152.
59. Kim JH, Kim MJ, Park SI, et al. MR cholangiography in symptomatic gallstones: diagnostic accuracy according to clinical risk group. *Radiology*. 2002;224:410–416.
60. Stiris MG, Tennoe B, Aadland E, et al. MR Cholangiopancreatography and endoscopic retrograde cholangiopancreatography in patients with suspected common bile duct stones. *Acta Radiol*. 2000;41:269–272.
61. Taylor AC, Little AF, Hennessy OF, et al. Prospective assessment of magnetic resonance cholangiopancreatography for non-invasive imaging of the biliary tree. *Gastrointest Endosc*. 2002;55:17–22.
62. Dittrick G, Lamont JP, Kuhn JA, et al. Usefulness of endoscopic ultrasound in patients at high risk of choledocholithiasis. *Proc (Bayl Univ Med Cent)*. 2005;18:211–213.
63. Latcher J, Rubin A, Shiller M, et al. Linear EUS for bile duct stones. *Gastrointest Endosc*. 2000;51:51–54.
64. Ainsworth AP, Rafaelsen SR, Wamberg PA, et al. Cost-effectiveness of endoscopic ultrasonography, magnetic resonance cholangiopancreatography and endoscopic retrograde cholangiopancreatography in patients suspected of pancreaticobiliary disease. *Scand J Gastroenterol*. 2004;39:579–583.
65. Montariol T, Msika S, Charlier A, et al. French Associations for Surgical Research. Diagnosis of asymptomatic common bile duct stones: preoperative endoscopic ultrasonography versus intraoperative cholangiography: a multicenter, prospective controlled study. *Surgery*. 1998;124: 6–13.

66. Garrow D, Miller S, Sinha D, et al. Endoscopic ultrasound: a meta-analysis of test performance in suspected biliary obstruction. *Clin Gastroenterol Hepatol*. 2007;5:616–623.
67. Tse F, Liu L, Barkun A, et al. EUS: a meta-analysis of test performance in suspected choledocholithiasis. *Gastrointest Endosc*. 2008;67:235–244.
68. Samaraee AA, Khan U, Almashta Z, et al. Preoperative diagnosis of choledocholithiasis: the role of MRCP. *Br J Hosp Med (Lond)*. 2009;70: 339–343.
69. Modifi R, Lee AC, Madhavan KK, et al. The selective use of magnetic resonance cholangiography in the imaging the axial biliary tree in patients with acute gallstone pancreatitis. *Pancreatology*. 2008;8:55–60.
70. Topal B, Van de Moortel M, Fieuws S, et al. The value of magnetic resonance cholangiopancreatography and ultrasound compared with direct cholangiography in the detection of choledocholithiasis. *Br J Surg*. 2003;90:42–47.
71. Ausch C, Hochwarter G, Taher M, et al. Improving the safety of laparoscopic cholecystectomy: the routine use of preoperatory magnetic resonance cholangiography. *Surg Endosc*. 2005;19:574–580.
72. Griffin N, Wastle ML, Dunn WK, et al. Magnetic resonance cholangiopancreatography versus endoscopic retrograde cholangiopancreatography in the diagnosis of choledocholithiasis. *Eur J Gastroenterol Hepatol*. 2003;15:809–813.
73. De Waele E, Op de Beeck B, Waele B, et al. Magnetic resonance cholangiopancreatography in the preoperative assessment of patients with biliary pancreatitis. *Pancreatology*. 2007;7:347–351.
74. Hallal AH, Amortegui JD, Jeroukhimov JM, et al. Magnetic resonance cholangiopancreatography accurately detects common bile duct stones in resolving gallstone pancreatitis. *J Am Coll Surg*. 2005;200: 869–875.
75. Makary MA, Duncan MD, Harmon JW, et al. The role of magnetic resonance cholangiopancreatography in the management of patients with gallstones pancreatitis. *Ann Surg*. 2005;241:119–124.
76. Moon JH, Cho YD, Cha AW, et al. The detection of bile duct stones in suspected biliary pancreatitis: comparison of MRCP, ERCP, and intraductal US. *Am J Gastroenterol*. 2005;100:1051–1057.
77. Verma D, Kapadia A, Eisen GM, et al. EUS vs MRCP for detection of choledocholithiasis. *Gastrointest Endosc*. 2006;64:248–254.
78. Ledro-Cano D. Suspected choledocholithiasis: endoscopic ultrasound or magnetic resonance cholangio-pancreatography? A systematic review. *Eur J Gastroenterol Hepatol*. 2007;19:1007–1011.
79. Whermann T, Martchenko K, Riphaus A. Catheter probe extraductal ultrasonography vs conventional endoscopic ultrasonography for detection of bile duct stones. *Endoscopy*. 2009;41:133–137.
80. Seifert H, Wehrmann T, Hilgers R, et al. Catheter probe extraductal EUS reliably detects distal common bile duct abnormalities. *Gastrointest Endosc*. 2004;60:61–67.
81. Catanzarro A, Pfau P, Isenberg GA, et al. Clinical utility of intraductal EUS for evaluation of choledocholithiasis. *Gastrointest Endosc*. 2003;57: 712–714.
82. Tsuchiya S, Tsuyuguchi T, Sakai Y, et al. Clinical utility of intraductal US to decrease early recurrence rate of common bile duct stones after endoscopic papillotomy. *J Gastroenterol Hepatol*. 2008;23:1590–1595.
83. Sotoudehmanesh R, Kolahdoozan S, Asgari AA, et al. Role of endoscopic ultrasonography in prevention of unnecessary endoscopic retrograde cholangiopancreatography: a prospective study of 150 patients. *J Ultrasound Med*. 2007;26:455–460.
84. Pollowski M, Regula J, Tilszer A, et al. Endoscopic ultrasound versus endoscopic retrograde cholangiography for patients with intermediate probability of bile duct stones: a randomized trial comparing two management strategies. *Endoscopy*. 2007;39:296–303.
85. Karakan T, Cindoruk M, Alagozlu H, et al. EUS versus endoscopic retrograde cholangiography for patients with intermediate probability of bile duct stones: a prospective randomized trial. *Gastrointest Endosc*. 2009; 69:244–252.
86. Petrov MS, Savides TJ. Systematic review of endoscopic ultrasonography versus endoscopic retrograde cholangiopancreatography for suspected choledocholithiasis. *Br J Surg*. 2009;96:967–974.
87. Cotton PB, Baillie J, Pappas TN, et al. Laparoscopic cholecystectomy and the biliary endoscopist [editorial]. *Gastrointest Endosc*. 1991;37:94–97.
88. Cotton PB. Endoscopic retrograde cholangiopancreatography and laparoscopic cholecystectomy. *Am J Surg*. 1993;165:474–478.
89. National Institutes of Health. Consensus development conference statement on gallstones and laparoscopic cholecystectomy. *Am J Surg*. 1993; 165:340–398.
90. O'Toole D, Palazzo L. Choledocholithiasis: a practical approach from the endosonographer. *Endoscopy*. 2006;38(suppl 1):S23–S29.
91. Sgouros S, Bergele C. Endoscopic ultrasonography versus other diagnostic modalities in the diagnosis of choledocholithiasis. *Dis Dig Sci*. 2006; S1:2280–2286.
92. Abboud PA, Malet PF, Berlin JA, et al. Predictors of bile duct stones prior to cholecystectomy: a meta-analysis. *Gastrointest Endosc*. 1996;44: 450–459.
93. Sahai AV, Mauldin PD, Marsi V, et al. Bile duct stones and laparoscopic cholecystectomy: a decision analysis to assess the roles of intraoperative cholangiography, EUS and ERCP. *Gastrointest Endosc*. 1999;49:334–343.
94. Das A, Chak A. EUS. Endoscopic ultrasonography. *Endoscopy*. 2004;36: 17–22.
95. Alhayaf N, Lalor E, Bain V, et al. The clinical impact and cost implications of endoscopic ultrasound on the use of endoscopic retrograde cholangiopancreatography in a Canadian university hospital. *Can J Gastroenterol*. 2008;22:138–142.
96. Arguedas MR, Dupont AW, Wilcox CM, et al. Where do ERCP, endoscopic ultrasound, magnetic resonance cholangiopancreatography, and intraoperative cholangiography fit in the management of acute biliary pancreatitis? A decision analysis model. *Am J Gastroenterol*. 2001;96: 2892–2899.
97. Rogmamuolo J, Currie C, Calgary Advanced Therapeutic Endoscopy Center study group. Noninvasive vs selective invasive biliary imaging for acute biliary pancreatitis: an economic evaluation by using decision tree analysis. *Gastrointest Endosc*. 2005;61:86–97.
98. Fabbri C, Polifemo AM, Luigiano C, et al. Single session versus separate session endoscopic ultrasonography plus endoscopic retrograde cholangiography in patients with low to moderate risk for choledocholithiasis. *J Gastroenterol Hepatol*. 2009;26:1107–1112.
99. Shea JA, Berlin JA, Escarce JJ, et al. Revised estimates of diagnostic test sensitivity and specificity in suspected biliary tract disease. *Arch Intern Med*. 1994;154:2573–2581.
100. Ko C, Sekijima J, Lee S. Biliary sludge. *Ann Intern Med*. 1999;130:301–311.
101. Dill JE, Hill S, Callis J, et al. Combined endoscopic ultrasound and stimulated biliary drainage in cholecystitis and microlithiasis: diagnoses and outcomes. *Endoscopy*. 1995;27:424–427.
102. Dahan P, Andant C, Levy P, et al. Prospective evaluation of endoscopic ultrasonography and microscopic examination of duodenal bile in the diagnosis of cholecystolithiasis in 45 patients with normal conventional ultrasonography. *Gut*. 1996;38:277–281.
103. Thorboll J, Vilmann P, Jacobsen B, et al. Endoscopic ultrasonography in detection of cholelithiasis in patients with biliary pain and negative transabdominal ultrasonography. *Scand J Gastroenterol*. 2004;39:267–269.
104. Mirbagheri SA, Mohamadnejad M, Nasiri J, et al. Prospective evaluation of endoscopic ultrasonography in the diagnosis of biliary microlithiasis in patients with normal transabdominal ultrasonography. *J Gastroenterol Surg*. 2005;9:961–964.
105. Kaw M, Brodmerkel GJ. ERCP, biliary crystal analysis, and sphincter of Oddi manometry in idiopathic recurrent pancreatitis. *Gastrointest Endosc*. 2002;55:157–162.
106. Lee SP, Hayashi A, Kim YS. Biliary sludge: curiosity or culprit? *Hepatology*. 1994;20:523–525.
107. Ros E, Navarro S, Bru C, et al. Occult microlithiasis in idiopathic acute pancreatitis: prevention of relapses by cholecystectomy or ursodeoxycholic acid therapy. *Gastroenterology*. 1991;101:1701–1709.
108. Venu RP, Geenen JE, Hogan W, et al. Is biliary microlithiasis a significant cause of idiopathic recurrent acute pancreatitis? A long-term follow-up study. *Clin Gastroenterol Hepatol*. 2007;5:75–79.
109. Chak A, Hawes RH, Cooper GS, et al. Prospective assessment of the utility of EUS in the evaluation of gallstone pancreatitis. *Gastrointest Endosc*. 1999;49:599–604.
110. Liu CL, Lo CM, Chan LK, et al. Detection of choledocholithiasis by EUS in acute pancreatitis: a prospective evaluation in 100 consecutive patients. *Gastrointest Endosc*. 2001;54:325–330.
111. Yusoff IF, Raymond G, Sahai AV. A prospective comparison of the yield of EUS in primary vs recurrent idiopathic acute pancreatitis. *Gastrointest Endosc*. 2004;60:673–678.
112. Wilcox CM, Varadarajulu S, Eloubeidi M. Role of endoscopic evaluation in idiopathic pancreatitis: a systematic review. *Gastrointest Endosc*. 2006; 63:1037–1045.
113. Wilcox CM, Kilgore M. Cost minimization analysis comparing diagnostic strategies in unexplained pancreatitis. *Pancreas*. 2009;38:117–121.
114. Lahde S. Helical CT in the examination of bile duct obstruction. *Acta Radiol*. 1996;37:660–664.
115. Park MS, Kim TK, Kim KW, et al. Differentiation of extrahepatic bile duct cholangiocarcinoma from benign stricture: findings at MRCP versus ERCP. *Radiology*. 2004;233:234–240.
116. Stewart CJ, Mills PR, Carter R, et al. Brush cytology in the assessment of pancreatico-biliary strictures: a review of 406 cases. *J Clin Pathol*. 2001; 54:449–455.
117. Ponchon T, Gagnon P, Berger F, et al. Value of endobiliary brush cytology and biopsies for the diagnosis of malignant bile duct stenosis: results of a prospective study. *Gastrointest Endosc*. 1995;42:565–572.

118. Schoefl R, Haefner M, Wbra F, et al. Forceps biopsy and brush cytology during endoscopic retrograde cholangiopancreatography for the diagnosis of biliary stenoses. *Scand J Gastroenterol*. 1997;32:363–368.
119. Farrell RJ, Jain AK, Wang H, et al. The combination of stricture dilation, endoscopic needle aspiration and biliary brushing significantly improves the diagnostic yield of malignant bile duct strictures. *Gastrointest Endosc*. 2001;54:587–594.
120. De Bellis M, Fogel EL, Sherman S, et al. Influence of stricture dilation and repeat brushing on the cancer detection rate of brush cytology in the evaluation of malignant biliary obstruction. *Gastrointest Endosc*. 2003; 58:176–182.
121. Tamada K, Ueno N, Tomiyama T, et al. Characterization of biliary strictures using intraductal ultrasonography: comparison with percutaneous cholangioscopic biopsy. *Gastrointest Endosc*. 1998;47:341–349.
122. Tamada K, Kurihara K, Tomiyama T, et al. How many biopsies should be performed during percutaneous transhepatic cholangioscopy to diagnose biliary tract cancer. *Gastrointest Endosc*. 1999;50:653–658.
123. Deveraux CE, Binmoeller KF. Endoscopic retrograde cholangiopancreatography in the next millennium. *Gastrointest Clin N Am*. 2000;10: 117–133.
124. Fogel EL, Sheman S. How to improve the accuracy of diagnosis of malignant biliary strictures. *Endoscopy*. 1999;31:758–760.
125. Tio TL, Cheng J, Wijers OB, et al. Endosonographic TNM staging of extrahepatic bile duct cancer: comparison with pathological staging. *Gastroenterology*. 1991;100:1351–1361.
126. Dancygier H, Nattermann C. The role of endoscopic ultrasonography in biliary tract disease: obstructive jaundice. *Endoscopy*. 1994;26:800–802.
127. Songur Y, Temucin G, Sahin B. Endoscopic ultrasonography in the evaluation of dilated common bile duct. *J Clin Gastroenterol*. 2001;33: 302–305.
128. Mukai H, Nakajima M, Yasuda K, et al. Evaluation of endoscopic ultrasonography in the preoperative staging of carcinoma of the ampulla of Vater and common bile duct. *Gastrointest Endosc*. 1992;38:676–683.
129. Menzel J, Poremba C, Dietl KH, et al. Preoperative diagnosis of bile duct strictures: comparison of intraductal ultrasonography with conventional endosonography. *Scand J Gastroenterol*. 2000;35:77–82.
130. Palazzo L, Roseau G, Gayet B, et al. Endoscopic ultrasonography in the diagnosis and staging of pancreatic adenocarcinoma: results of a prospective study with comparison to ultrasonography and CT scan. *Endoscopy*. 1993;25:143–150.
131. Hollerbach S, Klamann A, Topalidis T, et al. Endoscopic ultrasonography (EUS) and fine needle aspiration (FNA) cytology for diagnosis of chronic pancreatitis. *Endoscopy*. 2001;33:824–831.
132. Gress F, Gotlieb K, Sherman S, et al. Endoscopic ultrasonography-guided fine-needle aspiration biopsy of suspected pancreatic cancer. *Ann Intern Med*. 2001;134:459–464.
133. Harewood GC, Wiersema MJ. Endosonography-guided fine needle aspiration biopsy in the evaluation of pancreatic masses. *Am J Gastroenterol*. 2002;97:1386–1391.
134. Raut CP, Grau AM, Staerkel GA, et al. Diagnostic accuracy of endoscopic ultrasound-guided fine-needle aspiration in patients with presumed pancreatic cancer. *J Gastrointest Surg*. 2003;7:118–126.
135. Agarqal B, Abu-Hamda E, Molke KL, et al. Endoscopic ultrasound-guided fine needle aspiration and multidetector spiral CT in the diagnosis of pancreatic cancer. *Am J Gastroenterol*. 2004;99:844–850.
136. Varadarajulu S, Tamhane A, Eloubeidi MA. Yield of EUS-guided FNA of pancreatic masses in the presence or absence of chronic pancreatitis. *Gastrointest Endosc*. 2005;62:728–736.
137. Horwhat JD, Paulson EK, McGrath K, et al. A randomized comparison of EUS-guided FNA versus CT or US-guided FNA for the evaluation of pancreatic mass lesions. *Gastrointest Endosc*. 2006;63:966–975.
138. Lee JH, Salem R, Aslanian H, et al. Endoscopic ultrasound and fine needle aspiration of unexplained bile duct strictures. *Am J Gastroenterol*. 2004;99:1069–1073.
139. Byrne MF, Gerke H, Mitchell RM, et al. Yield of endoscopic ultrasound-guided fine-needle aspiration of bile duct lesions. *Endoscopy*. 2004;36: 715–719.
140. Fritscher-Ravens A, Broering DC, Sriram PV, et al. Endoscopic ultrasound-guided fine needle aspiration cytodiagnosis of hilar cholangiocarcinoma: a case series. *Gastrointest Endosc*. 2000;52:534–540.
141. Eloubeidi MA, Chen VK, Jhala NC, et al. Endoscopic ultrasound-guided fine needle aspiration biopsy of suspected cholangiocarcinoma. *Clin Gastroenterol Hepatol*. 2004;2:209–213.
142. Fritscher-Ravens A, Broering DC, Knoefel WT, et al. EUS-guided fine-needle aspiration of suspected hilar cholangiocarcinoma in potentially operable patients with negative brush cytology. *Am J Gastroenterol*. 2003;99:45–51.
143. Rösch T, Hofrichter K, Frimberger E, et al. ERCP or EUS for tissue diagnosis of biliary strictures? A prospective randomized trial. *Am J Gastroenterol*. 2004;60:390–396.
144. Meara RS, Jhala D, Eloubeidi MA, et al. Endoscopic ultrasound-guided FNA biopsy of bile duct and gallbladder: analysis of 53 cases. *Cytopathology*. 2006;17:42–49.
145. DeWitt J, Misra VL, LeBlanc JK, et al. EUS-guided FNA of proximal biliary strictures after negative ERCP brush cytology. *Gastrointest Endosc*. 2006; 64:325–333.
146. Larghi A, Lecca PG, Ardito F, et al. Evaluation of hilar biliary strictures by using a newly developped forward-viewing therapeutic echoendoscope: preliminary results of an ongoing experience. *Gastrointest Endosc*. 2009; 69:356–360.
147. Lefort C, Napoleón B, Ponchon T, et al. Interest of an intraductal ultrasonographic (IDUS) system in pancreatobiliary tract: results about our 100 first patients [abstract]. *Endoscopy*. 2002;34:A7.
148. Tamada T, Tomiyama T, Ischiyama M, et al. Influence of biliary drainage catheter on bile duct wall thickness as measured by intraductal ultrasonography. *Gastrointest Endosc*. 1998;47:28–33.
149. Vázquez-Sequeiros E, Baron TH, Clain JE, et al. Evaluation of indeterminate bile duct strictures by intraductal US. *Gastrointest Endosc*. 2002;56:372–379.
150. Tamada K, Nagai H, Yasuda Y, et al. Transpapillary intraductal US prior to biliary drainage in the assessment of longitudinal spread of extrahepatic bile duct carcinoma. *Gastrointest Endosc*. 2001;53:300–307.
151. Domag KD, Wessling J, Reamer P, et al. Endoscopic retrograde cholangiopancreatography, intraductal ultrasonography, and magnetic resonance cholangiopancreatography in bile duct strictures: a prospective comparison of imaging diagnostics with histopathological correlation. *Am J Gastroenterol*. 2004;99:1684–1689.
152. Stavropoulos S, Larghi A, Verna E, et al. Intraductal ultrasound for the evaluation of patients with biliary strictures and no abdominal mass on computed tomography. *Endoscopy*. 2005;37:715–721.
153. Krishna NB, Saripalli S, Safdar R, et al. Intraductal US in evaluation of biliary strictures without a mass lesion on CT scan or magnetic resonance imaging: significance of focal wall thickening and extrinsic compression at the stricture site. *Gastrointest Endosc*. 2007;66:90–96.
154. Varadarajulu S, Eloubeidi MA, Wilcos M. Prospective evaluation of indeterminate ERCP findings by intraductal ultrasound. *J Gastroenterol Hepatol*. 2007;22:2086–2092.
155. Inui K, Miyoshi H. Cholangiocarcinoma and intraductal sonography. *Gastrointest Endosc Clin N Am*. 2005;15:143–155.
156. Kuroiwa M, Tsukamoto Y, Naitoh Y, et al. New technique using intraductal ultrasonography for the diagnosis of bile duct cancer. *J Ultrasound Med*. 1994;13:189–195.
157. Gress F, Chen YK, Sherman S, et al. Experience with a catheter-based ultrasound probe in the bile duct and pancreas. *Endoscopy*. 1995;27:178–184.
158. Kuroiwa M, Goto H, Hirooka Y, et al. Intraductal ultrasonography for the diagnosis of proximal invasion in extrahepatic bile duct cancer. *J Gastroenterol Hepatol*. 1998;13:715–719.
159. Tamada K, Tomiyama T, Wada S, et al. Endoscopic transpapillary bile duct biopsy with the combination of intraductal ultrasonography in the diagnosis of biliary strictures. *Gut*. 2002;50:326–331.
160. Wehrmann T, Riphaus A, Martchenko K, et al. Intraductal ultrasonography in the diagnosis of Mirizzi syndrome. *Endoscopy*. 2006;38:717–722.
161. Lefort C, Napoléon B, Dumortier J, et al. Intraductal ultrasonography may modify the management of cholangiocarcinomas in diagnosing diffuse papillomatosis [abstract]. *Endoscopy*. 2003;35:A45.
162. Dumortier J, Scoazec JY, Valette PJ, et al. Successful liver transplantation for diffuse biliary papillomatosis. *J Hepatol*. 2001;35:542–543.
163. Tamada K, Tomiyama T, Oohashi A, et al. Bile duct wall thickness measured by intraductal US in patients who have not undergone previous biliary drainage. *Gastrointest Endosc*. 1999;48:199–203.
164. Tischendorrf JJW, Meier ON, Schneider A, et al. Transpapillary intraductal ultrasound in the evaluation of dominant stenoses in patients with primary sclerosing cholangitis. *Scand J Gastroenterol*. 2007;42:1011–1017.
165. Levy MJ, Baron TH, Clayton CL, et al. Prospective evaluation of advanced molecular markers and imaging techniques in patients with indeterminate bile duct strictures. *Am J Gastroenterol*. 2008;103:1263–1273.
166. Rösch T, Meining A, Fruhmorgen S, et al. A prospective comparison of the diagnostic accuracy of ERCP, MRCP, CT, and EUS in the biliary strictures. *Gastrointest Endosc*. 2002;55:870–876.
167. Sai JK, Suyama M, Kubokawa Y, et al. Early detection of extrahepatic bile-duct carcinomas in the nonicteric stage by using MRCP followed by EUS. *Gastrointest Endosc*. 2009;70:29–36.
168. Mishra G, Conway JD. Endoscopic ultrasound in the evaluation of radiologic abnormalities of the liver and biliary tree. *Curr Gastroenterol Rep*. 2009;11:150–154.
169. Fukuda Y, Tsuyuguchi T, Sakai Y, et al. Diagnostic utility of peroral cholangioscopy for various bile-duct lesions. *Gastrointest Endosc*. 2005;62:374–382.
170. Pleskow D, Parsi MA, Chen YK, et al. Biopsy of indeterminate biliary strictures: Does direct visualization help? A multicenter experience [abstract]. *Gastrointest Endosc*. 2008;67:AB103.

171. Napoléon B, Lefort C. IDUS: diagnosis of bile duct carcinoma. *Dig Endosc*. 2004;16:S230–S235.
172. Sato M, Inoue H, Ogawa S, et al. Limitations of transhepatic cholangioscopy for the diagnosis of intramural extension of bile duct carcinoma. *Endoscopy*. 1998;30:281–288.
173. Nimura Y. Staging cholangiocarcinoma by cholangioscopy. *HPB (Oxford)*. 2008;10:113–115.
174. Tamada K, Ueno N, Ischiyama M, et al. Assessment of pancreatic parenchymal invasion by bile duct cancer using intraductal ultrasonography. *Endoscopy*. 1996;28:492–496.
175. Tamada K, Ido K, Ueno N, et al. Assessment of hepatic artery invasion by bile duct cancer using intraductal ultrasonography. *Endoscopy*. 1995;27: 579–583.
176. Tamada K, Ido K, Ueno N, et al. Assessment of portal vein invasion by bile duct cancer using intraductal ultrasonography. *Endoscopy*. 1995;27: 573–578.
177. Chen CY, Lu CL, Chang FY, et al. Risk factors for gallbladder polyp in the Chinese population. *Am J Gastroenterol*. 1997;92:2066–2068.
178. Segawa K, Arisawa T, Niwa Y, et al. Prevalence of gallbladder polyps among apparently healthy Japanese: ultrasonographic study. *Am J Gastroenterol*. 1992;87:630–633.
179. Sugiyama M, Atomi Y, Kuroda A, et al. Large cholesterol of the gallbladder: diagnosis by means of US and endoscopic US. *Radiology*. 1995;196:493–497.
180. Aldridge MC, Bismuth H. Gallbladder cancer: the polyp-cancer sequence. *Br J Surg*. 1990;77:363–364.
181. Kozuka S, Tsubone M, Yasui A, et al. Relation of adenoma to carcinoma in the gallbladder. *Cancer*. 1982;50:2226–2234.
182. Silverstein B, Cecconello I, Ramos AC, et al. Hemobilia as a complication of laparoscopic cholecystectomy. *Surg Laparosc Endosc*. 1994;4:301–303.
183. Garcia-Olmo D, Vasquez P, Cifuentes J, et al. Postoperative gangrenous peritonitis after laparoscopic cholecystectomy: a new complication for a new technique. *Surg Laparosc Endosc*. 1996;6:224–225.
184. Black NA, Thombson E, Sanderson CFB, et al. Symptoms and health status before and 6 weeks after open cholecystectomy: a European cohort study. *Gut*. 1994;35:1301–1305.
185. Desautels SG, Slivka A, Hutson WR, et al. Post-cholecystectomy pain syndrome: pathophysiology of abdominal pain in sphincter of Oddi type III. *Gastroenterology*. 1999;116:900–905.
186. Sugiyama K, Atomi Y, Yamato T. Endoscopic ultrasonography for differential diagnosis of polypoid gallbladder lesions: analysis in surgical and follow-up series. *Gut*. 2000;46:250–254.
187. Shinkai H, Kimura W, Muto T. Surgical indications for small polypoid lesions of the gallbladder. *Am J Surg*. 1998;175:114–117.
188. Kubota K, Bandai Y, Noie T, et al. How should polypoid lesions of the gallbladder be treated in the era of laparoscopic cholecystectomy? *Surgery*. 1995;117:481–487.
189. Sadamoto Y, Oda S, Tanaka M, et al. A useful approach to the differential diagnosis of small polypoid lesions of the gallbladder, utilizing an endoscopic ultrasound scoring system. *Endoscopy*. 2002;34:959–965.
190. Sugiyama M, Xie XY, Atomi Y, et al. Differential diagnosis of small polypoid lesions of the gallbladder. *Ann Surg*. 1999;229:498–504.
191. Choi WB, Lee SK, Kim MH, et al. A new strategy to predict the neoplastic polyps of the gallbladder based on a scoring system using EUS. *Gastrointest Endosc*. 2000;52:372–379.
192. Azuma T, Yoshikawa T, Araida T, et al. Differential diagnosis of polypoid lesions of the gallbladder by endoscopic ultrasonography. *Am J Surg*. 2001;181:65–70.
193. Fujita N, Noda Y, Kobayashi GO, et al. Analysis of the layer structure of the gallbladder wall delineated by endoscopic ultrasound using the pinning method. *Dig Endosc*. 1995;7:353–356.
194. Fujita N, Noda Y, Kobayashi G, et al. Diagnosis of depth of invasion of gallbladder carcinoma by EUS. *Gastrointest Endosc*. 1999;50:659–663.
195. Morita K, Nakazawa S, Naito Y, et al. Endoscopic ultrasonography of the gallbladder compared with pathological findings. *Jpn J Gastroenterol*. 1986;83:86–95.
196. Matsumoto J. Endoscopic ultrasonography diagnosis of gallbladder lesions. *Endoscopy*. 1998;30(suppl 1):A120–A127.
197. Cho JH, Park JY, Kim YJ, et al. Hypoechoic foci on EUS are simple and strong predictive factors for neoplastic gallbladder polyps. *Gastrointest Endosc*. 2009;69:1244–1250.
198. Cheon YK, Cho WY, Lee TH, et al. Endoscopic ultrasonography does not differentiate neoplastic from non neoplastic small gallbladder polyps. *World J Gastroenterol*. 2009;15:2361–2366.
199. Kimura K, Fujita N, Noda Y, et al. Differential diagnosis of large-sized pedunculated polypoid lesions of the gallbladder by endoscopic ultrasonography: a prospective study. *J Gastroenterol*. 2001;36:619–622.
200. Chijiwa K, Sumiyoshi K, Nakayama F. Impact of recent advances in hepatobiliary imaging techniques on the preoperative diagnosis of carcinoma of the gallbladder. *World J Surg*. 1991;15:322–327.
201. Mizuguchi M, Kudo S, Fukahori T, et al. Endoscopic ultrasonography for demonstrating loss of multiple layer patterns of the thickened gallbladder wall in the preoperative diagnosis of gallbladder cancer. *Eur Radiol*. 1997;7:1323–1327.
202. Gallbladder. In: Edge SB, Byrd DR, Compton CC, et al, eds. *AJCC Cancer Staging Manual*, 7th ed. New York: Springer; 2010:255-262.
203. Sadamoto Y, Kubo H, Harada N, et al. Preoperative diagnosis and staging of gallbladder carcinoma by EUS. *Gastrointest Endosc*. 2003;58:536–541.
204. Fujimoto T, Kato Y, Kitamura T, et al. Hypoechoic area as an ultrasound finding suggesting subserosal invasion in polypoid carcinoma of the gallbladder. *Br J Radiol*. 2001;74:455–457.
205. Jacobson BC, Pitman MB, Brugge WR. EUS-guided FNA for the diagnosis of gallbladder masses. *Gastrointest Endosc*. 2003;57:251–254.
206. Varadarajulu S, Eloubeidi MA. Endoscopic ultrasound guided fine needle aspiration in the evaluation of gallbladder masses. *Endoscopy*. 2005;37: 751–754.
207. Meara RS, Jhala D, Eloubeidi MA, et al. Endoscopic ultrasound-guided FNA biopsy of bile duct and gallbladder: analysis of 53 cases. *Cytopathology*. 2006;17:42–49.
208. Fleming ID, Cooper JS, Henson DE, et al. *AJCC Cancer Staging Handbook*. 5th ed. Philadelphia: Lippincott-Raven; 1998.
209. Vilgrain V, Menu Y. *Imagerie du foie, des voies biliaires, du pancréas et de la rate*. Médecine Sciences. Paris: Flammarion; 2002.
210. Kim MY, Baik SK, Choi YJ, et al. Endoscopic sonographic evaluation of the thickened gallbladder wall in patients with acute hepatitis. *J Clin Ultrasound*. 2003;31:245–249.
211. Sato M, Ishida H, Konno K, et al. Segmental chronic cholecystitis: sonographic findings and clinical manifestations. *Abdom Imaging*. 2002;27:43–46.
212. Ishizuka D, Shirai Y, Tsukada K, et al. Gallbladder cancer with intratumoral anechoic foci: a mimic of adenomyomatosis. *Hepatogastroenterology*. 1998;45:927–929.
213. Nabatame N, Shirai Y, Nishimura A, et al. High risk of gallbladder carcinoma in elderly patients with segmental adenomyomatosis of the gallbladder. *J Exp Clin Cancer Res*. 2004;23:593–598.
214. Guzman-Valdivia G. Xanthogranulomatous cholecystitis: 15 years' experience. *World J Surg*. 2004;28:254–257.
215. Muguruma N, Okamura S, Okahisa T, et al. Endoscopic sonography in the diagnosis of xanthogranulomatous cholecystitis. *J Clin Ultrasound*. 1999;27:347–350.
216. Palazzo L, Ngo Y, Cellier C. Endosonographic features of primary cholangitis: study of 23 cases [abstract]. *Gastrointest Endosc*. 1997;45:A611.
217. Palazzo L, Hochain P, Helmer C, et al. Biliary varices on endoscopic ultrasonography: clinical presentation and outcome. *Endoscopy*. 2000; 32:520–524.
218. Tokiwa T, Iwai N. Early mucosal changes of the gallbladder in patients with anomalous arrangement of the pancreaticobiliary duct. *Gastroenterology*. 1996;110:1614–1618.
219. Tanno S, Obara T, Maguchi H, et al. Thickened inner hypoechogenic layer of the gallbladder wall in the diagnosis of anomalous pancreaticobiliary ductal union with endosonography. *Gastrointest Endosc*. 1997;46:520–526.
220. Kawakatsu M, Vilgrain V, Zins M, et al. Radiologic features of papillary adenoma and papillomatosis of the biliary tract. *Abdom Imaging*. 1997; 22:87–90.
221. Fockens P. The role of endoscopic ultrasonography in the biliary tract: ampullary tumors. *Endoscopy*. 1994;26:803–805.
222. Spigelman AD, Talbot IC, Penna C, et al. Evidence for adenoma-carcinoma sequence in the duodenum of patients with familial adenomatous polyposis. *J Clin Pathol*. 1994;47:709–710.
223. Napoléon B, Barthet M, Saurin JC, et al. Les risques de l'ampullectomie endoscopique sont-ils assez faibles pour en faire une alternative à la chirurgie? Résultats d'une étude rétrospective multicentrique [abstract]. *Gastrointest Clin Biol*. 2003;27:A79.
224. Burke CA, Beck GJ, Church JM, et al. The natural history of untreated duodenal and ampullary adenomas in patients with familial adenomatous polyposis followed in an endoscopic surveillance program. *Gastrointest Endosc*. 1999;49:358–364.
225. Hayes DH, Bolton JS, Willis GW, Bowen JC. Carcinoma of the ampulla of Vater. *Ann Surg*. 1987;206:572–577.
226. Knox RA, Kingston RD. Carcinoma of the ampulla of Vater. *Br J Surg*. 1986;73:72–73.
227. Baczako K, Buchler M, Beger H, et al. Morphogenesis and possible precursor lesions of invasive carcinoma of the papilla of Vater: epithelial dysplasia and adenoma. *Hum Pathol*. 1985;16:305–310.
228. Ponchon T, Berger F, Chavaillon A, et al. Contribution of endoscopy to diagnosis and treatment of tumors of the ampulla of Vater. *Cancer*. 1989;64:161–167.
229. Kimchi N, Mindrul V, Broide E, et al. The contribution of endoscopy and biopsy to the diagnosis of periampullary tumors. *Endoscopy*. 1998;30: 538–543.

230. Clary B, Tyler D, Dematos P, et al. Local ampullary resection with careful intraoperative frozen section evaluation for presumed benign ampullary neoplasms. *Surgery*. 2000;127:628–633.
231. Neoptolemos J, Talbot I, Carr-Locke D, et al. Treatment and outcome in 52 consecutive cases of ampullary carcinoma. *Br J Surg*. 1987;74:957–961.
232. Yamaguchi K, Enjoji M, Kitamura K. Endoscopic biopsy has limited accuracy in diagnosis of ampullary tumors. *Gastrointest Endosc*. 1990;36: 588–592.
233. Sivak MV. Clinical and endoscopic aspects of the tumors of the ampulla of Vater. *Endoscopy*. 1988;20:211–217.
234. Will U, Bosseckert H, Meyer F, et al. Correlation of endoscopic ultrasonography (EUS) for differential diagnostics between inflammatory and neoplastic lesions of the papilla of Vater and the peripapillary region with results of the histologic investigation. *Ultraschall Med*. 2008;29:275–280.
235. Keriven O, Napoléon B, Souquet JC, et al. Patterns of the ampulla of Vater at endoscopic ultrasonography [abstract]. *Gastrointest Endosc*. 1993;39:A290.
236. Rösch T, Braig C, Gain T, et al. Staging of pancreatic and ampullary carcinoma by endoscopic ultrasonography. *Gastroenterology*. 1992;102: 188–199.
237. Saurin JC, Chavaillon A, Napoléon B, et al. Long-term follow-up of patients with endoscopic treatment of sporadic adenomas of the papilla of Vater. *Endoscopy*. 2003;35:402–406.
238. Binmoeller K, Boaventura S, Ramsperger K, et al. Endoscopic snare excision of the benign adenomas of the papilla of Vater. *Gastrointest Endosc*. 1993;39:127–131.
239. Zadorova Z, Dvokaf M, Hajer J. Endoscopic therapy of benign tumors of the papilla of Vater. *Endoscopy*. 2001;33:345–347.
240. Norton I, Gostout C, Baron T, et al. Safety and outcome of endoscopic snare excision of the major duodenal papilla. *Gastrointest Endosc*. 2002; 56:239–243.
241. Napoléon B, Pialat J, Saurin JC, et al. Adénomes et adénocarcinomes débutants de l'ampoule de Vater: place du traitement endoscopique à but curatif. *Gastroenterol Clin Biol*. 2004;28:385–392.
242. Catalano M, Linder J, Chak A, et al. Endoscopic management of adenoma of the major duodenal papilla. *Gastrointest Endosc*. 2004;59:225–232.
243. Desilets D, Dy P, Ku P, et al. Endoscopic management of tumors of the major duodenal papilla: refined techniques to improve outcome and avoid complications. *Gastrointest Endosc*. 2001;54:202–208.
244. Ampulla of vater. In: Edge SB, Byrd DR, Compton CC, et al, eds. *AJCC Cancer Staging Manual*. 7th ed. New York: Springer; 2010:277-284.
245. Cannon M, Carpenter S, Elta G, et al. EUS compared with CT, magnetic resonance imaging, and angiography and the influence of biliary stenting on staging accuracy of ampullary neoplasms. *Gastrointest Endosc*. 1999; 50:27–33.
246. Tio TL, Sie LH, Kallimanis G, et al. Staging of ampullary and pancreatic carcinoma: comparison between endosonography and surgery. *Gastrointest Endosc*. 1996;44:706–713.
247. Yoshida T, Matsumoto T, Shibata K, et al. Patterns of lymph node metastasis in carcinoma of the ampulla of Vater. *Hepatogastroenterology*. 2000; 47:880–883.
248. Yamaguchi K, Enjoji M. Carcinoma of the ampulla of Vater: a clinicopathologic study and pathologic staging of 109 cases of carcinoma and 5 cases of adenoma. *Cancer*. 1987;59:506–515.
249. Nakao A, Harada A, Nonami T, et al. Prognosis of cancer of the duodenal papilla of Vater in relation to clinicopathological tumor extension. *Hepatogastroenterology*. 1994;41:73–78.
250. Shirai Y, Tsukada K, Ohtani T, et al. Carcinoma of the ampulla of Vater: histopathologic analysis of tumor spread in Whipple pancreatoduodenectomy specimens. *World J Surg*. 1995;19:102–107.
251. Rivadeneira DE, Pochapin M, Grobmyer SP, et al. Comparison of linear array endoscopic ultrasonography and helical CT for the staging of periampullary malignancies. *Ann Surg Oncol*. 2003;10:890–897.
252. Buscail L, Pages P, Bertelemy P, et al. Role of EUS in the management of pancreatic and ampullary carcinoma: a prospective study assessing resectability and prognosis. *Gastrointest Endosc*. 1999;50:34–40.
253. Midwinter MJ, Beveridge CJ, Wilsdon JB, et al. Correlation between spiral computed tomography, endoscopic ultrasonography, and findings at operation in pancreatic and ampullary tumors. *Br J Surg*. 1999;86: 189–193.
254. Artifon ELA, Counto D, Sakai P, et al. Prospective evaluation of EUS versus CT scan for staging of ampullary cancer. *Gastrointest Endosc*. 2009;70:290–296.
255. Chen CH, Yang CC, Yeh YH, et al. Reappraisal of endosonography of ampullary tumors: correlation with transabdominal sonography, CT and MRI. *J Clin Ultrasound*. 2009;37:18–25.
256. Maluf-Filho F, Sakai P, Cunha JEM, et al. Radial endoscopic ultrasound and spiral computed tomography in the diagnosis and staging of periampullary tumors. *Pancreatology*. 2004;4:122–128.
257. Ito K, Fujita N, Noda Y, et al. Preoperative evaluation of ampullary neoplasm with EUS and transpapillary intraductal US: a prospective study and histopathologically controlled study. *Gastrointest Endosc*. 2007;66: 740–747.
258. Morozumi A, Fujino MA, Sato T, et al. Endosonographic criteria for assessment of the depth of duodenal invasion in carcinoma of the papilla of Vater. *Dig Endosc*. 2001;13:149–158.
259. Menzel J, Hoepffner N, Sulkowski U, et al. Polypoid tumors of the major duodenal papilla: preoperative staging with intraductal US, EUS, and CT: a prospective histopathologically controlled study. *Gastrointest Endosc*. 1999;49:349–357.
260. Itoh A, Goto H, Naitoh Y, et al. Intraductal ultrasonography in diagnosing tumor extension of cancer of the papilla of Vater. *Gastrointest Endosc*. 1997;45:251–260.
261. Gress FG, Hawes RH, Savides TJ, et al. Endoscopic ultrasound-guided fine-needle aspiration biopsy using linear array and radial scanning endosonography. *Gastrointest Endosc*. 1997;45:243–250.
262. Napoleón B, Saurin JC, Scoazec JY, et al. Do endoscopic ultrasound and intraductal ultrasonography allow to orientate the treatment of ampullary tumour? [abstract]. *Endoscopy*. 2001;33:A2770.
263. Martin JA, Haber GB. Ampullary adenoma: clinical manifestations, diagnosis, and treatment. *Gastrointest Endosc Clin N Am*. 2003;13:649–669.
264. Vogt M, Jakobs R, Benz C, et al. Endoscopic therapy of adenomas of the papilla of Vater: a retrospective analysis with long-term follow-up. *Dig Liver Dis*. 2000;32:339–345.
265. Fukushina T, Fogel EL, Devereaux BM, et al. Use of ERCP and papillectomy in management of ampullary tumors: seven-year review of 75 cases at Indiana Medical Center [abstract]. *Gastrointest Endosc*. 2001;53:AB88.
266. Maguchi H, Takahashi K, Katanuma A, et al. Indication of endoscopic papillectomy for tumors of the papilla of Vater and its problems. *Dig Endosc*. 2003;15(suppl):S33–S35.
267. Cheng CL, Sherman S, Fogel EL, et al. Endoscopic snare papillectomy for tumors of the duodenal papillae. *Gastrointest Endosc*. 2004;60:757–764.
268. Hirroka Y, Itoh A, Goto H, et al. EUS/IDUS and endoscopic papillectomy. *Dig Endosc*. 2004;16(suppl):S176–S177.
269. Han J, Lee SK, Park DH, et al. Treatment outcome after endoscopic papillectomy of tumors of the major duodenal papilla. *Korean J Gastroenterol*. 2004;29:395.
270. Moon JH, Cha SW, Cho YD, et al. Wire-guided endoscopic snare papillectomy for tumors of the major duodenal papilla. *Gastrointest Endosc*. 2005;61:461–466.
271. Bohnacker S, Seitz U, Seewald S, et al. Endoscopic snare resection of benign ampullary tumor: can intraductal growth be treated endoscopically? [abstract]. *Gastrointest Endosc*. 2003;57:AB101.
272. Katsinelos P, Paroutoglou G, Koutouras J, et al. Safety and long-term follow-up of endoscopic snare excision of ampullary adenomas. *Surg Endosc*. 2006;20:608–613.
273. Irani S, Arai A, Ayub K, et al. Papillectomy for ampullary neoplasms: results of a single referral center over 10-year period. *Gastrointest Endosc*. 2009;70:923–932.
274. Yamao T, Isomoto H, Kohno S, et al. Endoscopic snare papillectomy with biliary and pancreatic stent placement for tumors of the major duodenal papilla. *Surg Endosc*. 2010;24:119–124.
275. Jung MK, Cho CM, Park SY, et al. Endoscopic resection of ampullary neoplasms: a single-center experience. *Surg Endosc*. 2009;23:2568–2574.
276. Quirk D, Rattner D, del Castillo CF, et al. The use of endoscopic ultrasonography to reduce the cost of treating ampullary tumors. *Gastrointest Endosc*. 1997;46:334–337.

CHAPTER 17 How to Perform Anorectal EUS

Paul Fockens | Steve Halligan | Robert H. Hawes | Shyam Varadarajulu

THE PERIANAL AREA

Examination of the perianal area is simplicity itself. No special patient preparation is required. The patient is told that any discomfort will be similar to having a finger in the anus and that the procedure will likely be less uncomfortable than digital rectal examination by a doctor. To the patient, the rigid probe is potentially a frightening piece of equipment, so it is worth mentioning that only the distal few centimeters will enter the anus (as opposed to rectal endosonography, in which insertion is obviously deeper). Some endosonographers place all patients in the left lateral position, whereas others prefer female patients to be in the prone position for examination. Placing women in the left lateral position can potentially distort anterior perineal anatomic features, with the result that the asymmetric images obtained will be difficult to interpret, especially with respect to perineal scarring.[1]

Proper equipment is essential for successful anal endoscopic ultrasonography (EUS). The standard (most commonly described in the literature) is the Bruel-Kjaer mechanical radial rigid probe. In the early days of EUS, when the principal instrument was the mechanical radial echoendoscope, examiners attempted to use this scope for anal EUS examination. However, the near-field imaging was poor, and the anal sphincters were often obscured by the ringdown artifact. Consequently, Olympus designed and marketed a rigid rectal probe compatible with their mechanical radial processor. However, with the introduction of electronic radial echoendoscopes, a flexible instrument is now available that can deliver high-quality images of anal anatomy and has rendered the dedicated rigid probe obsolete.

The rigid probe is prepared as necessary for the transducer being used. Some systems, for example, require the transducer head to be filled with degassed water to achieve acoustic coupling. This is accomplished by injection using a syringe through a side port. The probe must be maneuvered during filling so that all air is expelled through a pinhole located at the tip of the cone.

Whether or not water filling is required, the rigid probe tip is lubricated with ultrasound jelly and then is covered with a condom, which is itself lubricated to facilitate insertion. The probe is then inserted into the anus, and image acquisition is started by the operator. The probe is inserted so that its tip lies just in the distal rectum. The probe is then withdrawn gently, to examine the anal sphincters. As for all ultrasound examinations, the clinical findings are generally based on the image displayed on the monitor screen in real time (with the exception of three-dimensional acquisition, in which case the examination in its entirety can be replayed later). However, still images are usually required, and it is convenient to obtain these at three levels: the proximal, middle, and distal anal canal. These three anatomic levels are imaged at standard magnification, and the examination is then repeated at a higher magnification, so that six images are obtained, three at each magnification. The probe is oriented so that anterior (i.e., the 12 o'clock position) is uppermost and is then withdrawn. The examination is normally very quick, perhaps only a minute or so for the experienced operator who is familiar with normal and abnormal anatomy, especially when the sphincters are normal. The technique for imaging does not vary whether a rigid probe or an electronic radial flexible probe is used.

THE RECTUM

EUS of the rectum is mainly performed to examine suspicious rectal polyps or to stage rectal cancer. From country to country, huge differences exist in the use of EUS for this indication. Patients should be prepared with an enema or complete bowel preparation to evacuate all stool from the area to be investigated. For the start of the examination, the patient is usually placed in the left lateral position. The position may be changed during the examination. For noncircumferential masses or laterally spreading polyps, the patient should be positioned so that the mass or polyp is in the dependent position, to allow easy submersion in water. This is also an easy way to determine which wall of the rectum is involved (anterior, posterior, left, or right). Sedation is not usually necessary because the rectosigmoid junction is not passed with the instrument.

The examination is usually begun with a therapeutic endoscope with a built-in washing function. This equipment allows inspection of the mass and provides an opportunity to clear any residual stool that could degrade imaging. It also allows filling of the rectum, to indicate position of the patient that will optimize water filling.

There is no standard advice for the equipment to be used. For staging of tumors located very distally in the rectum, rigid radial scanning probes are often used. An alternative is a radial scanning echoendoscope, as used in the upper gastrointestinal tract. The advantage of echoendoscopes is that they can be advanced higher up into the rectum with help of the (oblique-viewing) optics. Linear echoendoscopes can also be used, with the advantage of enabling the examiner to perform EUS fine-needle aspiration (FNA) biopsy of extrarectal abnormalities such as lymph nodes or suspected tumor recurrences after surgery. The linear probes sometimes offer a further advantage, because the tumor and mural layers can be followed in the same image. This sometimes makes it easier to determine the exact involvement of the deeper layers. Finally, mini-probes can be used in patients with superficial lesions. With 12-MHz mini-probes, a penetration depth of 2 cm is generally possible.

Using a balloon around the tip of the rigid probe or echoendoscope removes the air and allows for good acoustic coupling between probe and tumor. Filling of the rectum with water is sometimes helpful, especially in the case of smaller lesions that would otherwise be compressed with a balloon. Complete filling of the rectum with water is usually not possible and should not be attempted because it is much easier to change the patient's position. When the bowel has been prepared with an enema, care should be taken not to fill the colon extensively with water, because this may mobilize stool located in the proximal colon.

Usually, the instrument is positioned proximal to the tumor, the balloon is slowly inflated, and the lumen is filled with water (Video 17.1). From this position, the transducer should be positioned in the center of the colon, to achieve perpendicular imaging of the rectal wall layers (Fig. 17.1). One should then look for the perirectal anatomic features. The universal landmark is the urinary bladder. Once the bladder has been identified, the image should be mechanically rotated so the bladder is located at the 12 o'clock position (Fig. 17.2). The instrument should be withdrawn slowly, with the transducer kept in the middle of the colon. The left/right and up/down dials should be used to adjust the transducer to maintain its position in the middle of the colon. The examiner must *not* torque the instrument because this will cause tangential imaging and potentially lead to inaccurate assessment of the depth of tumor penetration. When withdrawing the probe in the male, the seminal vesicles will be seen as echo-poor, elongated structures at the 12 o'clock position (see Fig. 17.2). Further withdrawal will bring the prostate in view. The prostate is seen as a hypoechoic, bean-shaped structure at the 12 o'clock position (Fig. 17.3). In female patients, withdrawal of the scope from the bladder first reveals the uterus (Fig. 17.4A), which is a rounded, hypoechoic structure at the 12 o'clock position. Then the vagina is seen as an elongated oval, hypoechoic structure with a characteristic hyperechoic band in the center that represents air (see Fig. 17.4B). It is important to recognize perirectal structures because invasion into any of them represents T4 disease. In addition, one must distinguish these structures, especially the seminal vesicles, from lymph nodes.

Once the tumor is seen with EUS, the lesion is examined extensively, and all layers of the colon wall are followed underneath the tumor. Houston's valves and the rectosigmoid junction make it almost impossible to maintain a perpendicular view of the rectal wall at all times with a radial instrument scan. Adaptation of the plane of scanning with the controls of the echoendoscope is important to prevent overstaging by nonperpendicular imaging.

After imaging of the tumor, the echoendoscope is advanced to the rectosigmoid junction to look for suspicious perirectal lymph nodes. Although it may be possible to advance the echoendoscope higher up, this maneuver is generally not advised. Images of the lesion and all other findings should be made; there are no standard positions at which images should be captured in every examination.

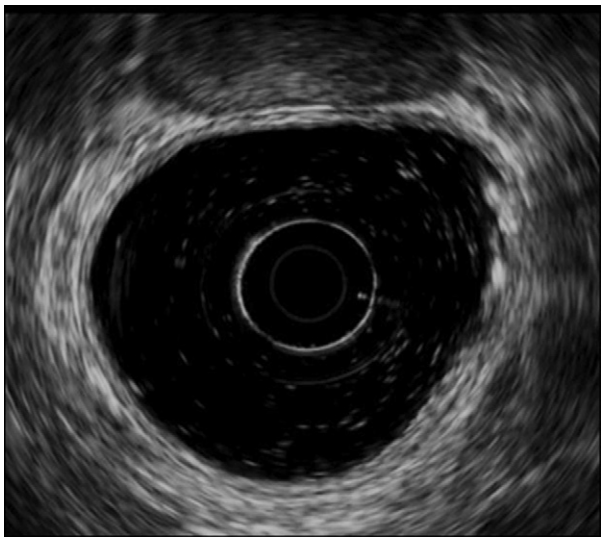


FIGURE 17.1 Rectal wall layers as imaged using a radial echoendoscope.

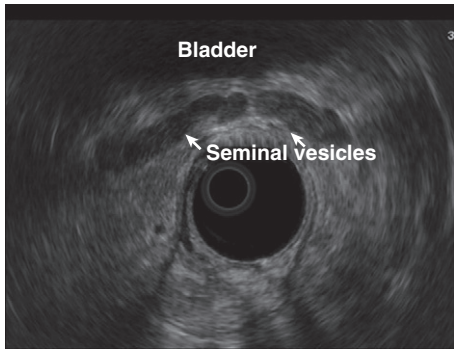


FIGURE 17.2 The anechoic structure at the 12 o'clock position represents the urinary bladder. In men, the echo-poor elongated structures seen below the urinary bladder represent the seminal vesicles.

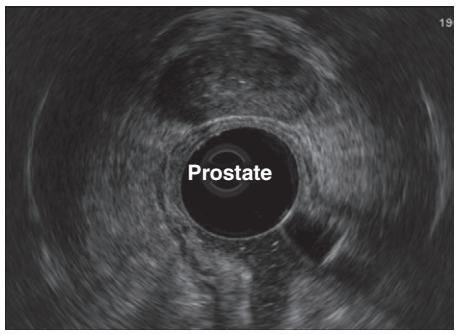


FIGURE 17.3 The prostate. On gradual withdrawal of the echoendoscope, a hypoechoic, bean-shaped structure is seen in men, which represents the prostate.

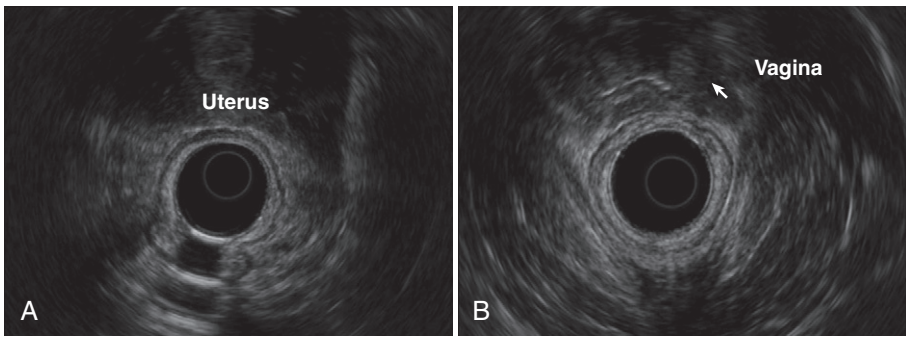


FIGURE 17.4 The uterus and vagina. In the female patient, withdrawal from the bladder first reveals the uterus (**A**), which is a rounded, hypoechoic structure at 12 o'clock, and then the vagina (**B**), which is seen as an elongated oval, hypoechoic structure with a characteristic hyperechoic band in the center that represents air.

In cases of small mucosal or submucosal lesions of the rectum, the practitioner may find it easier to use a dual-channel endoscope and a mini-probe. This equipment allows simultaneous water instillation, endoscopic visualization of the lesion, and ultrasound imaging.

Transrectal EUS FNA is feasible and safe. Antibiotic administration is recommended before the needle is passed. Indications for transrectal EUS FNA include suspicious lymph nodes associated with known primary rectal cancer when the lymph nodes are not "protected" by the primary tumor (tumor lies between the transducer and the lymph node) and perirectal masses of unknown origin.

REFERENCE

1. Frudinger A, Bartram CI, Halligan S, et al. Examination techniques for endosonography of the anal canal. *Abdom Imaging*. 1998;23:301–303.

CHAPTER 18 EUS IN RECTAL CANCER

Gavin C. Harewood

Key Points

The overall accuracy of EUS for T and N staging in rectal cancer is 85% and 75%, respectively. The addition of fine-needle aspiration increases the accuracy of nodal staging to 87%.

Studies have demonstrated a reduction in recurrence rates among patients with locally advanced rectal cancer who undergo preoperative neoadjuvant therapy. Therefore, EUS is recommended for all patients with newly diagnosed nonmetastatic rectal cancer.

When performing EUS examination of the rectum, it is important not only to evaluate the tumor and peritumoral areas for lymph nodes, but also to the study relationship of the tumor with surrounding organs and vasculature.

For evaluation of small tumors, instillation of deaerated water in the rectum may be required to obtain better acoustic coupling. It is sometimes necessary to change the position of a patient to supine to submerge the lesion completely under water.

INTRODUCTION

Accurate assessment of the extent of rectal cancer has important implications for the management of patients. Conventionally, initial staging is accomplished by means of computed tomography (CT) of the abdomen and pelvis; this serves to exclude distant metastatic (M1) disease. In patients without distant metastases (M0), endoscopic ultrasonography (EUS) is the most accurate imaging modality for determining locoregional stage (both T and N stages) of rectal tumors.

Rationale for Use of EUS in Staging Rectal Cancer

In 1990, the National Institutes of Health Consensus Conference recommended that patients with locally invasive rectal tumors (T3, T4N0, or TxN1 to TxN2 or stage II to III) should receive adjuvant therapy.[1] In large part, these recommendations reflected the findings of the Swedish Rectal Cancer trials, which demonstrated a reduction in recurrence rates among patients with locally advanced disease following the administration of preoperative radiation therapy compared with postoperative radiation therapy.[2,3] Since then, further studies corroborated these findings,[4–8] and they confirmed an improvement in recurrence-free survival and comparable toxicity when adjuvant therapy is given preoperatively. This is the rationale for accurately staging rectal tumors with EUS before operation: identification of patients with locally advanced nonmetastatic disease permits the selection of a subgroup of patients who will benefit maximally from preoperative neoadjuvant therapy (Fig. 18.1).

EUS TECHNIQUE

Transrectal EUS is conventionally performed with the patient in the left lateral decubitus position. Occasionally, repositioning of the patient is necessary to image lesions adequately. The use of a full colonoscopy preparation solution facilitates optimal ultrasonic visualization. This also allows colonoscopy to be performed at the same setting, if necessary. In that case, it is preferable to sequence the EUS first, to minimize the introduction of colonic air, which impedes ultrasound imaging. After the echoendoscope is advanced to the rectosigmoid junction and all the air is suctioned, the scope is slowly withdrawn, and a thorough examination is undertaken (Video 18.1). In patients with locally advanced disease, care must be taken to study the relationship of the tumor with adjacent organs such as the prostate, bladder, and seminal vesicles in men. In female patients, the relationship of the tumor with the bladder, vagina, cervix, and uterus should be studied. The perirectal area should be evaluated for the presence of lymph nodes and involvement of the iliac vasculature. Regional vasculature may mimic a lymph node, and this can be differentiated by using color or flow Doppler imaging. In addition, vessels tend to elongate and can be traced by EUS, whereas the lymph nodes are visualized as discrete structures that disappear with scope movement.

Smaller tumors and those located near the rectal folds may be difficult to evaluate by EUS and are best examined using the water-filling technique. In this technique, deaerated water is instilled into the rectum to submerge the lesion fully, and air is aspirated completely, to obtain better acoustic coupling. This maneuver permits ultrasonographic evaluation of the lesion without direct apposition of the echoendoscope balloon or tip over the lesion, which could result in compression of tissue planes and inaccuracy in T staging. Occasionally, changing the patient to a supine position permits complete immersion of the lesion under water and thereby makes the examination easier.

Endosonographically, the rectal wall is seen as five alternating hyperechoic and hypoechoic layers (Fig. 18.2). The histologic correlations of the echo layers are as follows:

- First layer (hyperechoic): interface between the water-filled balloon and the superficial mucosa
- Second layer (hypoechoic): deep mucosa and the muscularis mucosa
- Third layer (hyperechoic): submucosa
- Fourth layer (hypoechoic): muscularis propria
- Fifth layer (hyperechoic): interface between the serosa and perirectal fat

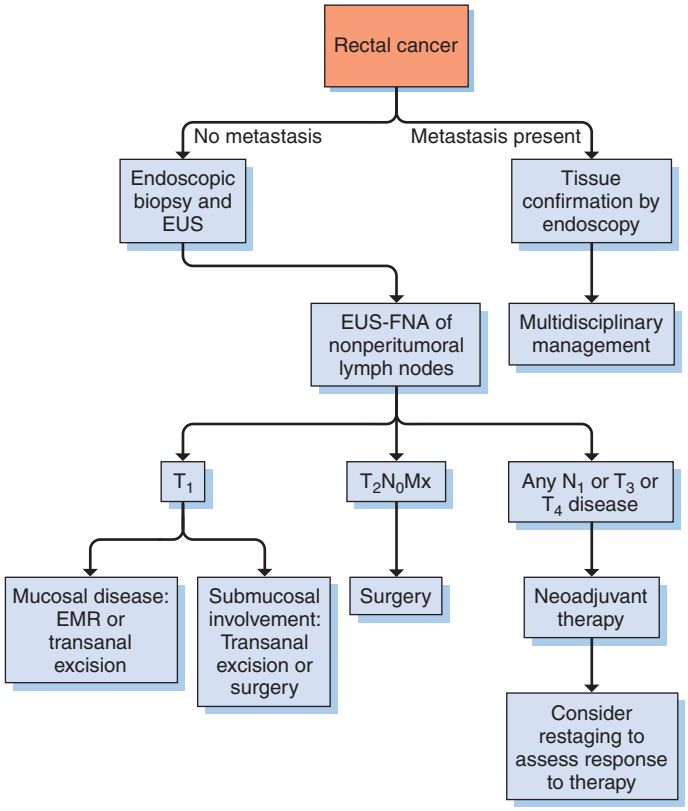


FIGURE 18.1 Algorithm denoting the role of EUS in rectal cancer management. EMR, endomucosal resection; FNA, fine-needle aspiration.

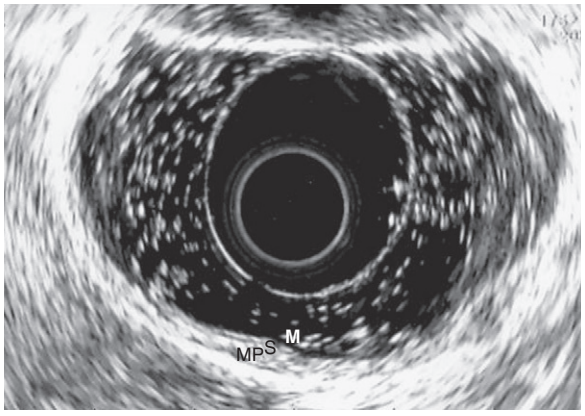


FIGURE 18.2 Normal rectal wall layers as visualized using a radial echoendoscope with water in the lumen. M, mucosa; MP; muscularis propria; S, submucosa.

Rectal cancer appears as a hypoechoic lesion that disrupts the normal wall echo layer pattern. A tumor that by EUS appears to be limited to the mucosa or the submucosa (first three echo layers) is classified as a T1 lesion (Fig. 18.3). A tumor that invades the muscularis propria (the hypoechoic fourth EUS layer) is a T2 lesion (Fig. 18.4). A T3 lesion penetrates the muscularis propria and extends beyond the five echo layers and into the surrounding perirectal fat (Fig. 18.5). A T4 lesion displays direct invasion into an adjacent organ such as the prostate gland, sacrum, vagina, and bladder (Fig. 18.6).

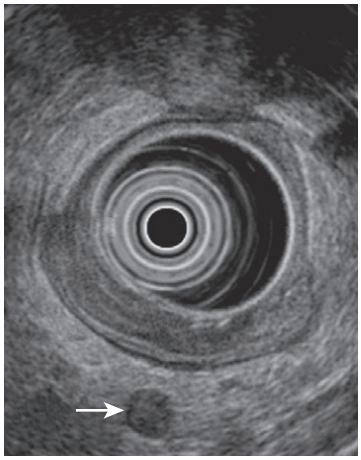


FIGURE 18.3 T1N1 tumor confined within submucosa and adjacent perirectal lymph node *(arrow).*

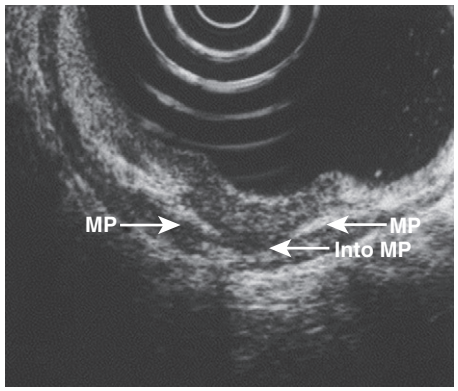


FIGURE 18.4 T2N0 rectal tumor invading the muscularis propria (MP).

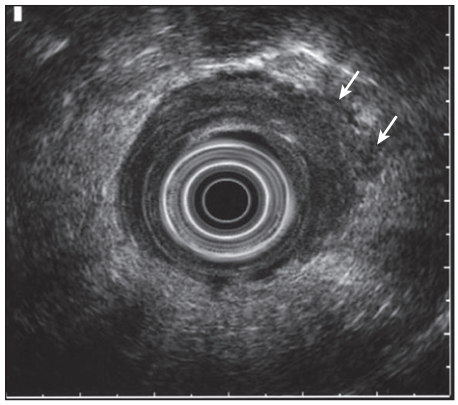


FIGURE 18.5 T3 rectal tumor with extension of tumor through muscularis propria *(arrows).*

EQUIPMENT

Both radial and curvilinear echoendoscopes are used for performing transrectal EUS. The radial instrument is available in both rigid and flexible models. Although the rigid instrument is cheaper, the flexible version has the advantage of an oblique viewing mechanism, which allows tumor visualization and

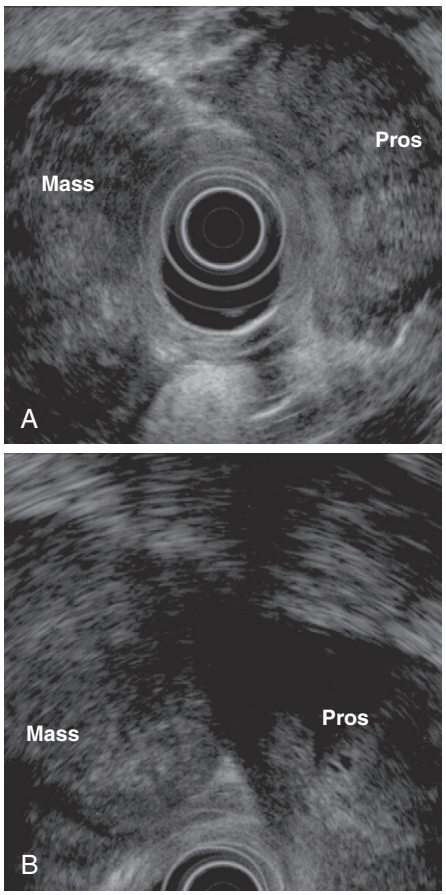


FIGURE 18.6 **T4 rectal cancer. A,** Rectal cancer invading the adjacent organ (prostate [Pros]) as seen with a radial echoendoscope. **B,** Magnified EUS image of the rectal cancer invading the prostate (Pros).

thereby facilitates traversal of stenotic tumors. The flexible instrument also allows deeper intubation to allow imaging of the iliac lymph nodes. This carries significant clinical implications because nodal metastases in the iliac region confer M1 status on the patient. Scanning is performed at a frequency of 7.5 or 12 MHz. If suspicious perirectal lymph nodes are detected on radial imaging, the linear scanning instrument is then used to target these nodes for EUS-guided fine-needle aspiration (FNA). Because of the low risk of infectious complications after FNA of perirectal lymph nodes, prophylactic administration of preprocedure antibiotics is not warranted.[9] For rectal lesions that measure less than 1 or 2 cm in diameter, the use of high-frequency ultrasonic miniprobes (20 MHz) is another option (water-filling technique) because these probes allow for the lesion to be targeted under direct endoscopic visualization (Fig. 18.7).

STAGING

T Staging

The superiority of EUS over other imaging modalities, such as CT and magnetic resonance imaging (MRI), for local tumor (T) and nodal (N) staging has been convincingly demonstrated in multiple clinical studies. As illustrated in Table 18.1, 41 studies evaluating EUS in this setting have been published in the peer-reviewed literature. Overall, the experience in 4118 subjects was reported as follows: mean EUS T-staging accuracy, 85.2% (median, 87.5%); mean sensitivity, 87.5% (median, 89.0%); and mean specificity, 83.5% (median, 86%). These findings

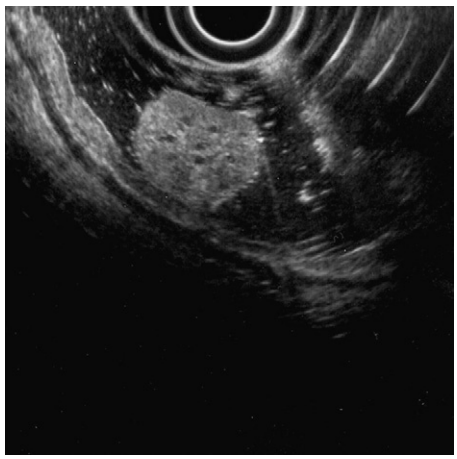


FIGURE 18.7 **A malignant polyp confined to the mucosal region as visualized using a high-frequency catheter probe.**

TABLE 18.1

Studies Reporting the Accuracy of EUS in Staging Rectal Cancer

		Accuracy (%)	
Authors	Patients (n)	T Stage	N Stage
Saitoh et al[39]	88	90	75
Feifel et al[40]	79	89	—
Beynon et al[41]	100	93	83
Yamashita et al[42]	122	78	—
Rifkin et al[43]	102	72	81
Hildebrandt et al[44]	113	—	78
Cho et al[45]	76	82	70
Herzog et al[46]	118	89	80
Glaser et al[47]	154	86	81
Nielsen et al[48]	100	85	—
Sailer et al[49]	160	77	83
Nishimori et al[50]	70	76	69
Norton and Thomas[51]	121	92	65
Akasu et al[52]	154	96	72
Garcia-Aguilar et al[53]	545	69	64
Marusch et al[54]	422	63	—
Beynon et al[55]	44	91	—
Boyce et al[56]	45	89	79
Massari et al[57]	85	91	76
Adams et al[58]	70	89	—
Spinelli et al[59]	131	75	—
Meyenberger et al[12]	21	83	—
Kaneko et al[60]	38	76	—
Osti et al[61]	63	83	66
Akasu et al[62]	164	79	76
Ramana et al[63]	10	100	83
Kim et al[64]	89	90	54
Gualdi et al[65]	26	77	76
Shami et al[66]	48	89	85
Hsieh et al[67]	67	88	73
Starck et al[68]	18	89	—
Harewood et al[15]	80	91	82
Thaler et al[11]	37	88	80
Waizer et al[69]	13	85	—
Pappalardo et al[70]	14	100	86
Romano et al[71]	23	87	—
Kramann et al[72]	29	93	—
Hildebrandt et al[73]	25	92	—
Mackay et al[74]	356	85	66
Marone et al[75]	63	81	70
Sentovich et al[76]	35	79	73
Maor et al[77]	66	86	71

Adapted from Harewood GC. Assessment of publication bias in the reporting of EUS performance in staging rectal cancer. *Am J Gastroenterol.* 2005;100:808-816. With permission of Blackwell Publishing Ltd.

compare with an accuracy of 65% to 75% for CT and 75% to 85% for MRI.[10–13] A more recent meta-analysis of 42 studies estimated the following respective sensitivities and specificities of EUS for determining T stages: T1, 88% and 98%;, T2, 81% and 96%; T3, 96% and 91%; and T4, 95% and 98%.[14]

In terms of the growing importance of outcomes research, not only does EUS demonstrate superior staging performance, but also this more accurate staging translates into a change in patient management. In a prospective clinical study of 80 consecutive patients with nonmetastatic rectal cancer, investigators found that the incremental staging information provided by EUS resulted in a change in management, usually the addition of neoadjuvant treatment, in 31% of patients.[15] This change was often the result of understaging of these rectal tumors by pelvic CT; when local invasion was missed by CT, candidates were not offered preoperative neoadjuvant therapy. Decision-analysis studies also demonstrated that the most cost-effective strategy for evaluation of proximal rectal cancer is the combination of initial abdominal CT (to exclude distant metastatic disease) and EUS (for local staging) in patients without distant disease.[16]

A concern exists that patients with early-stage disease (T1N0 to T2N0) may be erroneously overstaged by EUS, thereby leading to administration of unnecessary preoperative treatment. However, in the study by Harewood et al,[15] no patients were overstaged by EUS, and other investigators demonstrated similar findings.[17] These studies reassuringly indicate that EUS-based treatment decisions rarely expose patients to unnecessary overtreatment.

In clinical practice, it is not uncommon for patients to be referred for evaluation of a polypectomy site to assess for completeness of tumor removal. This situation is usually encountered in the context of routine colonoscopy in which, following polypectomy, the histopathologic examination reveals carcinoma. In such circumstances, it is usually not feasible to differentiate by EUS a polypectomy scar from residual tumor. Only biopsy of the area can confirm the presence or absence of residual disease.

N Staging

The medical literature has not demonstrated convincing superiority of EUS over other imaging modalities in assessing the nodal (N) stage of rectal cancer. A meta-analysis of 35 studies estimated that the pooled sensitivity and specificity of EUS in diagnosing nodal involvement by rectal cancers were 73% (95% confidence interval [CI], 71% to 76%) and 76% (95% CI, 74% to 78%), respectively (Video 18.2).[18] This finding is not significantly superior to the accuracy of CT and MRI.

The incorporation of FNA into EUS represented a promising advance in N staging of tumors elsewhere in the gastrointestinal tract.[19–27] A prospective study of 76 patients with rectal cancer highlighted the poor reliability of echo characteristics of lymph nodes for determining malignant involvement.[28] In this study, only 68% of malignant perirectal nodes displayed three or more features characteristic of malignancy (short axis length $\geq$5 mm, hypoechoic appearance, round shape, sharp border).[28] These findings supported the value of FNA for further characterization of perirectal lymph nodes in the context of rectal cancer. The major benefit of FNA is the high specificity of this sampling technique; false-positive aspirates are rarely, if ever, obtained from benign lymph nodes. A study of 51 patients with rectal cancer who were undergoing EUS staging and of whom 15 had EUS-guided FNA of perirectal nodes illustrated the value of FNA sampling.[29] Staging accuracy of EUS for detecting N1 disease was 70% compared with the gold standard of histologic examination at surgical resection; in contrast, the addition of EUS-guided FNA increased nodal staging accuracy to 87%. A theoretical concern is that traversing tumor tissue when accessing peritumoral lymph nodes may yield a false-positive result. For this reason, FNA of peritumoral lymph nodes is generally avoided.

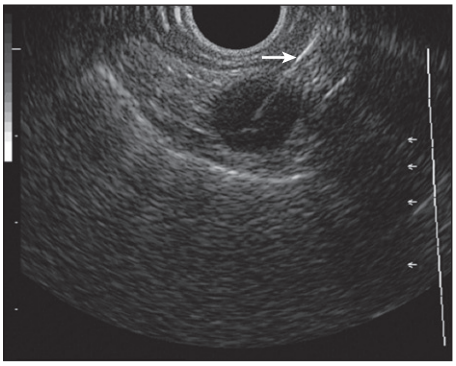


FIGURE 18.8 Perirectal node with malignant-appearing features (large, round, hypoechoic, sharp border) being sampled by FNA needle *(arrow)*.

An important practical consideration relates to the EUS appearance of perirectal lymph nodes. Generally, perirectal nodes are not visualized in healthy patients. Therefore, visualization of perirectal lymph nodes alone is sufficient to warrant sampling by FNA. This contrasts with benign lymph nodes in, for example, the periesophageal region, which can be seen by EUS. In that context, endosonographers rely on the echo characteristics of the lymph node to determine malignancy (size, shape, border, echogenicity). All visualized perirectal lymph nodes should be considered suspicious and should be sampled (Fig. 18.8).

The incorporation of EUS FNA into the staging workup of patients with rectal cancer appears to improve patient outcome directly by achieving superior staging accuracy.[30] A comparison of patients with rectal cancer who underwent staging with EUS FNA with a similarly matched patient group not undergoing EUS FNA demonstrated that EUS FNA was associated with reduced tumor recurrence risk (hazard ratio, 0.72; 95% CI, 0.52 to 0.97). This result was likely achieved by more accurate staging, which, in turn, facilitated more appropriate patient selection for preoperative neoadjuvant therapy.

LEARNING CURVE

An important factor in EUS performance in any region of the gastrointestinal tract is the level of experience of the endoscopist. Experienced endosonographers demonstrate superior performance, a finding that underscores the learning curve for mastering EUS. Transrectal EUS is no exception. The improvement with experience was shown by Orrom et al,[31] who found that the staging accuracy of rectal cancer increased from 58% in the initial 12 examinations to 88% for the subsequent 24 procedures.

RECURRENT RECTAL CANCER

Rectal cancer recurrence rates generally range from 20% to 50%, with higher rates in patients with a more advanced initial tumor stage. One of the challenging aspects of rectal cancer recurrence is its occasional extraluminal nature, which hinders early endoscopic detection.[32,33] Because of its ability to discern extramucosal structures, EUS may play an important role in this setting. Two studies demonstrated superior performance characteristics of EUS when compared with pelvic CT in the detection of local recurrence of rectal cancer.[34,35] The sensitivity of EUS for detecting recurrence was higher (100%) in both studies compared with that of CT (82% and 85%).

One limitation of EUS in the postradiation setting relates to the inflammatory soft tissue changes induced by radiation therapy.

These changes often obscure the detail of mucosal layers and diminish EUS sensitivity.[34] For this reason, FNA may offer greater utility in the detection of recurrent rectal cancer. By sampling any suspicious areas, cytologic examination overcomes the limitation of relying on EUS appearance alone. Hunerbein et al[36] evaluated 312 patients with a history of rectal cancer and demonstrated a significantly improved accuracy for EUS FNA (92%) in the detection of tumor recurrence compared with EUS (75%). Predictably, this superiority was primarily a reflection of the better specificity of FNA. Similarly, Lohnert et al[37] documented the superiority of EUS FNA in the detection of rectal cancer recurrence in a cohort of 116 patients (100% versus 79% for EUS alone).

FOLLOW-UP AFTER RESECTION

Although EUS, especially EUS FNA, offers a benefit in the detection of rectal tumor recurrence, no consensus exists regarding the standard practice for postresection surveillance. In the study by Lohnert et al,[37] EUS was performed at 3-month intervals for 2 years and subsequently at 6-month intervals for a further year postoperatively. Generally, recurrence rates are related to initial tumor stage. Therefore, it would appear prudent to perform the most aggressive surveillance in patients with locally advanced tumor stage at the outset, because such patients have the highest risk of recurrence.[38]

REFERENCES

1. National Institutes of Health Consensus Conference. Adjuvant therapy for patients with colon and rectal cancer. *JAMA*. 1990;264:1444–1450.
2. Pahlman L, Glimelius B. Pre- or postoperative radiotherapy in rectal and rectosigmoid carcinoma: report from a randomized multicenter trial. *Ann Surg*. 1990;211:187–195.
3. Frykholm GJ, Glimelius B, Pahlman L. Preoperative or postoperative irradiation in adenocarcinoma of the rectum: final treatment results of a randomized trial and an evaluation of late secondary effects. *Dis Colon Rectum*. 1993;36:564–572.
4. Swedish Rectal Cancer Trial. Improved survival with preoperative radiotherapy in resectable rectal cancer. *N Engl J Med*. 1997;336:980–987.
5. Medical Research Council Rectal Cancer Working Party. Randomised trial of surgery alone versus radiotherapy followed by surgery for potentially operable locally advanced rectal cancer. *Lancet*. 1996;348:1605–1610.
6. Minsky BD. Adjuvant therapy for rectal cancer: a good first step. *N Engl J Med*. 1997;336:1016–1017.
7. Grann A, Feng C, Wong D, et al. Preoperative combined modality therapy for clinically resectable uT3 rectal adenocarcinoma. *Int J Radiat Oncol Biol Phys*. 2001;49:987–995.
8. Hyams DM, Mamounas EP, Petrelli N, et al. A clinical trial to evaluate the worth of preoperative multimodality therapy in patients with operable carcinoma of the rectum: a progress report of National Surgical Breast and Bowel Project Protocol R-03. *Dis Colon Rectum*. 1997;40:131–139.
9. Levy MJ, Norton ID, Clain JE, et al. Prospective study of bacteremia and complications with EUS FNA of rectal and perirectal lesions. *Clin Gastroenterol Hepatol*. 2007;5:684–689.
10. Kwok H, Bissett IP, Hill GL. Preoperative staging of rectal cancer. *Int J Colorectal Dis*. 2000;15:9–20.
11. Thaler W, Watzka S, Martin F, et al. Preoperative staging of rectal cancer by endoluminal ultrasound vs. magnetic resonance imaging: preliminary results of a prospective, comparative study. *Dis Colon Rectum*. 1994;37:1189–1193.
12. Meyenberger C, Huch Boni RA, Bertschinger P, et al. Endoscopic ultrasound and endorectal magnetic resonance imaging: a prospective, comparative study for preoperative staging and follow-up of rectal cancer. *Endoscopy*. 1995;27:469–479.
13. Guinet C, Buy JN, Ghossain MA, et al. Comparison of magnetic resonance imaging and computed tomography in the preoperative staging of rectal cancer. *Arch Surg*. 1990;125:385–388.
14. Puli SR, Bechtold ML, Reddy JB, et al. How good is endoscopic ultrasound in differentiating various T stages of rectal cancer? Meta-analysis and systematic review. *Ann Surg Oncol*. 2009;16:254.
15. Harewood GC, Wiersema MJ, Nelson H, et al. A prospective, blinded assessment of the impact of preoperative staging on the management of rectal cancer. *Gastroenterology*. 2002;123:24–32.
16. Harewood GC, Wiersema MJ. Cost-effectiveness of endoscopic ultrasonography in the evaluation of proximal rectal cancer. *Am J Gastroenterol*. 2002;97:874–882.
17. Hawes RH. New staging techniques: endoscopic ultrasound. *Cancer*. 1993;71(suppl):4207–4213.
18. Puli SR, Reddy JB, Bechtold ML, et al. Accuracy of endoscopic ultrasound to diagnose nodal invasion by rectal cancers: a meta-analysis and systematic review. *Ann Surg Oncol*. 2009;16:1255.
19. Wiersema MJ, Kochman ML, Cramer HM, et al. Endosonography-guided real-time fine-needle aspiration biopsy. *Gastrointest Endosc*. 1994;40:700–707.
20. Chang KJ, Nguyen P, Erickson RA, et al. The clinical utility of endoscopic ultrasound-guided fine-needle aspiration in the diagnosis and staging of pancreatic carcinoma. *Gastrointest Endosc*. 1997;45:387–393.
21. Rodriguez J, Kasberg C, Nipper M, et al. CT-guided needle biopsy of the pancreas: a retrospective analysis of diagnostic accuracy. *Am J Gastroenterol*. 1992;87:1610–1613.
22. Gress FG, Savides TJ, Sandler A, et al. Endoscopic ultrasonography, fine-needle aspiration biopsy guided by endoscopic ultrasonography, and computed tomography in the preoperative staging of non–small-cell lung cancer: a comparison study. *Ann Intern Med*. 1997;127:604–612.
23. Wiersema MJ, Vilmann P, Giovannini M, et al. Endosonography-guided fine-needle aspiration biopsy: diagnostic accuracy and complication assessment. *Gastroenterology*. 1997;112:1087–1095.
24. Giovannini M, Seitz JF, Monges G, et al. Fine-needle aspiration cytology guided by endoscopic ultrasonography: results in 141 patients. *Endoscopy*. 1995;27:171–177.
25. Williams DB, Sahai AV, Aabakken L, et al. Endoscopic ultrasound guided fine needle aspiration biopsy: a large single centre experience. *Gut*. 1999;44:720–726.
26. Catalano MF, Alcocer E, Chak A, et al. Evaluation of metastatic celiac axis lymph nodes in patients with esophageal carcinoma: accuracy of EUS. *Gastrointest Endosc*. 1999;50:352–356.
27. Giovannini M, Monges G, Seitz JF, et al. Distant lymph node metastases in esophageal cancer: impact of endoscopic ultrasound-guided biopsy. *Endoscopy*. 1999;31:536–540.
28. Gleeson FC, Clain JE, Papachristou GI, et al. Prospective assessment of EUS criteria for lymphadenopathy associated with rectal cancer. *Gastrointest Endosc*. 2009;69:896–903.
29. Park HH, Nguyen PT, Tran Q, et al. Endoscopic ultrasound-guided fine needle aspiration in the staging of rectal cancer [abstract]. *Gastrointest Endosc*. 2000;51:AB171.
30. Harewood GC. Assessment of clinical impact of endoscopic ultrasound on rectal cancer. *Am J Gastroenterol*. 2004;99:623.
31. Orrom WJ, Wong WD, Rothenberger DA, et al. Endorectal ultrasound in the preoperative staging of rectal tumors: a learning experience. *Dis Colon Rectum*. 1990;33:654–659.
32. Mascagni DCL, Urciuoli P, De Matteo G. Endoluminal ultrasound for early detection of local recurrence of rectal cancer. *Br J Surg*. 1989;76:1176–1180.
33. Ramirez J, Mortensen NJ, Takeuchi N, et al. Endoluminal ultrasonography in the follow-up of patients with rectal cancer. *Br J Surg*. 1994;81:692–694.
34. Novell F, Pascual S, Viella P, et al. Endorectal ultrasonography in the follow-up of rectal cancer: is it a better way to detect early local recurrence? *Int J Colorectal Dis*. 1997;12:78–81.
35. Rotondano G, Esposito P, Pellecchia L, et al. Early detection of locally recurrent rectal cancer by endosonography. *Br J Radiol*. 1997;70:567–571.
36. Hunerbein M, Totkas S, Moesta KT, et al. The role of transrectal ultrasound-guided biopsy in the postoperative follow-up of patients with rectal cancer. *Surgery*. 2001;129:164–169.
37. Lohnert M, Doniec JM, Henne-Bruns D. Effectiveness of endoluminal sonography in the identification of occult local rectal cancer. *Dis Colon Rectum*. 2000;43:483–491.
38. Mellgren A, Sirivongs P, Rothenberger DA, et al. Is local excision adequate therapy for early rectal cancer? *Dis Colon Rectum*. 2000;43:1064–1071.
39. Saitoh N, Okui K, Sarashina H, et al. Evaluation of echographic diagnosis of rectal cancer using intrarectal ultrasonic examination. *Dis Colon Rectum*. 1986;29:234–242.
40. Feifel G, Hildebrandt U, Dhom G. Assessment of depth of invasion in rectal cancer by endosonography. *Endoscopy*. 1987;19:64–67.
41. Beynon J, Foy DM, Temple LN, et al. The endosonic appearances of normal colon and rectum. *Dis Colon Rectum*. 1986;29:810–813.
42. Yamashita Y, Machi J, Shirouzu K, et al. Evaluation of endorectal ultrasound for the assessment of wall invasion of rectal cancer: report of a case. *Dis Colon Rectum*. 1988;31:617–623.
43. Rifkin MD, Ehrlich SM, Marks G. Staging of rectal carcinoma: prospective comparison of endorectal US and CT. *Radiology*. 1989;170:319–322.
44. Hildebrandt U, Klein T, Feifel G, et al. Endosonography of pararectal lymph nodes: in vitro and in vivo evaluation. *Dis Colon Rectum*. 1990;33:863–868.
45. Cho E, Nakajima M, Yasuda K, et al. Endoscopic ultrasonography in the diagnosis of colorectal cancer invasion. *Gastrointest Endosc*. 1993;39:521–527.

46. Herzog U, von Flue M, Tondelli P, et al. How accurate is endorectal ultrasound in the preoperative staging of rectal cancer? *Dis Colon Rectum*. 1993; 36:127–134.
47. Glaser F, Kuntz C, Schlag P, et al. Endorectal ultrasound for control of preoperative radiotherapy of rectal cancer. *Ann Surg*. 1993;217:64–71.
48. Nielsen MB, Qvitzau S, Pedersen JF, et al. Endosonography for preoperative staging of rectal tumours. *Acta Radiol*. 1996;37:799–803.
49. Sailer M, Leppert R, Kraemer M, et al. The value of endorectal ultrasound in the assessment of adenomas, T1- and T2-carcinomas. *Int J Colorectal Dis*. 1997;12:214–219.
50. Nishimori H, Sasaki K, Hirata K, et al. The value of endoscopic ultrasonography in preoperative evaluation of rectal cancer. *Int Surg*. 1998;83:157–160.
51. Norton SA, Thomas MG. Staging of rectosigmoid neoplasia with colonoscopic endoluminal ultrasonography. *Br J Surg*. 1999;86:942–946.
52. Akasu T, Kondo H, Moriya Y, et al. Endorectal ultrasonography and treatment of early stage rectal cancer. *World J Surg*. 2000;24:1061–1068.
53. Garcia-Aguilar J, Pollack J, Lee SH, et al. Accuracy of endorectal ultrasonography in preoperative staging of rectal tumors. *Dis Colon Rectum*. 2002;45:10–15.
54. Marusch F, Koch A, Schmidt U, et al. Routine use of transrectal ultrasound in rectal carcinoma: results of a prospective multicenter study. *Endoscopy*. 2002;34:385–390.
55. Beynon J, Mortensen NJ, Foy DM, et al. Pre-operative assessment of local invasion in rectal cancer: digital examination, endoluminal sonography or computed tomography? *Br J Surg*. 1986;73:1015–1017.
56. Boyce GA, Sivak Jr MV, Lavery IC, et al. Endoscopic ultrasound in the preoperative staging of rectal carcinoma. *Gastrointest Endosc*. 1992;38:468–471.
57. Massari M, De Simone M, Cioffi U, et al. Value and limits of endorectal ultrasonography for preoperative staging of rectal carcinoma. *Surg Laparosc Endosc*. 1998;8:438–444.
58. Adams DR, Blatchford GJ, Lin KM, et al. Use of preoperative ultrasound staging for treatment of rectal cancer. *Dis Colon Rectum*. 1999;42:159–166.
59. Spinelli P, Schiavo M, Meroni E, et al. Results of EUS in detecting perirectal lymph node metastases of rectal cancer: the pathologist makes the difference. *Gastrointest Endosc*. 1999;49:754–758.
60. Kaneko K, Boku N, Hosokawa K, et al. Diagnostic utility of endoscopic ultrasonography for preoperative rectal cancer staging estimation. *Jpn J Clin Oncol*. 1996;26:30–35.
61. Osti MF, Padovan FS, Pirolli C, et al. Comparison between transrectal ultrasonography and computed tomography with rectal inflation of gas in preoperative staging of lower rectal cancer. *Eur Radiol*. 1997;7:26–30.
62. Akasu T, Sugihara K, Moriya Y, et al. Limitations and pitfalls of transrectal ultrasonography for staging of rectal cancer. *Dis Colon Rectum*. 1997; 40(suppl):S10–S15.
63. Ramana KN, Murthy PV, Rao KP, et al. Transrectal ultrasonography versus computed tomography in staging rectal carcinoma. *Indian J Gastroenterol*. 1997;16:142–143.
64. Kim JC, Yu CS, Jung HY, et al. Source of errors in the evaluation of early rectal cancer by endoluminal ultrasonography. *Dis Colon Rectum*. 2001; 44:1302–1309.
65. Gualdi GF, Casciani E, Guadalaxara A, et al. Local staging of rectal cancer with transrectal ultrasound and endorectal magnetic resonance imaging: comparison with histologic findings. *Dis Colon Rectum*. 2000;43:338–345.
66. Shami VM, Parmar KS, Waxman I. Clinical impact of endoscopic ultrasound and endoscopic ultrasound-guided fine-needle aspiration in the management of rectal carcinoma. *Dis Colon Rectum*. 2004;47:59–65.
67. Hsieh PS, Changchien CR, Chen JS, et al. Comparing results of preoperative staging of rectal tumor using endorectal ultrasonography and histopathology. *Chang Gung Med J*. 2003;26:474–478.
68. Starck M, Bohe M, Simanaitis M, et al. Rectal endosonography can distinguish benign rectal lesions from invasive early rectal cancers. *Colorectal Dis*. 2003;5:246–250.
69. Waizer A, Powsner E, Russo I, et al. Prospective comparative study of magnetic resonance imaging versus transrectal ultrasound for preoperative staging and follow-up of rectal cancer: preliminary report. *Dis Colon Rectum*. 1991;34:1068–1072.
70. Pappalardo G, Reggio D, Frattaroli FM, et al. The value of endoluminal ultrasonography and computed tomography in the staging of rectal cancer: a preliminary study. *J Surg Oncol*. 1990;43:219–222.
71. Romano G, de Rosa P, Vallone G, et al. Intrarectal ultrasound and computed tomography in the pre- and postoperative assessment of patients with rectal cancer. *Br J Surg*. 1985;72(suppl):S117–S119.
72. Kramann B, Hildebrandt U. Computed tomography versus endosonography in the staging of rectal carcinoma: a comparative study. *Int J Colorectal Dis*. 1986;1:216–218.
73. Hildebrandt U, Feifel G. Preoperative staging of rectal cancer by intrarectal ultrasound. *Dis Colon Rectum*. 1985;28:42–46.
74. Mackay SG, Pager CK, Joseph D, et al. Assessment of the accuracy of transrectal ultrasonography in anorectal neoplasia. *Br J Surg*. 2003;90:346–350.
75. Marone P, Petrulio F, de Bellis M, et al. Role of endoscopic ultrasonography in the staging of rectal cancer: a retrospective study of 63 patients. *J Clin Gastroenterol*. 2000;30:420–424.
76. Sentovich SM, Blatchford GJ, Falk PM, et al. Transrectal ultrasound of rectal tumors. *Am J Surg*. 1993;166:638–641, discussion 641–642.
77. Maro Y, Nadler M, Barshack I, et al. Endoscopic ultrasound staging of rectal cancer: diagnostic value before and following chemoradiation. *J Gastroenterol Hepatol*. 2006;21:454–458.

CHAPTER 19 EVALUATION OF THE ANAL SPHINCTER BY ANAL EUS

Steve Halligan

Key Points

Anal endosonography (AES) is simple to perform and visualizes the anal sphincter complex, notably the external and internal anal sphincters.

AES is able to image sphincter tears and defects.

AES can also characterize sphincter morphology and determine muscular quality.

AES is the single most important investigation in patients with anal incontinence.

INTRODUCTION

First described in 1989,[1] anal endosonography (AES) was the first technique to visualize the anal sphincter complex with enough spatial resolution to resolve the individual components of the sphincter mechanism. Despite the advent of endoanal magnetic resonance imaging (MRI), AES remains the technique with the highest spatial resolution, and it is also quick and easy to perform. The introduction of AES precipitated a significant reappraisal of the causes of anal incontinence (and its treatment), which had hitherto been thought to be mainly the result of pelvic neuropathy.[2] When incontinent patients were studied with AES, it rapidly became clear that occult anal sphincter disruption was present in many cases. Patients with disrupted sphincters can be scheduled for surgical procedures that aim to restore integrity to the sphincter ring, whereas patients whose sphincters are intact, or whose muscles are thought to be of poor quality, can be directed toward conservative measures or alternative surgical approaches.

At present, AES has replaced physiologic testing as the pivotal examination in the clinical decision-making process for these patients. Although AES is probably used most often following obstetric injury, it has also facilitated the anatomic characterization of other causes of fecal incontinence. For example, with AES, the examiner can identify neurogenic incontinence by way of specific patterns of sphincter atrophy and can identify occult and unintended sphincter damage following anal surgical procedures.

EQUIPMENT AND EXAMINATION TECHNIQUE

Although it is possible to perform AES using an echoendoscope, the best results by far are obtained using a dedicated anal probe. The anus is a very superficial structure, and an echoendoscope is both cumbersome when compared with a probe designed specifically for the purpose and more expensive. AES first employed a 7.5-MHz transducer that had been designed initially for rectal cancer staging and prostatic imaging. The transducer was covered by a rubber balloon, it was inserted through the anus into the rectum, the balloon was inflated with degassed water, and the transducer was mechanically rotated to produce 360-degree images of the rectal wall. Professor Clive Bartram of St. Mark's Hospital, London, realized that by simply replacing the soft rubber balloon with a rigid plastic cone, the rotating transducer could be safely withdrawn into the anus.[1] This maneuver was previously impossible because the balloon would be torn when compressed by the anus against the rotating metal transducer.

Modern probes encapsulate a fixed transducer within a permanent hard cover and are of higher frequency (Fig. 19.1). Some also possess three-dimensional capacity, achieved either by withdrawing the probe during image acquisition (e.g., EUP-R54AW-19/33, Hitachi Medical Systems, Wellingborough, UK) or by incorporating a transducer that moves along the *Z*-axis of the probe, inside the exterior capsule, while the head is held stationary within the anal canal (e.g., 2052 transducer, BK Medical, Herlev, Denmark).

The examination is simple, easily tolerated by the patient, and very rapid when performed by an experienced operator. No special patient preparation is required. The patient is told that discomfort, if any, will be similar to having a small finger in the anus, and the procedure will likely be much less uncomfortable than digital rectal examination by a doctor. To the patient, the probe is potentially quite a frightening piece of equipment, so it is worth mentioning that only the distal few centimeters will enter the anus (as opposed to rectal endosonography, in which insertion is obviously deeper).

Men are examined in the left lateral patient position, but the prone patient position is preferable for examining women. Placing women in the left lateral position can occasionally distort anterior perineal anatomy and can induce an asymmetrical image, which makes it difficult to distinguish perineal scarring from normal anatomic features.[3] In the past, it was necessary to fill the transducer head with degassed water to achieve acoustic coupling, accomplished by injection using a syringe through a side port and then maneuvering the probe so that all air was expelled through a pinhole located at the tip of the cone. However, most modern probes merely require the tip to be lubricated with ultrasound jelly and then covered with a condom, which is itself lubricated to facilitate insertion. The probe is then inserted into the anus, and image acquisition is commenced. The aim is to insert the probe so that the transducer lies just in the distal rectum. The probe is then withdrawn gently and slowly to examine the anal sphincters.

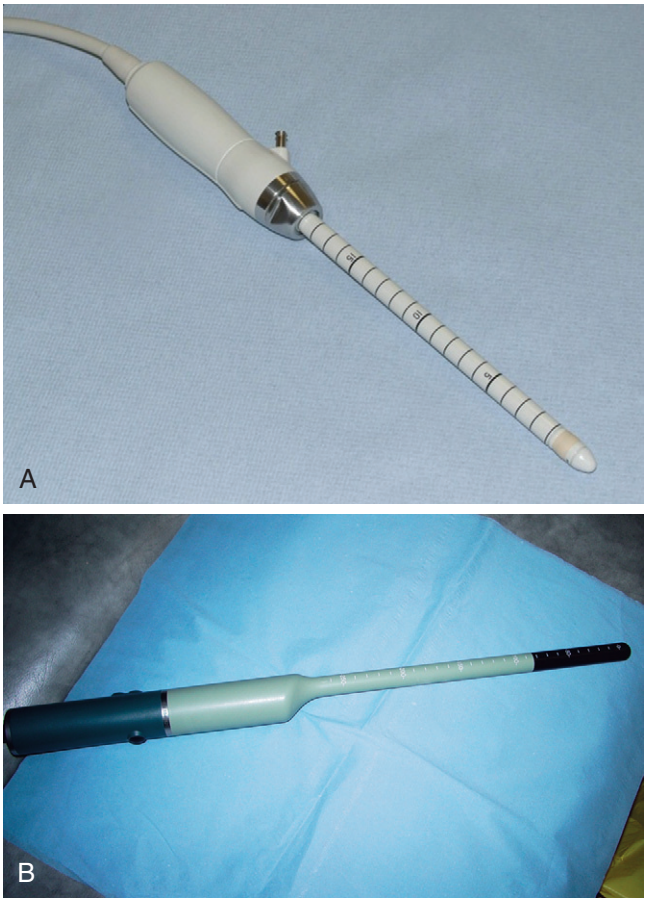


FIGURE 19.1 Probes for ultrasound examination of the anal sphincter complex. A, Hitachi EUP-R54AW-19/33 electronic radial probe. **B,** B and K medical 1846 probe. *(**A,** Courtesy of Hitachi Medical Systems, Wellingborough, UK; **B,** Courtesy of BK Medical, Herlev, Denmark.)*

As for all ultrasound examinations, clinical findings are generally based on the image displayed on the monitor screen in real time (with the exception of three-dimensional acquisition, in which case the examination in its entirety can be replayed later). However, still images are usually required for archival purposes, and it is convenient to obtain these still images at three levels: the proximal, middle, and distal anal canal (see later). These three anatomic levels are imaged at standard magnification, and the examination is then repeated at a higher magnification, for a total of six images, three at each magnification. The probe is oriented so that anterior (i.e., the 12 o'clock position) is uppermost. The examination is normally very quick, perhaps only a minute or so for the experienced operator who is familiar with normal and abnormal anatomy, and especially if the sphincters are normal.

ANAL SPHINCTER ANATOMY

Clearly, a sound understanding of basic anal anatomy is a prerequisite for accurate interpretation of endosonographic findings. There are two anal sphincters: the external anal sphincter (EAS) is composed of striated muscle, whereas the internal anal sphincter (IAS) is smooth muscle. These form two cylindrical layers, with the IAS innermost (Fig. 19.2).

The EAS arises from the striated muscles of the pelvic floor and is composed of three cylindrical bundles lying on top of one another (deep, superficial, and subcutaneous) that are difficult to distinguish in practice. The deep portion is fused with the puborectalis (or pubococcygeus) muscle, which itself merges with the levator plate of the pelvic floor. The EAS extends approximately 1 cm distal to the IAS, where it forms the subcutaneous part of the EAS muscle. Anteriorly, the EAS is closely related to several surrounding structures, such as the superficial transverse muscle of the perineum and the perineal body. Posteriorly, it is continuous with the anococcygeal ligament, a structure that is often more prominent in men and should not be mistaken for a posterior sphincter defect. The EAS is much shorter anteriorly in women than in men, and this feature should not be confused with a sphincter defect.

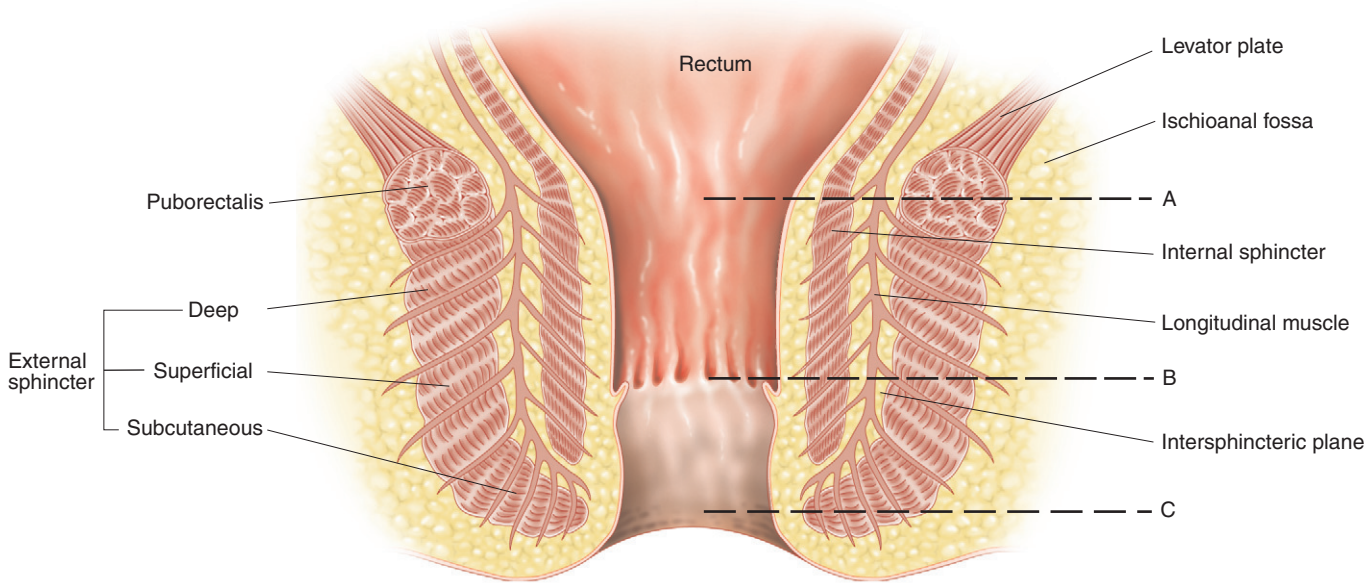


FIGURE 19.2 Coronal diagrammatic representation of important anal canal structures. Scan levels indicated correspond to Figure 19.3.

The IAS is the distal termination and condensation of the circular smooth muscle of the gut tube. It extends from the anorectal junction to approximately 1 to 1.5 cm below the dentate line (see Fig. 19.2). The longitudinal muscle of the gut tube also terminates in the anal canal, but it is less obvious than the IAS. The longitudinal muscle interdigitates between the EAS and the IAS and terminates in the subcutaneous EAS and subcutaneous anus. Its exact sphincteric action, if any, is much less clear than that of the EAS and IAS, and it is thought that its main purpose is to brace the anus and thus prevent anal eversion during defecation.[4] Lying between the EAS and the longitudinal muscle is a potential plane, the intersphincteric space, which may contain fat. The components of the anal sphincter are surrounded by the ischioanal space (often referred to as the ischiorectal fossa), which contains fat predominantly.

Directly anterior to the anal sphincter is the central perineal tendon or perineal body. In men, this lies posterior to the bulbospongiosus and corpus cavernosum and their related muscles, whereas in women, it lies within the anovaginal septum. Many structures insert fibers into the perineal body, such as the EAS, the deep and superficial transverse muscles of the perineum, the bulbocavernous muscle, and the puborectalis muscle. These structures should not be confused with sphincter defects. For example, normal variants of anal sphincter anatomy have been identified, such as differing relationships between the superficial transverse perineal muscle and the EAS.[5]

The distal anal canal is lined with stratified squamous epithelium, richly supplied by sensory receptors. These receptors are most concentrated at the dentate line, which demarcates the junction with proximal columnar epithelium. The anal subepithelial tissues are relatively thick, and this lining and its underlining vascular spaces—the anal cushions—also play a role in maintaining continence.

NORMAL ENDOSONOGRAPHIC FINDINGS

Because the anus and surrounding sphincter muscles are cylindrical, a 360-degree field of view is optimal, and the axial plane is also the most relevant surgically when considering sphincter defects. As stated earlier, it is convenient to obtain baseline images at three levels: the proximal, middle, and distal anal canal.

The proximal anal canal is primarily identified by the puborectalis and transverse perineal muscles (Fig. 19.3A). The puborectalis slings around the anorectal junction and can be distinguished from the EAS, with which it blends imperceptibly, because its anterior ends splay outward as they travel toward their fusion with the pubic arch (see Fig. 19.3A). The IAS is visible as a continuous hyperechoic ring and is generally the easiest structure to differentiate from other adjacent anal canal components because it is normally very hyporeflective. The subepithelial tissues, EAS, and longitudinal muscle all normally show varying degrees of hyperreflectivity, and their margins can often be difficult to define precisely, although direct comparisons with endoanal MRI have helped tremendously.[6] Increases in transducer frequency that improve spatial resolution have also helped to clarify the sonographic anatomy,[7] as has three-dimensional imaging.[8]

Sultan et al[9] carefully imaged cadaveric specimens following sequential histologic dissection of anal layers and thereby validated the sonographic appearances. These investigators found that the echogenicity of normal muscle changed as its orientation was altered with respect to the transducer. Thus, normal variant striated muscle slips may appear hypoechoic, depending on their orientation to the transducer, and should not be confused with sphincter tears or scars.

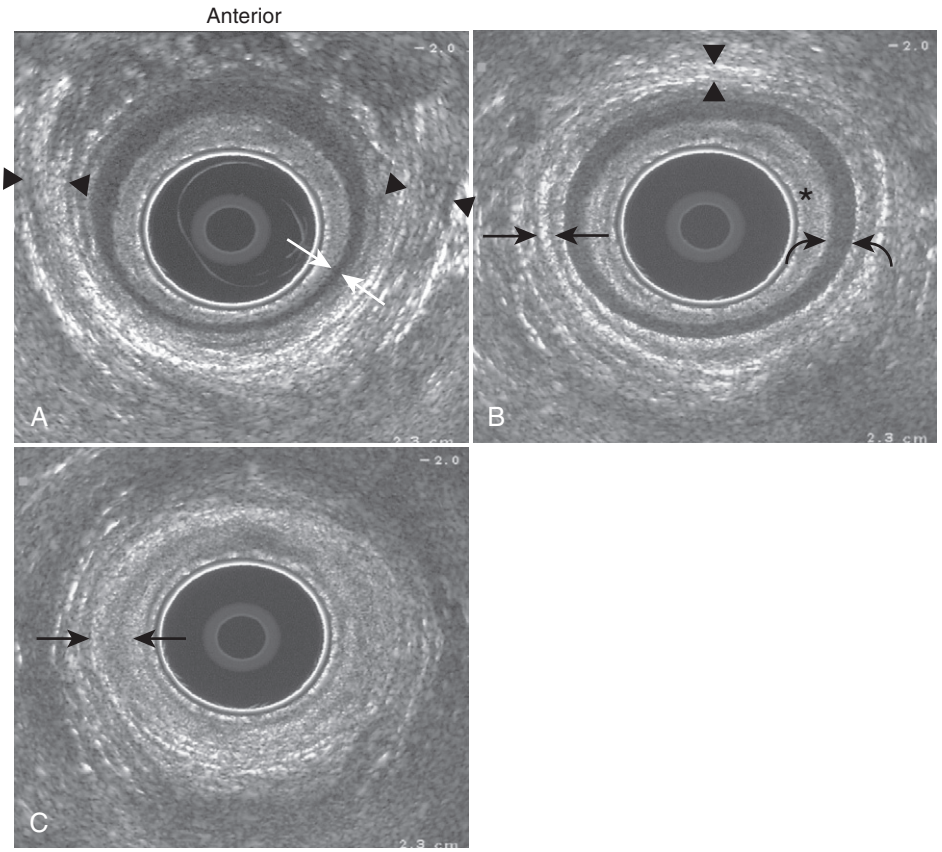


FIGURE 19.3 Normal endosonographic anatomy of the anal canal in a woman. This scan was obtained using a 10-Mhz 360-degree probe. **A,** Proximal anal canal level. At this level, the anterior ends of puborectalis muscle are well seen bilaterally *(between arrowheads)* as the muscle fibers course forward toward the pubis. The hyporeflective internal anal sphincter is also clearly seen *(between arrows)*. **B,** Midanal canal level. At this level, the external sphincter (superficial part) forms a complete ring around the anal canal, notably anteriorly *(between arrowheads)*. The internal sphincter is also at its thickest *(between curved arrows)*. The intersphincteric plane and longitudinal muscle *(between arrows)* lie between the external and internal sphincters. The subepithelial tissues *(asterisk)* lie medial to the internal sphincter. **C,** Distal anal canal level. At this level, the predominant muscle is the subcutaneous external sphincter *(between arrows)* because the scan plane is caudal to the termination of the internal sphincter.

If the probe is withdrawn just a centimeter or so from the proximal anal canal position, the anterior ends of the puborectalis muscle will converge anteriorly as they segue imperceptibly into the EAS. The midanal canal is thus defined where the EAS forms a complete ring anteriorly (see Fig. 19.3B). The IAS is also normally thickest and best seen at this location. At this level, the intersphincteric plane and longitudinal muscle may be resolved as two distinct layers, with the longitudinal muscle forming distinct bundles of smooth muscle fibers.

Withdrawing the probe slightly more will move the field of view into the subcutaneous EAS (see Fig. 19.3C). This structure is below the termination of the IAS, so this muscle is either not visualized or only partially visualized if its termination is irregular (a common normal variant). It is usually impossible to visualize the longitudinal muscle reliably at this level because it has thinned out as it interdigitates into the EAS, and it is mainly composed of fibroelastic tissue rather than the smooth muscle found more proximally.

Correct interpretation of AES is possible only if the operator has a firm grasp of the normal sonographic anatomy described earlier. Disorder is defined by either muscular discontinuity (i.e., from sphincter tears or lacerations, secondary to a variety of causes) or abnormal muscular quality (which is usually caused by neuromuscular atrophy or degeneration). To appreciate muscular quality correctly, it is important to realize that normal sonographic appearances are contingent on both age and sex. Frudinger et al[7] examined 150 nulliparous women with high-frequency AES to define normal age-related differences in sphincter morphology and found a highly significant positive correlation between IAS thickness and increasing age. In contrast, EAS thickness showed a highly significant negative correlation with increasing age.[7] Some evidence also suggested that the reflectivity of the IAS increased with age. No significant correlation was noted between age and thickness of subepithelial tissues, the longitudinal muscle, or the puborectalis muscle.[7]

On average, the IAS measures 2 to 3 mm thick (measured at either the 3 o'clock or 9 o'clock position in the midanal canal) in normal adults, but a thin IAS has more significance in an older person with symptoms (see later sections). In addition, although the IAS can be measured easily because it contrasts with adjacent structures, other muscles may be more difficult to measure and are subject to greater interobserver variation. Gold et al[10] measured anal canal structures in 51 consecutive referrals. These investigators found that although intraobserver agreement was superior to interobserver agreement, the 95% limits of agreement for EAS measurements spanned 5 mm, whereas those for the IAS spanned 1.5 mm.[10] More important from a diagnostic viewpoint, interobserver agreement for diagnosis of sphincter disruption and IAS echogenicity was very good ($\kappa = 0.80$ and 0.74, respectively).[10]

Clear sonographic differences exist between men and women with respect to the dimensions of anal canal structures and their sonographic appearances. Most importantly, the anterior complete ring of the EAS is shorter in women. This difference has been widely appreciated for some time, and Williams et al[8] used three-dimensional AES to show that the craniocaudal length of the EAS was approximately 17 mm in women, as opposed to 30 mm in men. A short anterior canal in a woman should not be misinterpreted as a sphincter defect. In addition the various muscular components in men have a generally more striated appearance (Fig. 19.4).

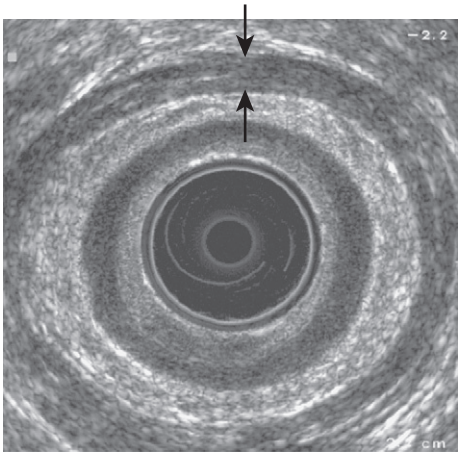


FIGURE 19.4 Anal endosonography at the midanal canal in an asymptomatic man. Note the generally more striated appearance when compared with Figure 19.3. The external sphincter *(between arrows),* in particular, is relatively hyporeflective.

ANAL SPHINCTER FUNCTION

Most clinical referrals for AES are in response to patients' complaining of anal incontinence, either to gas alone or to both gas and feces. It is therefore important to have some basic understanding of normal anal sphincter function.

The anal sphincter is the most complex sphincter in the human body. Continence is maintained by a multifaceted interrelationship between anal and pelvic floor musculature, integrating somatic and autonomic nervous pathways, the effects of which must be temporarily overcome during the act of defecation. The IAS is innervated by sympathetic presacral nerve fibers and is not under conscious control. It is primarily responsible for closing the anal canal at rest, at which time it is in a state of continuous involuntary contraction. Despite being striated muscle, the puborectalis and EAS also display some resting tone and can contract rapidly without conscious control in response to any sudden increase in intra-abdominal pressure, to prevent anal incontinence. The EAS is innervated by the pudendal nerves (S2, S3, and S4).

Defecation is initiated by colonic smooth muscle contractions, which are provoked by waking and eating. These contractions propel stool from the sigmoid colon into the normally empty rectum and stimulate rectal sensory nerves that produce an urge to defecate. These nerves are also able to determine the nature of rectal content (i.e., solid, liquid, or gas). The sensation of a full rectum and the ability to discriminate among gaseous, liquid, and solid content are important components of continence, in addition to sphincter integrity. Sensation is retained after rectal excision, a finding suggesting that some sensory receptors reside in the pelvic floor itself.[11] Rectal filling causes reflex IAS relaxation (the rectoanal inhibitory reflex), rectal contraction, and contraction of the puborectalis and the EAS, both of which are heavily modulated by conscious control. Stool within the anal canal contacts sensory receptors concentrated at the dentate line and greatly intensifies the urge to defecate, which is resisted by vigorous striated muscle contraction until circumstances for defecation are appropriate. When this is so, pelvic floor relaxation and increased intra-abdominal pressure create a positive pressure gradient from rectum to anus to allow evacuation.

The normal function and contribution of the EAS and IAS to anal continence can be used to predict which muscles are abnormal in incontinent patients. For example, IAS abnormality generally results in passive incontinence (i.e., the patient is unaware that leakage is about to occur), whereas EAS abnormality is more frequently manifest as urge incontinence (i.e., the patient is unable consciously to defer defecation).[12]

ANORECTAL PHYSIOLOGIC TESTING

Before the advent of AES, sphincter integrity and function were determined by anorectal physiologic testing, which tests nervous integrity, conduction, and muscular performance. Few physiologic tests are absolutely diagnostic, and most need to be considered together with symptoms, clinical findings, and imaging. However, these tests provide valuable complementary information and continue to be requested in combination with AES. Because of this, endosonographers working in this field need to be aware of these tests. Normal values vary among laboratories.

Manometry

Because digital assessment is unreliable, manometry is used to determine rectal and anal pressures. Systems vary in complexity, from simple balloons connected to a pressure transducer to perfused multichannel catheters capable of measuring pressure at several sites simultaneously, and even ambulatory systems that record over 24 hours or more. The pressure recorded rises when a rectal catheter is withdrawn into the anus, and it falls again when it reaches the anal margin. This zone defines the functional anal canal length (as opposed to anatomic length, which is usually shorter). The high-pressure zone generated at the anus is frequently diminished in incontinent patients. A static anal catheter can measure resting anal canal pressure, and it predominantly reflects IAS function. In general, reduced resting pressure points to IAS disease. In contrast, the squeeze pressure is the incremental rise over resting pressure elicited when the patient is asked to contract the anus voluntarily, and it reflects EAS function. This pressure is frequently reduced when incontinence is the result of EAS laceration, as occurs with obstetric injury. Dual-sphincter disease is implicated when both resting and squeeze pressures are abnormal, and neither finding is absolutely specific in an individual patient.

Pudendal Nerve Latency

The pudendal nerve terminal motor latency can be determined from the time taken for a digitally delivered pudendal nerve stimulus to elicit anal sphincter contraction. This is achieved by using a disposable glove with a stimulating electrode at the fingertip coupled with a pressure sensor at its base.[13] The nerve is stimulated near the ischial spine and has both sensory and motor components. Slow conduction is thought to be predominantly the result of stretch-induced injury. This may follow childbirth[2,14] or chronic straining,[15] and it can even be transiently demonstrated in physiologically normal individuals if they are asked to strain excessively. The clinical relevance of pudendal neuropathy remains unclear, especially because the degree of neuropathy, pelvic floor descent, and anal sensation should be directly related, but studies cannot demonstrate this.[16] Nevertheless, patients with abnormal latencies but intact sphincters usually have their incontinence attributed to neuropathic sphincter degeneration, and sphincter repair is less successful if underlying neuropathy is present.[17]

Electromyography

A needle electrode inserted into the EAS can determine both its activity and its muscular quality. Sphincter denervation is followed by reinnervation by neighboring healthy axons, which can be quantified electromyographically because the recorded action potentials become polyphasic. Until the advent of AES, electromyography was the only reliable way to diagnose sphincter tears preoperatively; the needle was inserted into the suspected defect, which was confirmed if no muscular potentials could be recorded subsequently (also possible if the needle tip missed the normal muscle because of incorrect placement—easily done when insertion is blind!). Needle passes were then made circumferentially around the anus until normal potentials were encountered, thus mapping the sphincter defect. Electromyography is painful because local anesthetic interferes with recording. Fortunately, AES is superior for detecting sphincter defects when the two modalities are compared directly.[18]

SONOGRAPHIC FINDINGS IN ANAL INCONTINENCE

As mentioned earlier, most clinical referrals for AES are in response to patients' complaints of anal incontinence. Anal incontinence may have a variety of causes, many of which relate to the integrity and quality of the sphincter mechanism. AES has assumed a central role in the diagnostic workup for assessment of this problem because AES reliably identifies those patients who have a sphincter tear, selects individuals likely to benefit from surgery that aims to restore integrity to the sphincter ring, and prevents unnecessary surgery in other patients. Physical examination cannot reliably detect anal sphincter defects, and although anal canal pressures can help to determine whether sphincter function is normal, they cannot indicate whether the cause is loss of sphincter integrity or neuropathy.

Anal incontinence is common, especially in women, and its prevalence increases with age. Two percent of the general population older than 45 years have anal incontinence,[19] and the prevalence rises to 7% of persons more than 65 years old.[20] In retirement homes or hospitals, approximately one third of individuals have anal incontinence.[19] Prevalence is also likely to be higher because of underreporting. Anal incontinence has considerable economic impact. A 1988 study estimated that more than $400 million annually was spent on incontinence appliances in the United States alone, and anal incontinence was the second most common cause of placement in a nursing home.[21] Several clinical grading systems for anal incontinence have been developed.

Obstetric Injury

Childbirth is a common cause of anal incontinence, either directly, from anal sphincter laceration, or indirectly, from damage to sphincter innervation. Until the advent of AES, it was assumed that neuropathy resulting from damage to sphincter innervation was the primary cause of obstetric-related incontinence because impaired pudendal nerve conduction can be demonstrated after vaginal delivery, presumably from stretch-induced injury.[2] Anal sphincter laceration was thought to be a relatively rare event because it could be identified clinically in only 1 out of 200 vaginal deliveries.[22] However, AES revealed that anal sphincter tears were far more common than initially assumed. An early study of 11 women with a diagnosis of neurogenic fecal incontinence revealed that 4 had also sustained unsuspected anal sphincter tears.[23] A further study of 62 women whose incontinence was related to childbirth found EAS tears in 56 (90%).[24]

In a landmark study, Sultan et al[25] used AES to study 202 consecutive unselected women before and after vaginal delivery and found anal sphincter tears in 28 of 79 of primiparous subjects (35%) and in 21 of 48 of multiparous subjects (44%). Furthermore, endosonographic evidence of sphincter laceration was associated with symptoms of anal incontinence 6 weeks following delivery and correlated with evidence of physiologic impairment, namely reduced anal resting and squeeze pressures. No primiparous woman had a sphincter defect before childbirth, and no subject undergoing cesarean section developed a new defect. These findings confirmed that sphincter injury was caused by vaginal delivery, especially forceps extraction. Moreover, the study confirmed that clinical examination of the perineum immediately after vaginal delivery misses most sphincter tears.

Anal incontinence may occur immediately after delivery if trauma is substantial, but many women present later in life,

presumably because the cumulative effects of multiple deliveries, progressive neuropathy, aging, and menopause overcome their compensatory mechanisms. Many women are also too embarrassed to complain, or they or their doctors believe that the condition is incurable. The accuracy of endosonography has been validated both histologically[9] and intraoperatively,[18] and it approaches 95%.[23,26,27] For example, a study of 44 patients found that all 23 EAS defects and 21 of 22 IAS defects visualized on preoperative AES were subsequently confirmed surgically.[26]

The sphincters are cylindrical structures, and discontinuity is diagnostic of a sphincter tear. A break in the hypoechoic IAS ring indicates an IAS defect, whereas EAS defects are defined by discontinuity of the more heterogeneous EAS, located peripheral to the intersphincteric plane and the longitudinal muscle. Obstetric injury is practically always anterior, because this is where the vagina lies. Because the EAS and IAS are in very close proximity, it usual for obstetric injury to involve both sphincters. Isolated EAS injury is relatively uncommon, and isolated IAS injury is rarely the result of obstetric injury alone.

In severe disruptions, the entire sphincter mechanism is completely absent anteriorly, with a cloacal defect between the vagina and anal canal (Fig. 19.5). However, it is usual for a primary repair of some sort to have been performed immediately after childbirth, to close the perineum to a variable degree. The competence with which these repairs are performed varies enormously. Scar tissue forms between the sphincter ends and creates a sonographic defect (Figs. 19.6 to 19.8). It is unclear how symptoms relate to the sonographic extent of the injury. For example, a study of 330 women found that although women with an EAS tear had lower basal squeeze pressures than those without a tear, beyond this no consistent relationship was seen between the morphology of the tear (in terms of both its longitudinal and circumferential extent) and either symptoms or impaired anal pressures.[28] Patients may first present several years after the initial injury (see Fig. 19.8), and some patients with large defects may be entirely asymptomatic initially (see Fig. 19.6). Supporting this finding, a prospective study found that some women with clear evidence of sphincter disruption on AES were entirely asymptomatic following delivery,[29] and a study of 124 consecutive women with late-onset anal incontinence after vaginal delivery found that 71% had sonographic sphincter defects that were believed to be the cause of symptoms despite the temporal separation between childbirth and symptoms.[30]

It also seems that perineal tears that do not involve the sphincter muscles directly are much less likely to be associated with immediate symptoms (Fig. 19.9). A prospective study of 55 nulliparous women that used three-dimensional AES found postpartum trauma in 29%. However, those women whose damage was limited to the puboanalis or transverse perineal muscles did not have symptoms, and no association with reduced anal pressures was noted.[31] It is also possible that anal canal morphology may change post partum without any direct tearing of the perineum or sphincters. In particular, both two-dimensional and three-dimensional studies found that the anterior EAS may shorten following vaginal delivery but without any sonographic evidence of a tear (i.e., stretching of the sphincter during delivery changes its shape permanently but without frank tearing).[32,33] At the other extreme, AES may be used to examine women who have an anovaginal fistula following delivery because gas within the fistula is highly reflective and allows delineation of the tract and its relationship with the sphincter mechanism (Fig. 19.10).

Perineal and sphincter trauma following vaginal delivery is generally repaired immediately afterward, usually using local anesthesia unless a significant disruption has been detected clinically. This sphincter surgery is known as a primary repair, and considerable attention has been focused on the sonographic

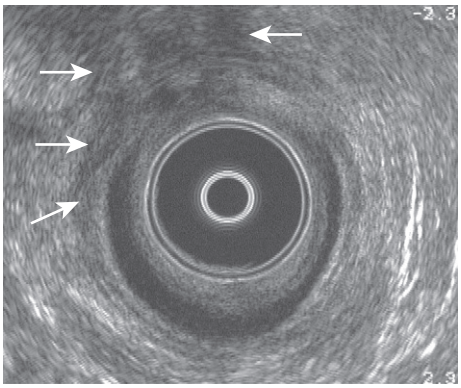


FIGURE 19.6 Typical anterior obstetric injury affecting both the external and internal anal sphincters. This 29-year-old woman was completely asymptomatic and was examined as part of a research study. The primary repair following delivery has opposed the external sphincter to some degree, but a sonographic defect remains *(arrows)*.

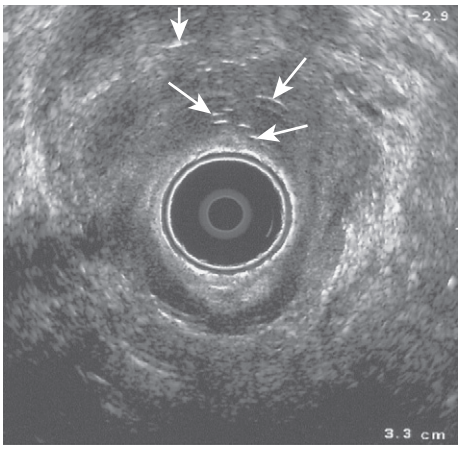


FIGURE 19.5 Obstetric injury. Anterior cloacal defect in a woman following vaginal delivery of a 5-kg baby. Note there is no external or internal sphincter anteriorly, and air within the defect *(arrows)* extends right to the probe surface.

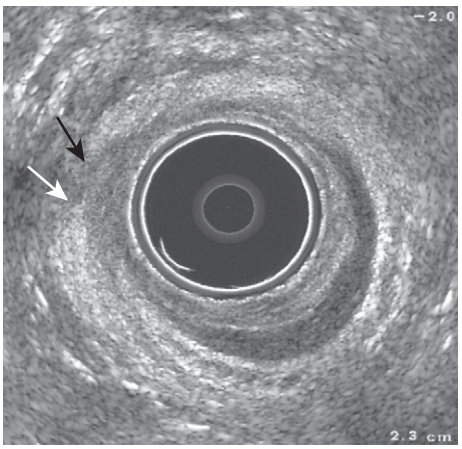


FIGURE 19.7 Typical anterior obstetric injury affecting both the external and internal sphincters. The sphincters have been reasonably well approximated *(arrows)* by primary repair, but the patient complained of anal incontinence immediately following childbirth.

assessment of such repairs. It is clear that many women suffer symptoms of anal incontinence following primary repair, despite recognition of the tear and attempted repair. A study of 156 such women found that 40% of respondents were anally incontinent and that this was associated with a persistent sphincter defect on AES.[34] Another study found that 44 of 56 (79%) women who had undergone primary sphincter repair for a clinically recognized EAS tear following vaginal delivery had persistent sphincter defects on AES and were more symptomatic than those whose repair showed no sonographic defect.[35] These findings were confirmed by other workers.[36]

Primary sphincter repair aims to restore integrity to the sphincter ring but seems unable to achieve this objective in a significant proportion of cases (Fig. 19.11). This may be because the perineum is very edematous and bruised immediately following vaginal delivery, factors that may conspire against successful repair. A study of 48 women 2 to 7 days following primary repair found that 90% had sonographic defects. Many of these defects were confined to the proximal anal canal, a finding suggesting that the initial repair had been incomplete.[37] The investigators concluded that inadequate repair was caused by surgical inexperience, rather than by the extent of sphincter damage, because junior doctors or midwives had undertaken many of the procedures.

If symptoms remain following primary repair and there is clear sonographic evidence of a persistent sphincter defect, then patients may be offered formal sphincter repair. An increasingly common option is to perform an anterior overlap repair, in which the disrupted EAS ends are mobilized, overlapped (thus tightening the anal canal), and then sutured together. Symptoms improve in approximately 85% of women immediately afterward, but this improvement is not sustained, and the percentage drops to approximately 50% at 5 years.[38] The cause of this deterioration is unclear, but concomitant progressive neuropathy is implicated, possibly resulting from pudendal damage or perhaps sphincter denervation and ischemia during the surgical procedure. However, repeated attempts at secondary sphincter repair are possible and can improve symptoms, even after many previous attempts, and delayed sphincter repair is also possible, with good symptomatic outcome.[39,40]

Endosonography has also assumed a role in the assessment of such secondary repairs. For example, the sonographic integrity of the repair correlates with symptoms and improved physiologic status.[41] Endosonography following a good anterior sphincter repair reveals sphincter ends that are well overlapped (Fig. 19.12), whereas poor repairs are detected by persistent sphincter defects (Fig. 19.13). Only the EAS is repaired, because attempts at IAS repair have not proved worthwhile. Residual IAS defects in the presence of a good EAS repair may underpin persistent symptoms, especially those of passive incontinence.

Endosonography has also been used to identify those women most at risk of obstetric injury. For example, some investigators have suggested that AES should be used routinely following

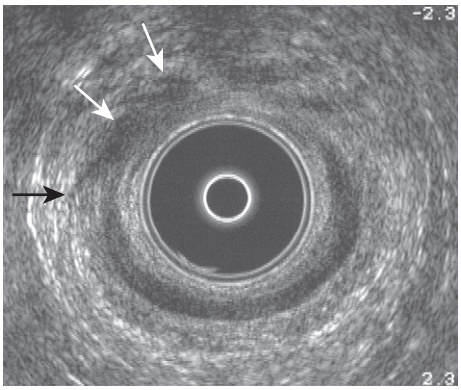


FIGURE 19.8 Typical anterior obstetric injury affecting both the external and internal anal sphincters. This 55-year-old woman had symptoms of anal incontinence that developed several years after vaginal delivery. Although it would be easy to ascribe this deterioration to progressive neuropathy, endosonography clearly reveals a sonographic defect centered on the right anterior quadrant *(arrows)*.

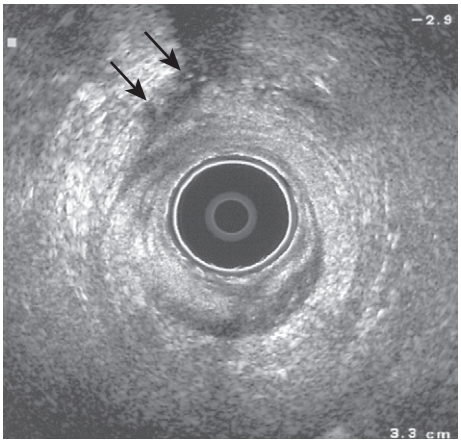


FIGURE 19.10 Anterior anovaginal fistula *(arrows)* in a woman following prolonged vaginal delivery.

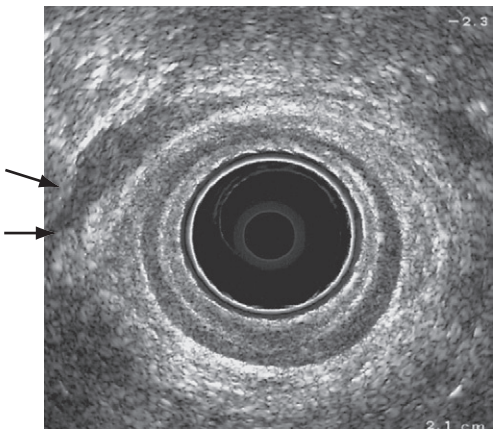


FIGURE 19.9 Perineal scar. Endosonography following vaginal delivery reveals a right anterior quadrant perineal scar *(arrows)* in this asymptomatic woman.

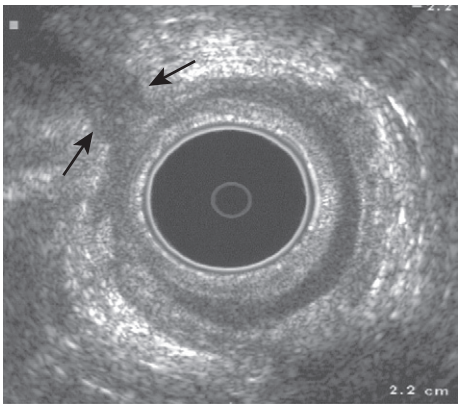


FIGURE 19.11 Anal endosonography following primary repair of a clinically recognized third-degree tear following vaginal delivery. A persistent external sphincter defect is visible *(arrows)*.

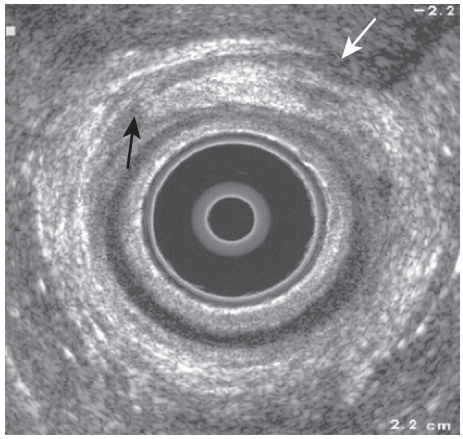


FIGURE 19.12 Good sonographic appearances following anterior overlapping sphincter repair. The external sphincter ends are well overlapped *(between arrows)*, and there is no residual defect.

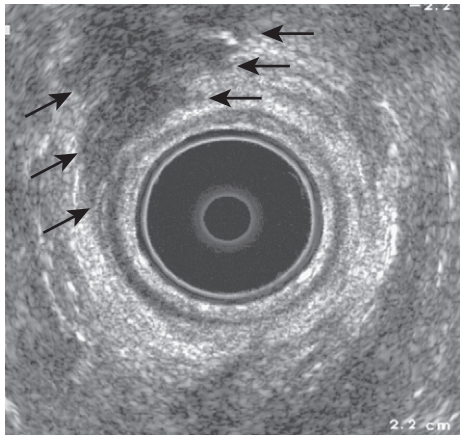


FIGURE 19.13 Poor sonographic appearances in a woman who remained symptomatic following a formal sphincter repair. A large persistent defect is visible *(arrows)*.

vaginal delivery to identify those women with clinically occult sphincter tears whose sphincter may be at further risk from subsequent deliveries,[42] which is known to increase the risk of cumulative damage.[43,44] Endosonography has also been used to determine which routinely collected obstetric information best indicates the likelihood of associated sphincter disruption.

A study of 159 women found no correlation between sonographic tears and head circumference, baby weight, episiotomy, or the duration of active pushing.[45] However, forceps delivery was strongly associated with sphincter tears,[45] an association recognized by other workers.[25,46] Other investigators were able to identify a link between sphincter tears and a second stage of labor prolonged by epidural anesthesia, which increased the risk of disruption by an odds ratio of 2:1.[46] Where access to AES is limited, it may be possible to identify women who harbor sphincter tears by administering a simple incontinence questionnaire following delivery. Frudinger et al[29] found that such an approach was able to identify 60% of women who sustained EAS tears following vaginal delivery.

AES revolutionized the management of women who sustain sphincter damage following vaginal delivery, but it is fair to say that some controversy persists regarding the exact incidence of EAS tears. For example, although the landmark study by Sultan et al[25] found an incidence of 35% in primiparous women, Varma et al[47] suggested that the true incidence was closer to 9%, and

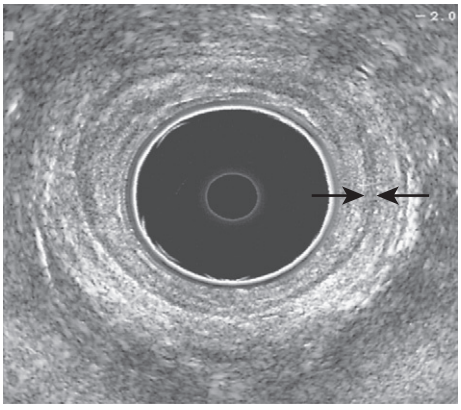


FIGURE 19.14 Anal endosonography in a 69-year-old woman with passive anal incontinence. The internal sphincter *(between arrows)* is intact but barely visible and measured 0.7 mm at its thickest. The findings suggest idiopathic degeneration of the internal anal sphincter.

other investigators suggested 17%.[48] In an attempt to resolve this uncertainty, a meta-analysis of 717 vaginal deliveries found a 27% incidence of sphincter defects in nulliparous women, and 30% of these were symptomatic. The investigators concluded that the probability that postpartum anal incontinence was caused by sphincter disruption was on the order of 80%.[49]

Idiopathic Internal Anal Sphincter Degeneration and External Anal Sphincter Atrophy

Not all anal incontinence is caused by sphincter disruption. Many incontinent patients have intact sphincters, but the functional quality of their sphincter muscle is impaired by neuromuscular degeneration. Vaizey et al[50] reported 52 patients with anal incontinence who had an intact EAS and IAS on endosonography but whose IAS was thinned and hyperreflective. Resting pressures, reflecting IAS function, were significantly lowered in this group, but squeeze pressures and pudendal nerve latencies were normal. The investigators concluded that discrete and isolated primary degeneration of the IAS was likely responsible for anal incontinence in these patients. Because the IAS normally thickens with age,[7] IAS thinning is relatively easy to diagnose using EAS, and the diagnosis should be considered in any older patient whose IAS measures 1 mm or less in thickness (Fig. 19.14). A rare cause of isolated IAS thinning is systemic sclerosis (scleroderma).[51]

The EAS may also degenerate, a process termed *atrophy*. This phenomenon was first recognized using endoanal MRI because the striated fibers of the EAS contrast strongly against ischioanal fat, and it is therefore easier to appreciate muscular bulk than on AES.[52] Although the mechanisms are unclear, one possibility being long-standing pudendal neuropathy, EAS atrophy is important because it adversely affects the outcome of sphincter repair. Briel et al[52] found that surgical procedures for concomitant EAS defects in this group were unsuccessful because the functional quality of the EAS was compromised by atrophy. Using both endoanal MRI and AES, Williams et al[53] were able to define the sonographic features of EAS atrophy and found that the EAS in these patients was patchy and poorly defined. In particular, the lateral edge of the EAS was indistinct, and the muscle was thinner than normal.[53] IAS degeneration and EAS atrophy may be combined in the same patient, and these are probably the sonographic features of what has long been termed *neurogenic* fecal incontinence (Fig. 19.15). Indeed, atrophy of both sphincters and concomitant tears can be found in the same patient.

Although endoanal MRI is likely superior to AES for diagnosis of EAS atrophy, investigators found that both modalities are equivalent for diagnosis of sphincter tears. AES is particularly

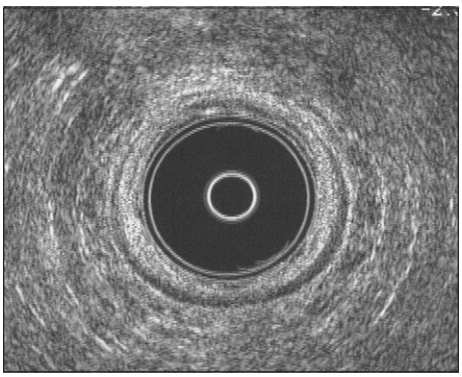


FIGURE 19.15 Anal endosonography in a 50-year-old-woman complaining of anal incontinence. Both sphincters are intact but are very poorly seen. The lateral margins of the external anal sphincter (EAS) are indistinct, suggesting EAS atrophy, and the internal anal sphincter is very thin, suggesting degeneration.

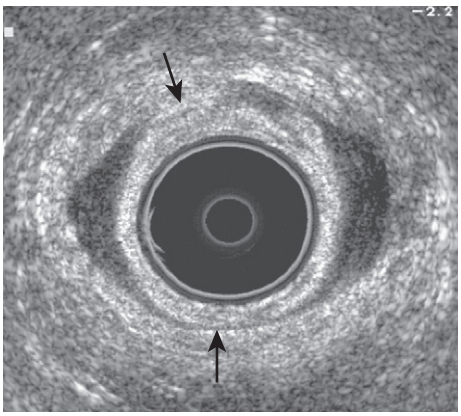


FIGURE 19.16 Endosonography in a man who became incontinent following hemorrhoidectomy. The scan reveals extensive internal sphincter division, with large anterior and posterior defects *(arrows)*.

adept at the diagnosis of IAS degeneration because this muscle is normally well visualized during endosonography and is thinned in these patients, whereas it is normally thicker in older people, an observation that facilitates a distinction between normal and abnormal.[54] EAS atrophy is more difficult to diagnose reliably with AES, not only because the sphincter is difficult to define, but also because the normal EAS tends to thin with age.[7]

Iatrogenic Sphincter Injury and Anal Trauma

Unfortunately, iatrogenic damage is a relatively common cause of anal incontinence. A study of 50 patients following a variety of anal surgical procedures found subsequent sphincter defects in 46%.[55] Although some procedures purposely seek to divide the sphincter mechanism, most obviously IAS sphincterotomy, other procedures should not normally cause sphincter damage. An association between unintentional sphincter division and hemorrhoidectomy is now well recognized (Fig. 19.16). A study of 16 patients undergoing hemorrhoidectomy found subsequent sphincter defects in 50%.[56] Quadrantic IAS division is relatively common in symptomatic patients, but occasionally the incision is sufficiently deep to lacerate the longitudinal muscle and the EAS as well.

The IAS may also be damaged in patients who have undergone procedures that require anal dilatation. In these cases, the appearances tend to be those of generalized IAS fragmentation around the circumference (Fig. 19.17). Anal stretch (the Lord procedure) for anal fissure is a common cause of such disruption, as is

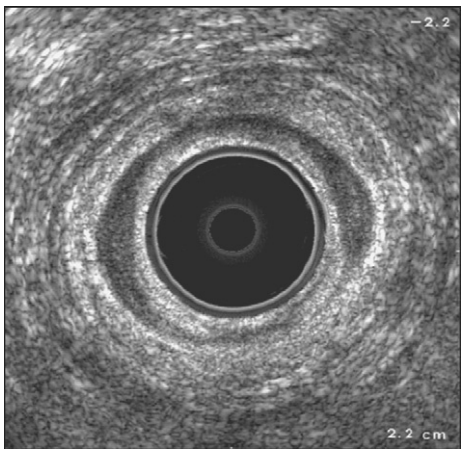


FIGURE 19.17 Internal anal sphincter fragmentation. Endosonography reveals internal sphincter fragmentation in this woman who had anal dilatation for an anal fissure and who now complains of anal incontinence.

manual rectal evacuation for intractable constipation, if it is not carefully performed.[57] Transanal stapling instruments, such as those used for low anterior resection, may also unintentionally incorporate the IAS in their firing path and result in IAS defects and subsequent passive incontinence.[58,59] Whereas the IAS is purposefully divided during lateral sphincterotomy, the intent is usually to divide the muscle for only the most caudal one third of its length. However, prospective sonographic studies of IAS morphology following this procedure revealed that division is often more extensive than actually intended, notably in women, probably because their anatomic anal canal is shorter than in men.[60] Such studies have increased physician awareness of overextensive IAS division, and operators are probably now more cautious than they were before the advent of AES. The result is that sonographic studies have revealed that some patients whose anal fissure persisted after sphincterotomy may not actually have had any muscle divided during the procedure.[61]

A current role is also emerging for AES in the treatment of anal incontinence, although this work is largely preliminary. For example, AES is necessary to monitor injection of bulking material, such as silicone, into the anal sphincter that may possibly treat incontinence.[62,63] More recent work has used AES to deliver autologous myoblasts into EAS defects, with the hope that the engineered cells will integrate into their surroundings and restore functionality to the damaged striated muscle.[64]

SONOGRAPHIC FINDINGS IN OTHER ANAL DISORDERS

Although the main role for AES is in patients with anal incontinence, AES has other useful applications. The most prominent of these is probably for imaging fistula-in-ano. Surgeons operating on these patients need to know the relationship of the fistula tract with the anal sphincter mechanism because treatment usually involves cutting down onto the fistula and laying it open, so that infection can drain and heal subsequently. This practically always necessitates a degree of unavoidable sphincter division, the extent of which may be predicted by AES.

Early attempts to use AES for preoperative assessment of fistula-in-ano were relatively disappointing, and assessment was no better than that achieved by digital examination by an experienced colorectal surgeon.[65] However, more recent studies using 10-MHz AES were more optimistic. A study of 108 fistulas in 104 patients found that AES correctly classified the primary fistula tract in 81% of cases, as opposed to 61% for digital examination

by an experienced surgeon.[66] Endosonography was particularly accurate in predicting the site of the internal enteric opening in the anal canal; the prediction was correct in 91% of cases.[66] The reason is that the internal opening is inevitably close to the transducer surface and is therefore visualized with high spatial resolution. However, AES has specific disadvantages in several areas. For example, insufficient penetration beyond the EAS, especially with high-frequency transducers, limits the ability to resolve tracts and abscesses that are remote from the anal canal. Unfortunately, these lesions are especially common in patients with recurrent disease.[67] Moreover, AES cannot reliably distinguish infection from fibrosis, given that both appear hypoechoic on ultrasound. This inability causes particular difficulties in patients with recurrent disease because active tracts and fibrotic scars are frequently combined. Attempts have been made to clarify the course of patent tracts by injecting hydrogen peroxide or ultrasound contrast agents into the external opening during examination.[68]

Another disadvantage of AES is the inability to image in the surgically important (for fistulas) coronal plane, so that it may be very difficult to distinguish supralevator from infralevator extensions. Some investigators have attempted to overcome this disadvantage by employing three-dimensional acquisition[69,70] (Fig. 19.18), but this technique remains relatively experimental. However, there is little doubt that MRI is a superior technique overall, and, therefore, the major role of AES in fistula disease is probably to assess the degree of sphincter disruption in those patients who become anally incontinent following fistula repair operations. AES also has a particular role in those patients who may have a small intersphincteric abscess that could be difficult to resolve using standard body or phased array surface coil MRI (Fig. 19.19).

Endosonography has revealed sphincter abnormalities in patients who are severely constipated, although the significance of these abnormalities remains largely uncertain. For example, patients with solitary rectal ulcer syndrome are known to have an abnormally thickened IAS (Fig. 19.20),[71] and this finding has been correlated with the presence of high-grade prolapse of rectal mucosa.[72] IAS hypertrophy has also been demonstrated by AES in children with intractable constipation.[73] A study of 144 constipated children found that this finding correlated with duration and severity of symptoms, size of megarectum, and amplitude of rectal contraction.[74] The investigators suggested that IAS thickening was caused by hypertrophy as a result of chronic stimulation owing to the presence of feces in the rectum.[74]

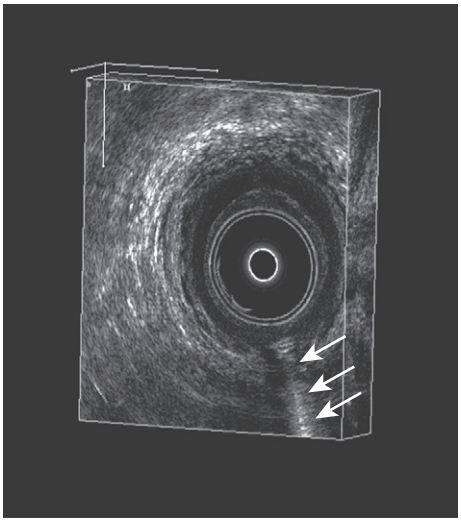


FIGURE 19.18 Three-dimensional anal endosonography following hydrogen peroxide injection through the external opening of a fistula-in-ano. Echogenic gas is present within an intersphincteric tract *(arrows).*

Endosonography may also be useful when it is necessary to determine the correct anatomic position of the neoanus with respect to any residual musculature in children with imperforate anus and, unlike MRI, can be easily performed perioperatively.[75,76]

Endosonography may also be used to stage anal tumors locally because it can determine the depth of penetration into surrounding tissues (Fig. 19.21).[77] However, some investigators have found the technique less useful for detecting local recurrence because all 14 recurrences in a series of 82 patients were detected by visual inspection and digital examination alone.[78]

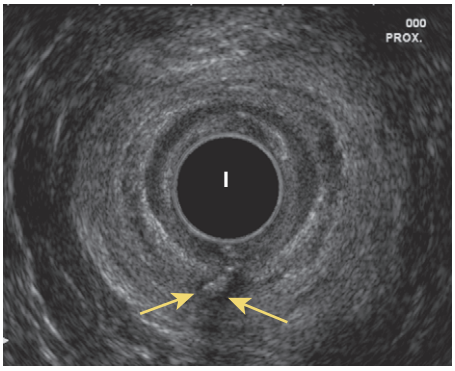


FIGURE 19.19 Endosonography clearly reveals a posterior intersphincteric abscess *(arrows)* in this patient with anal pain. The digital rectal examination had been normal.

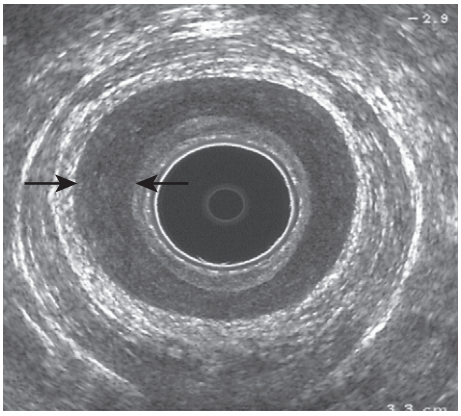


FIGURE 19.20 Male patient with solitary rectal ulcer syndrome. The internal sphincter *(between arrows)* measured 7.5 mm, far greater than normal.

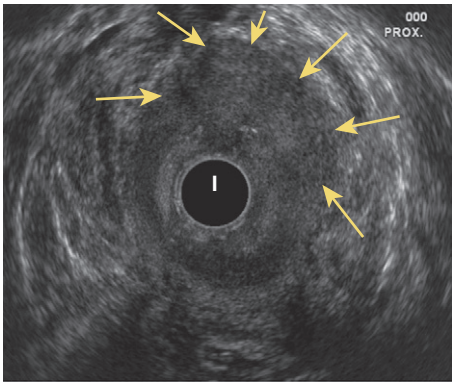


FIGURE 19.21 Anal squamous tumor. Endosonography in a man with a primary anal squamous tumor reveals a large left anterior quadrant mass *(arrows)* that has breached the anal sphincter complex to reach the surrounding tissues.

REFERENCES

1. Law PJ, Bartram CI. Anal endosonography: technique and normal anatomy. *Gastrointest Radiol*. 1989;14:349–353.
2. Snooks SJ, Setchell M, Swash M, Henry MM. Injury to the innervation of the pelvic floor sphincter musculature in childbirth. *Lancet*. 1984;2: 546–550.
3. Frudinger A, Bartram CI, Halligan S, Kamm M. Examination techniques for endosonography of the anal canal. *Abdom Imaging*. 1998;23:301–303.
4. Lunniss PJ, Phillips RK. Anatomy and function of the anal longitudinal muscle. *Br J Surg*. 1992;79:882–884.
5. Stoker J, Rociu E, Zwamborn AW, et al. Endoluminal MR imaging of the rectum and anus: technique, applications, and pitfalls. *Radiographics*. 1999;19:383–398.
6. Williams AB, Bartram CI, Halligan S, et al. Endosonographic anatomy of the normal anal canal compared with endocoil magnetic resonance imaging. *Dis Colon Rectum*. 2002;45:176–183.
7. Frudinger A, Halligan S, Bartram CI, et al. Female anal sphincter: age-related differences in asymptomatic volunteers with high-frequency endoanal US. *Radiology*. 2002;224:417–423.
8. Williams AB, Bartram CI, Halligan S, et al. Multiplanar anal endosonography: normal anal canal anatomy. *Colorectal Dis*. 2001;3:169–174.
9. Sultan AH, Nicholls RJ, Kamm MA, et al. Anal endosonography and correlation with in vitro and in vivo anatomy. *Br J Surg*. 1993;80:508–511.
10. Gold DM, Halligan S, Kmiot WA, Bartram CI. Intraobserver and interobserver agreement in anal endosonography. *Br J Surg*. 1999;86:371–375.
11. Lane RH, Parks AG. Function of the anal sphincters following colo-anal anastomosis. *Br J Surg*. 1977;64:596–599.
12. Engel AG, Kamm MA. Relationship of symptoms in faecal incontinence to specific sphincter abnormalities. *Int J Colorectal Dis*. 1995;10:152–155.
13. Rogers J, Henry MM, Misiewicz JJ. Disposable pudendal nerve stimulator: evaluation of the standard instrument and new device. *Gut*. 1988;29: 1131–1133.
14. Kiff ES, Swash M. Slowed conduction in the pudendal nerves in idiopathic (neurogenic) faecal incontinence. *Br J Surg*. 1984;71:614–616.
15. Parks AG, Porter NH, Hardcastle JD. The syndrome of the descending perineum. *Proc R Soc Med*. 1966;59:477–482.
16. Jorge JMN, Wexner SD, Ehrenpreis ED, et al. Does perineal descent correlate with pudendal neuropathy? *Dis Colon Rectum*. 1993;36:475–483.
17. Gilliand R, Altomare DF, Moreira H, et al. Pudendal neuropathy is predictive of failure following anterior overlapping sphincteroplasty. *Dis Colon Rectum*. 1998;41:1516–1522.
18. Sultan AH, Kamm MA, Talbot IC, et al. Anal endosonography for identifying external sphincter defects confirmed histologically. *Br J Surg*. 1994;81: 463–465.
19. Denis P, Bercoff E, Bizien MF. Etude de la prevalence di l'incontinence anale chez l'adulte. *Gastroenterol Clin Biol*. 1992;16:344–350.
20. Talley NJ, O'Keefe EA, Zinsmeister AR, Melton JL. Prevalence of gastrointestinal symptoms in the elderly: a population based study. *Gastroenterology*. 1992;102:895–901.
21. Lahr CJ. Evaluation and treatment of incontinence. *Pract Gastroenterol*. 1988;12:27–35.
22. Sultan AH, Kamm MA, Hudson CN, Bartram CI. Third degree obstetric tears: risk factors and outcome of primary repair. *BMJ*. 1994;308: 887–891.
23. Law PJ, Kamm MA, Bartram CI. Anal endosonography in the investigation of faecal incontinence. *Br J Surg*. 1991;78:312–314.
24. Burnett SJD, Spence-Jones C, Speakman CTM, et al. Unsuspected sphincter damage following childbirth revealed by anal endosonography. *Br J Radiol*. 1991;64:225–227.
25. Sultan AH, Kamm MA, Hudson CN, et al. Anal sphincter disruption during vaginal delivery. *N Engl J Med*. 1993;329:1905–1911.
26. Deen KI, Kumar D, Williams JG, et al. Anal sphincter defects: correlation between endoanal ultrasound and surgery. *Ann Surg*. 1993;218:201–205.
27. Sentovich SM, Wong WD, Blatchford GJ. Accuracy and reliability of transanal ultrasound for anterior anal sphincter injury. *Dis Colon Rectum*. 1998; 41:1000–1004.
28. Voyvodic F, Rieger NA, Skinner S, et al. Endosonographic imaging of anal sphincter injury: does the size of the tear correlate with the degree of dysfunction? *Dis Colon Rectum*. 2003;46:735–741.
29. Frudinger A, Halligan S, Bartram CI, et al. Assessment of the predictive value of a bowel symptom questionnaire in identifying perianal and anal sphincter trauma after vaginal delivery. *Dis Colon Rectum*. 2003;46: 742–747.
30. Oberwalder M, Dinnewitzer A, Baig MK, et al. The association between late-onset fecal incontinence and obstetric anal sphincter defects. *Arch Surg*. 2004;139:429–432.
31. Williams AB, Bartram CI, Halligan S, et al. Anal sphincter damage after vaginal delivery using three-dimensional endosonography. *Obstet Gynaecol*. 2001;97:770–775.
32. Frudinger A, Halligan S, Bartram CI, et al. Changes in anal anatomy following vaginal delivery revealed by anal endosonography. *Br J Obstet Gynaecol*. 1999;106:233–237.
33. Williams AB, Bartram CI, Halligan S, et al. Alteration of anal sphincter morphology following vaginal delivery revealed by multiplanar anal endosonography. *BJOG*. 2002;109:942–946.
34. Poen AC, Felt-Bersma RJ, Strijers RL, et al. Third-degree obstetric perineal tear: long-term clinical and functional results after primary repair. *Br J Surg*. 1998;85:1433–1438.
35. Davis K, Kumar D, Stanton SL, et al. Symptoms and anal sphincter morphology following primary repair of third-degree tears. *Br J Surg*. 2003; 90:1573–1579.
36. Savoye-Collet C, Savoye G, Koning E, et al. Endosonography in the evaluation of anal function after primary repair of a third-degree obstetric tear. *Scand J Gastroenterol*. 2003;38:1149–1153.
37. Starck M, Bohe M, Valentin L. Results of endosonographic imaging of the anal sphincter 2-7 days after primary repair of third- or fourth-degree obstetric sphincter tears. *Ultrasound Obstet Gynecol*. 2003;22:609–615.
38 Malouf AJ, Norton CS, Engel AF, et al. Long-term results of overlapping anterior anal-sphincter repair for obstetric trauma. *Lancet*. 2000;355: 260–265.
39. Pinedo G, Vaizey CJ, Nicholls RJ, et al. Results of repeat anal sphincter repair. *Br J Surg*. 1999;86:66–69.
40. Giordano P, Renzi A, Efron J, et al. Previous sphincter repair does not affect the outcome of repeat repair. *Dis Colon Rectum*. 2002;45:635–640.
41. Felt-Bersma RJ, Cuesta MA, Koorevaar M. Anal sphincter repair improves anorectal function and endosonographic image: a prospective clinical study. *Dis Colon Rectum*. 1996;39:878–885.
42. Faltin DL, Boulvain M, Irion O, et al. Diagnosis of anal sphincter tears by postpartum endosonography to predict fecal incontinence. *Obstet Gynecol*. 2000;95:643–647.
43. Fines M, Donnelly V, Behan M, et al. Effect of second vaginal delivery on anorectal physiology and faecal continence: a prospective study. *Lancet*. 1999;354:983–986.
44. Faltin DL, Sangalli MR, Roche B, et al. Does a second delivery increase the risk of anal incontinence? *BJOG*. 2001;108:684–688.
45. Varma A, Gunn J, Lindow SW, Duthie GS. Do routinely measured delivery variables predict anal sphincter outcome? *Dis Colon Rectum*. 1999;42: 1261–1264.
46. Donnelly V, Fynes M, Campbell D, et al. Obstetric events leading to anal sphincter damage. *Obstet Gynecol*. 1998;92:955–961.
47. Varma A, Gunn J, Gardiner A, Lindow SW, Duthie GS. Obstetric anal sphincter injury: prospective evaluation of incidence. *Dis Colon Rectum*. 1999;42:1537–1543.
48. Abramowitz L, Sobhani I, Ganansia R, et al. Are sphincter defects the cause of anal incontinence after vaginal delivery? Results of a prospective study. *Dis Colon Rectum*. 2000;43:590–596; discussion 596–598.
49. Oberwalder M, Connor J, Wexner SD. Meta-analysis to determine the incidence of obstetric anal sphincter damage. *Br J Surg*. 2003;90:1333–1337.
50. Vaizey CJ, Kamm MA, Bartram CI. Primary degeneration of the internal anal sphincter as a cause of passive faecal incontinence. *Lancet*. 1997; 349:612–615.
51. Engel AF, Kamm MA, Talbot IC. Progressive systemic sclerosis of the internal anal sphincter leading to passive faecal incontinence. *Gut*. 1994;35: 857–859.
52. Briel JW, Stoker J, Rociu E, et al. External anal sphincter atrophy on endoanal magnetic resonance imaging adversely affects continence after sphincteroplasty. *Br J Surg*. 1999;86:1322–1327.
53. Williams AB, Bartram CI, Modhwadia D, et al. Endocoil magnetic resonance imaging quantification of external anal sphincter atrophy. *Br J Surg*. 2001;88:853–859.
54. Malouf AJ, Williams AB, Halligan S, et al. Prospective assessment of accuracy of endoanal MR imaging and endosonography in patients with fecal incontinence. *AJR Am J Roentgenol*. 2000;175:741–745.
55. Felt-Bersma RJ, van Baren R, Koorevaar M, et al. Unsuspected sphincter defects shown by anal endosonography after anorectal surgery: a prospective study. *Dis Colon Rectum*. 1995;38:249–253.
56. Abbasakoor F, Nelson M, Beynon J, et al. Anal endosonography in patients with anorectal symptoms after haemorrhoidectomy. *Br J Surg*. 1998;85:1522–1524.
57. Gattuso JM, Kamm MA, Halligan SM, Bartram CI. The anal sphincter in idiopathic megarectum: effects of manual disimpaction under general anesthetic. *Dis Colon Rectum*. 1996;39:435–439.
58. Ho YH, Tsang C, Tang CL, et al. Anal sphincter injuries from stapling instruments introduced transanally: randomized, controlled study with endoanal ultrasound and anorectal manometry. *Dis Colon Rectum*. 2000; 43:169–173.
59. Farouk R, Duthie GS, Lee PW, Monson JR. Endosonographic evidence of injury to the internal anal sphincter after low anterior resection: long-term follow-up. *Dis Colon Rectum*. 1998;41:888–891.

60. Sultan AH, Kamm MA, Nicholls RJ, Bartram CI. Prospective study of the extent of internal anal sphincter division during lateral sphincterotomy. *Dis Colon Rectum*. 1994;37:1031–1033.
61. Garcia-Granero E, Sanahuja A, Garcia-Armengol J, et al. Anal endosonographic evaluation after closed lateral subcutaneous sphincterotomy. *Dis Colon Rectum*. 1998;41:598–601.
62. Tjandra JJ, Lim JF, Hiscock R, Rajendra P. Injectable silicone biomaterial for fecal incontinence caused by internal anal sphincter dysfunction is effective. *Dis Colon Rectum*. 2004;47:2138–2146.
63. Maeda Y, Vaizey CJ, Kamm MA. Long-term results of perianal silicone injection for faecal incontinence. *Colorectal Dis*. 2007;9:357–361.
64. Frudinger A, Kölle D, Schwaiger W, et al. Muscle-derived cell injection to treat anal incontinence due to obstetric trauma: pilot study with 1 year follow-up. *Gut*. 2010;59:55–61.
65. Choen S, Burnett S, Bartram CI, Nicholls RJ. Comparison between anal endosonography and digital examination in the evaluation of anal fistulae. *Br J Surg*. 1991;78:445–447.
66. Buchanan GN, Halligan S, Bartram CI, et al. Clinical examination, endosonography, and magnetic resonance imaging for preoperative assessment of fistula-in-ano: comparison to an outcome based reference standard. *Radiology*. 2004;233:674–681.
67. Buchanan G, Halligan S, Williams A, et al. Effect of MRI on clinical outcome of recurrent fistula-in-ano. *Lancet*. 2002;360:1661–1662.
68. Kruskal JB, Kane RA, Morrin MM. Peroxide-enhanced anal endosonography: technique, image interpretation, and clinical applications. *Radiographics*. 2001;21:173–189.
69. Buchanan GN, Bartram CI, Williams AB, et al. Value of hydrogen peroxide enhancement of three-dimensional endoanal ultrasound in fistula-in-ano. *Dis Colon Rectum*. 2005;48:141–147.
70. West RL, Zimmerman DD, Dwarkasing S, et al. Prospective comparison of hydrogen peroxide-enhanced three-dimensional endoanal ultrasonography and endoanal magnetic resonance imaging of perianal fistulas. *Dis Colon Rectum*. 2003;46:1407–1415.
71. Halligan S, Sultan A, Rottenberg G, Bartram CI. Endosonography of the anal sphincters in solitary rectal ulcer syndrome. *Int J Colorectal Dis*. 1995;10:79–82.
72. Marshall M, Halligan S, Fotheringham T, et al. Predictive value of internal anal sphincter thickness for diagnosis of rectal intussusception in patients with solitary rectal ulcer syndrome. *Br J Surg*. 2002;89:1281–1285.
73. Hosie GP, Spitz L. Idiopathic constipation in childhood is associated with thickening of the internal anal sphincter. *J Pediatr Surg*. 1997;32:1041–1043; discussion 1043–1044.
74. Keshtgar AS, Ward HC, Clayden GS, Sanei A. Thickening of the internal anal sphincter in idiopathic constipation in children. *Pediatr Surg Int*. 2004;20:817–823.
75. Jones NM, Humphreys MS, Goodman TR, et al. The value of anal endosonography compared with magnetic resonance imaging following the repair of anorectal malformations. *Pediatr Radiol*. 2003;33:183–185.
76. Yamataka A, Yoshida R, Kobayashi H, et al. Intraoperative endosonography enhances laparoscopy-assisted colon pull-through for high imperforate anus. *J Pediatr Surg*. 2002;37:1657–1660.
77. Tarantino D, Bernstein MA. Endoanal ultrasound in the staging and management of squamous-cell carcinoma of the anal canal: potential implications of a new ultrasound staging system. *Dis Colon Rectum*. 2002;45:16–22.
78. Lund JA, Sundstrom SH, Haaverstad R, et al. Endoanal ultrasound is of little value in follow-up of anal carcinomas. *Dis Colon Rectum*. 2004;47:839–842.

CHAPTER 20

How to Perform EUS-Guided Fine-Needle Aspiration and Biopsy

Anand V. Sahai | Sarto C. Paquin

Key Points

Because movement of the needle is easier when the echoendoscope is straight, the endosonographer should try to achieve a position in which up/down and left/right tip angulation is minimal and no elevator is required.

Before insertion of a needle, the needle pathway should be scanned using color Doppler mode.

Excessive force should never be used to pass the needle sheath past an acute bend in the endoscope tip.

The needle is kept in the visual plane at all times during EUS FNA.

During aspiration of cysts without a mass component, the endosonographer should fully aspirate all fluid, make only one pass, use antibiotics, and not try to perform aspiration cytology from the cyst wall.

INTRODUCTION

Fine-needle aspiration (FNA) provides some of the most clinically powerful information that endoscopic ultrasonography (EUS) has to offer: pathologic confirmation of the presence or absence of malignancy or metastasis to secondary sites (histologic staging). As with any procedure, proficiency requires adequate experience, but EUS FNA is not a universally difficult technique to master. Some cases are more technically demanding than others. Sampling a 5-mm pancreatic nodule buried deep in the uncinate process is certainly more challenging than sampling a 4-cm subcarinal lymph node. Some of the easiest cases provide information that can have a tremendous impact on patient management (e.g., avoidance of surgery by documentation of mediastinal lymph node involvement in a patient with non–small cell lung cancer).

This chapter provides a detailed description of a generic EUS FNA technique that can be applied to most lesions. EUS-guided Tru-Cut biopsy (TCB) and special situations are also discussed.

EUS FNA can be broken down into a series of steps. Proper execution of each step makes EUS FNA easier and probably increases the yield for malignancy. Experts likely have varying opinions on the best way to perform EUS FNA, but few or no data show clearly which procedural variables predict success.

STEPS FOR EUS FINE-NEEDLE ASPIRATION

1. Verify the indication.
2. Localize the lesion and position the echoendoscope.
3. Choose the correct needle size.
4. Insert the EUS FNA needle into the echoendoscope.
5. Prepare the needle:
   a. Use of the stopping device
   b. Stylet issues
   c. How to hold the needle
6. Puncture the lesion.
7. Consider use of suction.
8. Withdraw the needle and process the aspirate.
9. Prepare the needle for subsequent passes.
10. FNA considerations by site:
    a. Esophagus
    b. Stomach
    c. Duodenal bulb
    d. Duodenal sweep (D2)

Verify the Indication

Before EUS FNA, the indication should be clear, and the endoscopy suite and team should be adequately prepared. Like any test, EUS FNA does not need to change management to be useful. However, before EUS FNA is considered in a given patient, it should be clear that the information obtained has a reasonable chance of being clinically useful to those managing the patient or to the patient. If the endosonographer is not in charge of the patient's management, his or her opinion on the value of the information need not affect the decision to perform EUS FNA unless compelling evidence indicates that the risks of the procedure will likely far outweigh the possible benefits. If any doubt exists, these issues should be addressed with the referring physician before the procedure or even *during* the procedure, if necessary.

Localize the Lesion and Position the Echoendoscope

Optimal positioning of the echoendoscope with respect to the lesion should make EUS FNA easier, safer, and more effective. Once the lesion is identified, the echoendoscope should be positioned as much as possible within the natural path of the needle (i.e., the path taken by the needle when no elevator is applied) (Fig. 20.1). This position varies depending on the instrument used. If this is not possible, the echoendoscope should be

positioned within the range of deflection offered by the elevator (if present) (Fig. 20.2). The elevator can be used to *increase* the angle formed between the echoendoscope shaft and the needle. It cannot *reduce* this angle. The effectiveness of the elevator is also diminished if the distance that the sheath of the needle extends beyond the opening of the biopsy channel is excessively long (Fig. 20.3). Depending on the needle used, this distance can be adjusted by using a system integrated into the needle or by using spacers that Luer-lock onto the opening of the biopsy channel.

When elevator adjustment is required, it may be helpful first to lock the up/down dial to immobilize the echoendoscope tip.

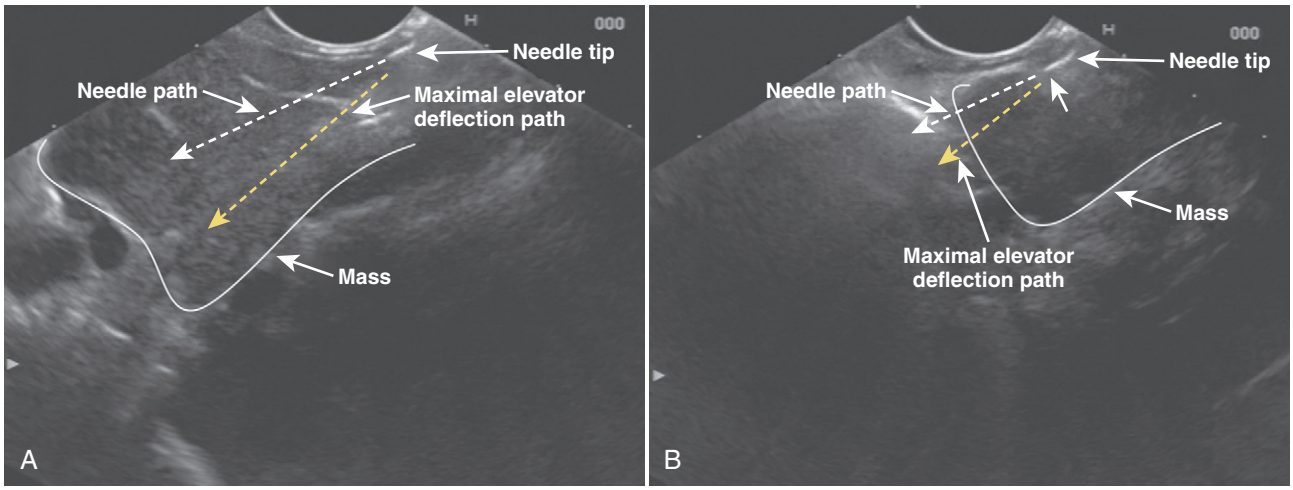


FIGURE 20.1 **Correct positioning of a subcarinal lymph node before FNA. A,** Lesion in needle and elevator path. **B,** Incorrect positioning.

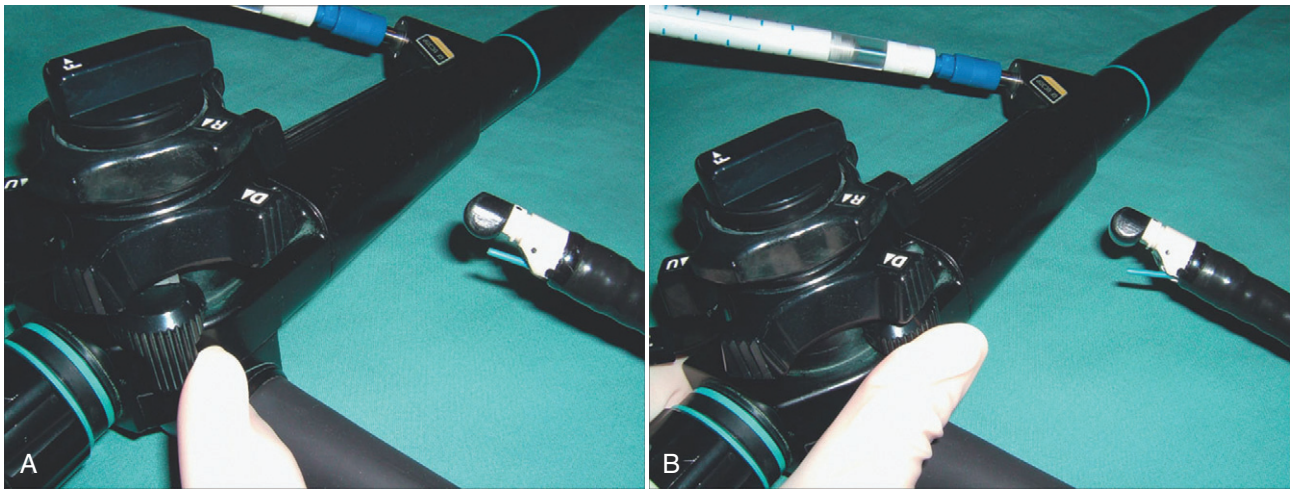


FIGURE 20.2 **Elevator range of movement. A,** No elevator. **B,** Maximum deflection of elevator.

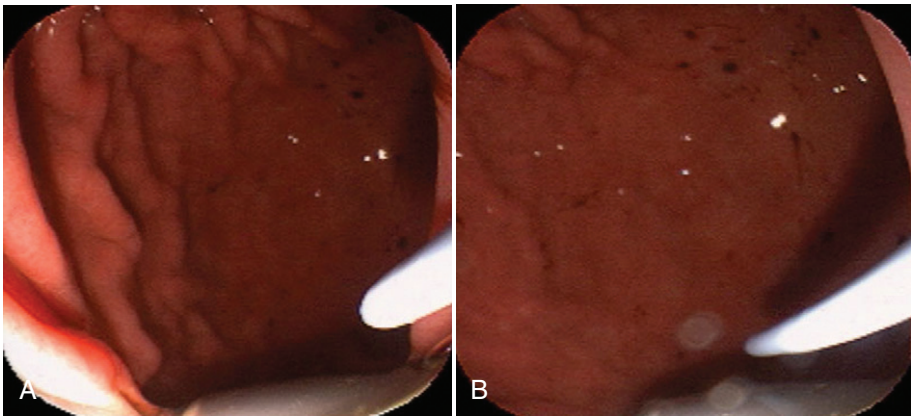


FIGURE 20.3 **Endoscopic view of a needle sheath. A,** Correct distance. **B,** Excessively long distance.

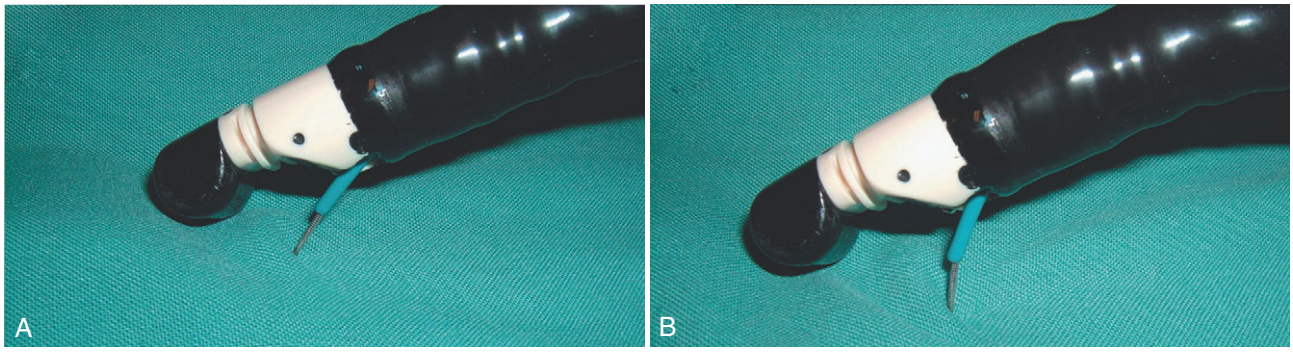


FIGURE 20.4 Planting and pushing to deflect the needle. A, Planting the needle. **B,** Advancing the echoendoscope.

If no elevator is available or if the tip deflection obtainable using the elevator is insufficient, the angle can be increased by implanting the needle tip into the gut wall and then gently advancing the echoendoscope (Fig. 20.4).

Movement of the EUS FNA needle is always easier if the needle is straight. Any bend in the needle induced by the echoendoscope position or the elevator increases the resistance in the needle system and makes needle movement more difficult. This is problematic primarily for sampling lesions with the probe in the duodenal bulb or the duodenal sweep. However, wedging the echoendoscope in the duodenal bulb (a maneuver that requires a long, bent scope) provides a mechanical advantage when one is trying to puncture indurated lesions in the region of the pancreatic head. Conversely, when the scope is in a short, straight position in the second duodenum, it may limit the ability to exert strong force in the direction of the lesion when advancing the needle because the needle is well out of the long axis of the echoendoscope shaft. Therefore, finding the most effective position may require some compromise between maintaining a fairly straight needle and not losing the mechanical advantage that is provided by the long echoendoscope position.

Given the risks inherent in needle puncture of any retroperitoneal structure, it is logical to assume that limiting the distance the needle must travel to reach the target will reduce the risk of complications related to trauma of the surrounding tissues and organs. One should also avoid puncturing undrained, obstructed ducts, because of the risk of inducing cholangitis or pancreatitis. Although not proven, it is also logical to assume that if a liquid-containing structure such as a blood vessel or bile duct is punctured, the risk of leakage will be lower if the needle enters perpendicular to the vessel or duct wall and produces only a pinhole defect, as opposed to passing tangentially and causing a linear laceration. Therefore, contact with all vessels should be avoided, but particularly when passing the needle laterally to a vessel. Before insertion of the needle, it is always reasonable to scan the biopsy path with the Doppler function to identify any significant blood vessels in the vicinity.

Choose the Correct Needle Size

EUS FNA is most commonly used to obtain specimens for *cytologic* analysis. At present, three needle sizes available for EUS FNA can be used to obtain material for cytologic examination: 19 gauge (G), 22 G, and 25 G. Largest is not necessarily best. Large-diameter needles tend to be more difficult to maneuver (particularly the 19-G needle), are more traumatic, and may provide bloodier samples. These factors may actually reduce the effectiveness of large-diameter needles when compared with smaller-diameter needles. Traditionally, 22-G needles were used for solid lesions, and 22 G was the first size that was commercially available. However, 25-G needles eventually came on the market, and some investigators hypothesized that a 25-G needle would be better (easier to penetrate hard lesions, more maneuverable, associated with less bloody aspirates), particularly for challenging pancreatic head lesions.[1–5] The first retrospective comparisons of the 22-G and 25-G needles showed the 25-G needle to be more sensitive for cancer in pancreatic masses.[1,2] Subsequent, prospective studies, however, failed to show statistically significant advantages.[3,4] Further work is required before one needle can be formally recommended over the other. Endosonographers should probably familiarize themselves with both 22-G and 25-G needles. If one needle fails, switching to the other may help.

Cytologic specimens are adequate for diagnostic purposes in most cases. These specimens can be used to confirm or exclude epithelial malignancies, to allow for immunochemical staining (e.g., to diagnose neuroendocrine tumors and small cell lung cancer or to look for specific tumor receptors), and to permit flow cytometry, which can help diagnose or exclude monoclonal lymphoid processes. Cytologic specimens may also be sufficient to identify granulomas, which may help diagnose diseases such as sarcoidosis. However, in some cases, true histologic specimens may be required, and core specimens should be sought using larger-gauge needles (see the later section on EUS-guided biopsy).

Insert the EUS Fine-Needle Aspiration Needle into the Echoendoscope

Whether or not the needle system is inserted into the biopsy channel before or after the echoendoscope is in position for FNA is a matter of personal preference. However, once the echoendoscope is in position, it may be difficult or impossible to pass the needle system completely into position if the echoendoscope is not sufficiently straight. In this situation, the sheath may become stuck in the bending portion of the instrument near the tip. One should *never* use excessive force to push the sheath past an excessive bend at this location because the needle sheath may perforate the inner sheath of the biopsy channel. Instead, the echoendoscope should be withdrawn into a straight configuration before the examiner attempts to reinsert the needle system completely.

In some cases, a lesion that is clearly visible before needle deployment may become difficult to see once the needle assembly is in place. The needle or sheath may produce artifact or may slightly reduce complete coupling between the ultrasound probe and the gut wall, thus producing air artifact. Slight repositioning of the echoendoscope, application of suction, or reinsertion of the needle assembly may help correct the problem.

Prepare the Needle

Once the needle assembly and lesion are in proper position, tissue sampling may begin. The goal is to insert the needle into the lesion under constant real-time ultrasound guidance and to make

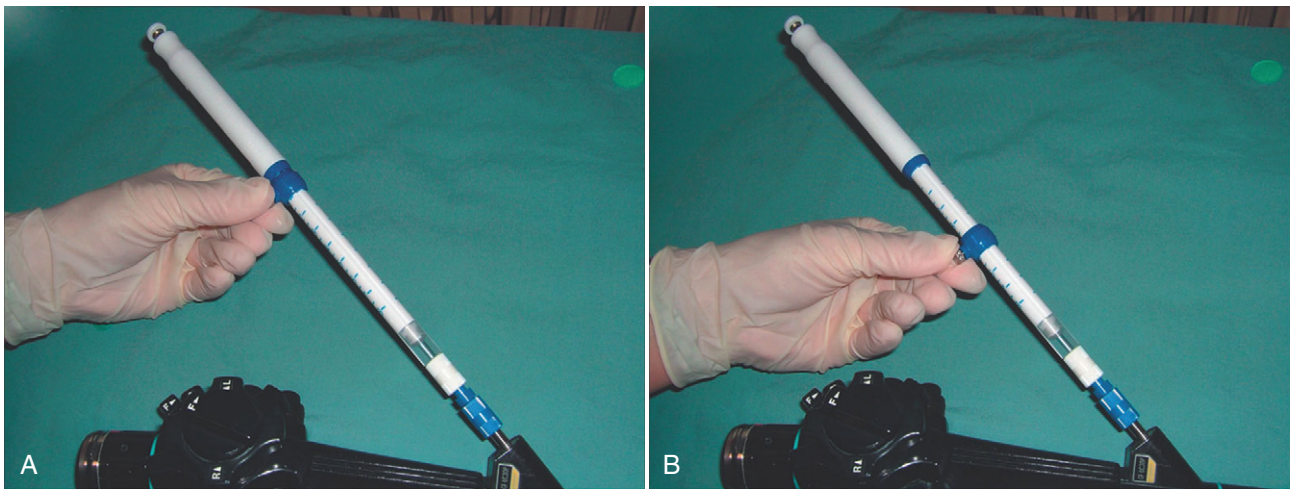


FIGURE 20.5 Stopper adjustment. A, Stopper off. **B,** Stopper on.

repetitive thrusting movements to shear off cells and collect them within the needle lumen. This technique requires that the needle be kept in the ultrasound imaging plane and that thrusting movements be deliberate, but not so fast as to make the needle difficult to see. Care should be taken to ensure that the needle does not leave the confines of the lesion during sampling, to avoid contaminating the specimen with tissue other than that from the target lesion.

Use of the Stopping Device

If the needle system includes a stopping device, it can be set to limit the maximum distance that the needle can travel (Fig. 20.5). This technique can be helpful in situations in which inserting the needle beyond the limits of the target lesion would be dangerous (e.g., the target lies directly over a vascular structure). Once the target lesion is in position on the screen, the caliper function can be used to measure the distance between the ultrasound probe and the center of the target lesion. The stopping device can then be set to this distance.

Stylet Issues

Depending on the needle system, stylet adjustment may be required before the target lesion is punctured. The stylet tip may be pointed or blunt and may or may not protrude beyond the tip of the hollow needle. If the stylet is flush with the needle tip, it can be left in place. If it protrudes beyond the needle tip (i.e., if the stylet is longer than the needle) and is blunt, the stylet must be withdrawn into the needle lumen to expose the sharp tip of the needle (Fig. 20.6). Even if the stylet tip is pointed, it may help to withdraw this tip into the needle because the stylet tip may be less effective at puncturing the gut wall than the beveled needle tip (e.g., it may be less pointed and may become dull more easily after multiple passes).

All commercially available EUS FNA systems include a removable stylet. It is believed that the stylet helps prevent clogging of the needle by gut wall tissue, a situation that could limit the ability to aspirate cells from the target lesion. Although this assumption is logical, no data have demonstrated clearly that the use of a stylet increases the yield of EUS FNA. Manipulation of the stylet increases the time and energy required to perform EUS FNA, increases the risks of needle stick injury, and likely raises the costs of EUS FNA needle systems. In some circumstances, the stylet may actually make EUS FNA impossible. Occasionally, it may not be possible to advance or to remove the stylet once the target has been punctured. This problem tends to occur only when the echoendoscope is bent (particularly when sampling from the bulb or duodenal sweep) and a large (19-G) needle is used. In this situation, consideration should be given to removing the stylet completely before attempting to perform EUS FNA.

Data show that EUS FNA performed without the stylet provides samples at least as valuable as samples acquired with the stylet in place.[5–7] Sahai and Paquin completely stopped using the stylet and performed more than 4000 EUS FNAs without the stylet, without any deterioration of results (unpublished observations). EUS FNA without the stylet is also technically much simpler and faster because the stylet withdrawal and reinsertion maneuvers are eliminated.

How to Hold the Needle

The fixed component of the needle handle should be grasped between the palm and the last three fingers of the examiner's right hand (Fig. 20.7). The movable portion should be held with the thumb and index finger. This position allows either fine or vigorous needle movements to be performed, but with control. Any method that does not allow such control should be avoided.

Puncture the Lesion

As stated earlier, it is reasonable to look for blood vessels by using the Doppler function before inserting the needle. Before beginning to move the needle, firm upward tip deflection should be applied using the up/down dial. This maneuver brings the lesion closer to the echoendoscope and reduces the tendency of the needle to push the ultrasound probe away from the gut wall, an action that can reduce ultrasound image quality by allowing air to seep in between the probe and the gut wall. It also provides a mechanical advantage during attempts to puncture an indurated lesion. Firm upward tip deflection also increases tension on the gut wall and thereby facilitates the puncture of mobile and thick walls such as the stomach body.

The needle should first be advanced approximately 1 cm out of the sheath, just enough to localize the tip in the ultrasound field. Once the tip has been identified, the elevator can be used to adjust the needle trajectory if needed. The needle can then be advanced into the lesion under ultrasound guidance. If, for some reason, the needle tip can no longer be seen once the lesion has been punctured, all *forward* movement of the needle should be stopped. Continuing to advance the needle in the hope that the tip will become visible is a mistake and can result in inadvertent puncture of structures deep to the target lesion. Instead, the first reflex should be to *withdraw* the needle slowly. This maneuver will help localize the tip without risking puncture of deep structures. If this approach is ineffective, slow left and right movement

of the shoulders can help bring the needle into the ultrasound imaging plane.

If both of these techniques fail, the needle should be withdrawn completely from the lesion into the sheath. If it is possible that the scope position could have caused the needle to be bent, the needle assembly should be removed from the echoendoscope and the needle straightened if needed (see later). The puncture can then be attempted again. This situation may be frequently encountered when the scope is torqued, especially in the duodenal bulb or sweep.

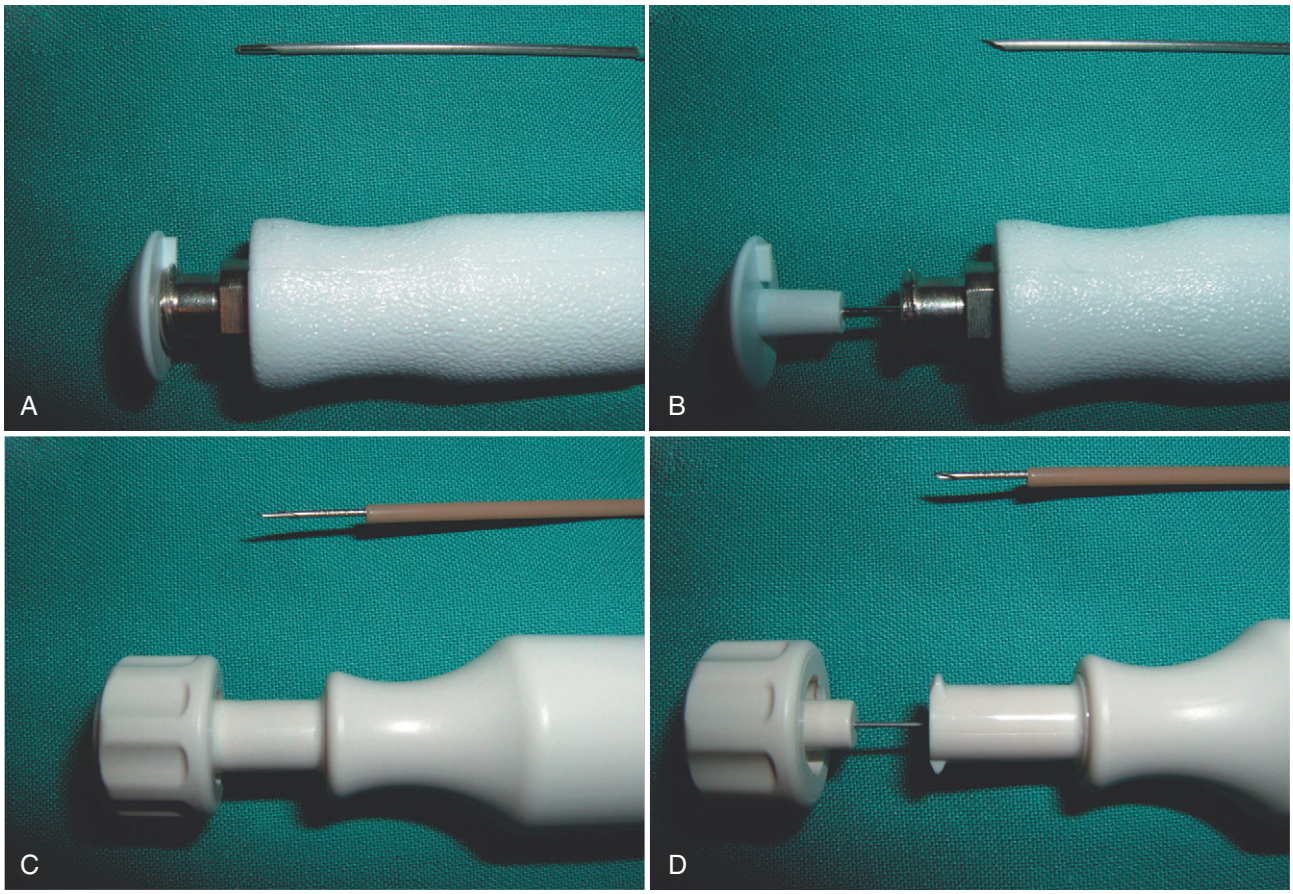


FIGURE 20.6 **Stylets. A,** Stylet blunt and longer than needle. **B,** Blunt stylet withdrawn to expose needle tip. **C,** Stylet pointed and longer than needle. **D,** Pointed stylet withdrawn to expose needle.

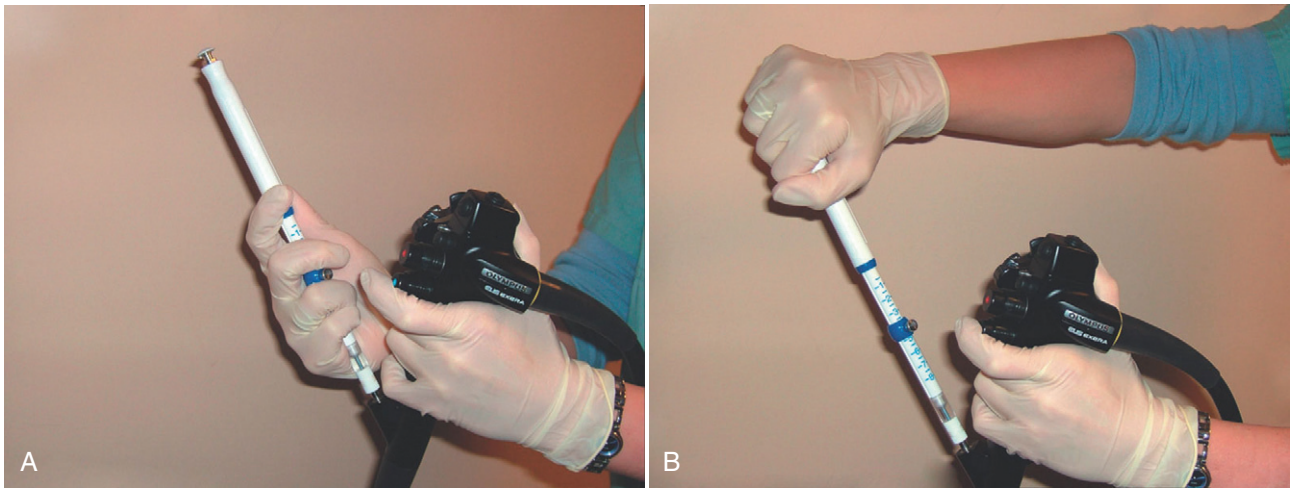


FIGURE 20.7 **How to hold the needle. A,** Correct method. **B,** Incorrect method.

Once the needle is in the lesion and the tip is clearly seen, the needle is moved back and forth several times within the lesion, with adequate thrusting force to shear off cells. In some cases, movement of the needle separates the ultrasound transducer from the gut wall and reduces needle visibility because of air artifact. To correct this problem, slight inward pressure should be applied to the shaft of the echoendoscope to push the probe against the gut wall. It may also be helpful to have an assistant prevent the echoendoscope from coming out by bracing the shaft as it exits the patient's mouth. (To do this, it is probably best for the assistant to stand on the opposite side of the bed from the echoendoscopist.) Constant gut lumen suctioning with the echoendoscope during FNA can also decrease the risk of air seepage between the probe and the gut wall.

If elevator deflection was used to adjust the needle angle, it may be helpful to return the elevator to the relaxed position once the needle is well inside the lesion. This technique allows the needle to move more freely.

Sampling Different Areas of the Same Lesion: "Fanning" versus "Multiple Pass" Techniques

To sample different areas of the same lesion during the same pass, a "fanning" technique may be possible if the lesion is sufficiently soft. Fanning is obtained by manipulation of the elevator or up/down tip deflection to guide the needle into different regions of the target lesion or to orient the needle into the long axis of an oval or oblong lesion without withdrawing the needle from the lesion. However, if the lesion is too hard, adequate fanning may be impossible. In this case, the "multiple pass" technique may be used. Instead of fanning, the examiner simply samples one area of the lesion, withdraws the needle into the gut lumen, and then traverses the gut wall again into a completely different area of the lesion. This can be repeated as needed to sample the entire lesion during the same pass. This technique can be used successfully without reintroducing the stylet into the needle each time the needle is withdrawn into the gut lumen.[6]

Consider Use of Suction

Evidence in the literature concerning the use of suction to obtain adequate material is conflicting.[8–11] Whereas some authors recommend the use of suction,[8,11] others state that it may actually hinder adequate cytologic analysis by causing aspirates to become diluted with blood.[9] It may be reasonable to perform FNA initially without suction. However, if in-room cytologic analysis of aspirates shows inadequate cellularity, it may be helpful to apply 5 to 10 mL of suction for a few seconds immediately before withdrawing the needle from the lesion or to use continuous suction.

Withdraw the Needle and Process the Aspirate

Once a pass has been completed, the needle is withdrawn completely into the sheath. If a locking device is present, the examiner slides it to the highest position and locks it, to prevent the needle from coming out of the sheath accidentally during removal of the needle assembly from the operating channel.

To avoid clotting in the needle, the aspirate should be expressed from the needle with a 10-mL air-filled syringe as quickly as possible. If the needle is blocked, the aspirate can be forced out by inserting the stylet. Once the clot has been expressed onto a slide or in to a container, the syringe should be used to express any remaining material from the needle. The slide with the cytology aspirate is then "smeared" against a second clean slide to distribute the material over the two slides as thinly as possible. Some examiners prepare only two slides per pass, whereas others express the material from each pass onto several slides before smearing.

Prepare the Needle for Subsequent Passes

The same needle can be used for several passes and need not be changed unless it malfunctions or the needle tip becomes too dull. If previous aspirates were bloody, it may be helpful to rinse the lumen with normal saline before the next pass. If the stylet is considered useful, it can then be reinserted into the needle.

If the needle is bent, it must be straightened; otherwise, it will deflect out of the ultrasound beam on subsequent passes. To straighten the needle, the endosonographer pushes it completely out of the sheath and then uses his or her fingers to straighten it manually (Fig. 20.8). An alcohol swab can then be used to clean the outer surface of the needle.

If a cytologist is available, passes should be performed until adequate material or a diagnosis is obtained. If not, the available data suggest that approximately three passes for lymph nodes and five passes for pancreatic masses should be sufficient to obtain a diagnosis (if cancer is indeed present).[9,12,13] There is no absolute limit to the number of passes that can be performed with the same needle. However, the needle should be changed if it malfunctions or if reinsertion of the stylet becomes too difficult.

Fine-Needle Aspiration Considerations by Site

The site in the gut from which EUS FNA is performed may make the technique easier or more difficult. The following sections describe common pitfalls and solutions based on EUS FNA site.

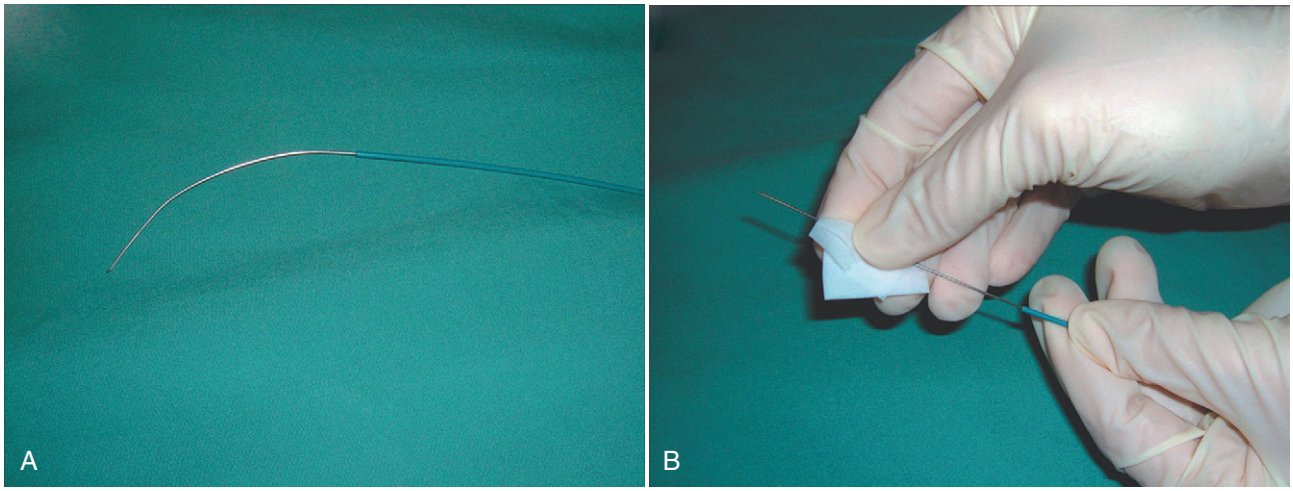


FIGURE 20.8 Straightening the needle. A, Bent needle. **B,** Straightening the needle.

Esophagus

This region is commonly the easiest area from which to perform EUS FNA. Most lesions accessed through this site are mediastinal lymph nodes or masses. The echoendoscope is virtually always in a straight position, and the tubular anatomy of the esophagus naturally prevents the scope from bending.

Stomach

The stomach probably has the thickest wall of all the sites from which EUS FNA is commonly performed. It is also very compliant, meaning that it tends to recoil during needle advancement. This characteristic can make traversing the gastric wall difficult and targeting perigastric lesions problematic, particularly if lesions are small or mobile (e.g., gastrohepatic ligament lymph nodes). If this problem arises, it may be helpful to divide the EUS FNA maneuver into two stages. First, the focus is on traversing the gastric wall. To facilitate wall puncture, the stomach is collapsed by sucking out the air. The wall will be more stable if the echoendoscope is withdrawn into position (from the antrum) rather than if it is pushed into position from the region of the gastroesophageal junction. A strong tip-up maneuver will also help hold the echoendoscope close to the gastric wall. Successful gastric puncture may require an unusually quick, strong, yet controlled jab. If present, the safety stopper on the needle may be used to prevent inadvertent advancement of the needle too far. Once the needle has successfully been passed through the gastric wall into the perigastric space, the focus is on the second stage, which is puncture of the target lesion.

Duodenal Bulb

When the echoendoscope is positioned in the duodenal bulb, it naturally assumes a "long-scope" position. Although this position may offer a mechanical advantage for more forceful puncture of an indurated lesion, the bend in the scope may render needle insertion into the scope difficult (Video 20.1). To avoid this situation, the needle is inserted into the echoendoscope while the scope is still in the stomach antrum. Once the needle is loaded into the scope, the pylorus is intubated, and the examiner repositions the scope in the bulb.

Accessing hilar lesions from the bulb usually requires a large amount of counterclockwise torquing. When excessive torquing is applied, it creates a bend in the needle. As the needle is deployed out of the sheath, it may deflect out of the ultrasound plane and may not be visible. Removing the needle from the scope and correcting any bend should be attempted at this point. If the problem recurs, the needle is deployed a few millimeters out of the sheath into the gut lumen with the examiner facing the lesion. Gently rotating *left* usually makes the needle tip appear. After realizing how much left rotation was needed to identify the needle, the examiner withdraws the needle back into its sheath and repositions himself or herself at the level of the lesion. The examiner rotates away from the lesion by torquing *clockwise*. The needle is deployed for a few millimeters and is counterrotated *counterclockwise*. If a sufficient amount of extra rotation is applied, the needle should be in front of the lesion.

Ideally, the needle should be visualized at *all times* during FNA. Moreover, it may be easier to access hilar lesions from the stomach, because the echoendoscope is in a straight configuration and little torque is needed.

Duodenal Sweep (D2)

Similar difficulties can be encountered when performing FNA from the duodenal sweep. Needle scope insertion can be problematic. To avoid this issue, the scope is withdrawn completely into a "short scope" position while it remains in the sweep. This maneuver should remove any bend in the scope and make initial needle insertion easy. One may still encounter some resistance a few centimeters before being able to Luer-lock the needle. At this point, the examiner removes any locks applied to the dials of the echoendoscope and generates a large amount of tip deflection downward using the up/down dial. This technique should remove any resistance to scope needle insertion. Once the needle is properly Luer-locked to the scope shaft, the scope can be repositioned as wanted into the duodenal sweep. This technique can permit needle insertion of any caliber, including the 19-G needle in most situations.

Needle bending can also occur in this location, based on the amount of torquing needed to visualize the lesion. The same technique described for duodenal bulb lesions can be applied.

EUS-GUIDED BIOPSY

Certain lesions may necessitate more information than cytologic examination can provide. Such may be the case for lymphomas, well-differentiated neoplasias, sarcoidosis, subepithelial lesions such as gastrointestinal stromal tumors (GISTs), and autoimmune pancreatitis. When tissue architecture is required for an appropriate diagnosis, histologic examination is required.

The Tru-Cut biopsy (TCB) needle (Quick-Core; Wilson-Cook Medical, Inc, Winston-Salem, NC) is a device containing a spring-loaded mechanism that can be used to procure a core biopsy specimen by EUS.[14] Its design is similar to that of a percutaneous liver biopsy needle, with a disposable 19-G needle and an 18-mm specimen tray (Fig. 20.9). Several studies have shown the safety and utility of the TCB needle for EUS-guided biopsies.[15–18]

To use the TCB needle properly and to maximize adequate histologic sampling, several steps must be taken before biopsy. Before the needle is inserted in the scope, the spring-loaded mechanism must be retracted. This maneuver enables the cutting sheath to withdraw itself from the specimen tray. The needle tip then needs to be advanced just above the level of the outer catheter sheath and secured with the stopping device. The TCB needle can then be inserted into the scope when the examiner is about to perform the biopsy. Finally, the apparatus must be correctly aligned with the base of the operating channel by using an adjustment wheel. This permits the specimen tray to align itself correctly with the transducer[14] (Fig. 20.10).

Once the lesion has been punctured with the TCB needle, the spring handle located at the handle portion of the apparatus should be gently retracted until resistance is felt. This maneuver enables the specimen tray to advance further into the lesion (for approximately 2 cm). Complete retraction of the spring handle then causes the spring-loaded mechanism to "fire." As a result,

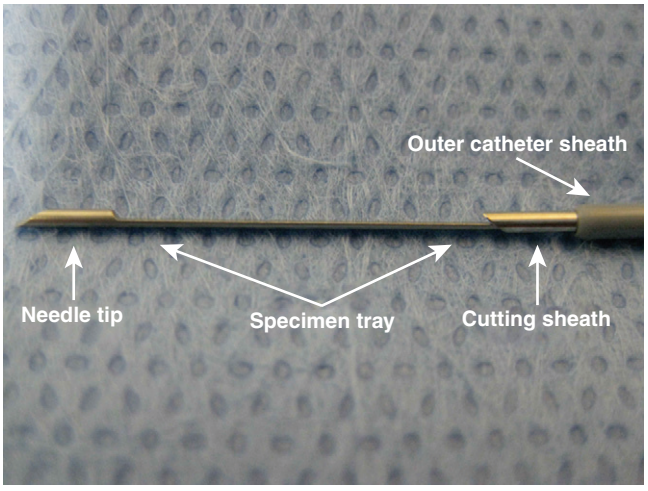


FIGURE 20.9 Tru-Cut biopsy needle.

the cutting sheath rapidly covers the specimen tray and thereby secures a core sample.

Because of its rigidity and more cumbersome use, the TCB needle has some limitations. To produce adequate samples, one should minimize any torquing and bending of the scope. TCB use is primarily indicated for lesions located near the esophagus, gastric body, and rectum. Because scope bending creates sluggish advancement of the needle sheath when fired (thereby causing inadequate sampling), TCB sampling yields inadequate results when the procedure is performed from the stomach fundus, antrum, and duodenum. Because the TCB needle needs to be deployed 2 cm further into the lesion to fire the mechanism, smaller lesions or lesions adjacent to important structures or ducts are more difficult to sample with this technique.

Overall, use of TCB for selected indications can produce histologic core specimens that can provide more information than cytology specimens. Endosonographer experience with the device and relative positioning of the needle both play important roles in acquiring adequate tissue. It is also possible to harvest core specimens with conventional FNA needles (particularly the 19-G needle).[19,20] Given that these needles are considerably cheaper than the TCB needle, they maybe an interesting alternative.

SPECIAL ISSUES

Biopsy of Multiple Lesions

When an individual patient has several potential biopsy sites or lesions (e.g., pancreatic mass, celiac node, liver lesion, mediastinal node), biopsies should be performed starting with the lesion that, if positive, will confirm the most advanced stage. If the first lesion tests negative, the lesion offering the next highest stage should be sampled. If a metastatic lesion is confirmed, the primary lesion need not undergo biopsy unless a compelling reason exists to do so. If the foregoing sequence of biopsy sites is employed (i.e., from distant lesions toward the primary lesion), then several lesions can be sampled using a single EUS FNA needle. If not, a new needle should be used for each lesion, to avoid the risk of creating false-positive results or seeding distant sites.

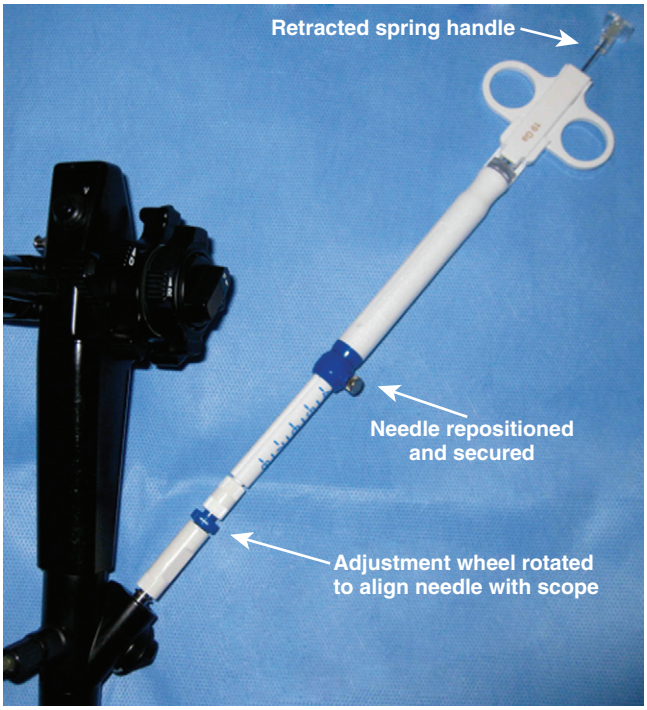


FIGURE 20.10 **Tru-Cut biopsy needle inserted into the scope before biopsy.**

Cystic Lesions

Cystic lesions may be punctured for cyst fluid analysis, biopsy of the cyst wall, or treatment. Primary concerns relate to the risks of infection and bleeding. Bleeding is alarming, but rarely serious, because it is usually contained by the cyst cavity. Infections, however, can lead to serious morbidity and mortality. Therefore, perhaps more than with other lesions, cysts should not be punctured unless it is clear that the information obtained will likely be useful to someone. Prophylactic antibiotics are indicated before FNA of a cystic lesion.[21]

Unless clear evidence of a mass component exists, sampling of the wall is rarely productive and only increases the risk of bleeding. Similarly, results of cyst fluid cytologic examination are almost always negative. Therefore, for cysts *without* a significant mass component, the primary goal should be to aspirate sufficient fluid to perform tumor marker analysis. Conversely, if the cystic lesion has a significant mass component, it is reasonable to perform EUS FNA of the mass alone and avoid the risks of cyst puncture. Biochemistry laboratory personnel should be consulted to determine the minimum quantity of cyst fluid that will be required to perform the desired analyses.

For larger-diameter lesions (>1 to 2 cm), a 19-G needle is preferred to smaller-gauge needle, to allow for more rapid and complete cyst fluid aspiration, especially if the fluid is viscous. One should always use a *new* needle to puncture a cyst and, if possible, perform only one pass. If more than one pass is required, a change to a new needle will be required.

Many experts believe that the risk of infection is lower if the cyst is drained completely, so this is probably a reasonable goal. However, in the case of a multiloculated cyst, it may be safer to focus on draining only a single, superficial loculation, one that appears to contain sufficient fluid for marker analysis.

Once the cyst has been punctured, the examiner should try to place the tip in the center of the cavity before aspiration. During aspiration and as the cyst collapses, the needle should be repositioned as needed to stay away from the wall or any debris that may clog the needle lumen. If the needle clogs before the cyst has collapsed completely, one may halt suction and try to reposition the needle gently, *without removing it from the cyst*. When the cyst is almost completely collapsed, drainage frequently stops, and it often becomes difficult to locate the needle tip. Attempts to reposition the needle to obtain "every last drop" should be avoided, because this may lead to bleeding. Once adequate fluid has been obtained for analysis, the remaining fluid can be drained by repeatedly filling a syringe or by connecting the aspiration port of the needle to wall suction. After cyst drainage, the cyst should be observed for a short time to look for early recurrence or bleeding.

Mobile Lesions

Lesions that are not fixed, such as retroperitoneal lymph nodes, can be difficult to puncture because they tend to bounce off the needle tip. This problem may be compounded if the lesion is not directly adjacent to the gut wall, if it is small, or if there is excessive respiratory movement. To puncture these lesions effectively, it may be helpful first to focus on traversing the gut wall with the needle. Once the needle tip is in the extraluminal space, one can then focus on puncturing the lesion.

To puncture the lesion, the needle tip is advanced so that it abuts the lesion wall. Coordination with respiratory movement may be required. To enter the lesion, a rapid single thrust is used to stab the lesion effectively. It may be necessary actually to pass the needle completely through the lesion. If this occurs, the lesion will be immobilized, and the needle tip can then be withdrawn slowly until it is within the confines of the lesion.

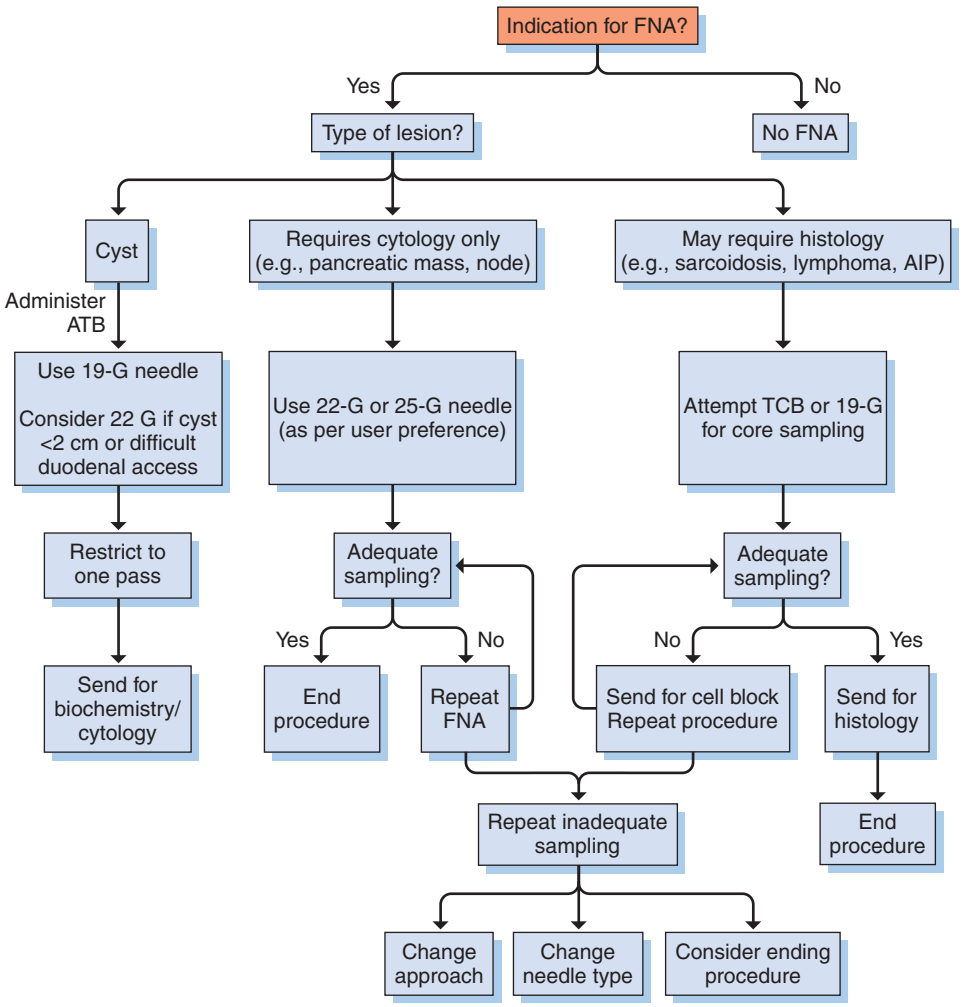


FIGURE 20.11 Algorithm for EUS FNA. AIP, autoimmune pancreatitis; ATB, antibiotic prophylaxis; TCB, Tru-Cut biopsy.

Indurated Lesions

Occasionally, it may be difficult to penetrate a lesion because it is indurated. If a lesion is difficult to penetrate, one must first verify that the needle is functioning correctly. The needle tip may have become dull, for example, from multiple previous passes, or it may not be exiting the sheath effectively. The stylet tip may also be too dull or, if it is blunt, may not have been withdrawn sufficiently to expose the needle tip.

If the needle is functioning properly, the lesion can be punctured by using more forceful stabbing maneuvers. However, this should be a last resort because it is difficult to stab forcefully *and* simultaneously control the depth of penetration. Instead, firm upward tip deflection should be applied, the needle tip should be placed against the leading edge of the lesion, and firm, progressively increasing pressure should be applied to the needle. If this approach fails, it may be helpful to apply force by actually advancing the echoendoscope (assuming that the echoendoscope is in a position that ensures that pressure can be applied in the same axis as the needle).

Tumor Seeding

Tumor seeding has been described with EUS FNA.[22–25] In the presence of a potentially resectable malignant lesion, EUS FNA should be reconsidered if the biopsy tract will not be included in the surgical specimen (e.g., FNA through the gastric wall in the case of a pancreatic body lesion). Instead, if at all possible, an attempt should be made to perform biopsies through a part of the gut wall that will be removed should the patient go to surgery (e.g., lesions of the pancreatic genu should undergo biopsy through the duodenum if possible). To avoid seeding extraluminal sites, such as lymph nodes, EUS FNA should never be performed through an area of the gut wall that is overtly or possibly infiltrated by malignancy or dysplasia.

SUMMARY

EUS FNA and biopsy are powerful clinical tools. They can be technically challenging, but the procedures are often straightforward if the lesion can be located, is sufficiently large, and can be brought into the needle path with the echoendoscope in a fairly straight position. The primary goal of these procedures is to obtain sufficient material to obtain a cytologic diagnosis. When cytology is insufficient to provide a reliable answer, a core biopsy with larger needles or TCB should be contemplated. As a guide for endosonographers who perform EUS-guided FNA and biopsies, a basic algorithm was designed to facilitate decision making based on the type of lesion to sample (Fig. 20.11).

REFERENCES

1. Yusuf TE, Ho S, Pavey DA, et al. Retrospective analysis of the utility of endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) in pancreatic masses, using a 22-gauge or 25-gauge needle system: a multicenter experience. *Endoscopy*. 2009;41:445–448.

2. Nguyen TT, Lee CE, Whang CS, et al. A comparison of the diagnostic yield and specimen adequacy between 22 and 25 gauge needles for endoscopic ultrasound guided fine-needle aspiration (EUS-FNA) of solid pancreatic lesions (SPL): is bigger better? [abstract]. *Gastrointest Endosc*. 2008;67: AB100.
3. Lee JH, Stewart J, Ross WA, et al. Blinded prospective comparison of the performance of 22-gauge and 25-gauge needles in endoscopic ultrasound-guided fine needle aspiration of the pancreas and peri-pancreatic lesions. *Dig Dis Sci*. 2009;54:2274–2281.
4. Siddiqui UD, Rossi F, Rosenthal LS, et al. EUS-guided FNA of solid pancreatic masses: a prospective, randomized trial comparing 22-gauge and 25-gauge needles. *Gastrointest Endosc*. 2009;70:1093–1097.
5. Paquin SC, Gariepy G, Sahai AV. A prospective, randomized, controlled trial of EUS-FNA with and without a stylet: no stylet is better [abstract]. *Gastrointest Endosc*. 2007;65:AB198.
6. Wyse JM, Paquin SC, Joseph L, et al. EUS-FNA without the stylet: the yield is comparable to that with the stylet and sampling of multiple sites during the same pass may improve sample quality and yield [abstract]. *Gastrointest Endosc*. 2009;69:AB330–AB331.
7. Devicente NM, Hawes RH, Hoffman BJ, et al. The yield of endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) is not affected by leaving out the stylet [abstract]. *Gastrointest Endosc*. 2009;59:AB335.
8. Bhutani MS, Suryaprasad S, Moezzi J, et al. Improved technique for performing endoscopic ultrasound guided fine needle aspiration of lymph nodes. *Endoscopy*. 1999;31:550–553.
9. Wallace MB, Kennedy T, Durkalski V, et al. Randomized controlled trial of EUS-guided fine needle aspiration techniques for the detection of malignant lymphadenopathy. *Gastrointest Endosc*. 2001;54:441–447.
10. Storch IM, Sussman DA, Jorda M, et al. Evaluation of fine needle aspiration vs. fine needle capillary sampling on specimen quality and diagnostic accuracy in endoscopic ultrasound-guided biopsy. *Acta Cytol*. 2007;51: 837–842.
11. Puri R, Vilmann P, Săftoiu A, et al. Randomized controlled trial of endoscopic ultrasound-guided fine-needle sampling with or without suction for better cytological diagnosis. *Scand J Gastroenterol*. 2009;44:499–504.
12. LeBlanc JK, Ciaccia D, Al-Assi MT, et al. Optimal number of EUS-guided fine needle passes needed to obtain a correct diagnosis. *Gastrointest Endosc*. 2004;59:475–481.
13. Savides TJ. Tricks for improving EUS-FNA accuracy and maximizing cellular yield. *Gastrointest Endosc*. 2009;69(suppl):S130–S133.
14. Levy MJ, Wiersema MJ. EUS-guided Trucut biopsy. *Gastrointest Endosc*. 2005;62:417–426.
15. Levy MJ, Jondal ML, Clain J, et al. Preliminary experience with an EUS-guided trucut biopsy needle compared with EUS-guided FNA. *Gastrointest Endosc*. 2003;57:101–106.
16. Varadarajulu S, Fraig M, Schmulewitz N, et al. Comparison of EUS-guided 19-gauge Trucut needle biopsy with EUS-guided fine-needle aspiration. *Endoscopy*. 2004;36:397–401.
17. Kien-Fong Vu C, Chang F, Doig L, Meenan J. A prospective control study of the safety and cellular yield of EUS-guided FNA or Trucut biopsy in patients taking aspirin, nonsteroidal anti-inflammatory drugs, or prophylactic low molecular weight heparin. *Gastrointest Endosc*. 2006;63: 808–813.
18. Thomas T, Kaye PV, Ragunath K, et al. Efficacy, safety, and predictive factors for a positive yield of EUS-guided Trucut biopsy: a large tertiary referral center experience. *Am J Gastroenterol*. 2009;104:584–591.
19. Möller K, Papanikolaou IS, Toermer T, et al. EUS-guided FNA of solid pancreatic masses: high yield of 2 passes with combined histologic-cytologic analysis. *Gastrointest Endosc*. 2009;70:60–69.
20. Jenssen C, Dietrich CF. Endoscopic ultrasound-guided fine-needle aspiration biopsy and Trucut biopsy in gastroenterology: an overview. *Best Pract Res Clin Gastroenterol*. 2009;23:743–759.
21. ASGE Guideline. Antibiotic prophylaxis for GI endoscopy. *Gastrointest Endosc*. 2008;67:791–798.
22. Hirooka Y, Goto H, Itoh A, et al. Case of intraductal papillary mucinous tumor in which endosonography-guided fine-needle aspiration biopsy caused dissemination [letter]. *J Gastroenterol Hepatol*. 2003;18:1323–1324.
23. Shah JN, Fraker D, Guerry D, Feldman M, Kochman ML. Melanoma seeding of an EUS-guided fine needle track. *Gastrointest Endosc*. 2004;59: 923–924.
24. Paquin SC, Gariépy G, Lepanto L, et al. A first report of tumor seeding because of EUS-guided FNA of a pancreatic adenocarcinoma. *Gastrointest Endosc*. 2005;61:610–611.
25. Doi S, Yasuda I, Iwashita T, et al. Needle tract implantation on the esophageal wall after EUS-guided FNA of metastatic mediastinal lymphadenopathy. *Gastrointest Endosc*. 2008;67:988–990.

CHAPTER 21 A CYTOLOGY PRIMER FOR ENDOSONOGRAPHERS

Darshana Jhala | Nirag Jhala

Key Points

Communication between the endosonographer and the cytopathologist is the key to a successful EUS-FNA service.

A cytopathology service should be involved early in the planning process for establishing EU-guided FNA service.

Using an algorithmic approach to diagnosing a patient will facilitate a correct diagnosis.

INTRODUCTION

Conceptual breakthroughs that are based on developed theories and discoveries in science bring accolades. Advances in the biotechnology field are signs of the dominance of creative imagination expressed through technology over abstract conceptual thinking. Despite such subtle differences in the concepts put forth, most clinicians involved in patient care agree that advances in the biomedical sciences have significantly broadened horizons and have redefined patient management.

The field of endoscopic ultrasonography (EUS)-guided fine-needle aspiration (FNA) should be viewed as no different. It could be said that the keystone events in the development of modern endosonography were the conceptualization and production of flexible endoscopes for human use in late 1950s.[1] In the 1980s, ultrasound probes were attached to endoscopes, and Doppler imaging capability was introduced. These improvements allowed better visualization of lesions and an understanding of vascular flow. These powerful scopes could characterize lesions not only of the luminal gastrointestinal tract, but also of the gastrointestinal tract wall, the periluminal lymph nodes (intrathoracic and intra-abdominal), the pancreas, the liver (mostly the left side), the left kidney, the spleen, and the adrenal glands. The list continues to grow.[2–5] EUS imaging alone, however, may not be sufficient to differentiate benign from malignant lesions. Further advances in technology made since early 1990s permit the performance of FNA under EUS guidance.[6,7] The ability to obtain cytologic material safely under real-time visualization makes this a powerful modality that offers an opportunity for prompt and accurate diagnosis and staging.

The outcome of the EUS FNA diagnosis depends on effective collaboration between the cytopathologist and endoscopist. The best results are achieved by those clinicians who really believe in cytology for their own patients and who work in close cooperation with cytologists. Thus, an understanding of relevant issues by both endosonographers and cytopathologists involved in obtaining and interpreting cytologic specimens optimizes the diagnostic yield. When such visions are synchronized, the diagnostic performance of EUS FNA far exceeds expectations. As predicted earlier,[2] this technique has now become a standard of care at many institutions and continues to replace other modalities for tissue diagnoses, staging, and adequate management of patients.

The objective of this chapter is to help both endosonographers and cytopathologists to learn the technical aspects of cytology procedures and to understand the basic principles of interpretive cytopathology diagnosis. Thus, the chapter reviews pertinent technical aspects that may influence cytology interpretation and affect outcome. It also discusses the algorithmic approach and salient cytologic features of benign and malignant lesions commonly sampled by EUS FNA.

TECHNICAL ASPECTS OF EUS THAT IMPROVE DIAGNOSTIC YIELD

Fundamental to the success of the EUS FNA is the procurement of adequate cells to provide the most effective diagnosis. This requires careful planning and understanding of factors that can affect cellularity of the target lesion.

Preliminary Planning

Ideally, an interested pathologist should be involved in the development of the EUS FNA service from the earliest stages of the planning process. This includes such crucial factors as the location of the endosonography suite, the type of instrument and needle used, the personnel involved, the scheduling of FNA, the type of preparation, the transport medium, the need for immediate cytologic evaluation (ICE) for determination of adequacy and diagnosis, the need for performing ancillary studies, and the role of the procedure in the patient management algorithm (Table 21.1). Further planning should also involve ordering of supplies, stocking and provision of the FNA cart or cabinet, or maintenance of a permanent small space for supplies in the endoscopy suite area.

The type of tissue specimen preparation (direct smear, liquid-based cytologic preparation, cell block, core biopsy, or a combination) depends on institutional practice, staffing issues, and the physical distance between the pathologist and the endoscopy suite, in addition to the relative sensitivity, specificity, and diagnostic accuracy of the various choices. Developing adequate skills for accurate interpretation of EUS samples not only depends on an experienced cytopathologist but may also require additional specific experience in interpreting these samples. Experience indicates that cytopathologists who are specifically interested in

gastrointestinal diseases tend to be more effective in providing accurate diagnosis.[8]

For the pathologist and laboratory staff, a comprehensive understanding of their direct role in the EUS procedure and the patient care algorithm ensures appropriate support. Diagnostic strategies depend on whether the procedure is a screening test, a diagnostic test in a patient who may not undergo further diagnostic workup, or a test to procure material for performance of ancillary studies to enhance patient management decisions.

A further preliminary planning step is consideration of database archives of cytology and diagnostic data. In combination with the EUS characteristics of lesions and other clinical information, these data can provide valuable feedback regarding diagnostic accuracy, individual practitioner competency, utility of ICE, and other quality assurance measures.

Professional staff should be properly trained and should understand the limitations of their expertise and of the technique. In the United States, both the technical and the interpretive services in the cytology laboratory are regulated at state and federal levels by the provisions of the Clinical Laboratory Improvement Amendments of 1988 (CLIA 1988), the Laboratory Accreditation Program of the College of American Pathologists (CAP), and others. Such mandatory and voluntary standards ensure high-quality laboratories.

TABLE 21.1

Factors to Consider in Preliminary Planning for Cytology Services

Factor	Details
Type of biopsy	Needle core or cytology (fine needle)
Size of needle	25, 22, 19 G or other
Fixation or processing for cores	Formalin, other
Type of preparation of cells for FNA	Direct smears, transport media (proprietary, culture media [RPMI-1640], formalin, other)
Type of smear	Air dried, alcohol fixed, or both
Personnel	GI suite staff, laboratory staff, training
Immediate cytologic assessment	Cytopathologist, cytotechnologist, advanced trainee, not performed
Database archives for cytology information	Diagnosis, number of passes, pathologist, type of smears prepared, cell block available, special studies

FNA, fine-needle aspiration; GI, gastrointestinal.

The following sections discuss technical factors that may improve diagnostic yield for EUS biopsy procedures, including needle type and size, suction or "capillary" aspiration, number of passes, and direction of passes. These factors are listed in Table 21.2.

Fine-Needle Aspirates

Fine-needle biopsies are used widely for EUS, computed tomography (CT), and other image-guided biopsy techniques, as well as for percutaneous biopsies of palpable masses. The material contained within a fine needle is usually smeared onto slides, and the resulting monolayer of cells is fixed or dried and stained. Material obtained from a fine needle is generally dispersed as single and small groups of cells, rather than intact tissue cores. Because the preparation is not sectioned, the cells represented on an aspirate smear are intact, and they round up or splay out depending on how they are treated in further processing steps. The monolayer smear created from a fine-needle biopsy allows resolution of microarchitecture and of details of the nucleus and cytoplasm that is superior to many other modalities.

Choice of Needles

Fine-needle biopsies are defined as being performed with a 22-G or smaller needle. Varying sizes of EUS instruments and needles are available on the market, and the choice of needle may also influence cytology findings. The cutting edge of the needle plays a role in obtaining samples; for example, a beveled edge requires less force in comparison with circular edges. Similarly, needle sizes also have an impact on the procurement of tissue samples. EUS needles range from 19 to 25 G.[9] Contrary to intuitive thinking that larger size is always better for FNA samples, sometimes the smaller-bore needle provides better sampling.

Several prospective studies compared samples obtained by the various EUS FNA needle types.[9–12] Some of these investigators suggested that needle aspirates from 25-G needles provide less hypocellular or acellular and bloody specimens, have better diagnostic performance, and perhaps induce less tissue injury in comparison with samples from a 22-G needle.[10,12] Another independent study, however, could not confirm a difference between 22-G and 25-G needles with regard to cellularity and the ability to render a diagnosis.[11]

FNA samples are also increasingly used for ancillary studies. In a study designed to determine the optimum needle size and number of passes to obtain material for RNA quantitation, the number of cells obtained from needles of varying sizes was

TABLE 21.2

Technical Aspects that May Positively Influence Diagnostic Yield

Technical Feature	Advantage	Disadvantage
Preliminary planning	Optimal laboratory support	None
Endoscopist skill	More likely to procure adequate specimen	None
Pathologist skill	Few if any false-positive or "atypical" diagnoses	None
Core biopsy	Histologic diagnosis	Possible more tissue injury
	Tissue for special stains	No capacity for on-site evaluation for adequacy
	Does not require on-site laboratory personnel for specimen processing or evaluation	
Aspiration biopsy	More cells	Few disadvantages
		Risk of inadequate sample for some lesions or sites
Smaller needle size	Less tissue injury	Relatively fewer cells
Suction	Retrieves more cells	Increases bleeding in tissue
		May compromise some cell features
More passes	More cells	Injury to tissue
Cytopathologist in room	Specimens adequate for diagnosis	Time and cost
Air-dried and alcohol-fixed smears	Complementary stains yield optimal nuclear and cytologic detail	Increased technical effort required
Cell block	Tissue available for special stains	Not a stand-alone preparation; best in combination with smears

counted. With 10 needle excursions into a tumor, 32,000 cells were obtained with a 25-G needle.[13] Although large numbers of cells are important for some tests, such as RNA extraction, it is generally accepted that diagnoses can be made on smears containing fewer than 100 cells. Investigators have suggested that a larger needle (e.g., 22 G) may be useful for lesions associated with less risk of complication or that require large numbers of cells for classification.

Given the tradeoff between more cells and more complications with larger fine needles, the choice of needle size should be based on the site and type of lesion to be aspirated. Indications for a smaller needle (e.g., 25 G) include patients with coagulopathy, organs in which leakage of fluid or air may occur, organs in which tissue trauma may increase complications (pancreas), and vascular organs or lesions. A smaller needle size decreases potential complications such as bleeding into the tissue and hemodilution or obscuring of the cytology sample by excessive blood. Smaller needles also cause less tissue damage and thus possibly less risk of pancreatitis.

Needle Core Biopsy versus Fine-Needle Aspiration

For numerous reasons—rational and not—some clinicians and pathologists believe that a tissue core yields unequivocally better diagnostic material. This belief perhaps stems from the concept that tissue cores techniques may obtain samples with fewer needle passes, they do not involve on-site specimen assessment,[14] they provide architecture, and ancillary studies can be performed on these samples.[2] It is also true that needle core biopsies (14 to 19 G) have been used for a long time to obtain tissue samples.[9,14,15] Sections made from these core biopsies are thin, 3- to 5-μm slices of the tissue that, when stained and viewed microscopically, show cells or portions of cells within their intact tissue stroma. Most histopathologists are very familiar with this method of tissue-based assessment.

Conversely, however, one should also be aware that analysis of tissue core may not always provide adequate diagnostic clues. Tru-Cut biopsy also induces greater tissue injury than a fine-needle biopsy and is considered more invasive. Such considerations should deter clinicians from using large-bore Tru-Cut needles routinely. It is also true that needle core biopsies can pose greater challenges for diagnosing well-differentiated carcinomas of the pancreas in comparison with FNA samples. In preliminary analyses, the success of FNA sampling using EUS guidance led to a sharp decline in performance of percutaneous needle core biopsies and CT-guided FNA. Such a change dramatically altered practice management decisions for pancreatic neoplasms.

A possible explanation for the failure of core needles to sample the lesion may be the attributes of the lesion itself, given that a larger needle may deflect from the surface of a firm or rubbery lesion. In addition, a Tru-Cut biopsy represents a single pass into the tissue and is not able to sample the lesion widely without further passes into the tissue. The use of larger needles increase the risk of bleeding and complications, although these risks remain very low. In addition, technical limitations of the currently available EUS-guided Tru-Cut biopsy equipment limit the anatomic regions that can be sampled for biopsy successfully.

Although studies of the pancreas show mixed results, the use of EUS-guided Tru-Cut biopsies showed significant promise in a review of lymphadenopathy. Tru-Cut biopsy is useful not only to establish the diagnosis of lymphoma, but also to characterize cellular architecture, which is more important in disorders such as follicular center cell lymphomas. Tru-Cut biopsy also may be more useful in cases in which flow cytometry results can provide false-negative results, such as large B-cell lymphomas. EUS-guided Tru-Cut biopsy may also be helpful in establishing the difficult diagnosis of Hodgkin lymphoma, in which morphology is varied and often challenging to identify.

The decision to obtain cores instead of, or in addition to, aspirates rests on certain factors, including the available equipment and personnel, the training and expertise of the pathologists and staff, and the endoscopist's preference. Each type of biopsy has advantages and disadvantages that must be considered for individual lesions or patients. Overall, FNA is considered a more sensitive diagnostic method, and it can be complemented by core biopsy or cell block.

To Apply or Not to Apply Suction

For many fine-needle biopsies, suction is applied to the needle to attempt to increase cell yield. This is the origin of the term *fine-needle aspirate*, which is often used more generally for any fine-needle biopsy. The purpose of suction is not to draw cells into the needle, but rather to "hole" the tissue against the cutting edge of the needle. Suction should be turned off before the needle is withdrawn.

In another technique, the cells are obtained without applying suction. The lumen is filled with cells by the direct cutting action of the needle through the tissue or capillary action. A study of 670 superficial and deep lesions sampled by biopsy with a fine needle without suction showed that diagnostic material was obtained in more than 90% of the cases.[16] Specific to EUS FNA, a study by Wallace et al[17] found no difference in suction versus no suction in terms of overall diagnostic yield for lymph nodes, but these investigators noted excess blood in the specimens to which suction was applied. Another study demonstrated that EUS-guided fine-needle sampling with suction increased the number of slides (17.8 ± 7.1 slides) needed to be prepared as compared with a significantly ($P < .0001$) reduced number of slides to be prepared for samples in which no suction was applied.[18]

In general, applying suction to the needle increases cellular yield but potentially increases artifact and blood, especially in vascular organs and lesions. Suction is commonly used, however, because the increased cellular yield of specimens often outweighs the disadvantages. Some clinicians attempt up to three passes without suction and add further passes with suction if the cellular yield is low.

When a large amount of blood is aspirated and the specimen clots, a less desirable, but useful, salvage of material is with gentle microdissection of the clot or fragment with a small scalpel blade or separate needle tip. The fragments are then lifted from the slide and are placed in formalin for subsequent cell block preparation. Forceful smearing of the clot to disperse the cells may cause significant crush artifact and may render the cells uninterruptible.

Number of Passes

A pass usually comprises 10 or more needle excursions or movements of the needle to and fro once the needle is within the lesion. The number of passes needed to obtain diagnostic material depends on multiple factors, including experience of endosonographer, location of the lesion, type of lesion, cellularity of the lesion, and risk of complications. Many investigators suggest that after a certain number of passes, the procedure reaches a state of diminishing returns for obtaining diagnostic cellularity.

In an analysis of more than 204 cases, diagnostic cellularity was obtained after five passes in more than 90% cases. It also emerged in this study that the rate of diminishing returns was reached earlier for lymph nodes and later for pancreas. For solid pancreatic lesions, adequate cellularity was achieved with fewer numbers of passes when the lesion was smaller ($\leq$25 mm) compared with larger lesions.[19] In comparison, observations suggested that after five passes, lymph nodes offered little benefit in obtaining diagnostic cells. It was also evident that for lymph nodes, a mean of only three passes was needed for obtaining diagnostic cellularity. LeBlanc et al[20] determined that at least

seven passes were needed in pancreatic lesions to obtain a sensitivity and specificity of 83% and 100%, respectively, although only five passes were needed in lymph node aspirates for a respective sensitivity and specificity of 77% and 100%. Wallace et al[17] deemed two to three passes sufficient for lymph nodes. In a study in which a cytopathologist was present at the time of the FNA, Erickson et al[21] demonstrated that only tumor site and differentiation influenced the number of passes.

A well-known advantage of real time image-guided biopsies, especially EUS, is the ability to direct the needle to a small point of interest. Selection of the exact site of biopsy may influence the cytologic yield. Biopsy of the necrotic center of a tumor may be nondiagnostic, whereas the edge may contain viable tumor cells. Conversely, biopsy of the edge of a pancreatic carcinoma may show only chronic pancreatitis, a common reactive change in the surrounding pancreatic tissue.

Depending on the anatomic site, directing the needle to specific portions of the lesion may be advantageous. Metastatic tumor in lymph nodes may be histologically more apparent in the subcapsular sinus, but in lymph node aspirates evaluated by EUS FNA, aspiration of the edge of the node did not increase the likelihood of a correct diagnosis. Nonetheless, because EUS allows visualization of the lesion, biopsy of a necrotic area can be avoided, and, as discussed later, on-site evaluation of the specimen can provide guidance to another location if the first site is necrotic.

A main advantage of the FNA technique is the wide sampling of a lesion by maneuvering the needle in different directions with each to-and-fro movement. Small redirections of the needle to make a fan shape result in sampling of new areas of the lesion each time. Repeated needle excursions in the same direction, along the same needle tract, result in biopsy of the blood or fluid that can fill the area with blood.

Immediate Cytologic Evaluation

One way to ensure adequate material from an FNA procedure is the use of immediate cytologic evaluation (ICE) (Video 21.1). The goal of ICE is to provide real-time feedback about the content and quality of the smears, to reduce the number of nondiagnostic or atypical biopsies, and to maximize the efficiency of the procedure. ICE also yields a highly reliable preliminary diagnosis.[22,23] Investigators have demonstrated that specimen adequacy is more than 90% when a cytopathologist is present in the endoscopy suite for ICE.[19,24,25] Such high specimen adequacy rates drop when cytopathologists are not present in the endoscopy suite for ICE.[24,26] In a direct comparison of EUS FNA procedures performed by the same endoscopist at two institutions, with and without a pathologist present during the procedure, ICE was more likely to result in a definitive diagnosis and less likely to involve an inadequate specimen.[24] Most false-negative EUS results are caused by inadequate sampling, which may necessitate a second procedure. It is also true that the most effective way to reduce sampling error is ICE.

A retrospective analysis was conducted of changes noted after the transition from CT-guided FNA to EUS-guided FNA sampling from the pancreas. Cytopathologists were present to provide ICE in an endoscopy suite, whereas this practice was not in place for samples obtained under CT guidance. The results demonstrated that EUS FNA provided more definitive diagnoses and fewer unsatisfactory or equivocal diagnoses. The investigators also were able to procure additional samples for ancillary studies. Such efforts at other institutions have also seen greater than 90% specimen adequacy rates and reductions in equivocal diagnosis. When ICE is performed, selected air-dried slides are stained in the endoscopy suite or an adjacent room and are reviewed immediately by the pathologist, so that feedback can be given to the endoscopist regarding the adequacy of the pass. If diagnostic material is present, additional passes are not made, and the procedure is stopped. If the smears are nondiagnostic, further passes are made. If there are no cells or only necrosis, the needle can be redirected for the next pass, and the procedure can be continued until adequate material for diagnosis is obtained.

In addition to minimizing the number of passes needed to obtain diagnostic material, another advantage of ICE is the triage of specimens for special studies. Such a practice may allow procurement of samples for ancillary studies such as lymphoma workup or for cell block when the initial smears show a tumor that may need classification by immune histochemistry, in situ hybridization, or other studies for better patient management. Thus, obtaining additional directed passes is encouraged for making an adequate cell block.

Although ICE clearly improves diagnostic yield, this practice is variable throughout the world. The use of ICE is influenced by the physical location of the laboratory and gastrointestinal suite, personnel, and cost issues. Reluctance of a pathologist to attend EUS FNA procedures may relate to lack of time and inadequate reimbursement for the time investment required.

Layfield and colleagues[27] studied a series of 142 non-EUS FNA procedures for which immediate, on-site evaluations were performed in a variety of clinical settings. The series included bronchoscopic, endoscopic, ultrasound-guided, and CT-guided biopsies. The investigators studied the attendance time of the pathologist and correlated it with the target organ, guidance technique, and the nature of the aspirator. For purposes of comparison, the costs of the cytopathologist were calculated using the 80th percentile pay level of an associate professor with full-time clinical duties. Medicare rate schedules were used to calculate compensation. In this analysis, with the exception of FNA performed in the clinic by the cytopathologist, the time costs exceeded compensation by $40 to $50 per procedure. From these data, it seems that intraprocedural consultations by cytopathologists for CT-guided, ultrasound-guided, bronchoscopic, or endoscopic procedures are compensated insufficiently by current Medicare compensation schedules for on-site evaluation.

A more recent analysis of cost effectiveness was performed at a large academic center.[28] This study assumed an average reported rate of nondiagnostic FNA without ICE of 20%. This rate included both image-guided and non–image-guided biopsies. The study also assumed that if patients were to undergo a repeat FNA for each nondiagnostic specimen, the estimated additional cost in the United States in direct institutional charges would be $2,022,626 over 5 years or $404,525 dollars annually without ICE. This potential cost savings could be realized by using ICE despite the additional fee, because of the higher rate of specimen adequacy. Unfortunately, however, lack of will on the part of consumers of these services has not helped to change the conventional stance on reimbursements in the United States. Instead, the reimbursement rates are increasingly becoming more cost prohibitive. All institutions and regions of any country are different, and they need to develop their own cost-effective strategies for the sake of providing optimal health care for their patients.

In an attempt to minimize the impact of the lack of ICE, additional alternatives were investigated by different investigators, with variable success. These alternatives included assessment of cellularity by visual inspection, performance of smears and evaluation by endosonography personnel, and the use of services of advanced cytotechnologists or advanced trainees in cytopathology. In this context, the use of dynamic telecytology for adequacy assessment was also investigated.

Regardless of whether ICE is used or not, an adequate sample is the foundation of the diagnosis. The needle must be placed into the lesion, and the technical aspects of the sampling must be optimized to obtain cells for evaluation, and the smears must be free of crush, drying, staining, or other artifact and obscuring blood, inflammation, or necrosis.

FACTORS ASSOCIATED WITH IMPROVED CYTOLOGIC PREPARATION

The material from EUS-guided biopsy can be prepared in many different ways, each of which has advantages and disadvantages. Some preparations are complementary, and two or three types are often prepared from the same biopsy specimen. The following sections define preparation of air-dried and alcohol-fixed smears, cell block, and the stains used for highlighting various cell features.

Cytology Smears and Cell Block

A smear slide is the standard method of preparing cells obtained from a fine-needle biopsy for viewing. As in a blood smear, the biopsy material is dispersed or "smeared" onto a glass slide, stained, and viewed as individual cells. For EUS FNA, after the needle is removed from the endoscope, the tip is placed near the frosted end of a labeled slide, and a single small drop is expressed onto the slide by slowly advancing the stylet into the needle. Dropping the material from a distance, squirting, or spraying it onto the slide can result in drying of the specimen and unwanted artifact. A second slide is then drawn over the drop of material, to pull the material into a monolayer. The technique requires practice. When the smear is too thick, the cells are obscured by one another or by background cells; if too much pressure is applied, the cells are artificially disrupted from their normal microarchitecture or are lysed. Imperfect smears may reduce the diagnostic yield.

In contrast to smears, a cell block is a preparation in which the cells are placed into a liquid medium or fixative, transported to the laboratory, spun into a pellet, formalin fixed, paraffin embedded, and selected for standard hematoxylin and eosin (H&E) staining. This routine formalin fixation and paraffin embedding is not optimal for preserving cytologic detail. A cell block is often made from leftover material rinsed from the needle. Its value as an adjunct to diagnosis can improve if an additional directed pass is obtained at the end of the procedure. This technique is highly recommended, especially for lesions that may require special stains.

Air-Dried or Alcohol-Fixed Smears

Generally, smears prepared from FNA material are either air dried or alcohol fixed. Air-dried smears are stained rapidly (using a modified Romanowsky stain [e.g., Diff-Quik]) and are typically used for ICE. Some institutions use H&E or rapid Papanicolaou (Pap) stains for ICE.

Diff-Quik–stained, air-dried smear preparations highlight intracytoplasmic material and extracellular substances. Alcohol fixation causes cells to shrink and round up, but it preserves nuclear features and is followed by Pap or H&E staining. The Pap stain highlights nuclear detail and chromatin quality, as well as demonstrating keratinization of squamous cells. The cytoplasm appears more transparent in Pap-stained slides. Slides can be fixed in preparation for a Pap stain by immersing or spraying them with alcohol. The Pap and Diff-Quik stains are complementary, and optimal cytologic detail is provided when both alcohol-fixed and air-dried smears are prepared from the FNA.

Transport Media and Liquid-Based Preparations

Samples are frequently collected in transport media for subsequent preparations. Although many media are available, Hank's balanced salt solution is preferred. This medium allows for preparation of cytospins and cell blocks, and should one require lymphoma consideration later, this medium can also be used for flow cytometric analysis. For consideration of any lymphoma workup, many institutions also collect their samples in RPMI 1640. This is also a useful medium to collect for cytogenetic analysis, as well as gene rearrangement studies.

Liquid-based cytology is increasingly being investigated. Currently, two methods have been approved by the Food and Drug Administration: ThinPrep (Cytyc Co, Marlborough, MA) and SurePath (TriPath Inc, Burlington, NC). There are slight differences between the two methods, but both offer advantages of monolayer cell dispersion, elimination of obscuring mucus and blood, and consistent cell preparation without artifacts of preparation, as noted with smear preparations.

These techniques, however, increase the cost of preparation and cannot be used for ICE. Because the preparations may disaggregate cells (loss of architecture) and alter some cytologic details, they offer challenges to interpretation. Some of the proprietary liquid fixatives contain methanol, a coagulative fixative (rather than a protein cross-linking fixative such as formalin), which may lead to suboptimal fixation for immunohistochemistry. Liquid-based cytology preparations do not fare as well as direct smear preparations. However, liquid-based cytology offers a viable alternative when ICE is not a consideration. Samples from pancreas prepared using liquid-based cytology preparations demonstrated smaller cell clusters, smaller cell size in comparison with air-dried smears, better nuclear characteristics, and diminished or absent mucin. Furthermore, these samples could not be used at a later time for flow cytometry analysis. Such considerations should be taken into account during selection of transport media and preparations. A detailed model of an optimized EUS FNA procedure is shown in Table 21.3.

Cytology Interpretation

Evaluation of the biopsy begins the moment material is expressed from the needle onto a slide or into a fixative. An adequate aspirate, or one that is likely to yield a diagnosis, is cellular, so that when placed on the slides and smeared out, a finely granular quality is apparent. In contrast, in a hypocellular or purely bloody smear, the thin sheen of material is smooth. When the material is placed in fixative, visible particulate matter or cloudiness is usually present. Mucus, pus, and necrosis may also be apparent grossly.

Adequacy

Once under the microscope, the smear is first assessed for adequacy. For an aspirate to be interpretable, it must be free of technical artifacts and must contain cells for evaluation. A global assessment of cellularity as a measure of adequacy, however, may be misleading in FNA, because the number of cells relates to the lesion. For example, aspiration of neuroendocrine tumors usually yields highly cellular smears, whereas aspiration of a gastrointestinal stromal tumor (GIST) may yield few cells, but both may be equally adequate for diagnosis.

For diagnostic nongynecologic cytology specimens, a sample is adequate when it explains the clinical situation or target lesion. The aspirator must be certain that the lesion has been sampled, and the pathologist must be able to interpret the slides. The concept of the "triple test" is also applicable to EUS FNA. The clinical, imaging, and FNA findings should agree and correlate on whether the lesion is benign or malignant. Some lesions have characteristic morphologic features, and therefore a cell number criterion for such tumors is not a requirement.

Diagnostic Evaluation of the Slide

Whether on site or in the laboratory, the cytotechnologist or pathologist begins the slide evaluation by assessing the cell types, cell arrangement, and cellular features on the smear. Central to a cytology diagnosis is the appearance of the nuclear and cytoplasmic features of individual cells; these are quite distinct, depending on the lesion sampled. No single feature is diagnostic of malignancy, but rather the composite picture of cell type, microarchitecture, and nuclear and cytoplasmic characteristics determines the diagnosis. It is useful to know the common pathologic diagnoses as well as the characteristic of the normal tissue in the region sampled (Table 21.4 and Fig. 21.1).

TABLE 21.3

Optimized EUS Fine-Needle Aspiration Model Technique

Stage	Description
Preparation	When the procedure is scheduled, arrangements are made for the cytology technician and pathologist to be at the site. Clinical findings are discussed with the pathologist at the start of the procedure. The locations of the lesions or other details must be known, based on previous imaging studies. Conscious sedation is provided to the patient with intravenous meperidine and midazolam.
Needle preparation	The stylet is removed completely from a 22-G EUS FNA needle, and the needle is flushed with heparin. Air is then flushed through the needle to expel the excess heparin. The stylet is replaced, and the needle is ready for use. The needle may also be straightened manually between passes if necessary.
Radial EUS	A radial echoendoscope is first used for an overview of appropriate anatomic landmarks. The location of lesions is noted.
Linear array EUS FNA	The radial echoendoscope is replaced with a linear array echoendoscope. The scope is advanced to the distance at which the lesion of interest was identified with radial endosonography. The lesion is visualized, and color Doppler is used if there is concern about intervening blood vessels. The EUS FNA needle is inserted and fastened to the biopsy channel of the echoendoscope, and then it is advanced just slightly beyond the scope into the gut lumen. At this point, the stylet is retracted approximately 1 cm. The needle is passed into the lesion. The stylet is replaced into the needle to expel any tissue from normal structures and then is removed completely, and a suction syringe is attached. Sampling is performed with and without suction. The needle is moved into various locations throughout the lesion ("fanning the lesion") to improve sampling. After approximately 20 back-and-forth movements, the suction is turned off, the needle is retracted back into the catheter, and the entire assembly is removed.
Expressing material on slide	A dedicated cytology technician holds the end of the catheter over a labeled glass slide. The needle is advanced approximately 1 cm from the catheter by the endoscopy technician, and a stylet is slowly advanced back into the needle. This produces a controlled passage of drops of material out from the tip. The cytology technician alternately places drops onto a slide and into transport medium. Finally, the needle is flushed with a few milliliters of saline and then air to expel any remaining material into the liquid medium.
Preparing and staining cytologic material	Slides are prepared depending on the amount of material. As rapidly as possible, the drops of aspirated material are spread downward onto the slides by using another clean glass slide. Half of the slides are air dried, and the remaining slides are immediately immersed in 95% ethyl alcohol for later Papanicolaou staining. The air-dried slides are stained with Diff-Quik stain for immediate cytologic evaluation by the pathologist (see below). When the procedure is finished, an additional dedicated pass may be placed in transport medium (e.g., Hank's balanced salt solution) and transported to the laboratory, and a cell block is prepared. The material in cell suspension is centrifuged into a pellet, to which thrombin is added. The pellet is resuspended, and the resulting clot is removed, wrapped in lens paper, placed in a tissue cassette, fixed in formalin, and routinely processed for paraffin embedding and H&E or immunostaining. If indicated, material for flow cytometric immunophenotyping or other studies is removed from the medium, and the cell block is prepared. The alcohol-fixed slides are stained with a standard Papanicolaou stain.
Immediate cytologic evaluation	A pathologist, advanced trainee, or experienced cytotechnologist examines air-dried Diff-Quik–stained slides prepared at the site and provides assessment of specimen adequacy. Based on this report, the endoscopist may continue with the same technique or may change needle position to procure more tissue. Immediate cytologic evaluation also helps triage the specimen or obtain additional passes for special studies.

FNA, fine-needle aspiration; H&E, hematoxylin and eosin.

TABLE 21.4

Some Common EUS Cytologic Diagnoses in Specific Sites

Site	Cytologic Diagnoses
Lung	Adenocarcinoma Squamous carcinoma Small cell carcinoma Granuloma or infection
Esophagus	Squamous carcinoma Adenocarcinoma Granular cell tumors Leiomyoma or other spindle cell tumor (GIST or neurofibroma)
Stomach	Carcinoma Carcinoid GIST MALT lymphoma
Pancreas	Ductal adenocarcinoma Chronic pancreatitis Autoimmune pancreatitis Pancreatic endocrine neoplasm Metastatic carcinoma Intraductal papillary mucinous neoplasm Mucinous cystic neoplasm Solid pseudopapillary tumor
Rectum and perirectal lymph nodes	Metastatic adenocarcinoma or squamous carcinoma GIST
Liver	Metastatic carcinoma, melanoma, sarcoma Lymphoma Primary hepatocellular tumors

GIST, gastrointestinal stromal tumor; MALT, mucosa-associated lymphoid tissue.

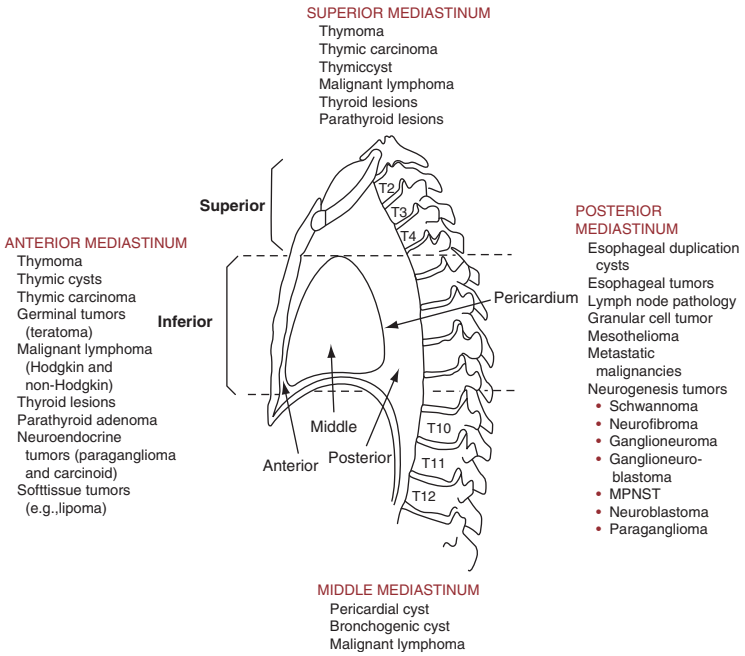


FIGURE 21.1 Common lesions of the mediastinum. MPNST, malignant peripheral nerve sheath tumor.

As in histologic sections, order and aesthetics reign in cytologic preparations of benign tissue. The appearance and composition of a benign aspirate reflect the various cell populations in normal tissue. Epithelial cells are round to oval, have moderate to abundant cytoplasm, and are cohesive. Benign epithelial cells show evidence of differentiation. Squamous cells acquire keratin as they mature, whereas their nuclei become progressively smaller and darker (pyknotic). A benign superficial squamous cell exfoliated from the esophagus has a large, polyhedral shape, with a small, uniformly dark, nucleus described as an "ink dot" (Fig. 21.2). The cytoplasm is orange-pink to blue, depending on the degree of keratin accumulation. Benign, mature squamous cells appear single, unless they are from the deeper layers of the epithelium, in which case they may remain together as large sheets of cells with less keratinization of the cytoplasm. Benign glandular epithelium from the stomach (Fig. 21.3), intestine, and pancreas also demonstrates an orderly arrangement of differentiated cells with organ-specific variations. In smears, duodenal epithelium consists of folded or draped sheets of columnar cells, with interspersed goblet cells appearing as clear spaces among the absorptive cells (Fig. 21.4). Glandular cells are polarized, with the nucleus present at one end of each cell in the sheet of epithelium. The cytoplasm may be filled with a single mucin droplet (the goblet cell); smaller, more finely divided vacuoles; or other secretory products such as zymogen granules. Classically, benign columnar epithelium has a honeycomb pattern. Changing the microscope plane to focus reveals the hexagonal borders of the apical cytoplasm and polarized, orderly nuclei at the base of the honeycomb sheet. In contrast, benign stromal or mesenchymal cells have elongated nuclei and usually abundant cytoplasm. Occasionally, small vascular structures are visible in smears of benign tissue.

The cells represented in an aspirate of normal tissue are proportionate to their mixture in the organ. For example, benign pancreatic tissue is composed mostly of acini (Fig. 21.5), with relatively few ductal structures (see Fig. 21.5) and islets usually represented on FNA smears. A benign reactive lymph node (Fig. 21.6) contains a polymorphic mixture of cell types, with large and small lymphocytes, macrophages, and sometimes identifiable germinal centers, whereas lymphoid malignancy is usually monomorphic. In contrast to the order inherent in benign tissue, malignant cells deviate in their organization and demonstrate predictable unpredictability in architecture.

Normal epithelial cells exhibit cohesion, whereas malignant epithelial cells are loosely aggregated or single cells. The degree of dyshesion is relative and is an important criterion in the overall assessment of malignancy. In contrast to epithelial cells, some tissue types are normally dyshesive. Unlike carcinomas, which reveal cohesive cell clusters and many single cells, FNA from noncarcinoid tumors and melanoma are usually noted as single cells. An overzealous smearing technique may artificially separate epithelial cells and may lead to overestimation of dyshesion.

Malignant cells also exhibit disorganization of their normal arrangement of polarity. The loss of polarity is a particular diagnostic feature in lesions arising in columnar epithelium. An important EUS FNA example is the diagnosis of atypia or malignancy in mucinous neoplasms. Once the low-power assessment of the general characteristic of the smear has been evaluated for cell types, overall organization, and cohesion, detailed analysis of the nucleus and cytoplasm allows characterization of a cell as benign or malignant. Specific nuclear features determine malignancy, whereas cytoplasmic features and microarchitecture demonstrate differentiation of the cell.

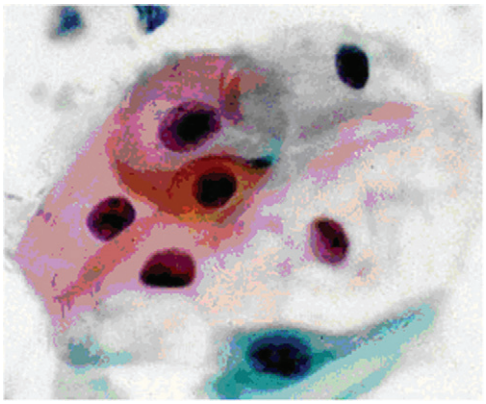


FIGURE 21.2 Sample from the esophageal squamous mucosa showing polygonal cells with abundant hard cytoplasm with hyperchromatic nuclei. Squamous cells also show maturation, as evidenced by keratinization.

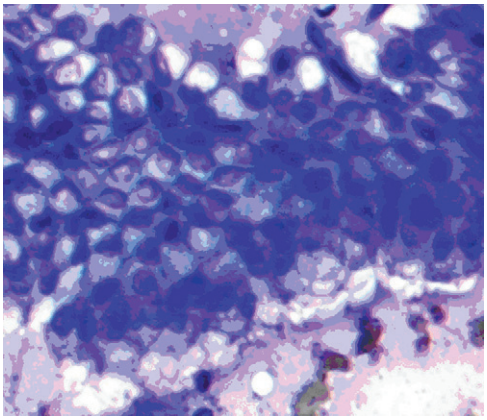


FIGURE 21.3 Smears from the gastric mucosa reveal foveolar cells with cohesive cell groups with minimal overlapping. The cells show a columnar shape with nuclei lined at the base. They also show a round, regular nuclear membrane and inconspicuous nucleoli, if any (Diff-Quik stain; magnification ×20).

EUS FINE-NEEDLE ASPIRATION OF SPECIFIC SITES

The usefulness of EUS FNA in various organ systems and the associated pitfalls in diagnostic interpretation are discussed in the following sections.

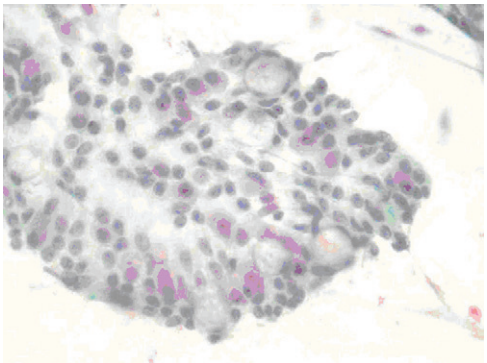


FIGURE 21.4 Smear reveals a cohesive two-dimensional group of epithelial cells with a honeycomb appearance. The group also reveals interspersed goblet cells *(arrow)* consistent with surface duodenal mucosal cells (Papanicolaou stain; magnification ×40)

Pancreas

EUS is, in itself, a highly effective modality for detecting, staging, and determining respectability of pancreatic carcinomas. FNA was documented to be as accurate as frozen section diagnosis and is less invasive, faster, and more cost effective for the diagnosis of both resectable as well as nonresectable pancreatic carcinomas. Investigators also showed that EUS FNA is better than percutaneous FNA for obtaining accurate preoperative diagnosis. The objectives of EUS FNA of lesions of the pancreas are to obtain the initial diagnosis of a clinically suspicious malignant neoplasm, to obviate the need for surgery for the purpose of obtaining tissue for diagnosis, and to obtain tissue confirmation of the diagnosis before surgical resection with curative intent or initiating adjuvant chemotherapy. As a result, this modality has now found its rightful place as a preferred technique for obtaining tissue diagnosis and confirmation by the members of the National Comprehensive Cancer Network.

Global Approach to Diagnosis

An algorithmic morphology–based approach to the diagnosis of pancreatic FNA may result in a better diagnostic work-up and determine the need for additional ancillary studies to confirm and support the diagnosis (Fig. 21.7). What treating clinicians want to know from a cytologist is whether a given lesion is benign or malignant. This determination and the associated differential diagnosis generally rest on the imaging characteristics of the lesion (solid versus cystic pancreatic lesion).

Table 21.5 demonstrates more common lesions that should be considered in the differential diagnosis of solid pancreatic lesions. When a solid pancreatic mass in an older patient is noted, the major differential diagnosis remains pancreatic adenocarcinoma versus chronic pancreatitis.

Pancreatic Adenocarcinoma and Chronic Pancreatitis

Distinguishing chronic pancreatitis from pancreatic carcinoma is not a diagnostic challenge when cellular features are characteristic. This is more challenging for cytopathologists when a well-differentiated pancreatic adenocarcinoma is aspirated. Diagnostic criteria for pancreatic adenocarcinoma have been well established,[29] and they include the following: increased cellularity; the predominance of a single cell type; three-dimensional groups (overlapping cells); a "drunken honeycomb" appearance (Fig. 21.8); the presence of many pleomorphic single cells (Fig. 21.9); tall cells with large nuclei (tombstones); and cells with an increased nuclear-to-cytoplasmic (N/C) ratio, irregular nuclear membrane, coarse and clumped chromatin, macronucleoli, and abnormal mitoses. The presence of abortive glands in a background of tumor-associated necrosis is another feature that may help suggest carcinoma over reactive ductal epithelium. Carcinomas may also show tumor diathesis, mucin production, occasional signet ring cells with mucin vacuoles, bizarre cells, and squamoid cells.[30] Cytologic features of pancreatic carcinoma vary by histologic subtype, including the presence of keratinization in adenosquamous carcinomas and many giant cells in giant cell tumors of the pancreas. In contrast, reactive ductal epithelial cells show many tight cohesive two-dimensional groups of ductal cells with minimal, if any, overlapping. Reactive cells show moderate cytoplasm, well-defined borders, nuclei with a round and regular nuclear membrane, and inconspicuous nucleoli. In some instances, however, nuclear enlargement may be more conspicuous, there may be more single cells, and occasional cytologic atypia may be noted. Chronic pancreatitis may also be characterized by dense fibrous connective tissue and few chronic inflammatory cells (Fig. 21.10).

Pitfalls. A polymorphous cell population as opposed to predominance of cells of one type is a major consideration when evaluating specimens for pancreatic adenocarcinoma. With EUS FNA, the pancreatic mass is approached from the gastrointestinal tract. The approach to the lesion in the pancreas using EUS varies with its topographic location. In addition, in EUS FNA, as with percutaneous FNA, the needle passes through a background of chronic pancreatitis before it reaches the target lesion. This may cause additional cells to be noted on the slide preparations and may give the false impression of a polymorphous cell population. The approaches taken by the endoscopist to lesions in different locations in the pancreas and the cells that may be observed by a cytopathologist are listed in Table 21.6.

Increased cellularity is one of the criteria used to distinguish well-differentiated adenocarcinoma from chronic pancreatitis. The cellularity of a sample is influenced by several factors, including operator technique and the anatomic location of the tumor. Trained operators usually obtain cellular samples from EUS FNA. Some of the possible reasons for the increased cellularity of the samples obtained with EUS FNA include the proximity to the lesion and the better visualization of the lesions. The use of

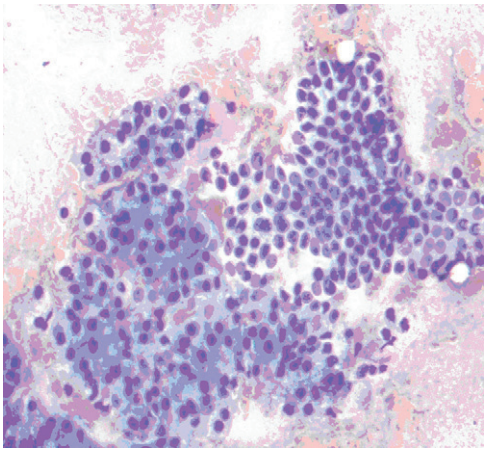


FIGURE 21.5 Smear from EUS fine-needle aspiration of pancreas reveals many acini and ductal cells. Acinar cells show moderate granular and two-toned amphophilic cytoplasm. The nuclei are centrally placed with a round, regular nuclear membrane. In comparison, the smear also reveals ductal epithelial cells. These cells show a cohesive two-dimensional honeycomb group of ductal epithelial cells. These cells reveal clear, well-demarcated cytoplasm (Diff-Quik stain; magnification ×20).

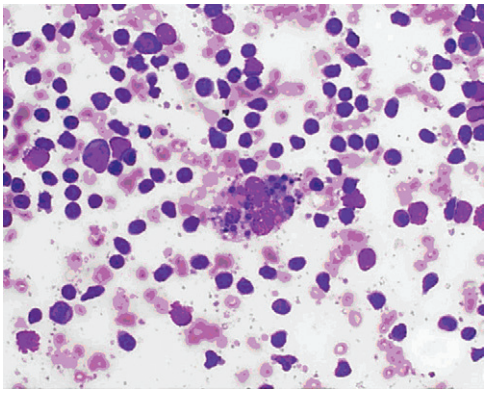


FIGURE 21.6 EUS fine-needle aspiration from a reactive mediastinal lymph node reveals many lymphocytes of varying sizes. Tingible body macrophages are also noted (Diff-Quik stain; magnification ×20).

cellularity as a criterion in the differentiation of chronic pancreatitis and well-differentiated adenocarcinoma should therefore be used with caution, especially when the samples have been obtained using EUS FNA.

Causes of False-Negative Diagnosis. False-negative diagnoses may result from technical difficulties, sampling error, or interpretive errors. For a cytopathologist, offering a diagnosis based on hypocellular samples is a common cause of false diagnosis. A sampling error may result from the technical difficulty associated with reaching the tumor, such as when a tumor is located in the uncinate process. It also is possible that the marked desmoplasia of pancreatic adenocarcinoma may result in an inadequate specimen or an inconclusive diagnosis (atypical or suspicious for malignancy), both of which require further investigations or repeat FNA.

Interpretative causes of false-negative diagnosis may include a tumor with mixed cellularity in which a component of chronic pancreatitis is also noted along with few tumor cells. It is also challenging to make a diagnosis of well-differentiated adenocarcinoma of the pancreas because of subtle morphologic changes. In such instances, the use of biomarkers may further aid in distinguishing reactive ductal epithelium from carcinoma cells. The list of such markers is ever increasing. Investigators have demonstrated that a lack of SMAD4 and clusterin in suspicious cells supports the diagnosis of carcinoma. In addition, mesothelin, p53, and MUC4 expression in suspicious cells further aids in supporting the diagnosis of carcinoma.[31]

Causes of False-Positive Diagnosis. Chronic pancreatitis and autoimmune pancreatitis are more common reasons for a false-positive diagnosis of malignancy. Some of the cytologic features that may mimic malignancy in chronic pancreatitis are occasional atypical cells, which include enlarged cells, enlarged nuclei with degenerative vacuoles, single cells, and occasional mitosis. Chronic pancreatitis may also be characterized by areas with necrosis, especially in patients with development of early pseudocysts.

Autoimmune pancreatitis is a relatively recently recognized entity in the field of cytopathology. Aspirations from these lesions often show marked stromal reaction with embedded small clusters of epithelial cells. These cells may show features of reactive atypia. However, autoimmune pancreatitis should be suspected if the patient has a history of autoimmune disease, a characteristic EUS image, and an associated increase in lymphoplasmacytic infiltrates. When in doubt, serum or tissue estimations of immunoglobulin G_4 (IgG_4) may further aid in suggesting this diagnosis. This value becomes more informative when elevated IgG_4 levels are interpreted in context of total IgG levels.

The cytologic features of primary pancreatic carcinomas are similar to the features of many other adenocarcinomas that can metastasize to the pancreas. Thus, it is crucial for endosonographers to provide adequate clinical information about any history of prior malignant diseases. It also may happen that a history of prior malignancy is obtained after EUS FNA sample is procured.

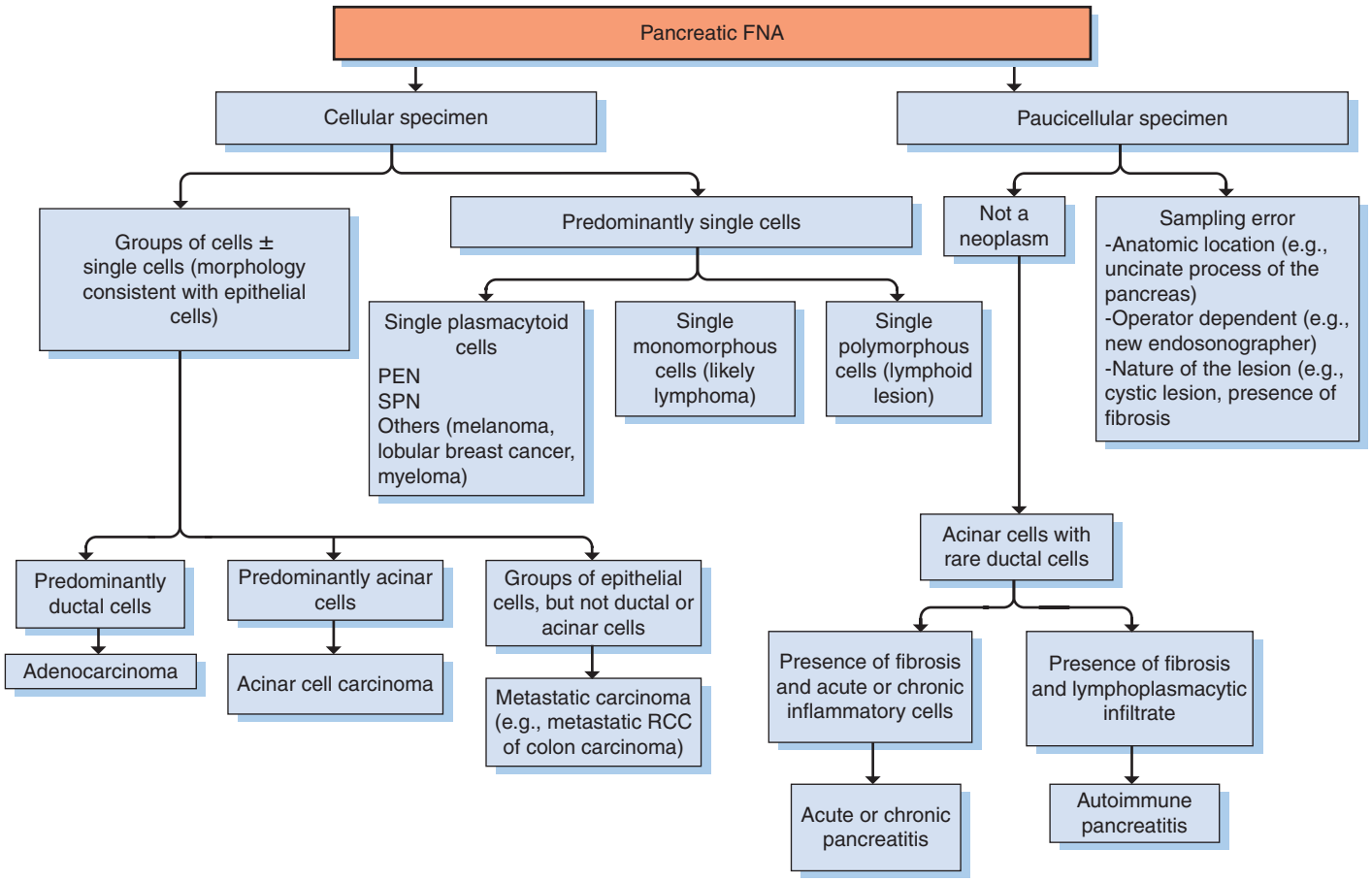


FIGURE 21.7 Morphology-based practical algorithm approach to pancreatic fine-needle aspiration (FNA). PEN, pancreatic endocrine neoplasm; RCC, renal cell carcinoma; SPN, solid pseudopapillary neoplasm.

In some cases, it becomes important to determine the primary site of origin. Several immunohistochemical stains can reliably suggest possible primary tumor sites. Therefore, some investigators suggested an additional dedicated pass, to make a cell block to aid in performing immunohistochemical stains if and when required.

Pancreatic Endocrine Neoplasm

Pancreatic endocrine neoplasms (PENs) more frequently manifest in the body or tail of the pancreas. They usually are well-demarcated solid lesions, although they may infrequently manifest as cystic lesions as well. Cytologic characteristics of these tumors include moderate to highly cellular smears.[32–34] These smears predominantly have single cells with occasional loose cellular aggregates, as well as rosette formation (Fig. 21.11A). Neoplastic cells are plasmacytoid without perinuclear huff, and the cytoplasm may show neurosecretory granules (see Fig. 21.11B). Nuclei show a round, regular nuclear membrane and usually do not reveal conspicuous nucleoli, although exceptions have been noted. Cells may also show marked anisonucleosis. Cytologic features usually cannot distinguish benign from malignant neoplasms. However, increased proliferative activity and necrosis have been associated with malignant lesions.

Pitfalls

1. A multi-institutional study noted that solid pseudopapillary neoplasms (SPNs) of the pancreas are not infrequently diagnosed as PENs on EUS FNA samples.[35] Both tumors share some morphologic features, including moderate cellularity, low N/C ratio, and plasmacytoid cells. Some of the features that suggest SPN over PEN include pseudopapillary groups, cytoplasmic hyaline globules, and a chromatic matrix material and nuclei with "coffee bean" appearance (Fig. 21.12). Investigators noted that SPNs frequently demonstrate large cytoplasmic vacuoles. These large cytoplasmic vacuoles serve as a valuable clue to distinguish these tumors from PENs.[36]
2. Cytologic features, however, are not always confirmatory. In such instances, a limited panel of immunohistochemical stains is needed to distinguish PEN from SPN. Chromogranin, synaptophysin, and CD56 stains highlight PEN.[37] All three stains may also be highlighted in SPN. Investigators showed that when FNA samples are extremely limited in quantity, a judicious use of immunohistochemistry stain may help to distinguish SPN from PEN. Accordingly,

TABLE 21.5

Differential Diagnosis of Common Solid Pancreatic Lesions

Benign	Malignant
Chronic pancreatitis	Pancreatic carcinoma
Autoimmune pancreatitis	Acinar cell carcinoma
Pancreatic endocrine neoplasm	Pancreatic endocrine neoplasm (well-differentiated endocrine carcinoma)
Acute pancreatitis	Metastatic malignancies
Infections	Non-Hodgkin's lymphoma

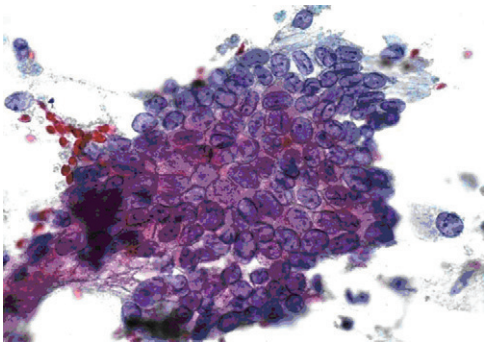


FIGURE 21.8 Smear from a well-differentiated adenocarcinoma of the pancreas reveals a tightly cohesive group of epithelial cells. Cells show mild overlapping with loss of cell polarity. Nuclei show coarse chromatin clumping, nuclear membrane irregularity, and conspicuous nucleus (Papanicolaou stain; magnification ×20).

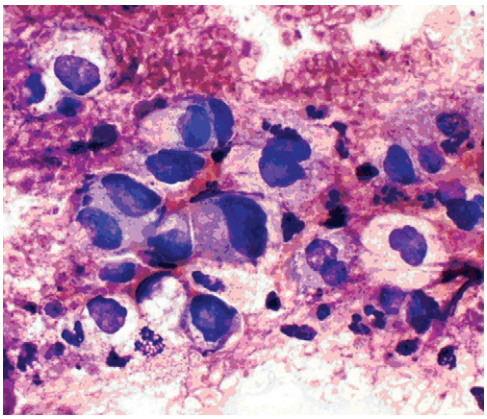


FIGURE 21.9 Pancreatic carcinoma. Smear from a poorly differentiated pancreatic carcinoma reveals many single cells with marked cytologic atypia including enlarged nuclei, marked nuclear membrane irregularity, and background necrosis (Papanicolaou stain; magnification ×40).

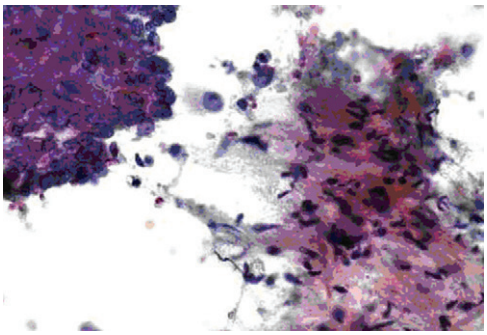


FIGURE 21.10 Smear from chronic pancreatitis. The smear reveals reactive ductal cells with tight cohesive groups, few inflammatory cells, and dense fibrous connective tissue (Papanicolaou stain; magnification ×40).

TABLE 21.6

Transluminal Approach to Pancreas and Gastrointestinal Mucosal Cells

EUS Approach	Lesion in the Pancreas	Contaminating Gastrointestinal Mucosal Cells
Transgastric	Body and tail, occasionally uncinate process	Foveolar cells, parietal cells, chief cells, smooth muscle cells
Transduodenal	Head and uncinate process	Villi, Bruner's glands, and smooth muscle

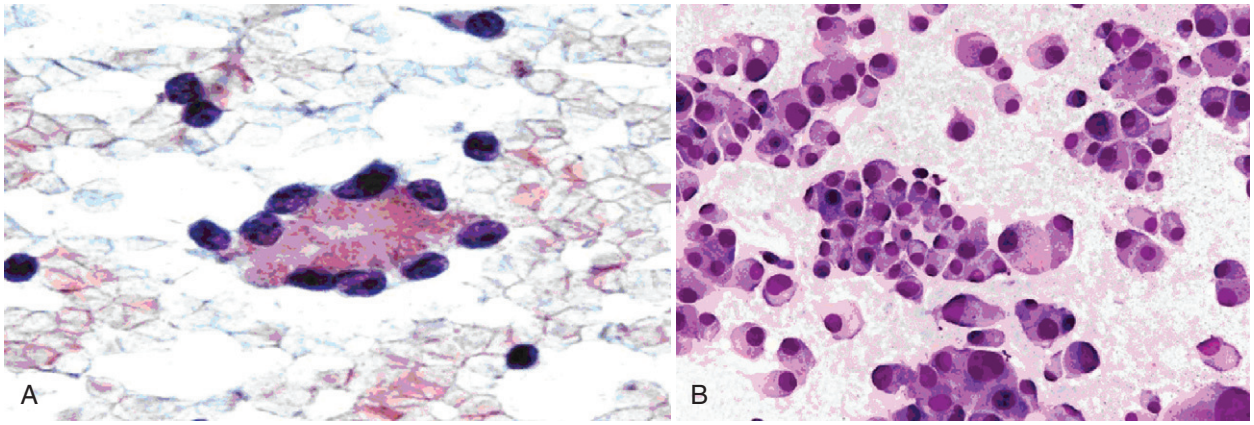
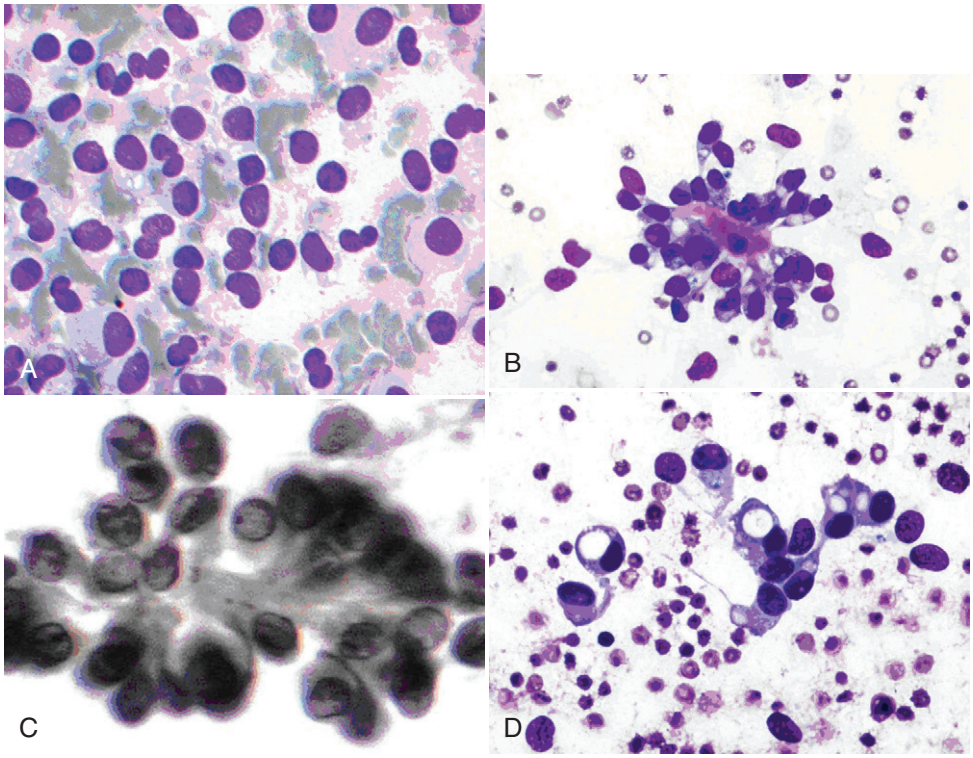


FIGURE 21.11 Pancreatic endocrine neoplasms. A, Smears from pancreatic endocrine neoplasms usually show moderate cellularity with rosette formation and many single cells with peripherally placed nuclei (Papanicolaou stain; magnification ×40). **B,** The nuclei reveal evenly dispersed chromation without conspicuous nucleoli. They also reveal coarse neurosecretory granules (Diff–Quik stain; magnification ×20).

FIGURE 21.12 A to D, Fine-needle aspirates from a solid pseudopapillary neoplasm of the pancreas show wispy nondescript cytoplasm with nuclei lined away from the stroma. These cells also show a preserved nuclear-to-cytoplasmic ratio, plasmacytoid cells (**A**, Diff-Quik stain; magnification ×20), an eosinophilic cytoplasmic globule (**A**, Diff–Quik stain; magnification ×20), a characteristic metachromatic matrix (**B;** Diff–Quik stain; magnification ×20), nuclei with a "coffee bean" appearance (**C;** Papanicolaou stain; magnification ×40), and large cytoplasmic vacuoles (**D;** Diff-Quik stain; magnification ×40).



membrane expression of E-cadherin and beta catenin is associated with PEN, whereas lack of membrane expression and nuclear beta catenin expression support the diagnosis of SPN.[38]

Cystic Pancreatic Lesions

Guidelines for performing FNA for cystic lesions and associated morphologic findings are changing, and as a result, not all cysts should be aspirated.[39] The role of the cytopathologist is also constantly evolving.

The diagnosis of cystic lesions requires a coordinated multispecialty team approach.[40] Cytologists are largely faced with assessment of five major cystic lesions of the pancreas that have characteristic demographic, EUS, and cytologic features. However, taken individually, clinical features, EUS findings, and cytologic features do not provide adequate sensitivity. Estimation of carcinoembryonic antigen (CEA), amylase, and lipase estimations from cyst fluid is a very valuable adjunct.[41] In addition, occasionally pseudocysts of the pancreas as well as epidermoid cysts of the pancreas may show spurious elevations of CEA. For adequate patient management, it appears that the distinction needs to be made between neoplastic mucinous cyst (intraductal papillary mucinous neoplasia [IPMN], mucinous cystic neoplasm, and mucin-secreting adenocarcinoma) and nonmucinous cyst (serous cystadenoma and pseudocyst). It is also important for further management to determine the cyst size and the diameter of the main pancreatic duct.

Assessment of Cystic Lesions. The algorithmic approach highlighted in Figure 21.13 is useful for distinguishing common

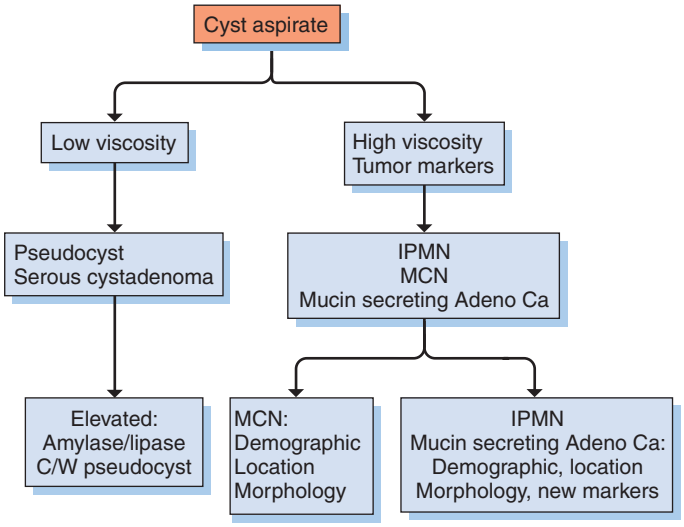


FIGURE 21.13 Algorithmic approach to the diagnosis of cystic pancreatic lesions. Ca, carcinoma; C/W, consistent with; IPMN, intraductal papillary mucinous neoplasia; MCN, mucinous cystic neoplasm.

cystic pancreatic lesions. A few studies also demonstrated how molecular analysis of the cysts can help improve the diagnosis of cystic lesions. This analysis used determinations of DNA quality and quantity, loss of heterozygosity of K-*ras* mutation and its amplification, and mutations in seven other loci.[42,43] Based on a set formula, the cysts are categorized into neoplastic versus nonneoplastic cysts. Although the preliminary data are promising, such tests may become cost prohibitive for the help they provide in the management of patients with cystic pancreatic lesions.

Intraductal Papillary Mucinous Neoplasia. IPMNs generally are noted in male patients near the head of the pancreas.[44] EUS and other imaging modalities reveal that the cysts communicate with the main pancreatic duct, and as a result these ducts are frequently larger in diameter. As a consequence of direct communication, mucin is often noted to ooze out from the ampulla in the second portion of the duodenum. When such lesions are aspirated, they characteristically have large papillary epithelial groups with a fibrovascular core lying in pools of mucin (Fig. 21.14). The neoplastic cells are columnar and show loss of cell polarity. A few single cells also may be seen. Individual cells may demonstrate a wide range of morphologic changes; however, IPMN adenomas usually reveal a preserved N/C ratio and a regular nuclear membrane. When malignant transformation occurs, neoplastic cells may show vacuolated cytoplasm, marked anisocytosis, an increased N/C ratio, and an irregular nuclear membrane with conspicuous nucleoli.

Causes of False Diagnosis. These tumors are lined by varied cell types including gastric foveolar epithelium, colonic epithelium, pancreaticobiliary epithelium, and oncocytic cells with granular eosinophilic cytoplasm. When a needle traverses either the stomach or the duodenum, it raises diagnostic difficulties, especially if cytopathologists and endosonographers do not interact. It is also important to note the type of mucin. Thick mucin that develops a ferning pattern when air dried is an important clue to being neoplastic mucin as opposed to mucin noted when the gastric mucosa is aspirated.

Mucinous Cystic Neoplasm. These tumors almost exclusively arise in female patients. They also are noted in young patients and are predominantly located in the tail of the pancreas. These tumors do not communicate with the main pancreatic duct.

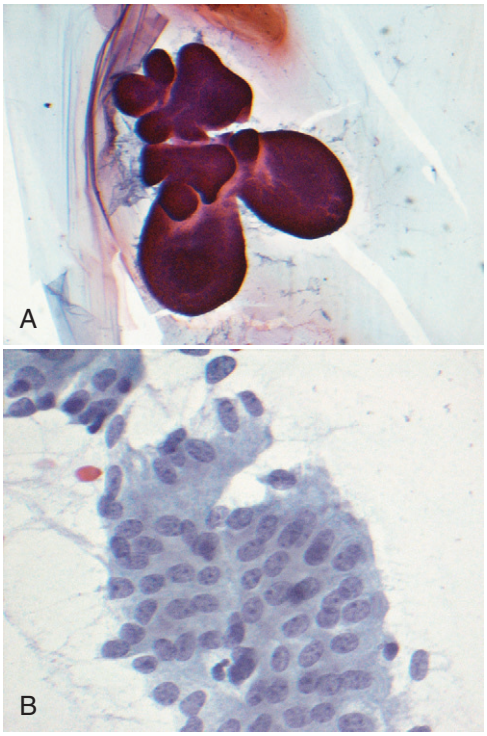


FIGURE 21.14 Intraductal papillary mucinous neoplasm. A, Smear from intraductal papillary mucinous neoplasia reveals pool of mucin with a large papillary epithelial group (Papanicolaou stain; magnification ×10). **B,** Higher magnification reveals columnar cells with a preserved nuclear-to-cytoplasmic ratio. The nuclei show a round, regular nuclear membrane with inconspicuous nucleoli (Papanicolaou stain; magnification ×40).

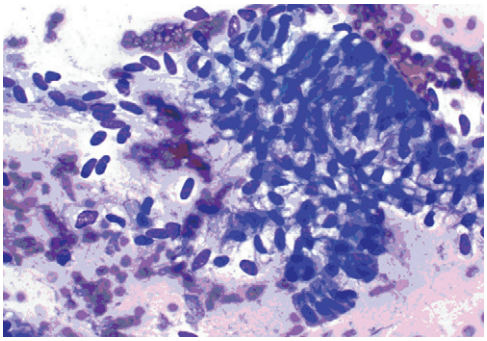


FIGURE 21.15 EUS fine-needle aspiration of the pancreas from a mucinous cyst adenoma reveals cuboidal neoplastic epithelial cells. These cells are in close proximity to the spindled cells representing the ovarian stroma (Papanicolaou stain; magnification ×40).

When cells are obtained from the center of the cyst, they reveal only cyst contents as suggested by cell debris, macrophages, and crystals. When the wall is aspirated, these tumors may show cuboidal or columnar mucin-secreting epithelial cells with a preserved N/C ratio. Smears from these tumors reveal elongated stromal cells in close approximation to bland cuboidal or columnar epithelial cells (Fig. 21.15). The stromal cells most likely represent ovarian stroma. When these cysts have dysplastic or malignant components, the cells begin to show atypia. Features of atypia include many single cells and hyperchromatic and enlarged nuclei with cell pleomorphism. The nuclei begin to look wrinkled and also may reveal prominent nucleoli.

Causes of false diagnosis

Paucicellular Aspirates. Aspiration of these cysts frequently reveals paucicellular aspirates. In this setting, a definitive diagnosis of mucinous cyst adenoma cannot be made with certainty. Mucinous cystic neoplasms also frequently reveal sloughed mucosa. Aspiration from such areas may reveal only acellular debris or necrotic debris with inflammatory cells reminiscent of pseudocysts.

Lining Cells. When aspirate reveals goblet cells, it becomes a challenge to differentiate these cells from duodenal cells. Knowledge of the point of needle entry is very useful in this setting to avoid false-negative interpretation.

Lymph Nodes

Many studies noted the importance of performing EUS FNA for mediastinal and intra-abdominal lymphadenopathy.[45] Most of these studies evaluated the use of EUS FNA for staging of malignancies including those from the lung, gastrointestinal tract, and pancreas. Determination of nodal metastasis by EUS FNA results in a change in preoperative staging that prevents unnecessary surgeries and a change in management strategies for patients with primary malignant neoplasms of the lung, gastrointestinal tract, and pancreas. EUS FNA of deep-seated lymphadenopathy can also be used to provide a diagnosis of primary lesions including granulomas, infections, and lymphomas (non-Hodgkin and Hodgkin lymphoma).

Sample Collection

If the clinical information or the rapid interpretation of on-site cytology suggests malignant non-Hodgkin lymphoma, the endoscopist should provide an additional sample for flow cytometric, gene rearrangement, or cytogenetic examination. Generally, these cells should be collected in RPMI 1640 solution for flow cytometric analysis or molecular genetic analysis. Experience suggests that simple Hank's balanced-salt solution can also be used as a transport medium to perform flow cytometric evaluation. If the sample has not been collected for flow cytometry, a sample collected for cell block can be stained with immunohistochemical stains for appropriate phenotyping. Gene rearrangement studies can also be performed on such samples.

Algorithmic Approach to Interpretation of Lymph Node Aspirates

Using a stepwise methodical approach for lymph node aspirations leads to improved accuracy[46] (Fig. 21.16). Earlier reports suggested that FNA was not always useful to test diagnoses of

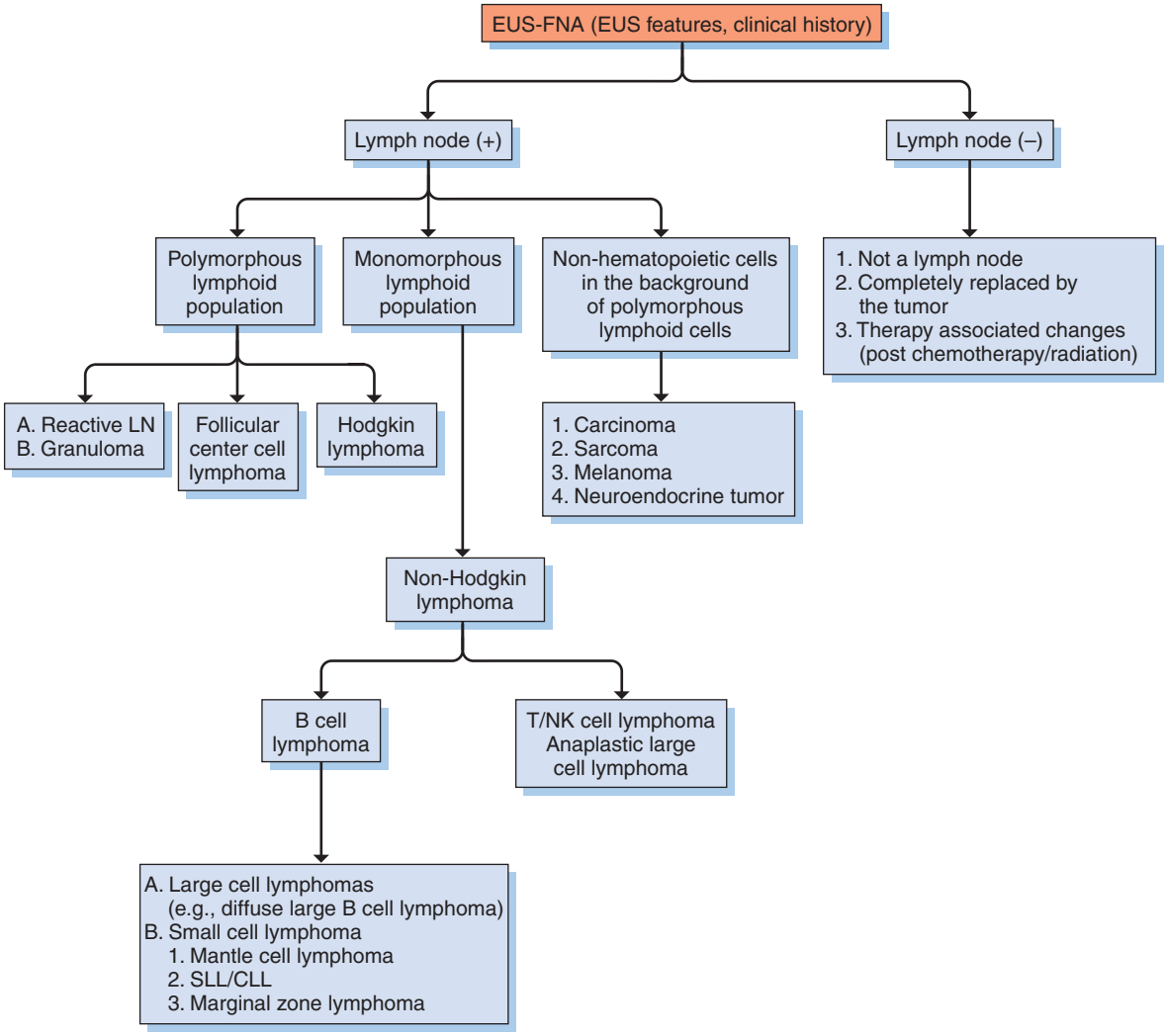


FIGURE 21.16 An algorithmic approach to the interpretation of lymph node aspirates. LN, lymph node; SLL/CLL, small lymphocytic lymphoma/chronic lymphocytic lymphoma.

malignant non-Hodgkin lymphoma. Many publications, however, challenged this view.[45,47] The power of EUS-guided tissue sampling is increasing exponentially. Use of aspirates combined with Tru-Cut biopsies can improve the diagnosis of difficult lesions such as Hodgkin lymphoma.

How to Confirm Lymph Nodes

Lymphoid tissue demonstrates cellular aspirates with many single dyscohesive cells composed of polymorphous lymphoid cells of varying sizes. These cells may have germinal centers with debris containing (tingible body) macrophages. Diff-Quik stain also highlights the presence of cytoplasmic fragments such as lymph glandular bodies (see Fig. 21.6).

Differential Diagnosis

When a range of small, medium, and large lymphocytes is noted in a lymph node aspirate in elderly patients from unexplained lymphadenopathy, one must be aware of conditions such as follicular center cell lymphoma and other small lymphocytic lymphomas. A similar pleomorphic cell type with plasma cells and eosinophils should raise suspicion for Hodgkin lymphoma. In such instances, additional samples should be obtained for flow cytometry, cytogenetics, or cell block analysis. Cell block analysis is more useful especially for the diagnosis of Hodgkin lymphoma, in which additional immunohistochemical stains rather than flow cytometry will provide a definitive answer.

Similarly, if lymph node aspirates reveal many polygonal cells that also have reniform nuclei with inconspicuous nucleoli, granuloma should be suspected. Granulomas show aggregates of epithelioid histiocytes (Fig. 21.17), with occasional multinucleated giant cells. In such instances, additional studies should be undertaken to determine possible causes.

Monomorphous Lymphoid Population

When a lymph node aspirate reveals a sea of monomorphic lymphoid population (small, intermediate, or large), the strong possibility of lymphoma should be considered, and additional samples should be obtained for ancillary studies.

Pitfalls. Diffuse large B-cell non-Hodgkin lymphomas have fragile cytoplasm and therefore frequently reveal large nuclei stripped of their cytoplasm. These cells also reveal prominent nucleoli that raise the suspicion of a differential diagnosis of melanoma.

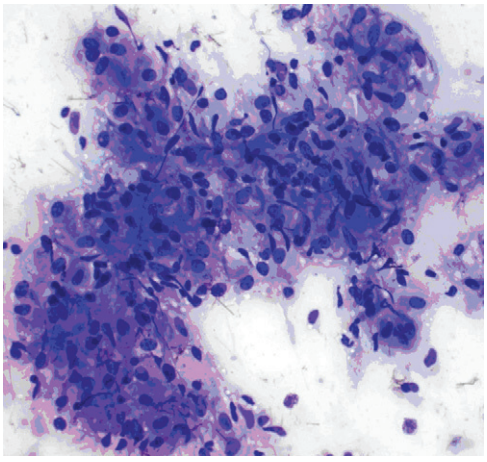


FIGURE 21.17 EUS fine-needle aspiration of mediastinal lymph node. The aspirate reveals aggregates of epithelioid histiocytes characteristic of granulomas (Diff-Quik stain; magnification ×40).

The cytoplasm with B-cell markers may be sheared while passing through the narrow capillary bore of a flow cytometer. Thus, it is not uncommon to see that flow cytometry may have a false-negative result. Immunohistochemical stains performed on cell block or gene rearrangement studies may aid in confirming this difficult diagnosis.

Small lymphocytic lymphomas fall on other end of the spectrum. The smears may contain only small, mature lymphocytes. These lesions cannot be distinguished from mature lymphocytes or lymphocyte-predominant Hodgkin lymphoma or other lymphomas with small lymphoid morphology such as mantle cell or marginal zone lymphomas. Therefore, in a patient with multiple groups of lymph node enlargement, it is advisable to obtain an additional sample for ancillary studies.

Nonhematopoietic Cells in Background of Lymphoid Cells

When nonhematopoietic cells are noted in lymph node aspirates, the diagnosis is metastatic malignancy unless proved otherwise. These metastases can be from carcinoma, melanoma, or neuroendocrine tumors. The characteristic morphologic features of each entity can distinguish these tumors.

Pitfalls

1. Although generally it is not difficult to distinguish metastatic malignancies, the diagnosis of small cell carcinomas may pose diagnostic challenges. Tumor cells in small cell carcinomas demonstrate an increased N/C ratio, nuclei that are hyperchromatic, and possibly also nuclear molding. These cells are fragile and reveal stretching of DNA material. They also show frequent apoptosis and absent or inconspicuous nucleoli. Although these features are easily recognizable, poorly prepared smears from lymph nodes may also reveal shearing of cells from overzealous spread. They may show loose aggregates of cells that reveal a low N/C ratio, hyperchromatic nuclei, and inconspicuous nucleoli. In such cases, the pattern of chromatin architecture may help to differentiate the two. Small cell carcinomas reveal a fine, evenly distributed chromatin pattern, whereas lymphocytes may have margination of the chromatin pattern.
2. One must also not overinterpret benign gastrointestinal tract epithelium noted in a background of lymph node aspirates as diagnostic of metastatic malignancy. When these aspirates are evaluated carefully, up to 60% may show some form of gastrointestinal contamination.

Nonhematopoietic Cells without the Background of Lymphoid Cells

Rarely, a lesion deemed as a lymph node on EUS imaging turns out to be tumor nodule. This possibility should be suspected when multiple passes reveal only neoplastic cells, and no lymphoid component is noted.[46] Tumor cells generally fall into one of four categories: (1) carcinoma, in which cells show cohesive groups with single cells; (2) melanoma, in which the cells are mostly single, with mild to moderate cytoplasm that may or may not have pigment; nuclei also reveal intranuclear cytoplasmic inclusions and prominent nucleoli; this tumor not infrequently has double mirror image nuclei; (3) carcinoid tumors, which are well-differentiated neuroendocrine carcinomas that reveal many single plasmacytoid cells with anisonucleosis; the cytoplasm may show neurosecretory granules, and occasionally these tumors also have a spindled appearance giving rise to a biphasic pattern of cells; these tumors may also form rosettes; and (4) sarcoma. In rare instances, patients treated with either chemotherapy or radiation therapy show transformational changes in lymph nodes; in such cases, they may only show mucinous or myxoid change with few inflammatory cells,[2] and these lesions often remain undetermined.

Spleen

FNA of the spleen has proven useful for the detection of malignant non-Hodgkin lymphoma, metastatic carcinoma, sarcoidosis, infectious conditions, and extramedullary hematopoiesis.[48] Percutaneous FNA of the spleen is highly specific (100%) and yields an overall accuracy of 84.9% to 88% for needle aspirates. Investigators noted that the diagnostic accuracy of splenic FNA can be increased by obtaining samples for flow cytometry.[49] Some investigators suggested, however, that a potential risk for increased bleeding contributes to the lack of use of FNA of the spleen in the United States. Preliminary experience suggested that judicious use of EUS FNA may permit the detection of unsuspected neoplasms, the determination of a preoperative diagnosis of splenic lesions, or both. However, further studies are needed to determine the safety and efficacy of this modality in the detection of splenic lesions.

Gastrointestinal Tract

For cytologic diagnosis, endoscopic brushing is a useful modality for the detection of surface lesions. However, this modality is not useful for the diagnosis of submucosal lesions. EUS with FNA offers the advantages of direct visualization of the mucosal surface and accuracy in determining the extent and size of the submucosal lesion. Therefore, EUS permits preoperative determination of the depth of tumor invasion, or T staging, as well as determination of the N status, and thus provides valuable information concerning the TNM staging of gastrointestinal tract malignancies. EUS also has been used to determine the extent of involvement and response to therapy of mucosa-associated lymphoid tissue (MALT) lymphomas of the stomach. Specifically, EUS FNA has shown value in the following areas for cytologic diagnosis.

Detection of Foregut Cysts

One of the major differential diagnoses for a patient with a posterior mediastinal lesion, which may manifest with dysphagia, is a foregut duplication cyst.[50] This category includes esophageal reduplication and bronchogenic cysts. These cysts may be differentiated based on the presence of complete muscle wall, the type of lining epithelium, and results of imaging studies. An esophageal reduplication cyst is a rare developmental anomaly that clinically and radiologically can mimic a neoplasm.

The cytologic features of the cysts show degenerated cell debris and hemosiderin-laden macrophages (Fig. 21.18). In addition, these aspirates also may contain detached ciliated cell fragments, which can be demonstrated by both light and electron microscopy. The presence of numerous squamous cells supports the diagnosis of an esophageal reduplication cyst. The presence of numerous goblet cells with an absence of squamous cells supports the diagnosis of a bronchogenic cyst. Cytologic features alone are not pathognomonic for the diagnosis of a foregut cyst but can be used to rule out malignant neoplasm and can help to support the diagnosis of foregut cyst when cytology is used in conjunction with imaging studies, including EUS findings.[51]

Gastrointestinal Stromal Tumors

GISTs usually are submucosal and cannot be detected by brush sampling or forceps biopsy. FNA is increasingly used for the diagnosis of GISTs. EUS helps to determine the site, size, and extent of the lesion, and some of these features are useful for determining the malignant potential of this tumor.[52] FNA samples from GISTs show hypercellular groups of spindled cells (Fig. 21.19A) and, rarely, epithelioid cells. The spindled cells also show blunt-ended nuclei and may have nuclear angulations. The major pitfall associated with EUS FNA of GISTs is the aspiration of muscle cells from the wall of the gastrointestinal tract or smooth muscle tumors. Because the definitive differentiation of GISTs from other spindle cell lesions influences subsequent therapy, every attempt

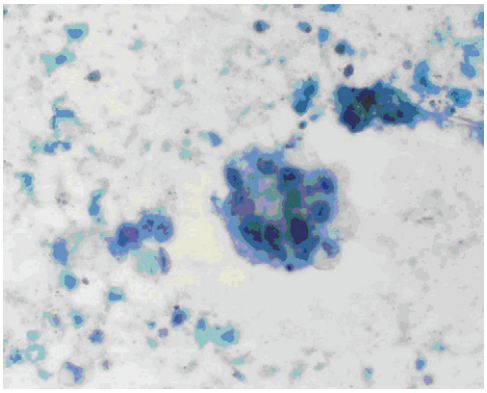
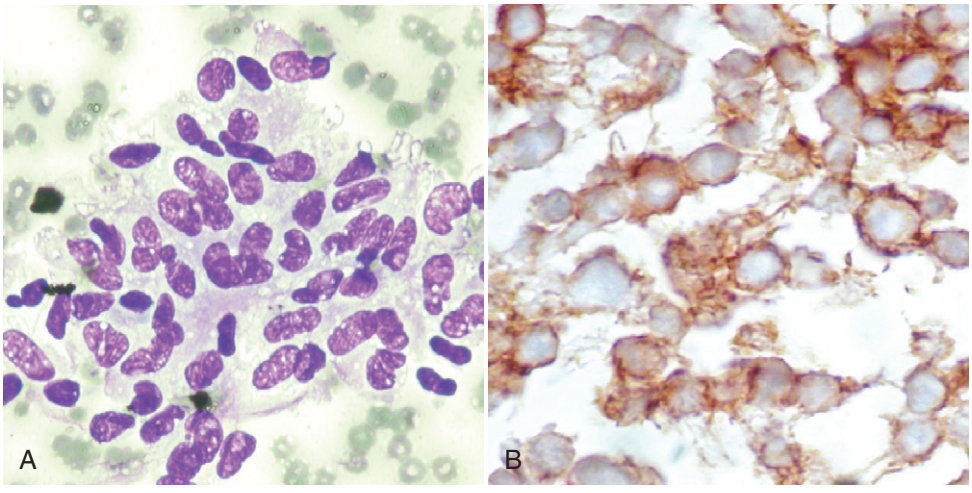


FIGURE 21.18 EUS fine-needle aspiration of an esophageal duplication cyst. The aspirate reveals macrophages, giant cells, and cell debris consistent with the cyst content (Papanicolaou stain; magnification ×40).

FIGURE 21.19 A and B, EUS fine-needle aspiration of a gastric submucosal tumor reveals a paucicellular aspirate with many spindled cells suggestive of gastrointestinal tract stromal tumor (GIST). These cells also were stained by CD117 (c-*kit*), which confirmed the diagnosis of GIST tumor (**A,** Diff-Quik stain; magnification ×40; **B,** immunohistochemical stain; magnification ×40).



should be made to distinguish among these lesions. A panel of immunohistochemical stains, including primary antibodies against c-*kit* (CD117) (see Fig. 21.19B), CD34, smooth muscle antigen, muscle-specific actin, and S-100, may be used to distinguish GISTs from muscle cells, smooth muscle tumors, and rare tumors, such as solitary fibrous tumors of the gastrointestinal tract. Additional c-*kit* mutational analysis is being investigated to determine utility of EUS FNA as a predictive tool in management for GIST tumors.

Hepatobiliary Tree

Liver

CT and ultrasound scans have been used to detect and guide the collection of FNA samples from hepatic masses. Several studies explored the usefulness of EUS in the diagnosis of hepatic lesions,[53] as well as the ability of EUS to promote early intervention. Investigators reported that EUS is able to identify hepatic lesions when a previous CT scan failed to detect a lesion. FNA is used generally to confirm the diagnosis of metastatic tumors or to diagnose primary tumors such as hepatocellular carcinoma and cholangiocarcinoma. Aspirates from hepatocellular carcinomas generally show adequately cellular samples. The neoplastic hepatocytes may be in groups or single cells. Two patterns of morphologic features are characteristic: (1) groups of hepatocytes with overlapping cells that are lined by sinusoids (basketing pattern) (Fig. 21.20A) and (2) overlapping cell groups with vessels transgressing these neoplastic cells. Neoplastic hepatocytes may have a range of morphologic features based on their cellular differentiation and histologic subtype. It may be difficult to distinguish well-differentiated hepatocellular carcinomas from hepatocellular adenoma, focal nodular hyperplasia, or macroregenerative nodules. In such instances, an altered architectural pattern highlighted on reticulin stain on cell block examination may prove to be a valuable adjunct.[54] Moderately or more poorly differentiated tumors may show many single atypical hepatocytes, the presence of bile, or single nuclei stripped of their cytoplasm. These cells also may have clear cytoplasmic vacuoles representing steatosis. Malignant cells show an increased N/C ratio, nuclear membrane irregularity, abnormal mitoses, and prominent nucleoli (see Fig. 21.20B). Similarly, EUS FNA has also been useful in the diagnosis of biliary and gallbladder carcinomas.[55,56] This modality has also been identified to be more sensitive and specific than biliary brushes in detection of these malignancies.[56,57]

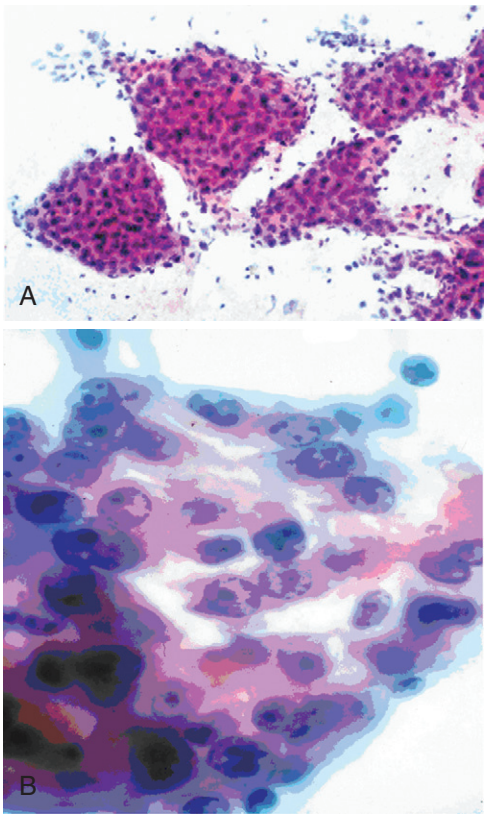


FIGURE 21.20 Hepatocellular carcinoma. A, Aspirate from hepatocellular carcinoma shows increased cellularity and reveals groups of hepatocytes with sinusoids around the periphery (basketing pattern) (Papanicolaou stain; magnification ×20). **B,** Individual tumor cells either show no or very little cytoplasm with increased nuclear-to-cytoplasmic ratio. Nuclei reveal irregular nuclear membranes and have prominent nucleoli (Papanicolaou stain; magnification ×40).

Adrenal Glands

EUS can detect adrenal gland lesions and can effectively obtain FNA samples from left-sided and some right-sided lesions.[58,59] This modality is useful for detecting metastatic malignant neoplasms to the adrenal gland, especially from the lung.[60] Samples from normal adrenal glands reveal single cells or small aggregates. The cells usually are uniform; however, anisocytosis sometimes can be noted. The nuclei generally have regular nuclear membranes. Some cells may reveal conspicuous nucleoli. The cytoplasm may be eosinophilic, foamy, or rich in lipids. Because the cytoplasm frequently is disrupted, naked nuclei often are identified, with lipid vacuoles noted in the background.

SUMMARY

EUS is a powerful modality that has forever changed practice patterns related to deep-seated malignant neoplasms.[61] Advances in this technology will continue to challenge conventional wisdom in the coming years. Effective use of this technique for patient management, however, requires that cytopathologists form an integral part of the patient management team. Although the diagnostic criteria for a majority of lesions are not affected, endosonographers as well as cytopathologists should be aware of the benefits, limitations, and pitfalls of evaluating samples obtained by EUS-guided FNA.

REFERENCES

1. Jhala N, Jhala D. Gastrointestinal tract cytology: advancing horizons. *Adv Anat Pathol*. 2003;10(5):261–277.
2. Jhala NC, Jhala DN, Chhieng DC, et al. Endoscopic ultrasound-guided fine-needle aspiration: a cytopathologist's perspective. *Am J Clin Pathol*. 2003;120(3):351–367.
3. Gress FG, Hawes RH, Savides TJ, et al. Endoscopic ultrasound-guided fine-needle aspiration biopsy using linear array and radial scanning endosonography. *Gastrointest Endosc*. 1997;45(3):243–250.
4. Fisher L, Segarajasingam DS, Stewart C, et al. Endoscopic ultrasound guided fine needle aspiration of solid pancreatic lesions: performance and outcomes. *J Gastroenterol Hepatol*. 2009;24(1):90–96.
5. Bardales RH, Stelow EB, Mallery S, et al. Review of endoscopic ultrasound-guided fine-needle aspiration cytology. *Diagn Cytopathol*. 2006;34(2):140–175.
6. Wiersema MJ, Hawes RH, Tao LC, et al. Endoscopic ultrasonography as an adjunct to fine needle aspiration cytology of the upper and lower gastrointestinal tract. *Gastrointest Endosc*. 1992;38(1):35–39.
7. Vilmann P, Hancke S. A new biopsy handle instrument for endoscopic ultrasound-guided fine-needle aspiration biopsy. *Gastrointest Endosc*. 1996;43(3):238–242.
8. Eltoum IA, Chhieng DC, Jhala D, et al. Cumulative sum procedure in evaluation of EUS-guided FNA cytology: the learning curve and diagnostic performance beyond sensitivity and specificity. *Cytopathology*. 2007;18(3):143–150.

9. Binmoeller KF, Thul R, Rathod V, et al. Endoscopic ultrasound-guided, 18-gauge, fine needle aspiration biopsy of the pancreas using a 2.8 mm channel convex array echoendoscope. *Gastrointest Endosc*. 1998;47(2): 121–127.
10. Sakamoto H, Kitano M, Komaki T, et al. Prospective comparative study of the EUS guided 25-gauge FNA needle with the 19-gauge Trucut needle and 22-gauge FNA needle in patients with solid pancreatic masses. *J Gastroenterol Hepatol*. 2009;24(3):384–390.
11. Lee JH, Stewart J, Ross WA, et al. Blinded prospective comparison of the performance of 22-gauge and 25-gauge needles in endoscopic ultrasound-guided fine needle aspiration of the pancreas and peri-pancreatic lesions. *Dig Dis Sci*. 2009;54(10):2274–2281.
12. Siddiqui UD, Rossi F, Rosenthal LS, et al. EUS-guided FNA of solid pancreatic masses: a prospective, randomized trial comparing 22-gauge and 25-gauge needles. *Gastrointest Endosc*. 2009;70(6):1093–1097.
13. Centeno BA, Enkemann SA, Coppola D, et al. Classification of human tumors using gene expression profiles obtained after microarray analysis of fine-needle aspiration biopsy samples. *Cancer*. 2005;105(2):101–109.
14. Storch I, Jorda M, Thurer R, et al. Advantage of EUS Trucut biopsy combined with fine-needle aspiration without immediate on-site cytopathologic examination. *Gastrointest Endosc*. 2006;64(4):505–511.
15. Varadarajulu S, Fraig M, Schmulewitz N, et al. Comparison of EUS-guided 19-gauge Trucut needle biopsy with EUS-guided fine-needle aspiration. *Endoscopy*. 2004;36(5):397–401.
16. Kate MS, Kamal MM, Bobhate SK, Kher AV. Evaluation of fine needle capillary sampling in superficial and deep-seated lesions: an analysis of 670 cases. *Acta Cytol*. 1998;42(3):679–684.
17. Wallace MB, Kennedy T, Durkalski V, et al. Randomized controlled trial of EUS-guided fine needle aspiration techniques for the detection of malignant lymphadenopathy. *Gastrointest Endosc*. 2001;54(4):441–447.
18. Puri R, Vilmann P, Saftoiu A, et al. Randomized controlled trial of endoscopic ultrasound-guided fine-needle sampling with or without suction for better cytological diagnosis. *Scand J Gastroenterol*. 2009;44(4):499–504.
19. Jhala NC, Jhala D, Eltoum I, et al. Endoscopic ultrasound-guided fine-needle aspiration biopsy: a powerful tool to obtain samples from small lesions. *Cancer*. 2004;102(4):239–246.
20. LeBlanc JK, Ciaccia D, Al-Assi MT, et al. Optimal number of EUS-guided fine needle passes needed to obtain a correct diagnosis. *Gastrointest Endosc*. 2004;59(4):475–481.
21. Erickson RA, Sayage-Rabie L, Beissner RS. Factors predicting the number of EUS-guided fine-needle passes for diagnosis of pancreatic malignancies. *Gastrointest Endosc*. 2000;51(2):184–190.
22. Eloubeidi MA, Tamhane A, Jhala N, et al. Agreement between rapid onsite and final cytologic interpretations of EUS-guided FNA specimens: implications for the endosonographer and patient management. *Am J Gastroenterol*. 2006;101(12):2841–2847.
23. Jhala NC, Eltoum IA, Eloubeidi MA, et al. Providing on-site diagnosis of malignancy on endoscopic-ultrasound-guided fine-needle aspirates: should it be done? *Ann Diagn Pathol*. 2007;11(3):176–181.
24. Klapman JB, Logrono R, Dye CE, Waxman I. Clinical impact of on-site cytopathology interpretation on endoscopic ultrasound-guided fine needle aspiration. *Am J Gastroenterol*. 2003;98(6):1289–1294.
25. Wiersema MJ, Vilmann P, Giovannini M, et al. Endosonography-guided fine-needle aspiration biopsy: diagnostic accuracy and complication assessment. *Gastroenterology*. 1997;112(4):1087–1095.
26. Shin HJ, Lahoti S, Sneige N. Endoscopic ultrasound-guided fine-needle aspiration in 179 cases: the M. D. Anderson Cancer Center experience. *Cancer*. 2002;96(3):174–180.
27. Layfield LJ, Bentz JS, Gopez EV. Immediate on-site interpretation of fine-needle aspiration smears: a cost and compensation analysis. *Cancer*. 2001;93(5):319–322.
28. Nasuti JF, Gupta PK, Baloch ZW. Diagnostic value and cost-effectiveness of on-site evaluation of fine-needle aspiration specimens: review of 5,688 cases. *Diagn Cytopathol*. 2002;27(1):1–4.
29. Ylagan LR, Edmundowicz S, Kasal K, et al. Endoscopic ultrasound guided fine-needle aspiration cytology of pancreatic carcinoma: a 3-year experience and review of the literature. *Cancer*. 2002;96(6):362–369.
30. Bellizzi AM, Stelow EB. Pancreatic cytopathology: a practical approach and review. *Arch Pathol Lab Med*. 2009;133(3):388–404.
31. Jhala N, Jhala D, Vickers SM, et al. Biomarkers in diagnosis of pancreatic carcinoma in fine-needle aspirates. *Am J Clin Pathol*. 2006;126(4): 572–579.
32. Gu M, Ghafari S, Lin F, Ramzy I. Cytological diagnosis of endocrine tumors of the pancreas by endoscopic ultrasound-guided fine-needle aspiration biopsy. *Diagn Cytopathol*. 2005;32(4):204–210.
33. Jhala D, Eloubeidi M, Chhieng DC, et al. Fine needle aspiration biopsy of the islet cell tumor of pancreas: a comparison between computerized axial tomography and endoscopic ultrasound-guided fine needle aspiration biopsy. *Ann Diagn Pathol*. 2002;6(2):106–112.
34. Labate AM, Klimstra DL, Zakowski MF. Comparative cytologic features of pancreatic acinar cell carcinoma and islet cell tumor. *Diagn Cytopathol*. 1997;16(2):112–116.
35. Bardales RH, Centeno B, Mallery JS, et al. Endoscopic ultrasound-guided fine-needle aspiration cytology diagnosis of solid-pseudopapillary tumor of the pancreas: a rare neoplasm of elusive origin but characteristic cytomorphologic features. *Am J Clin Pathol*. 2004;121(5):654–662.
36. Jhala N, Siegal GP, Jhala D. Large, clear cytoplasmic vacuolation: an under-recognized cytologic clue to distinguish solid pseudopapillary neoplasms of the pancreas from pancreatic endocrine neoplasms on fine-needle aspiration. *Cancer*. 2008;114(4):249–254.
37. Notohara K, Hamazaki S, Tsukayama C, et al. Solid-pseudopapillary tumor of the pancreas: immunohistochemical localization of neuroendocrine markers and CD10. *Am J Surg Pathol*. 2000;24(10):1361–1371.
38. Burford H, Baloch Z, Liu X, et al. E-cadherin/beta-catenin and CD10: a limited immunohistochemical panel to distinguish pancreatic endocrine neoplasm from solid pseudopapillary neoplasm of the pancreas on endoscopic ultrasound-guided fine-needle aspirates of the pancreas. *Am J Clin Pathol*. 2009;132(6):831–839.
39. Tanaka M, Chari S, Adsay V, et al. International consensus guidelines for management of intraductal papillary mucinous neoplasms and mucinous cystic neoplasms of the pancreas. *Pancreatology*. 2006;6(1–2):17–32.
40. Pitman MB, Lewandrowski K, Shen J, et al. Pancreatic cysts: preoperative diagnosis and clinical management. *Cancer Cytopathol*. 2010;118(1): 1–13.
41. Pitman MB, Michaels PJ, Deshpande V, et al. Cytological and cyst fluid analysis of small ($\leq$3 cm) branch duct intraductal papillary mucinous neoplasms adds value to patient management decisions. *Pancreatology*. 2008;8(3):277–284.
42. Shen J, Brugge WR, Dimaio CJ, Pitman MB. Molecular analysis of pancreatic cyst fluid: a comparative analysis with current practice of diagnosis. *Cancer Cytopathol*. 2009;117(3):217–227.
43. Khalid A, Zahid M, Finkelstein SD, et al. Pancreatic cyst fluid DNA analysis in evaluating pancreatic cysts: a report of the PANDA study. *Gastrointest Endosc*. 2009;69(6):1095–1102.
44. Stelow EB, Shami VM, Abbott TE, et al. The use of fine needle aspiration cytology for the distinction of pancreatic mucinous neoplasia. *Am J Clin Pathol*. 2008;129(1):67–74.
45. Pugh JL, Jhala NC, Eloubeidi MA, et al. Diagnosis of deep-seated lymphoma and leukemia by endoscopic ultrasound-guided fine-needle aspiration biopsy. *Am J Clin Pathol*. 2006;125(5):703–709.
46. Bakdounes K, Jhala N, Jhala D. Diagnostic usefulness and challenges in the diagnosis of mesothelioma by endoscopic ultrasound guided fine needle aspiration. *Diagn Cytopathol*. 2008;36(7):503–507.
47. Al-Haddad M, Savabi MS, Sherman S, et al. Role of endoscopic ultrasound-guided fine-needle aspiration with flow cytometry to diagnose lymphoma: a single center experience. *J Gastroenterol Hepatol*. 2009; 24(12):1826–1833.
48. Iwashita T, Yasuda I, Tsurumi H, et al. Endoscopic ultrasound-guided fine needle aspiration biopsy for splenic tumor: a case series. *Endoscopy*. 2009; 41(2):179–182.
49. Eloubeidi MA, Varadarajulu S, Eltoum I, et al. Transgastric endoscopic ultrasound-guided fine-needle aspiration biopsy and flow cytometry of suspected lymphoma of the spleen. *Endoscopy*. 2006;38(6):617–620.
50. Faigel DO, Burke A, Ginsberg GG, et al. The role of endoscopic ultrasound in the evaluation and management of foregut duplications. *Gastrointest Endosc*. 1997;45(1):99–103.
51. Fazel A, Moezardalan K, Varadarajulu S, et al. The utility and the safety of EUS-guided FNA in the evaluation of duplication cysts. *Gastrointest Endosc*. 2005;62(4):575–580.
52. Yoshida S, Yamashita K, Yokozawa M, et al. Diagnostic findings of ultrasound-guided fine-needle aspiration cytology for gastrointestinal stromal tumors: proposal of a combined cytology with newly defined features and histology diagnosis. *Pathol Int*. 2009;59(10):712–719.
53. Crowe DR, Eloubeidi MA, Chhieng DC, et al. Fine-needle aspiration biopsy of hepatic lesions: computerized tomographic-guided versus endoscopic ultrasound-guided FNA. *Cancer*. 2006;108(3):180–185.
54. Bergman S, Graeme-Cook F, Pitman MB. The usefulness of the reticulin stain in the differential diagnosis of liver nodules on fine-needle aspiration biopsy cell block preparations. *Mod Pathol*. 1997;10(12): 1258–1264.
55. Fritscher-Ravens A, Sriram PV, Schroder S, et al. Stromal tumor as a pitfall in EUS-guided fine-needle aspiration cytology. *Gastrointest Endosc*. 2000; 51(6):746–749.
56. Meara RS, Jhala D, Eloubeidi MA, et al. Endoscopic ultrasound-guided FNA biopsy of bile duct and gallbladder: analysis of 53 cases. *Cytopathology*. 2006;17(1):42–49.
57. Jacobson BC, Pitman MB, Brugge WR. EUS-guided FNA for the diagnosis of gallbladder masses. *Gastrointest Endosc*. 2003;57(2):251–254.

58. Stelow EB, Debol SM, Stanley MW, et al. Sampling of the adrenal glands by endoscopic ultrasound-guided fine-needle aspiration. *Diagn Cytopathol*. 2005;33(1):26–30.
59. Jhala NC, Jhala D, Eloubeidi MA, et al. Endoscopic ultrasound-guided fine-needle aspiration biopsy of the adrenal glands: analysis of 24 patients. *Cancer*. 2004;102(5):308–314.
60. Bodtger U, Vilmann P, Clementsen P, et al. Clinical impact of endoscopic ultrasound-fine needle aspiration of left adrenal masses in established or suspected lung cancer. *J Thorac Oncol*. 2009;4(12):1485–1489.
61. Shah JN, Ahmad NA, Beilstein MC, et al. Clinical impact of endoscopic ultrasonography on the management of malignancies. *Clin Gastroenterol Hepatol*. 2004;2(12):1069–1073.

CHAPTER 22

EUS-Guided Drainage of Pancreatic Pseudocysts

Hans Seifert | Shyam Varadarajulu

Key Points

Symptomatic pancreatic pseudocysts located adjacent to the gastrointestinal tract can be drained safely under EUS guidance as long as they are within the reach of the echoendoscope.

Randomized trials have shown that the technical success rate and safety profile of EUS are superior to those of gastroscopy for pancreatic pseudocyst drainage. EUS affects management by establishing an alternate diagnosis in 5% to 10% of patients.

EUS can be performed either to identify a site for subsequent transmural drainage by gastroscopy or as a one-step procedure entirely under EUS guidance.

Given the portability of EUS processors, the procedure can be undertaken safely at the patient's bedside or in the operating room. Moreover, in patients with multiple symptomatic fluid collections, more than one pseudocyst can be drained efficaciously at the same setting.

A fluoroscopy unit, a therapeutic echoendoscope, accessories such as 19-G needles, an endoscopic retrograde cholangiopancreatography cannula or needle-knife catheters, 0.035-inch guidewires, balloon dilators, and double-pigtail stents or biliary drainage catheters are essential for the procedure.

The procedure is very safe, with rates of technical and treatment success greater than 90% and 85%, respectively.

INTRODUCTION

Pancreatic fluid collections (PFCs) may occur as a result of acute or chronic pancreatitis, surgery, trauma, or neoplasia. With the exception of cyst neoplasias, collections form as a consequence of either a disruption of the pancreatic duct with subsequent leakage or maturation of pancreatic necrosis. Indications for drainage of these collections include pain, gastric outlet obstruction, obstruction of the biliary tract, and infection. The available current therapeutic options include surgery, endoscopy, and percutaneous drainage. Since the first reports of endoscopic drainage of PFCs in the 1980s, increasing experience has led to compelling results that support this approach to patient management. PFCs that complicate acute and chronic pancreatitis can be categorized into three types: (1) acute PFCs, (2) pseudocysts, and (3) walled-off pancreatic necrosis. Acute PFCs generally do not warrant any intervention because they occur early in the course of the disease, lack a well-defined wall, and are spontaneously reabsorbed within a few weeks after the onset of acute pancreatitis. Walled-off pancreatic necrosis is a well-defined collection of pancreatic juice and debris, which may be sterile or infected, that when managed endoscopically requires transluminal necrosectomy and not just drainage of cyst contents. Pancreatic pseudocysts that arise as a consequence of acute or chronic pancreatitis have a well-defined wall with a homogeneous fluid collection and no debris. Symptomatic pseudocysts can be managed effectively by endoscopic means if they are located adjacent to the gastrointestinal lumen.

In this chapter, the different approaches to endoscopic ultrasonography (EUS)-based management of pseudocysts, the advantages and limitations of the technique, and supportive outcomes data are reviewed. This chapter does not address the management of walled-off pancreatic necrosis because treatment includes endoscopic necrosectomy and not simply EUS-guided drainage.

CURRENT TREATMENT APPROACHES AND LIMITATIONS

Surgical Cystogastrostomy

Open surgical drainage entails the creation of a cystogastrostomy or cystenterostomy. This can also be accomplished laparoscopically through an anterior transgastric approach, which requires an anterior gastrotomy for access and a cystogastrostomy creation through the posterior gastric wall, or a posterior approach through the lesser sac.[1] The procedure can also be performed through a lesser sac approach, which is technically easier and is associated with less intraoperative bleeding.[2] Pancreatic pseudocysts that are not in close proximity to the stomach require the creation of a cystojejunostomy.[3] The cystojejunostomy is sometimes created through a Roux limb of jejunum. Although the technical and treatment success rates for surgery are high, the procedure is associated with a 10% to 30% morbidity rate and a 1% to 5% mortality rate.[4] The technique is invasive, associated with prolonged hospital stay, and more expensive than the alternatives[5] (Table 22.1).

TABLE 22.1

Comparison of Surgical, Percutaneous, and Endoscopic Approaches to Pseudocyst Management

Treatment Modality	Advantages	Disadvantages
Surgical cystogastrostomy	1. Effective therapy 2. Salvage therapy following failed endoscopic or percutaneous drainage	1. Invasive 2. High morbidity and 1%-5% mortality. 3. Longer hospital stay 4. Expensive
Percutaneous drainage	1. Less invasive 2. Useful adjunct to endoscopic drainage when pseudocyst is inaccessible by endoscopy 3. Can be undertaken in high-risk patients too sick to undergo surgical or endoscopic drainage	1. Cutaneous infections and local complications such as bleeding 2. Inadequate therapy in the presence of debris 3. Predisposes to pancreaticocutaneous fistula formation
Non–EUS-guided endoscopic drainage	1. Less invasive than surgery and organ-preserving intervention 2. Rescue measure in postoperative pancreatic fluid collections	1. Feasible only if the pseudocyst is adjacent to the gastrointestinal lumen and causes luminal compression 2. May only be a temporizing measure if the underlying anatomic predisposition requires surgical correction 3. Inability to visualize interposed vessels may cause hemorrhage 4. Possibility of perforation because of the relatively "blind" technique 5. Potential for misdiagnosing cyst neoplasms and necrotic collections as pseudocysts. 6. Infection
EUS-guided pseudocyst drainage	1. Ability to access pseudocysts that do not cause luminal compression 2. Distinguish cyst neoplasms and necrotic collections from pseudocysts 3. Real-time puncture minimizes bleeding, perforation risks	1. Limited availability and lack of dedicated accessories 2. Infection 3. Surgery may be required to correct underlying anatomic defects not amenable for endotherapy

TABLE 22.2

Studies Evaluating the Impact of EUS on Patients Undergoing Pseudocyst Drainage

Authors (yr)	Change in Management (%)	Alternate Diagnosis (%)	Pseudocyst Size Variation between Time of CT and EUS (%)	Other Impact (%)
Fockens et al[21] (1997)	37.5	6	9	22.5*
Varadarajulu et al[9] (2007)	16	8	8	—

*The presence of intervening vessels, normal pancreatic parenchyma, and distance between the pseudocyst and the gut lumen precluded transluminal drainage. In this study, all drainages were undertaken by esophagogastroduodenoscopy following assessment of the pancreatic fluid collection by EUS.
CT, computed tomography.

Percutaneous Drainage

Percutaneous drainage, which is performed under radiologic guidance, is less invasive than surgery. Major drawbacks of this technique include the inability to clear solid debris that necessitates surgical rescue in 50% to 60% of patients, the risk of puncture of adjacent viscera, infection, prolonged periods of external drainage, and predisposition to the development of pancreaticocutaneous fistula.[6] Nevertheless, percutaneous drainage is an important adjunctive therapy when the fluid collection is multifocal and extends to areas not accessible for endoscopic drainage or lacking a mature wall. Percutaneous drainage appears more likely to be successful in patients with normal pancreatic ducts and in patients with strictures but no communication between the duct and the pseudocyst, compared with patients with strictures and duct-cyst communication or those with complete cutoff of the duct. These features predispose patients to long-term pancreaticocutaneous fistula formation.[7]

Non–EUS-Guided Endoscopic Transmural Drainage

Non–EUS-guided endoscopic transmural drainage entails the creation of a fistulous tract between the pseudocyst and the gastric lumen (cystogastrostomy) or duodenal lumen (cystoduodenostomy). After establishing access, a nasocystic catheter or a transluminal stent is placed into the pseudocyst to facilitate drainage. The technical success rate of this approach is between 50% and 60%, and most treatment failures are caused by the lack of endoscopically visible luminal compression.[8,9] The risk of perforation is particularly high when luminal compression is absent.[10–12] Another major complication is hemorrhage, which is encountered in approximately 6% of cases.[10–15] There is also the potential for misdiagnosing a malignant cyst neoplasm or a necrotic collection as a pseudocyst and managing it inappropriately by transmural stenting.[9,16,17]

EUS-Guided Drainage of Pancreatic Pseudocysts: Presentation

EUS, by virtue of its ability to visualize outside the lumen of the gastrointestinal tract, enables drainage of pancreatic pseudocysts that do not cause luminal compression. The technical success rate of EUS for pancreatic pseudocyst drainage has been reported to be greater than 90%, and the complication rate is less than 5%.[9,18–20] Apart from issues related to access and safety, performing routine EUS before endoscopic drainage leads to a change in management in 5% to 37% of cases.[9,21,22] The reason is that EUS establishes an alternate diagnosis of cyst neoplasm in 3% to 5% of cases that were originally misclassified as a pseudocyst by CT[9,20,23] (Table 22.2). From a treatment point of view, the

differentiation of walled-off pancreatic necrosis from pseudocyst is very important, and EUS is much more sensitive than CT in making this distinction. Moreover, if a CT scan has not been performed recently, EUS can assess suitability for drainage because pseudocysts tend to resolve or become smaller over time.[9,21,22]

At some institutions, endoscopists first perform EUS to confirm the diagnosis and identify a site for subsequent transmural drainage by esophagogastroduodenostomy (EUS-assisted transmural drainage). In others, pseudocyst drainage is performed under EUS guidance as a one-step procedure (EUS-guided transmural drainage). This variation in practice pattern may result from the following factors:

- The endosonographer may not be proficient in performing therapeutic interventions. In such cases, after confirmation of the diagnosis and identification of an appropriate site, transmural drainage is subsequently undertaken by a therapeutic endoscopist.
- In most centers, although the endoscopic retrograde cholangiopancreatography (ERCP) suite has access to fluoroscopy, the EUS suite does not have fluoroscopy. This situation requires the manual transport of a patient to the ERCP suite following EUS, because maneuvers such as guidewire exchange and stent deployment require fluoroscopic guidance. In addition, if dedicated magnetic resonance cholangiopancreatography (MRCP) had not been undertaken to assess the pancreatic duct anatomy, most endoscopists perform a pancreatogram before pseudocyst drainage.
- Because most therapeutic interventions involve deployment of 7- or 10-French (Fr) transmural stents, a therapeutic echoendoscope with a large biopsy channel ($\geq$3.7 mm) is required for performing pseudocyst drainage. In centers that do not have access to a therapeutic echoendoscope, drainage procedures are undertaken using a side-view duodenoscope or the double-channel gastroscope.

EUS-Assisted Transmural Drainage

In all patients who undergo pseudocyst drainage, when available, it is preferable to perform EUS examinations using a curvilinear echoendoscope. This procedure enables aspiration of cyst fluid for analysis and performance of EUS-guided drainage or marking of a site for subsequent drainage by endoscopy. Marking of a site can be performed by tattooing or by any other convenient technique. The pseudocyst is first evaluated by EUS for confirmation of diagnosis, for assessment of size and cyst wall maturity, and to exclude the presence of any intervening vasculature. If required, a sample of the cyst aspirate is sent for tumor marker studies (carcinoembryonic antigen) and amylase and lipase levels. In patients with suspected infection, the aspirate may be sent for Gram staining and culture. Antibiotics are administered before the procedure for all patients. This section is categorized based on the following three presentations at endoscopy: (1) the presence of definitive luminal compression, (2) the presence of submucosal prominence but without definitive luminal compression, and (3) the absence of luminal compression.

Presence of Definitive Luminal Compression

In most (>90%) patients with definitive luminal compression, following EUS, drainage of the pseudocyst can be undertaken successfully by gastroscopy.[1,2] Only in patients with portal hypertension and gastric or duodenal varices does a safe site need to be identified and marked at EUS for subsequent drainage.[24]

Presence of a Submucosal Prominence but without Definitive Luminal Compression

In patients with multiple pancreatic pseudocysts, more than one luminal compression may be evident at endoscopy, and only the largest pseudocyst or the one that is infected requires drainage. In addition, extramural organs such as a distended gallbladder or spleen can cause luminal compression and may mimic a pseudocyst. In patients with severe hypoalbuminemia, the diffuse edema in the gastric mucosal layer can mask luminal compression caused by a pseudocyst. In these patients, the area of the gastrointestinal tract that is apposed to the wall of the pseudocyst is identified at EUS and is marked. It is important that after marking the site, drainage is undertaken in the same position the patient used for the EUS examination. This is particularly relevant in transgastric drainage because the site identified for puncture at EUS may not be apposed to the pseudocyst as a result of variation in patient positioning.[25] This situation is encountered when the size of the pseudocyst is intermediate (4 to 6 cm) or when the window of contact between the pseudocyst and the gastric wall is small. Patient positioning is not a major factor for transduodenal drainage because the luminal compression is more obvious. Placement of a guidewire within the pseudocyst at EUS can circumvent this problem with patient positioning.

Absence of Luminal Compression

In patients in whom no luminal compression is evident at endoscopy, the pseudocyst is best drained under EUS guidance or by alternate treatment modalities. Luminal compression may not be evident when the pseudocyst is small or the pseudocyst is located in the tail of the pancreas or in an atypical location such as the right upper quadrant.[9] In these patients, marking a site at EUS may still not guarantee access to the pseudocyst. In such cases, a 0.035-inch guidewire is coiled into the pseudocyst during EUS to guarantee definitive access for endoscopic drainage. In general, the distance between the pseudocyst and the EUS transducer should be no greater than 1.5 cm. A distance greater than 1.5 cm is considered a relative contraindication, out of concerns for perforation and leak.

Advantages. First, as stated earlier, EUS can establish an alternate diagnosis and can thereby affect patient management in a subset of patients. Second, if an endosonographer is not trained to perform therapeutic procedures, a safe site can be identified at EUS so that transmural drainage can be undertaken by a different endoscopist. Next, deploying 10-Fr stents and using the curvilinear echoendoscope can sometimes be technically challenging, given the small diameter of the biopsy channel (3.7 mm). In these patients, placing a guidewire at EUS enables easier deployment of 10-Fr stents by using a duodenoscope or a double-channel gastroscope. In addition, if the fluid collection is necrotic, placing a guidewire at EUS will enable subsequent access for débridement using a double-channel gastroscope. Finally, because the quality of an MRCP depends on the institution, most endoscopists still prefer ERCP to assess the integrity of the main pancreatic duct before they perform pseudocyst drainage. In such instances, both ERCP and transmural drainage can be undertaken in the same setting following assessment of the pseudocyst at EUS.

Disadvantages. The need to exchange the echoendoscope for a duodenoscope or a double-channel gastroscope prolongs the procedure and increases the patient's discomfort and the need for more sedation. Moreover, if a guidewire had been placed at EUS for subsequent access, there remains a potential for accidental dislodgment of the guidewire during scope exchange. In a minority of patients with intermediate-size pseudocysts (4 to 6 cm) in whom luminal compression is not definitive despite identification of a site at EUS, transgastric access to the pseudocyst may be unsuccessful at gastroscopy if any variation in patient positioning occurs.

EUS-Guided Transmural Drainage: One-Step Technique

When a therapeutic echoendoscope and access to fluoroscopy are available, pancreatic pseudocyst drainages can be performed as a one-step procedure under EUS guidance. The technique is

relatively straightforward but requires expertise with therapeutic maneuvers such as guidewire exchange and stent deployment. This section reviews the basic techniques and keys to success for EUS-guided pseudocyst drainage. Requisite accessories for the procedure include the following:

- Echoendoscope with a biopsy channel 3.7 mm or larger
- 19-gauge (G) fine-needle aspiration (FNA) needle (lumen of the 22-G needle does not permit a 0.035-inch guidewire)
- 0.035-inch guidewire
- 4.5- or 5-Fr ERCP cannula or an over-the-wire needle-knife catheter
- Over-the-wire biliary balloon dilator
- 7- or 10-Fr double-pigtail plastic stents

Graded Dilation Technique for EUS-Guided Drainage of Pancreatic Pseudocyst (Video 22.1)

After excluding the presence of vasculature in the path of the needle by using color Doppler ultrasound, a 19-G FNA needle is used to puncture the pseudocyst under EUS guidance (Fig. 22.1A). A 0.035-inch guidewire is introduced through the needle and is coiled within the pseudocyst under fluoroscopic guidance (see Fig. 22.1B). The tract is then sequentially dilated under fluoroscopic guidance (see Fig. 22.1C) by first passing a 4.5- or 5-Fr ERCP cannula over the guidewire (see Fig. 22.1D). Further dilation is then undertaken using a 6- to 15-mm over-the-wire biliary balloon dilator (see Fig. 22.1E). Following dilation, two 7- or 10-Fr double-pigtail stents are deployed within the pseudocyst under fluoroscopic guidance (see Fig. 22.1F). Multiple stents and a 7- or 10-Fr nasocystic drainage catheter have to be deployed in all patients with pancreatic abscess or necrosis for periodic flushing and evacuation of the cyst contents.

Technical Tips. A major advantage of the graded dilation technique is that electrocautery is not used during any step of the procedure. In the largest series reported to date on EUS-guided drainage of PFC using the foregoing technique, no major complication such as bleeding or perforation was encountered in any patient.[26] In patients with a thick pseudocyst wall, the ERCP cannula may "bounce off" if it is not aligned properly. It is important that the cannula be in line with the guidewire when it exits the echoendoscope, to penetrate the pseudocyst perpendicularly (see Fig. 22.1C and D). Once within the pseudocyst, the cannula should be withdrawn into the echoendoscope, and repeated penetration of the pseudocyst should be attempted, to dilate the transmural tract further.

Needle-Knife Technique for Pseudocyst Drainage (Video 22.2)

After a guidewire has been coiled within the pseudocyst by using a 19-G FNA needle, the transmural tract can be dilated using electrocautery administered through an over-the-wire needle-knife catheter (rather than dilating the tract with an ERCP cannula). Following access to the pseudocyst, dilation and stenting are performed as outlined earlier.

Another alternative includes the use of a dedicated commercially available cystotome. The cystotome is a modified needle-knife papillotome that consists of an inner wire with a needle-knife tip,

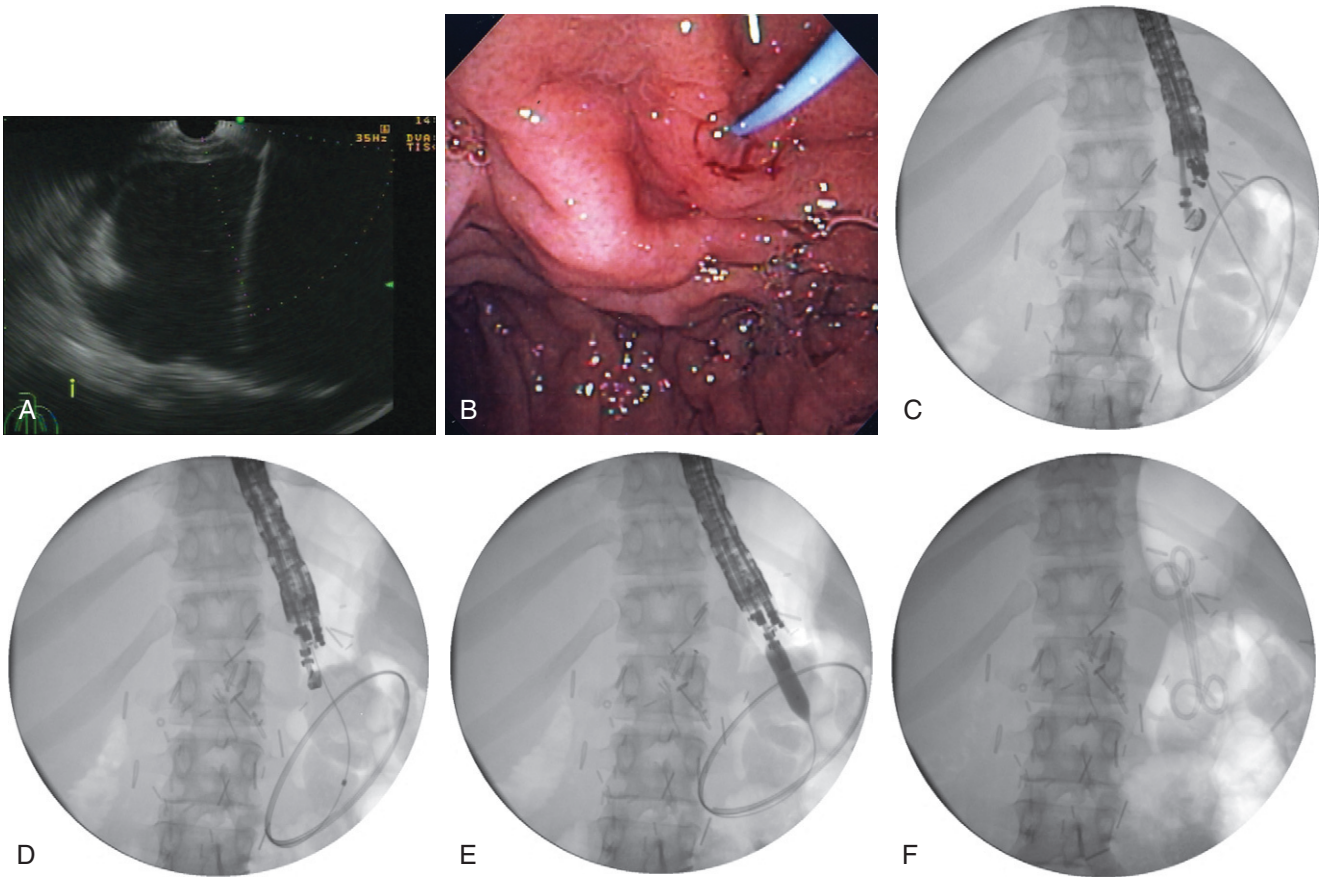


FIGURE 22.1 **A,** Pseudocyst accessed with a 19-G fine-needle aspiration needle. **B,** Passage of a 0.035-inch guidewire into the pseudocyst. Note the edematous gastric mucosa in severe hypoalbuminemia. **C,** Passage of a 0.035-inch guidewire under fluoroscopy. **D,** Passage of a 5-Fr endoscopic retrograde cholangiopancreatography catheter to dilate the transmural tract. **E,** Dilation of the transmural tract with use of a balloon. **F,** Placement of two transmural stents.

a 5-Fr inner catheter, and a 10-Fr outer catheter equipped with a diathermy ring at its distal tip. The proximal end of this device includes a handle with connectors for administration of electrocautery. The pancreatic pseudocyst is punctured with the cystotome by using the knife tip of the inner catheter, with administration of electrocautery, and is then entered with the inner catheter. The metal part of the inner catheter is then withdrawn, and a 0.035-inch guidewire is passed through the inner catheter into the cyst cavity. The outer 10-Fr sheath of the cystotome, which is equipped with a diathermy ring, is advanced through the puncture site by using electrocautery. The cystotome is then removed, leaving the guidewire in the cyst cavity. The transmural tract is then dilated followed by stent deployment.

Technical Tips. An advantage of the needle-knife technique is that it penetrates the pseudocyst wall with relative ease. The main disadvantage of the technique is that perforation was reported as a complication in several series.[8,20,27–29] Generally, EUS is performed for pseudocyst drainage in patients without luminal compression. Pseudocysts that do not cause luminal compression are usually located in the pancreatic tail region or in atypical locations such as the right upper quadrant.[9] The location of these pseudocysts is such that they are accessed from the gastric cardia or the fundus of the stomach. When a catheter is deployed at these locations, because of the acute angulation of the echoendoscope, the deployed needle-knife points tangentially and leads to an undesirable incision. Maintaining a degree of tension over the guidewire keeps the needle-knife catheter in plane with the guidewire as it exits the echoendoscope and can possibly minimize the risk of perforation.

A few technical modifications have been suggested to overcome the need to recannulate the pseudocyst following initial transmural stent placement. After the initial EUS-guided needle-knife puncture, a guidewire is inserted into the pseudocyst through the 5.5-Fr inner catheter of the cystotome after withdrawing the needle knife. The 10-Fr outer catheter of the cystotome is then advanced over the guidewire into the pseudocyst by using electrocautery. A second guidewire can be introduced through the 10-Fr outer catheter of the cystotome into the cavity, alongside the first guidewire after removal of the 5.5-Fr inner catheter.[30]

Another option is the use of a dilator technique. After initial placement of a guidewire into the pseudocyst through a 19-G needle, a wire-guided needle knife is used to dilate the puncture site by using electrocautery. A 10-Fr Soehendra dilator is inserted over the guidewire into the cavity (Video 22.3), and a second guidewire can be inserted through the dilator into the cavity.[31] This technique can potentially enable the placement of more guidewires for multiple stent placements.

Keys to Technical Success and Other Considerations

Stent Deployment

When pseudocyst drainages are performed through the cardia or fundus of the stomach and the duodenum, the tip of the echoendoscope is acutely angulated. Deployment of 10-Fr transmural stents at these sites can be technically challenging unless the tip of the echoendoscope can be kept straightened, under fluoroscopic guidance (Fig. 22.2). This limitation can also be overcome by placement of multiple 7-Fr double-pigtail stents. However, 10-Fr stents should be preferentially deployed if a pseudocyst is infected. Unlike the duodenoscope, which has a 4.2-mm biopsy channel, the biopsy channel of most therapeutic echoendoscopes is only 3.7 mm. When deploying 10-Fr stents, it is important not to have another 0.035-inch guidewire in the biopsy channel because it increases the friction and makes stent deployment very difficult.

Use of the Small Channel Curvilinear Echoendoscope for Pseudocyst Drainage

When a therapeutic echoendoscope is not available, pseudocyst drainage can still be undertaken using a small channel curvilinear echoendoscope by passing a 0.035-inch guidewire into the pseudocyst through a 19-G FNA needle. The echoendoscope is then exchanged over the guidewire for a double-channel gastroscope or duodenoscope, and pseudocyst drainage can be completed successfully.

Bedside EUS for Pseudocyst Drainage

For patients in the intensive care unit who are unstable and are deemed to be too sick to be transported safely to the endoscopy unit, drainage of PFCs can be undertaken at the bedside if a portable fluoroscopy machine is available. This concept was demonstrated in a study of six patients who underwent bedside EUS in the intensive care unit.[32] A pancreatic pseudocyst and a mediastinal abscess were drained successfully in two of these six patients. From the point of view of convenience, these procedures are easier to perform when the EUS processor is small and can be placed on the endoscopy cart.

Multiple Pancreatic Pseudocysts

Approximately 10% of patients have pseudocysts at multiple locations, and their management poses a clinical dilemma.[26] These patients are generally managed by surgery or percutaneous drainage. In a study reported in 2008, 6 of 60 patients with PFCs

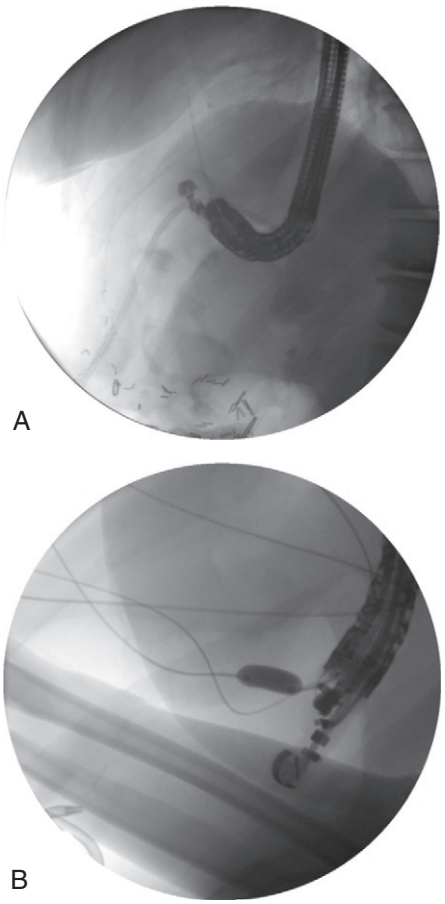


FIGURE 22.2 **A,** Acute angulation of the echoendoscope at drainage through the gastric fundus. A transpapillary pancreatic stent is seen in background. **B,** After guidewire passage, the tip of the echoendoscope is straightened for undertaking further endotherapy.

had multiple fluid collections (≥6 cm), and pancreatography revealed complete duct disruption in all 6 cases.[26] With EUS, 15 individual PFCs were drained successfully in these 6 patients, with a successful clinical outcome in all 3 patients with pancreatic pseudocysts (Fig. 22.3). Three pseudocysts were drained at 3 different sites in each of these 3 patients. Generally, the largest pseudocyst is drained at an index procedure. A repeat procedure is warranted for drainage of other pseudocysts if a patient has persistent symptoms with a noncommunicative fluid collection on follow-up imaging.

Patients with Altered Anatomy

In patients with postsurgical anatomy, identification of focal disorder at EUS can be technically challenging. However, EUS-guided drainage of pancreatic pseudocysts may still be technically feasible because symptomatic pseudocysts usually tend to be large and frequently communicate or extend to other areas in the lesser sac. Reviewing a CT scan before the procedure will provide important information on the landmarks and the best site from which the pseudocyst can be accessed. Caution must be exercised during navigation of the echoendoscope through different limbs because the presence of adhesions can increase the risk for perforation. In a study evaluating the clinical outcomes of patients undergoing EUS-guided drainage of PFCs, a pseudocyst was safely drained through the Roux-en-Y limb in one patient.[26]

Management of Small Symptomatic Pseudocysts

It is technically not feasible to place transmural stents in patients with pseudocysts that measure 4 cm or less. Therefore, symptomatic pseudocysts up to 4 cm in size that communicate with the main pancreatic duct are managed by transpapillary pancreatic stenting. In these patients, following pancreatic stenting, the pseudocyst is aspirated completely by EUS-guided FNA. Despite the lack of published data, observations indicate that these patients experience quick and better symptom relief.

Advantages. When the requisite accessories and technical expertise are available, EUS enables one-step drainage of pancreatic pseudocysts irrespective of the presence or absence of luminal compression. Because it is a one-step procedure, drainage can be undertaken in a timely manner with minimal discomfort to the patient and less need for additional sedation. Confirmation of diagnosis and therapy can be undertaken in the same setting. The ability to drain the pseudocyst in real time under ultrasound guidance minimizes the risk of complications. Intracystic hemorrhage is a rare but serious complication encountered during FNA of cystic lesions of the pancreas. During EUS, the bleeding manifests as hyperechoic foci within the pseudocyst.[33] Early identification of bleeding at EUS permits timely intervention and thereby minimizes the risk for serious adverse events. During non–EUS-guided endoscopic drainage, if a guidewire is accidentally dislodged after balloon dilation of the transmural tract, it may be difficult to access the pseudocyst again because the luminal compression may have disappeared. This is not a major problem with EUS-guided drainage because the pseudocyst is well visualized at all times and reentry to the pseudocyst can be easily accomplished.

Disadvantages. The EUS-guided pseudocyst drainage approach has no major disadvantages. Deployment of 10-Fr stents can sometimes be technically challenging when the tip of the

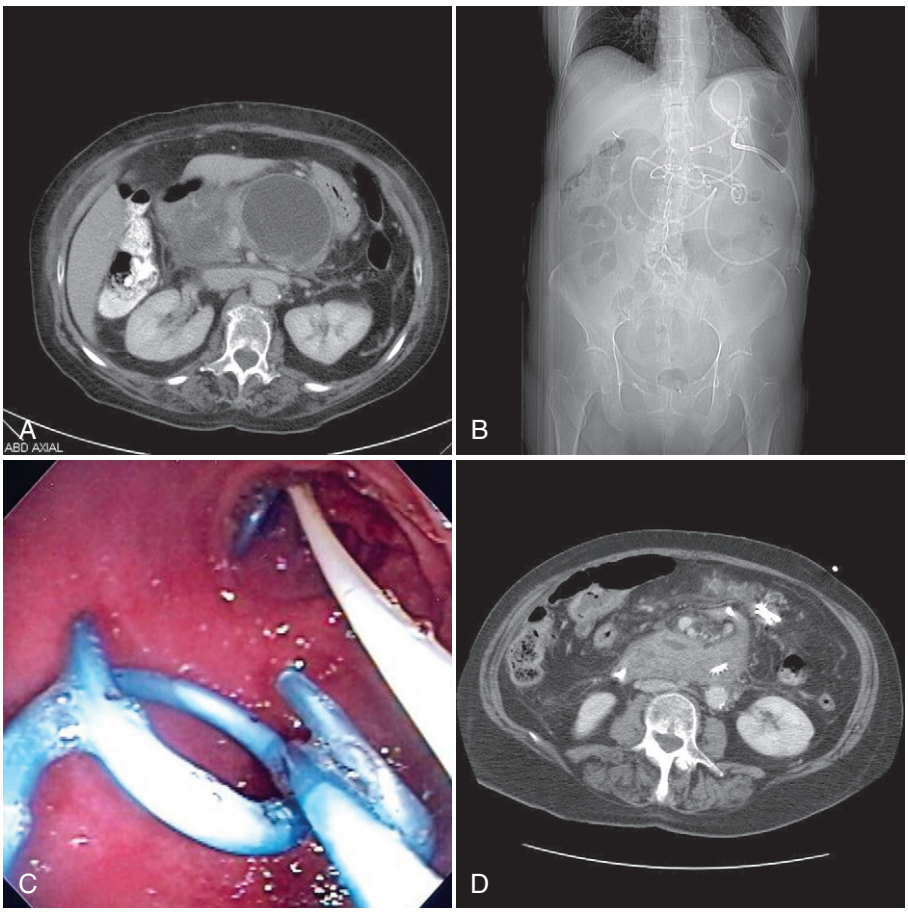


FIGURE 22.3 **A,** Computed tomography (CT) of the abdomen revealing multiple pancreatic fluid collections (PFCs) in this patient. **B,** Five transmural stents draining three large PFCs are evident on this scout image obtained at CT. One stent is transduodenal, three are transgastric, and one is transesophageal. **C,** The corresponding endoscopic image of multiple transgastric stents. **D,** CT of the abdomen revealing complete resolution of all PFCs at 6-week follow-up.

TABLE 22.3

Results of EUS-Guided Drainage from Large Series

Authors (yr)	*N*	Type of Fluid Collection (*n*)	Technical Success (%)	Treatment Success (%)	Complication Rates (and Complications [*n*])
Pfaffenbach et al[47] (1998)	11	Pseudocyst	91	82	0%
Giovannini et al[28] (2001)	35	Pseudocyst (15) Abscess (20)	100 90	100 80	3% (pneumoperitoneum: 1)
Seewald et al[48] (2005)	13	Abscess (8) Necrosis (5)	100	85	31% (minor bleeding: 4)
Kahaleh et al[8] (2006)	46	Pseudocyst	100	Short term: 93 Long term: 84	20% (bleeding: 2; stent migration: 1; infection: 4; pneumoperitoneum: 2)
Hookey et al[35] (2006)	51/116	Pseudocyst (94) Abscess (9) Necrosis (8) Acute fluid collection (5)	96	93	Without EUS: 11.7% With EUS: 10.8% Total: 11.2% (bleeding: 6; pneumoperitoneum: 4; systemic infection: 1; post-ERCP pancreatitis: 1; duodenal/surgical drain communication: 1)
Antillon et al[20] (2006)	33	Pseudocyst	94	Complete resolution: 82 Partial resolution: 12	Major: 6% (perforation: 1; major bleeding: 1) Minor: 9% (minor bleeding: 2; asymptomatic pneumoperitoneum: 1)
Azar et al[27] (2006)	23	Pseudocyst	91	82	4% (pneumoperitoneum: 1)
Kruger et al[18] (2006)	35	Pseudocyst (30) Abscess (5)	94	88	Immediate: 0% Delayed (infection): 31% (stent occlusion: 4; ineffective drainage: 3; secondary infection: 4)
Ahlawat et al[34] (2006)	11	Pseudocyst	100	82	18% (stent migration: 2)
Charnley et al[49] (2006)	13	Necrosis	100	92	0% (2 unrelated deaths after successful treatment and resolution)
Lopes et al[19] (2007)	51	Pseudocyst (36) Abscess (26; 51 patients with 62 collections)	100	94	Immediate: 3% (pneumoperitoneum: 1; stent migration: 1) Delayed: 18% (stent occlusion: 3; stent migration: 8)
Voermans et al[46] (2007)	25	Necrosis	100	93	Severe: 7% (perforation: 1; major bleeding: 1) Minor: 30% (minor bleeding: 8)
Seifert et al[50] (2007)	60	Necrosis	100	73	13% (perforation: 2; bleeding: 5; pneumoperitoneum: 1, with 1 death)
Varadarajulu et al[26] (2008)	60	Pseudocyst (36) Abscess (15) Necrosis (9)	95	93	0%

ERCP, endoscopic retrograde cholangiopancreatography.

echoendoscope is acutely angulated. This problem can be overcome by straightening the tip of the echoendoscope with aid of fluoroscopy or by deployment of 7-Fr stents.

CLINICAL OUTCOMES OF EUS-GUIDED DRAINAGE

Clinical data pertaining to drainage of only pseudocysts are scant, given that most studies evaluated patients with PFCs that also encompassed abscess and necrosis (Table 22.3). The success rate for pseudocyst drainage is higher compared with drainage of infected necrosis, which requires additional treatment measures such as endoscopic necrosectomy to remove necrotic and devitalized tissue. When assessing outcomes, one needs also to distinguish between technical success and resolution of the fluid collection. Technical success refers to achieving satisfactory access and drainage of the fluid collection, whereas PFC resolution pertains to complete resolution and recovery. This concept is important because one can be successful technically in terms of placing transmural stents for an infected walled-off necrosis. However, this procedure does not lead to resolution of the collection, given that additional steps such as endoscopic débridement and necrosectomy are needed. Another point is that when one compares EUS-guided with non–EUS-guided drainage, the difference exists only at the initial stage of attempting to puncture and access the fluid collection. All subsequent steps are similar in both approaches.

Pseudocysts and Abscesses

For pseudocysts, several case series have reported very high success rates for EUS-guided drainage ranging between 82% to 100%.[28,34–37] Clinical data on pancreatic abscess drainage are more limited. Nonetheless, high success rates ranging from 80% to 90% have been reported.[19,28,30]

Infected Walled-off Pancreatic Necrosis

The results of endoscopic drainage of infected walled-off necrosis are generally poorer than pseudocyst drainage, due to the need to remove the necrotic solid debris. Baron et al[38] showed that the success rate of pseudocyst drainage was 92%, compared with 72% in patients with necrosis. Although this study utilized non EUS-guided endoscopic drainage, it illustrated the principle that the outcome of endoscopic drainage for pseudocysts was superior when compared to infected necrosis. In fact, in another study, the success rate was only 25%.[35]

Comparison of EUS-Guided Drainage with Alternative Drainage Techniques

Surgical versus Percutaneous and Endoscopic Drainage

Vosoghi et al[39] reviewed and compared the results of case series of surgical, percutaneous, and endoscopic drainage of symptomatic pseudocysts. The success rates of surgical, percutaneous, non–EUS-guided transmural drainage, and EUS-guided transmural drainage were 100%, 84%, 90%, and 94%, respectively. Complication rates were higher for surgical (28% to 34%, with 1% to 8.5% mortality) and percutaneous drainage (18%, with 2% mortality) compared with non–EUS-guided (15%, with 0% mortality) and EUS-guided transmural (1.5%, with 0% mortality) drainage.

EUS-Guided Cystogastrostomy versus Surgical Cystogastrostomy

A retrospective study compared the clinical outcomes of EUS-guided cystogastrostomy with surgical cystogastrostomy for the management of patients with uncomplicated pancreatic pseudocysts and performed a cost analysis of each treatment modality.[5] The investigators showed that EUS-guided drainage was similar to surgery in terms of rates of treatment success (100% versus 95%), but it had advantages in terms of shorter hospital stay (mean length of stay, 2.7 versus 6.5 days) and lower costs.

Similar findings were reported in a randomized trial that compared EUS and surgery for pancreatic cystogastrostomy.[40] In this trial, which included 36 randomized patients, no difference was noted in the rates of technical (both cohorts, 100%) and treatment success (94.4% versus 100%) and of procedural complications (none in both cohorts) between EUS and surgery, respectively. At a median follow-up of 18 months, no difference was reported in rates of pseudocyst recurrence (0% versus 5.8%) or repeat interventions (5.2% versus 0%) between EUS and surgery, respectively. Although no long-term differences were reported, when EUS was compared with surgery, the average scores for pain and interference of general activity and mood were significantly better at 1 week for the EUS-treated cohort. Compared with surgery, the mean quality of life scores for general health, general vitality, and physical function were significantly better for the EUS group from immediately after the procedure up to 3 months. After 3 months, the improvement in quality of life was similar in both groups. Compared with surgery, the median length of postprocedure hospital stay and average costs were also significantly less for EUS-guided cystogastrostomy. The investigators concluded that EUS-guided cystogastrostomy should be the preferred treatment approach for patients with uncomplicated symptomatic pancreatic pseudocysts because the procedure was less costly, yielded quicker pain relief, was associated with shorter length of hospital stay, and had long-term clinical outcomes and quality of life comparable to those seen after surgery.

EUS-Guided versus Non–EUS-Guided Endoscopic Drainage

Direct comparison of EUS and non–EUS-guided endoscopic drainage has been made. Non–EUS-guided transmural drainage was compared with EUS-guided drainage in a study in which patients with pseudocysts with bulging and no obvious portal hypertension underwent conventional transmural drainage, whereas all remaining patients underwent EUS-guided drainage.[8] No significant differences were noted between both groups in terms of efficacy or safety. Indirectly, this study supported the concept that EUS-guided drainage is superior because it can be used to drain pseudocysts not amenable to conventional transmural drainage, without any increased risks.

In another study (Table 22.4), the rate of technical success between EUS and non–EUS-guided transmural drainage of pancreatic pseudocysts was directly compared prospectively.[23]

TABLE 22.4

Randomized Trials Comparing EUS and Non-EUS Endoscopic Techniques for Pseudocyst Drainage

Authors (yr)	EUS (%)	EGD (%)	*P*
TECHNICAL SUCCESS			
Varadarajulu et al[23] (2008)	100	33.3	<.001
Park et al[41] (2009)		7	
	94	2	.03
TREATMENT SUCCESS			
Varadarajulu et al[23] (2008)	100	87	.48
Park et al[41] (2009)	89	86	.6
COMPLICATIONS			
Varadarajulu et al[23] (2008)	0	13	.48
Park et al[41] (2009)	7	10	.6

EGD, esophagogastroduodenoscopy.

All the patients randomized to EUS ($n = 14$) underwent successful drainage; in contrast, the procedure was technically successful in only 33% randomized to non–EUS-guided drainage ($n = 15$). The reasons for technical failure were the absence of luminal compression in 9 and severe bleeding following attempted puncture of the pseudocyst in 1 patient. All 10 patients subsequently underwent successful drainage of the pseudocyst under EUS guidance. In another similar study, the technical success rate of pseudocyst drainage was higher in patients undergoing EUS-guided drainage compared with those without EUS guidance (94% versus 72%).[41] Several studies reported on the technical feasibility and safety profile of EUS to perform transesophageal drainage of PFCs (Fig. 22.4) even in the absence of luminal compression in the esophagus (Table 22.5).[42–45]

Technical Proficiency

Currently, in most parts of North America and Asia, dedicated devices to perform EUS-guided drainage are not commercially available. Endoscopists who want to perform pseudocyst drainages but who do not perform ERCPs need to be proficient with use of accessories such as 0.035-inch guidewires, needle-knife catheters, balloon dilators, and double-pigtail stents. In a study that evaluated performance of a single endosonographer, the technical proficiency for performing pseudocyst drainages improved significantly after 25 procedures.[23] The median procedural duration after performing 25 cases decreased from 70 to 25 minutes.

TECHNICAL LIMITATIONS

It is clear that EUS-guided drainage offers several advantages compared with traditional drainage techniques. However, the EUS procedure has limitations related to the echoendoscope design that result in technical difficulties during endoscopic drainage. An important limitation is that the size of the working channel of a therapeutic linear echoendoscope is 3.7 or 3.8 mm, smaller than that of a therapeutic duodenoscope (4.2 mm). This size limits the suction ability, which is important when copious fluid is draining from the pseudocyst cavity after the initial puncture. Additionally, although placing a 10-Fr stent is not an issue with a linear echoendoscope, one may need to place multiple stents or a nasocystic catheter for irrigation. In these situations, it may be faster and easier to use a double-wire technique. However, the smaller working channels of echoendoscopes limit the use of double-wire techniques in that the size of the first transmural stent inserted must be 8.5 Fr or smaller because of excessive resistance within a 3.7-mm working channel with two guidewires in place. The first stent that is placed cannot be the preferred, larger 10-Fr size.

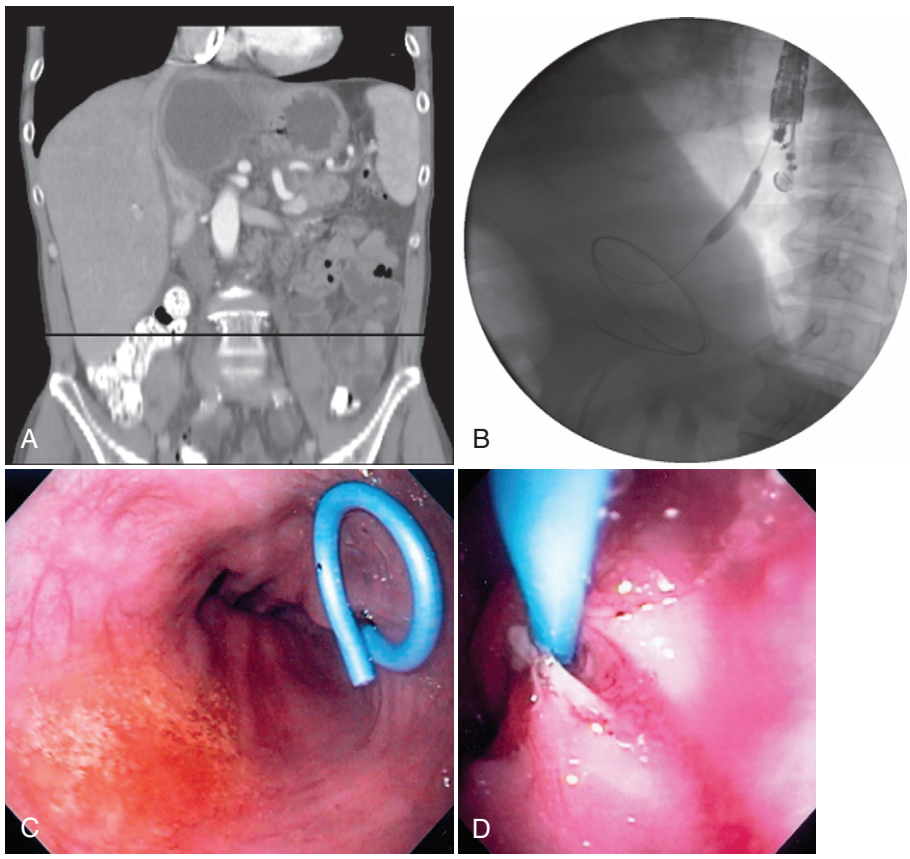


FIGURE 22.4 **A,** Computed tomography (CT) of the abdomen (coronal view) revealing a pancreatic fluid collection (PFC) at the liver hilum. **B,** The PFC is then accessed from the distal esophagus with a 19-G needle, and the tract is dilated to 6 mm using a balloon. **C,** A transesophageal stent or nasocystic drainage catheter is deployed. **D,** During transesophageal drainage, it is recommended to dilate the tract to only 6 mm and to deploy 7-Fr stents because of the increased risk of mediastinitis associated with the procedure.

TABLE 22.5
Reports on EUS-Guided Transesophageal Drainage of Pancreatic Fluid Collections

Authors (yr)	Etiology and PFC Type	Drainage Modality	Complications	Outcomes	Follow-up (mo)
Gupta et al[42] (2007)	Alcohol; pseudocyst	Only aspiration	None	Success	3
Saftouia et al[43] (2006)	Alcohol; pseudocyst	10-Fr stent	None	Success	3
Baron et al[44] (2000)	Alcohol; pseudocyst	7-Fr stent	Mediastinal free air on CT	Success	2
Trevino et al[45] (2009)	Alcohol; postsurgical	7-Fr stent, drainage catheter	None	Success	24

CT, computed tomography; PFC, pancreatic fluid collection.

Another limitation is the oblique view of current echoendoscopes. This configuration limits the endoscopic view and results in a tangential puncture axis. Puncturing at an angle may hamper successful completion of the procedure because the force that is applied when accessories are introduced through the working channel cannot be fully directed toward the puncture site. The tangential axis also makes subsequent cannulation of the pseudocyst cavity difficult, unless there was prior balloon dilatation of the puncture site or a double-wire technique was used.

A prototype forward-viewing therapeutic echoendoscope developed by Olympus allows a forward axis of needle puncture and insertion of accessories, parallel to the scanning axis. This facilitates forward transmission of force when inserting accessories, stents, and catheters. In a pilot study, all pseudocysts were successfully drained without complications, and some pseudocysts could be punctured only with the forward-viewing scope.[46] The forward-viewing echoendoscope is limited by a 3.7-mm working channel, a lack of elevator, and an ultrasonic view of only 90 degrees.

Endoscopic drainage is feasible only for PFCs located around the stomach and duodenum. When PFCs involve more distal locations such as the paracolic regions, then they are not accessible endoscopically, and other adjunctive measures such as percutaneous or surgical drainage need to be considered.

SUMMARY

It is clear from current evidence that EUS is the endoscopic modality of choice for drainage of pancreatic pseudocysts. EUS increases the rates of technical success, decreases complications, and affects patient management by establishing an alternative diagnosis in a small subset of patients. Although limited, current data suggest that for patients with uncomplicated pseudocysts located adjacent to the stomach or duodenum, the technical and treatment outcomes of EUS are comparable to those of surgery. The procedure is less costly, is associated with a shorter length of hospital stay, and yields long-term quality of life comparable to that experienced after surgery.

REFERENCES

1. Park AE, Heniford BT. Therapeutic laparoscopy of the pancreas. *Ann Surg*. 2002;236:149–158.
2. Davila-Cervantes A, Gomez F, Chan C, et al. Laparoscopic drainage of pancreatic pseudocysts. *Surg Endosc*. 2004;18:1420–1426.
3. Kohler H, Schafmayer A, Ludtke FE, et al. Surgical treatment of pancreatic pseudocysts. *Br J Surg*. 1987;74:813–815.
4. Bhattacharya D, Ammori BJ. Minimally invasive approaches to the management of pancreatic pseudocysts. *Surg Laparosc Endosc Percutan Tech*. 2003;13:141–148.
5. Varadarajulu S, Lopes TL, Wilcox CM. EUS versus surgical cyst-gastrostomy for management of pancreatic pseudocysts. *Gastrointest Endosc*. 2008;68: 649–655.
6. Bradley 3rd EL, Howard TJ, van Sonnenberg E, et al. Intervention in necrotizing pancreatitis: an evidence based review of surgical and percutaneous alternatives. *J Gastrointest Surg*. 2008;12:634–639.
7. Adams DB, Anderson MC. Percutaneous catheter drainage compared with internal drainage in the management of pancreatic pseudocyst. *Ann Surg*. 1992;215:571–576.
8. Kahaleh M, Shami VM, Conaway MR, et al. Endoscopic ultrasound drainage of pancreatic pseudocyst: a prospective comparison with conventional endoscopic drainage. *Endoscopy*. 2006;38:355–359.
9. Varadarajulu S, Wilcox CM, Tamhane A, et al. Role of EUS in drainage of peripancreatic fluid collections not amenable for endoscopic transmural drainage. *Gastrointest Endosc*. 2007;66:1107–1119.
10. Bejanin H, Liquory C, Ink O, et al. Endoscopic drainage of pseudocysts of the pancreas: study of 26 cases. *Gastroenterol Clin Biol*. 1993;17(11): 804–810.
11. Smits ME, Rauws EA, Tytgat GN, et al. The efficacy of endoscopic treatment of pancreatic pseudocysts. *Gastrointest Endosc*. 1995;42(3):202–207.
12. Sharma SS, Bhargawa N, Govil A. Endoscopic management of pancreatic pseudocyst: a long-term follow-up. *Endoscopy*. 2002;34(3):203–207.
13. Sahel J, Bastid C, Pellat B, et al. Endoscopic cystoduodenostomy of cysts of chronic calcifying pancreatitis: a report of 20 cases. *Pancreas*. 1987;2: 447–453.
14. Cremer M, Deviere J, Engelholm L. Endoscopic management of cysts and pseudocysts in chronic pancreatitis: long-term follow-up after 7 years of experience. *Gastrointest Endosc*. 1989;35:1–9.
15. Monkemuller KE, Baron TH, Morgan DE. Transmural drainage of pancreatic fluid collections without electrocautery using the Seldinger technique. *Gastrointest Endosc*. 1998;48:195–200.
16. Baron TH, Thaggard WG, Morgan DE, et al. Endoscopic therapy for organized pancreatic necrosis. *Gastroenterology*. 1996;111:755–764.
17. Papachristou GI, Takahashi N, Chahal P, et al. Per oral endoscopic drainage/debridement of walled-off pancreatic necrosis. *Ann Surg*. 2007; 245:943–951.
18. Kruger M, Schneider AS, Manns MP, et al. Endoscopic management of pancreatic pseudocysts or abscesses after an EUS-guided 1-step procedure for initial access. *Gastrointest Endosc*. 2006;63(3):409–416.
19. Lopes CV, Pesenti C, Bories E, et al. Endoscopic-ultrasound–guided endoscopic transmural drainage of pancreatic pseudocysts and abscesses. *Scand J Gastroenterol*. 2007;42:524–529.
20. Antillon MR, Shah RJ, Stiegmann G, et al. Single-step EUS-guided transmural drainage of simple and complicated pancreatic pseudocysts. *Gastrointest Endosc*. 2006;63(6):797–803.
21. Fockens P, Johnson TG, van Dullemen HM, et al. Endosonographic imaging of pancreatic pseudocysts before endoscopic transmural drainage. *Gastrointest Endosc*. 1997;46:412–416.
22. Norton ID, Clain JE, Wiersema MJ, et al. Utility of endoscopic ultrasonography in endoscopic drainage of pancreatic pseudocysts in selected patients. *Mayo Clin Proc*. 2001;76:794–798.
23. Varadarajulu S, Christein JD, Tamhane A, et al. Prospective randomized trial comparing EUS and conventional endoscopy for transmural drainage of pancreatic pseudocysts. *Gastrointest Endosc*. 2008;68:1102–1111.
24. Sriram PV, Kaffes AJ, Rao GV, et al. Endoscopic ultrasound-guided drainage of pancreatic pseudocysts complicated by portal hypertension or by intervening vessels. *Endoscopy*. 2005;37:231–235.
25. Bhasin DK, Rana SS, Nagi B, et al. Movement of the pancreas associated with change of posture. *JOP*. 2007;8:458–459.
26. Varadarajulu S, Tamhane A, Blakely J. Graded dilation technique for EUS-guided drainage of peripancreatic fluid collections: an assessment of outcomes, complications and technical proficiency. *Gastrointest Endosc*. 2008;68:656–666.
27. Azar RR, Oh YS, Janec EM, et al. Wire-guided pancreatic pseudocyst drainage by using a modified needle knife and therapeutic echoendoscope. *Gastrointest Endosc*. 2006;63:688–692.
28. Giovannini M, Pesenti CH, Rolland AL, et al. Endoscopic ultrasound guided drainage of pancreatic pseudo-cyst and pancreatic abscess using a therapeutic echoendoscope. *Endoscopy*. 2001;33:473–477.
29. Will U, Wegener C, Graf KI, et al. Differential treatment and early outcome in the interventional endoscopic management of pancreatic pseudocysts in 27 patients. *World J Gastroenterol*. 2006;12:4175–4178.
30. Jansen JM, Hanrath A, Rauws EA, et al. Intracystic wire exchange facilitating insertion of multiple stents during the endoscopic drainage of pancreatic pseudocysts. *Gastrointest Endosc*. 2007;66:157–161.
31. Ang TL, Teo EK, Fock KM, et al. EUS-guided drainage of infected pancreatic pseudocyst: use of a 20F Soehendra dilator to facilitate a double-wire technique for initial transgastric access (with videos). *Gastrointest Endosc*. 2008;68:192–194.
32. Varadarajulu S, Eloubeidi MA, Wilcox CM. The concept of bedside EUS. *Gastrointest Endosc*. 2008;67:1180–1184.
33. Varadarajulu S, Eloubeidi MA. Frequency and significance of acute intracystic hemorrhage during EUS-FNA of cystic lesions of the pancreas. *Gastrointest Endosc*. 2004;60:631–635.
34. Ahlawat SK, Charabaty-Pishvaian A, Jackson PG, Haddad NG. Single-step EUS-guided pancreatic pseudocyst drainage using a large channel linear array echoendoscope and cystotome: results in 11 patients. *JOP*. 2006;7: 616–624.
35. Hookey LC, Debroux S, Delhaye M, et al. Endoscopic drainage of pancreatic-fluid collections in 116 patients: a comparison of etiologies, drainage techniques, and outcomes. *Gastrointest Endosc*. 2006;63:635–643.
36. Weckman L, Kylanpaa ML, Puolakkainen P, et al. Endoscopic treatment of pancreatic pseudocysts. *Surg Endosc*. 2006;20:603–607.
37. Lopes CV, Pesenti C, Bories E, et al. Endoscopic ultrasound-guided endoscopic transmural drainage of pancreatic pseudocysts. *Arq Gastroenterol*. 2008;45:17–21.
38. Baron TH, Harewood GC, Morgan DE, et al. Outcome differences after endoscopic drainage of pancreatic necrosis, acute pancreatic pseudocysts, and chronic pancreatic pseudocysts. *Gastrointest Endosc*. 2002;56:7–17.
39. Vosoghi M, Sial S, Garrett B, et al. EUS-guided pancreatic pseudocyst drainage: review and experience at Harbor-UCLA Medical Center. *MedGenMed*. 2002;4:2.
40. Varadarajulu S, Trevino JM, Wilcox CM, et al. Randomized trial comparing EUS and surgery for pancreatic pseudocyst drainage [abstract]. *Gastrointest Endosc*. 2010;71, AB116 [abstract].
41. Park DH, Lee SS, Moon SH, et al. Endoscopic ultrasound-guided versus conventional transmural drainage for pancreatic pseudocysts: a prospective randomized trial. *Endoscopy*. 2009;41:842–848.
42. Gupta R, Munoz JC, Garg P, et al. Mediastinal pancreatic pseudocyst: a case report and review of the literature. *MedGenMed*. 2007;9:8–13.
43. Saftouia A, Cuirea T, Dumitrescu D, et al. Endoscopic ultrasound-guided transesophageal drainage of a mediastinal pancreatic pseudocyst. *Endoscopy*. 2006;38:538–539.
44. Baron TH, Wiersema MJ. EUS-guided transesophageal pancreatic pseudocyst drainage. *Gastrointest Endosc*. 2000;52:545–549.
45. Trevino JM, Christein JD, Varadarajulu S. EUS-guided transesophageal drainage of peripancreatic fluid collections. *Gastrointest Endosc*. 2009;70: 793–797.
46. Voermans RP, Eisendrath P, Bruno MJ, et al. Initial evaluation of a novel prototype forward-viewing ES endoscope in transmural drainage of pancreatic pseudocysts (with videos). *Gastrointest Endosc*. 2007;66: 1013–1017.
47. Pfaffenbach B, Langer M, Stabenow-Lohbauer U, et al. Endosonography controlled transgastric drainage of pancreatic pseudocysts [in German with English abstract]. *Dtsch Med Wochenschr*. 1998;123:1439–1442.
48. Seewald S, Groth S, Omar S, et al. Aggressive endoscopic therapy for pancreatic necrosis and pancreatic abscess: a new safe and effective treatment algorithm. *Gastrointest Endosc*. 2005;62:92–100.
49. Charnley RM, Lochan R, Gray H, et al. Endoscopic necrosectomy as primary therapy in the management of infected pancreatic necrosis. *Endoscopy*. 2006;38:925–928.
50. Seifert H, Biermer M, Schmitt W, et al. Long-term outcome of endoscopic pancreatic necrosectomy: final results of the first German multi-center trial [abstract]. *Gastrointest Endosc*. 2007;65:AB360.

CHAPTER 23

EUS-Guided Drainage of the Biliary and Pancreatic Ductal Systems

Michael J. Levy

Key Points

EUS-guided biliary and pancreatic ductal interventions are being developed as less invasive alternatives to surgical and interventional radiologic therapies. At present, more data are available on biliary than on pancreatic duct interventions.

EUS-guided biliary and pancreatic duct drainage can be undertaken either by transluminal stenting or by passage of a guidewire that, on exiting the major duodenal papilla, would facilitate therapy by the rendezvous approach.

Although the technical success rate of EUS-guided ductal drainages is greater than 85%, the rate of complications exceeds 15%, and complications are severe. The procedures are technically challenging and are time and personnel intensive.

Additional studies are needed to define the risks and long-term outcomes of these procedures more accurately. Dedicated EUS-specific devices are required to improve the safety profile of the technique and to promote its application in clinical practice.

INTRODUCTION

The role of endoscopic ultrasonography (EUS) has evolved since the 1980s, when use of the technique was restricted to the evaluation of subepithelial lesions and gastrointestinal luminal cancer staging. The development of linear instruments allowed fine-needle aspiration (FNA) with cytologic evaluation and Tru-Cut biopsy (TCB) with histologic assessment and thus further expanded the role of EUS.[1,2] Similarly, EUS is used to guide therapeutic interventions including celiac plexus and ganglia blockade and neurolysis,[3–5] pancreatic fluid drainage,[6–9] cholecystenterostomy,[10] and delivery of cytotoxic agents such as chemotherapy, radioactive seeds, and gene therapy.[11,12] In the mid-1990s, the concept of combining therapeutic endoscopic retrograde cholangiopancreatography (ERCP) with interventional EUS technology led to the concept of endoradiosonographic cholangiopancreatography (ERSCP).[13]

The continued need to develop less invasive alternatives to surgical and interventional radiologic therapies drove the development of EUS-guided methods for biliary and pancreatic intervention. The purposes of this chapter are to review existing data and to focus on the EUS techniques for obtaining access and subsequent drainage of biliary and pancreatic ducts.

GENERAL ROLE

ERCP is the method most commonly employed to access the bile duct or main pancreatic duct (MPD) and is routinely performed to obtain diagnostic information or provide therapy. Indications for ERCP include evaluation of benign disorders (e.g., inflammatory stricture, stone, congenital ductal anomalies) or malignancy (e.g., cholangiocarcinoma, pancreatic carcinoma). Percutaneous and surgical approaches are available for patients in whom access cannot be achieved by ERCP.[14,15] An emerging alternative to these more invasive and potentially risky interventions is EUS-guided access and drainage. EUS-guided techniques appear ideally suited following failed ERCP, which may occur secondary to a patients' underlying disease (e.g., gastric or duodenal obstruction, disrupted duct), the presence of anatomic variants (e.g., duodenal diverticulum), or surgically altered anatomy (e.g., Billroth II resection or pancreaticoduodenectomy). EUS approaches are also considered for patients who are poor operative candidates and for persons who decline surgical intervention.

PATIENT PREPARATION

Although EUS is typically performed in an ambulatory setting, most endosonographers perform interventional EUS examinations in a hospital setting within a fluoroscopy suite and using monitored anesthesia care or general anesthesia services. As for diagnostic EUS examinations, the initial evaluation should include a thorough history, physical examination, and review of medical record to identify factors that influence the need, risks, benefits, alternatives, and timing of EUS and for documenting acquisition of informed consent. Laboratory and radiologic studies are ordered as necessary for management of the underlying disorder and sometimes to clarify the anatomy and to help guide planned interventions. Antibiotics (e.g., levofloxacin or ciprofloxacin) are routinely administered before the procedure.

EQUIPMENT AND TECHNICAL CONSIDERATIONS

EUS is ideally performed with a therapeutic channel linear array echoendoscope to allow use of a broader array of accessories and insertion of large-caliber 10-Fr stents. Smaller-caliber diagnostic echoendoscopes may be used to perform rendezvous wire passage or to place 7-Fr or smaller stents. Duct access may be achieved with any of the currently available 25-, 22-, or 19-gauge (G) FNA needles in conjunction with a wide selection of available wires. Before a needle is used, it is important to verify that the selected FNA needle will allow passage of a particular guidewire. One cannot automatically assume that a needle of a particular gauge, or wire of a particular caliber, can replace a similarly sized needle or wire, because of the minor variations that exist in equipment among companies.[16,17] Use of a larger-caliber needle offers the ability to use a larger-gauge guidewire that may facilitate traversal of stenotic strictures and facilitate passage of other accessories. However, initial duct access may be more difficult when using larger-gauge and stiffer needles.

A clear understanding of the procedure goals can help guide equipment selection. For instance, it may be reasonable to use a 25-G needle if the intended goal is to obtain a cholangiogram or pancreatogram. Some endosonographers also prefer a smaller-gauge needle to determine whether contrast freely flows into the anastomosed bowel lumen, a finding suggesting absence of critical stenosis and thereby potentially obviating the need for therapeutic intervention (e.g., anastomotic dilation and stenting).

Guidewire use largely depends on needle selection. Use of a 0.035-inch guidewire requires selection of a 19-G needle. These stiffer wires may be more difficult to insert into the bile or pancreatic duct, but use of these wires may enable traversal of obstructed segments and may facilitate subsequent interventions. Thus, these wires are generally preferred in this setting. A 0.018-inch guidewire may be used with a 19- or 22-G needle. These wires are more flexible and may improve duct access and facilitate traversal of obstructed segments, but their floppy nature can make subsequent interventions more difficult. Similarly, one may select Teflon-coated hydrophilic wires or angled wires, which may facilitate traversal of narrowed or tortuous segments. The selected guidewire is advanced in an antegrade fashion across the site of stenosis and then papilla or anastomosis and then is coiled in the small bowel. These steps are performed under fluoroscopic guidance.

Various accessories may be used to create the fistula between the gut lumen (stomach, duodenum, or jejunum) and duct (bile or pancreatic) to facilitate passage of other accessories or for dilation of anastomotic strictures. A variety of standard biliary and pancreatic catheter dilators and pneumatic dilators may be used, based on the patient's anatomy. No formal comparative trials exist to clarify the relative value of available devices. Equipment use varies among endoscopists and often requires trial and error even within the same patient.

EUS-GUIDED ACCESS AND THERAPY OF THE BILIARY DUCTAL SYSTEM (VIDEOS 23.1 AND 23.2)

Wiersema et al[18] performed the first EUS-guided cholangiogram following unsuccessful ERCP and demonstrated successful opacification of the biliary tree in 7 of 10 patients. Subsequently, a porcine model was used to demonstrate EUS-guided hepaticogastrostomy to palliate obstructive jaundice.[19] Since then, the practice has gradually evolved, and many technical modifications have been reported. In broad terms, EUS-guided intrahepatic (i.e., hepaticogastrostomy) or extrahepatic (i.e., choledochoduodenostomy) drainage is achieved following transluminal access from the stomach or duodenum, respectively.

Indications

EUS-guided biliary access and therapy are most commonly indicated after failed ERC to evaluate and manage the following:

1. Malignant biliary obstruction (e.g., pancreatic carcinoma or cholangiocarcinoma)
2. Benign biliary obstruction (e.g., inflammatory stricture, stones, congenital ductal anomalies)

Technique

Transhepatic Approach (Hepaticogastrostomy)

Although EUS-guided biliary duct drainage is reviewed first, many of the techniques and principles also apply to the other routes and sites of drainage. To access the intrahepatic bile ducts, the echoendoscope must be positioned within the proximal stomach (cardia, fundus, or proximal body) and oriented along the lesser curve or more posterior position (Fig. 23.1). The liver is scanned to identify a dilated intrahepatic bile duct that is ideally oriented in a plane that facilitates access and passage of accessories.

A location is selected that allows the least distance between the transducer and a left intrahepatic bile duct branch to facilitate access and subsequent therapy. It is important to exclude intervening structures, such as blood vessels and undesired ducts. After bile is aspirated to confirm biliary access, contrast is injected to delineate the biliary anatomy fluoroscopically. Under fluoroscopic guidance, a guidewire is advanced through the FNA needle, which is passed in an antegrade fashion through the site of obstruction and into the duodenum. The guidewire is advanced further to form loops within the duodenal lumen to reduce the risk of wire dislodgment that may occur either during removal of the echoendoscope or when inserting the side-viewing duodenoscope. Passage of the wire across the site of obstruction and into the small bowel allows subsequent transpapillary or transanastomotic stenting.

Once the wire is adequately positioned within the small bowel, the echoendoscope is back-loaded, thus leaving the guidewire in place. The rendezvous portion of the procedure is then performed by passing a side- or forward-viewing endoscope to the papilla or site of anastomosis. The luminal end of the guidewire is grasped with a snare or biopsy cable, and the wire is withdrawn through the endoscope, to leave both ends of the guidewire exiting the patient's mouth and under the endoscopist's control. Alternatively, the duodenoscope may be passed over the guidewire, a maneuver that eliminates the need to grasp the guidewire and withdraw through the accessory channel. However, some endosonographers find this latter approach to be technically challenging or believe that this method places unacceptable tension on the wire and risks injury to the liver parenchyma, bile duct, or duodenum. The ERC (retrograde) portion of the procedure can be performed with a standard side-viewing duodenoscope in patients with unaltered gastroduodenal anatomy. In patients with an afferent jejunal limb or Roux-en-Y reconstruction following pancreaticoduodenectomy, an extended forward-viewing instrument such as a colonoscope is often employed.

Once the selected instrument is properly positioned and guidewire control is achieved, biliary stent insertion and other interventions may be performed in standard fashion. It is often necessary to work over the guidewire until initial dilation is performed. After the site of obstruction is dilated with a catheter or balloon, subsequent interventions may be performed over or alongside the guidewire (if desired), thereby maintaining access with a safety wire. Following dilatation, a cannula can be passed alongside the safety wire, to leave a separate wire within the bile duct and thus allow subsequent stent insertion and duct drainage.

In contrast, with the transpapillary approach, one may opt to perform the entire examination, including stent insertion, with an echoendoscope alone without a need for the rendezvous portion of the examination (Fig. 23.2). For this technique, tract

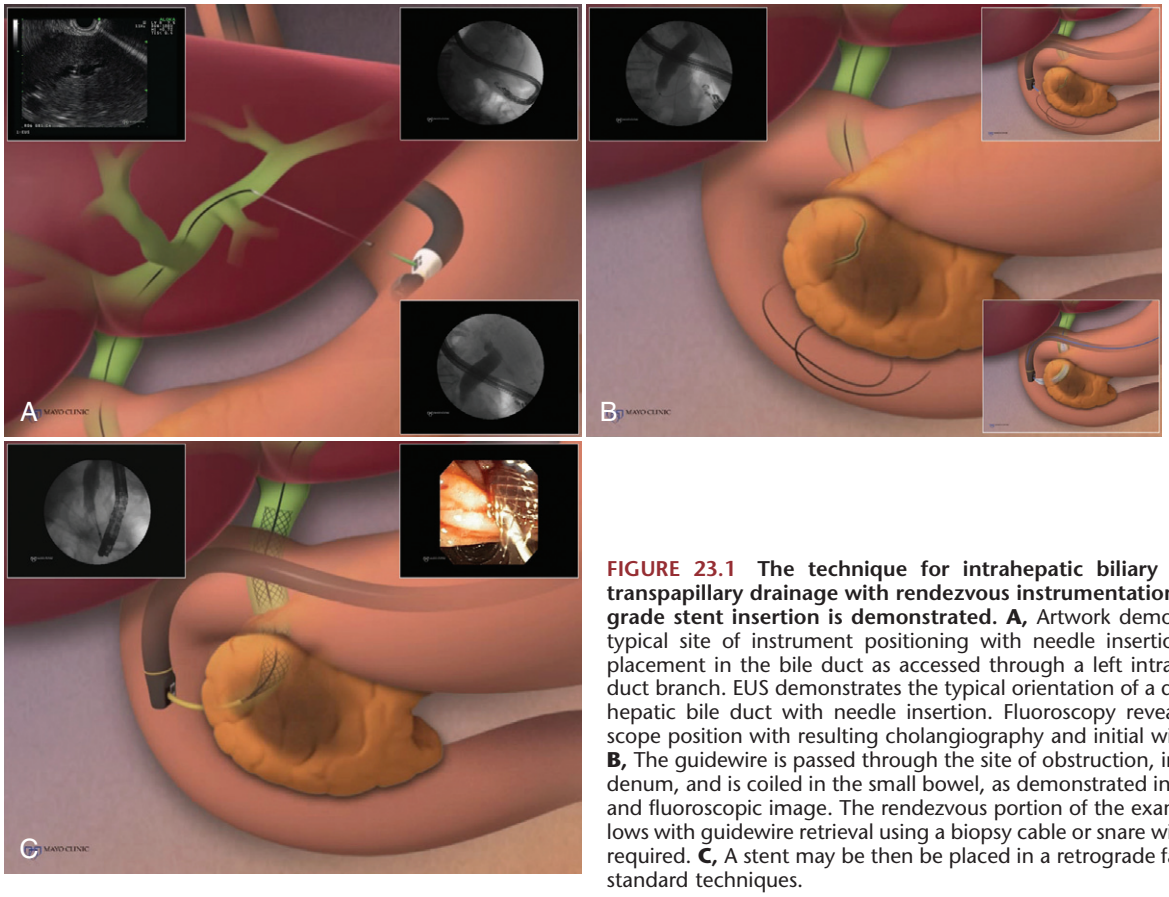


FIGURE 23.1 The technique for intrahepatic biliary access and transpapillary drainage with rendezvous instrumentation and retrograde stent insertion is demonstrated. A, Artwork demonstrates the typical site of instrument positioning with needle insertion and wire placement in the bile duct as accessed through a left intrahepatic bile duct branch. EUS demonstrates the typical orientation of a desired intrahepatic bile duct with needle insertion. Fluoroscopy reveals the ideal scope position with resulting cholangiography and initial wire insertion. **B,** The guidewire is passed through the site of obstruction, into the duodenum, and is coiled in the small bowel, as demonstrated in the artwork and fluoroscopic image. The rendezvous portion of the examination follows with guidewire retrieval using a biopsy cable or snare with dilation if required. **C,** A stent may be then be placed in a retrograde fashion using standard techniques.

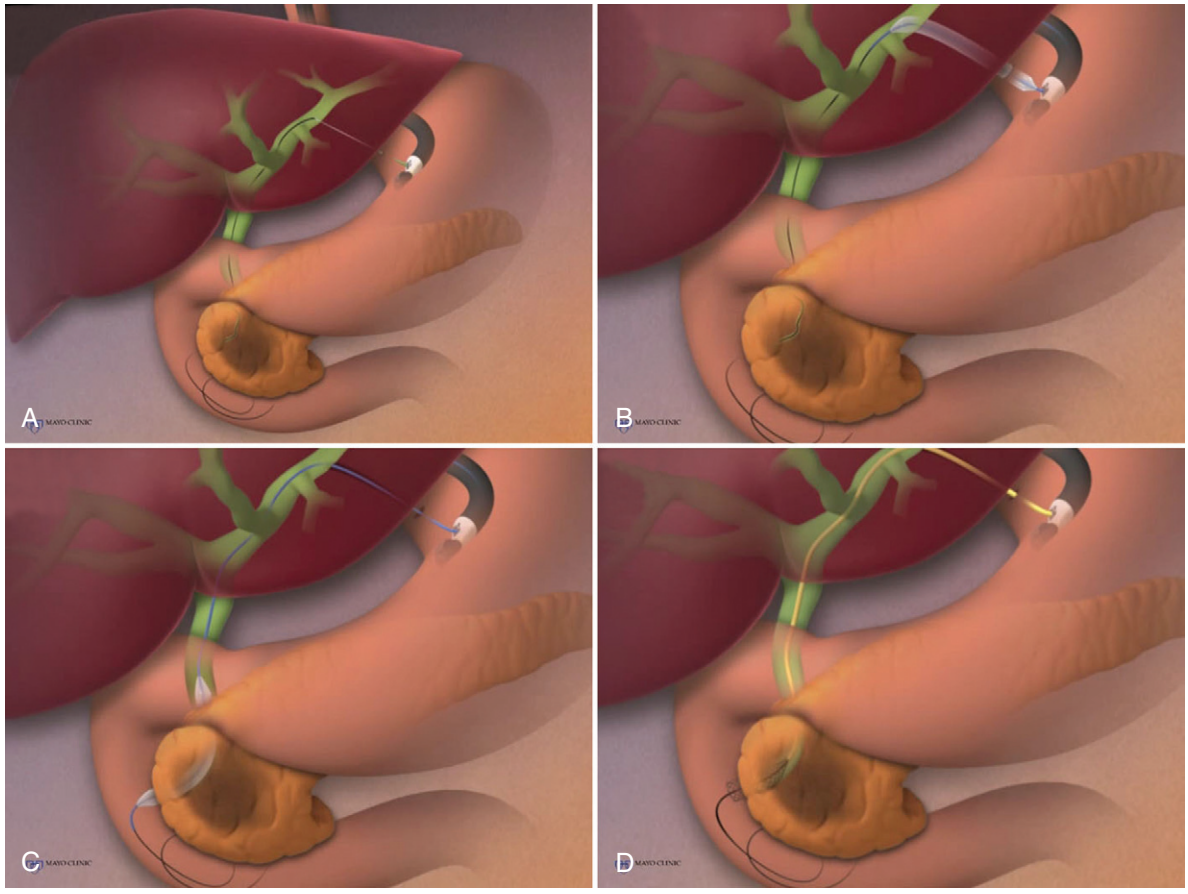


FIGURE 23.2 The technique for intrahepatic biliary access and transpapillary drainage with antegrade stent insertion to the small bowel, performed solely through an echoendoscope, is demonstrated. A, EUS is used to access a branch of the left intrahepatic bile duct. A guidewire is then passed into the biliary tree and duodenum. **B,** Tract dilation is required to include the gastric wall, hepatic parenchyma, and intrahepatic bile duct wall. **C,** The site of obstruction is then dilated to facilitate stent insertion. **D,** Plastic or metal stent placement may then be achieved in an antegrade direction, all performed through an echoendoscope under ultrasound and fluoroscopic guidance.

dilation is required, including the gastric wall, hepatic parenchyma, and intrahepatic bile duct wall. Tract dilation can be performed by many approaches, but the initial use of a dilating balloon, standard cannula, or tapered catheter is preferred. Adequate dilation may require use of several such devices. Although some endosonographers routinely rely on cystotome or needle-knife entry, it is more prudent to do so only as a rescue technique when other approaches fail, because of the perceived risk of cautery-induced injury. Whenever possible, the stent is advanced so that the distal tip rests within the small bowel and the proximal end of the stent lies within the stomach, to optimize duct drainage and diminish the risk of inadvertent stent migration. However, at times it may not be possible to advance the guidewire beyond the site of obstruction or papilla (or anastomosis). In this situation, the stent may be inserted so that the distal tip rests within the biliary tree while the proximal end lies within the gastric lumen, a procedure sometimes referred to as transluminal or transmural drainage (Fig. 23.3). Stents of varying caliber and length have been used. Although pigtail stents are generally favored, straight stents may be used as well. Extra side holes may be created within the intraductal portion of the stent to facilitate drainage.

Extrahepatic Approach (Choledochoduodenostomy)

Giovannini et al[20] performed the first clinical EUS-guided biliary drainage in a patient with pancreatic adenocarcinoma, by transduodenal access of the extrahepatic bile duct with plastic stent insertion. Other investigators expanded on their initial experiences.[17,21,25] With this approach, the echoendoscope is advanced to the duodenum, where the extrahepatic (either intrapancreatic or suprapancreatic) bile duct can be accessed. The FNA needle is inserted into the extrahepatic bile duct, and a guidewire is advanced in an antegrade direction into the duodenum (Fig. 23.4). The procedure is completed in a similar fashion to the transhepatic technique, with the stent advanced through the site of obstruction to provide transpapillary drainage into the duodenum. Depending on the orientation of the echoendoscope relative to the biliary anatomy, wire insertion from this position has a tendency for passage proximally into the intrahepatic bile ducts instead of distally through the papilla. This problem can usually be overcome by altering the scope position or by elevator deflection. Alternatively, the guidewire may be further advanced into the intrahepatic biliary tree to induce looping and eventual passage in the alternate direction toward the papilla. Fistula patency is maintained by the indwelling stent, and the result is the creation of an endoscopic choledochoduodenostomy with transluminal stenting and decompression of the proximal biliary tree without traversal of the obstructing mass or papilla (Fig. 23.5).

Technical Success, Outcomes, and Complications

Whereas the technical success of these procedures can be established, data pertaining to clinical success, therapeutic response, and complications are more difficult to discern from current reports. The paucity of data, study heterogeneity, and overall methodology limit the strengths of any conclusions regarding these techniques. Studies vary greatly in terms of the precise endoscopic procedures performed, the procedural goals, the technical and clinical end points, the definitions of success, the duration and extent of follow-up, and the overall extent and detail of documentation. Although rigorous study designs are not

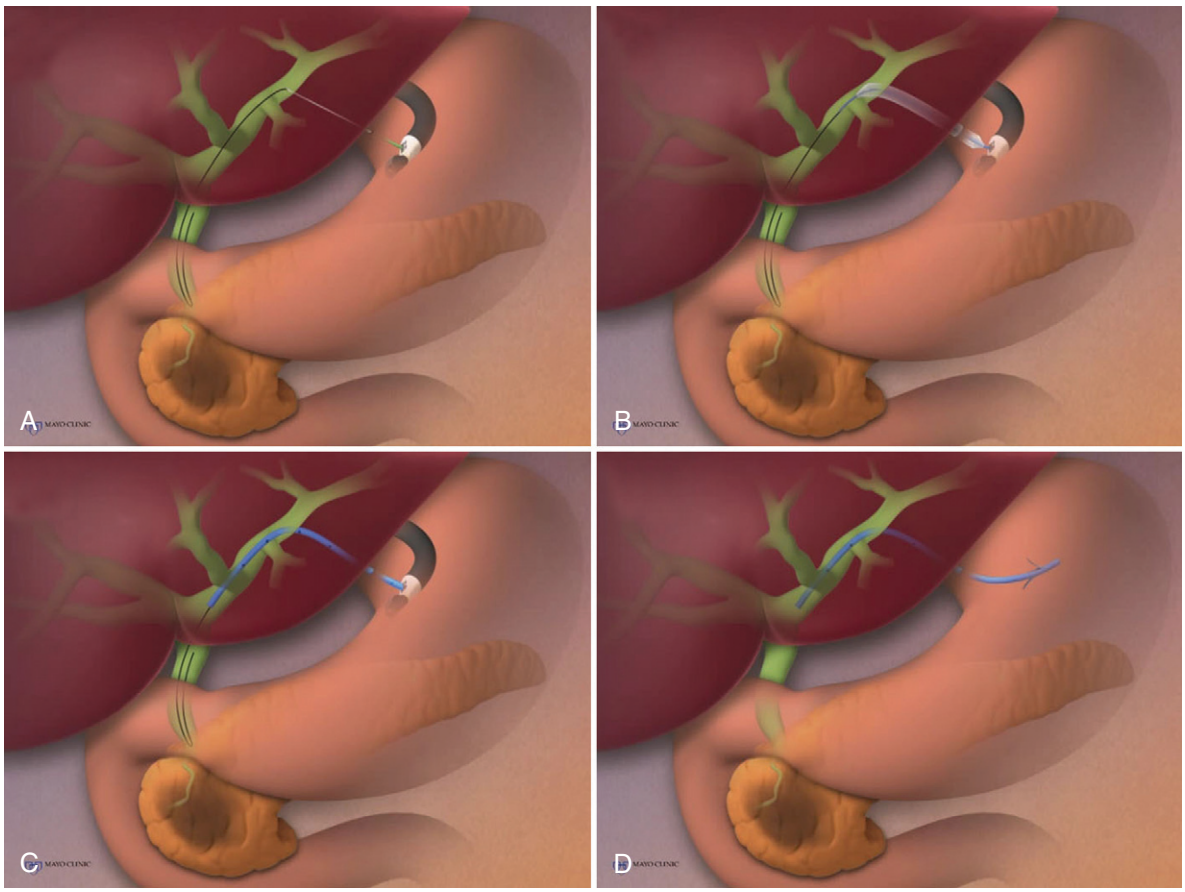


FIGURE 23.3 The technique for intrahepatic biliary access and antegrade stenting of the biliary tree to the stomach, as performed solely with an echoendoscope, is demonstrated. A, EUS is used to access a branch of the left intrahepatic bile duct followed by guidewire passage into the biliary tree. **B,** Tract dilation is required to include the gastric wall, hepatic parenchyma, and intrahepatic bile duct wall. **C** and **D,** The stent is advanced so that the distal tip rests within the biliary tree and the proximal end of the stent lies within the stomach.

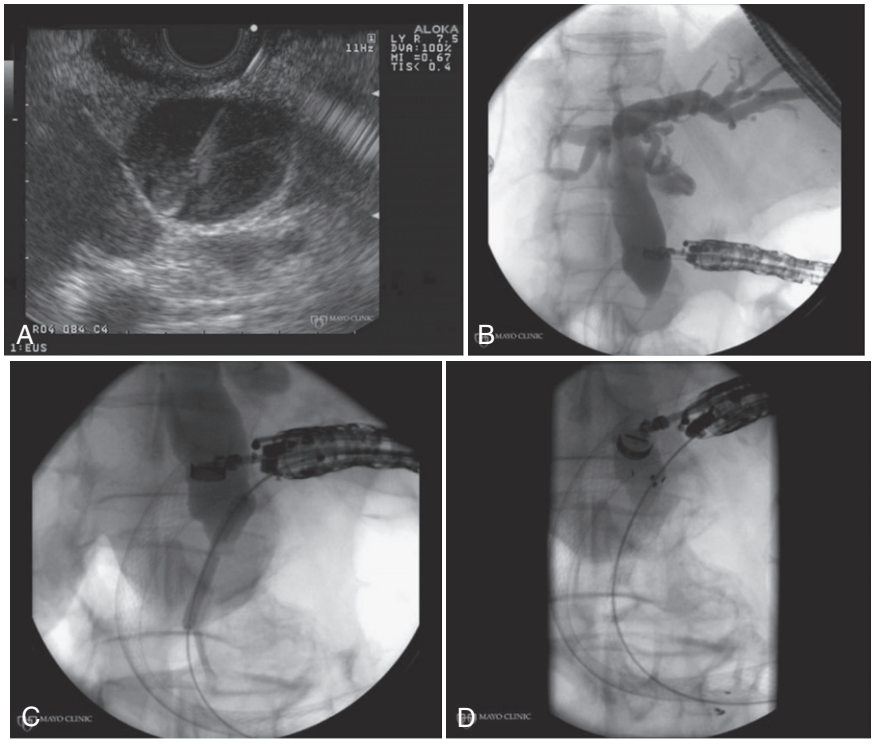


FIGURE 23.4 The technique for extrahepatic biliary access and transpapillary drainage following antegrade stent insertion, performed solely with an echoendoscope, is demonstrated. A, EUS-guided needle access into the extrahepatic bile duct allows initial cholangiography to aid needle insertion. **B,** Fluoroscopic imaging reveals a malignant-appearing distal biliary stricture in a patient with a duodenal stent placed as therapy for gastric outlet obstruction. **C,** The entire tract is dilated to facilitate stent insertion. **D,** A self-expandable metal stent is deployed in an antegrade manner using EUS and fluoroscopic guidance.

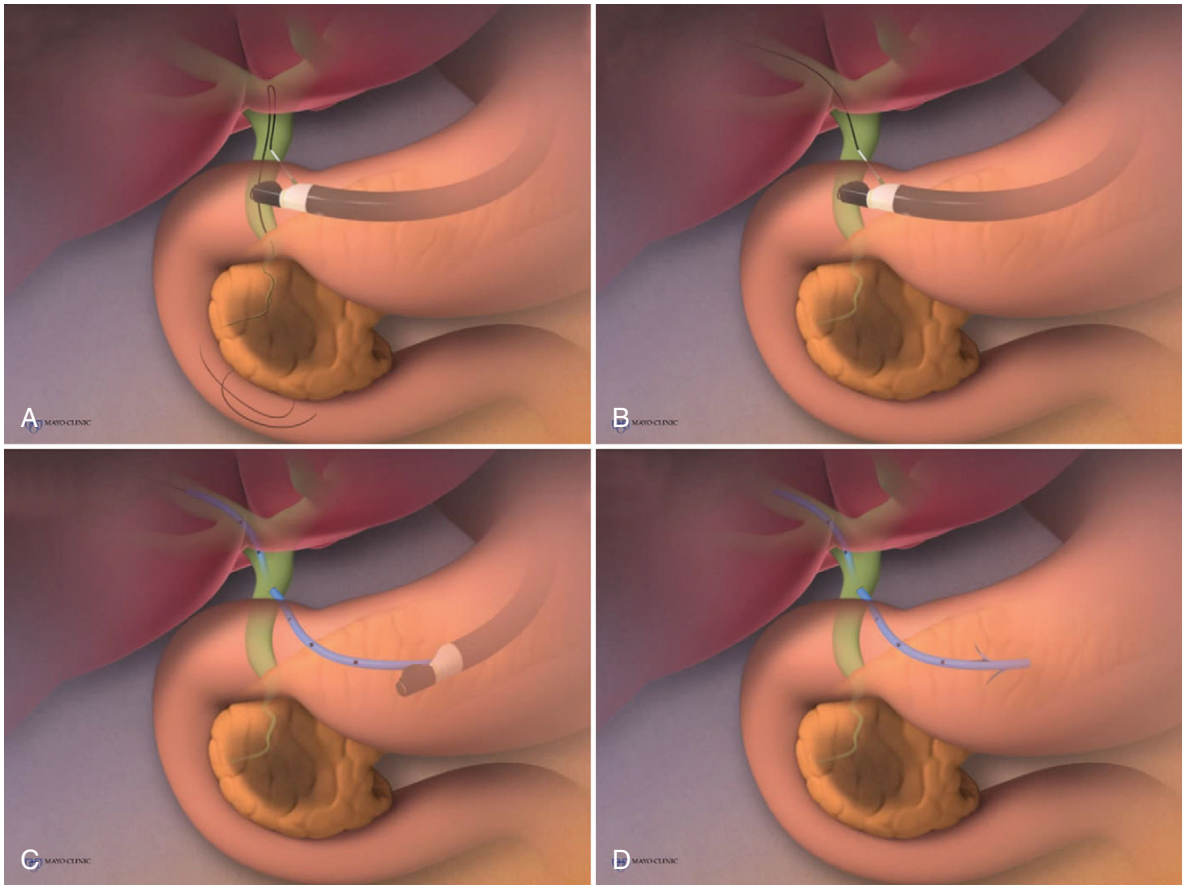


FIGURE 23.5 The technique for extrahepatic biliary access and transluminal drainage following antegrade stent insertion, performed solely with an echoendoscope, is demonstrated. A, EUS is used to access the extrahepatic bile duct with subsequent cholangiography and needle placement. **B,** The guidewire may be advanced into the intrahepatic bile ducts to provide a straight angle of access and stent delivery. **C** and **D,** The stent is advanced so that the distal tip rests within the biliary tree and the proximal end of the stent lies within the stomach or duodenum.

practical in this context, the lack of controlled, randomized, comparative data and the absence of blinding further limit our understanding of the utility and role of these techniques. Finally, there is likely reporting and publication bias, which affects these data. Despite the limitations, these studies offer preliminary data suggesting the relative efficacy of EUS-guided biliary access and drainage, but they raise concerns regarding the risks of these procedures.

Evaluating the collective literature from 2003 to 2009 ($n = 56$ patients), it appears that EUS-guided intrahepatic biliary access has a 77% ($n = 43$) technical success rate and a 16% ($n = 9$) complication rate when stent-specific complications are excluded (Table 23.1). Reported complications include the following: pneumoperitoneum ($n = 3$), cholangitis ($n = 2$), hemorrhage ($n = 1$), biloma ($n = 1$), ileus ($n = 1$), and aspiration pneumonia ($n = 1$). Grouped data for patients who underwent attempted EUS-guided extrahepatic biliary access from 1996 to 2009 ($n = 71$ patients) indicate an 87% ($n = 62$) success rate and a 15% ($n = 11$) complication rate (Table 23.2). Reported complications included the following: peritonitis ($n = 5$), pneumoperitoneum ($n = 3$), cholecystis ($n = 1$), abdominal pain ($n = 1$), and cardiopulmonary failure ($n = 1$).

As a result of study limitations, the need and timing of reintervention and long-term clinical outcomes cannot be accurately determined based on published reports. However, Yamao et al[26] noted that stents occluded from 4 weeks to 4 months. More recently Bories et al[27] described successful EUS-guided left hepaticogastrostomy in 10 of 11 patients with plastic or covered metal stent placement; the covered metal stents may provide more prolonged stent patency.

In the largest report to date, Maranki et al[28] reviewed their experience in patients undergoing attempted EUS-guided biliary access and therapy for obstructive jaundice following failed ERC. Whenever the second portion of the duodenum was accessible, the extrahepatic approach was preferred. If the guidewire could not be advanced across the obstruction, a transenteric fistula was created. These investigators initially attempted the intrahepatic approach in 40; patients, however, 5 patients were crossed over to the extrahepatic group because of an inability to advance the guidewire through the duct ($n = 4$) or because of failed access to a peripheral hepatic duct ($n = 1$).

In the final analysis, 35 patients underwent intrahepatic access, and 15 underwent extrahepatic access and attempted drainage. The overall success rate was 84% (41/49), with an overall complication rate of 16% (8/49). Among the 35 patients who underwent intrahepatic access, the stent traversed the major papilla ($n = 23$) or was positioned within the extrahepatic or intrahepatic bile duct in 1 and 3 patients, respectively. Biliary obstruction was relieved in 83% (29/35), but relief of obstruction was not possible in 6 patients because of failure to advance the guidewire through to a high-grade obstruction or tortuous duct ($n = 5$) or because of creation of a false channel ($n = 1$). Based on intention-to-treat analysis, clinical success was achieved in 29 of 40 (73%) patients undergoing the intrahepatic approach. Mild to moderate complications were managed conservatively and occurred in 5 of 35 patients. These complications included the following: pneumoperitoneum ($n = 3$), bleeding ($n = 1$), and aspiration pneumonia ($n = 1$). For the 14 patients undergoing an extrahepatic approach, biliary obstruction was relieved in 12 (86%) following stent placement across the major papilla ($n = 8$) or by transenteric stenting ($n = 4$).

TABLE 23.1

EUS-Guided Biliary Duct Access (Hepaticogastrostomy)

Authors (yr)	Approach	Cases (*n*)	Technical Success (*n*)	Complications
Burmester et al[21] (2003)	Transluminal	1	1/1	None
Puspok et al[41] (2005)	Transluminal	1	1/1	None
Kahaleh et al[16,22,23] (2004, 2005, 2006) Maranki et al[28] (2009)	Transluminal	35	24/35	Pneumoperitoneum ($n = 3$) Hemorrhage ($n = 1$) Aspiration pneumonia ($n = 1$)
Bories et al[27] (2007)	Transluminal	11	10/11	Ileus ($n = 1$) Cholangitis ($n = 1$) Biloma ($n = 1$)
Will et al[42] (2007)	Transluminal	8	7/8	Cholangitis ($n = 1$)

TABLE 23.2

EUS-Guided Biliary Duct Access (Choledochoduodenostomy)

Authors (yr)	Approach	Cases (*n*)	Technical Success (*n*)	Complications
Wiersema et al[18] (1996)	Opacification alone	10	7/10	Pancreatitis ($n = 1$)
Giovannini et al[20] (2001)	Transluminal	1	1/1	None
Burmester et al[21] (2003)	Transluminal	3	2/3	Bile peritonitis ($n = 1$)
Mallery et al[17] (2004)	Rendezvous	2	2/2	None
Puspok et al[41] (2005)	Transluminal	5	4/5	Subacute phlegmonous cholecystitis ($n = 1$)
Lai et al[25] (2005)	Rendezvous	1	1/1	None
Kahaleh et al[16,22,23] (2004, 2005, 2006) Maranki et al[28] (2009)	Transluminal	14	8/14	Pneumoperitoneum ($n = 1$) Biliary peritonitis ($n = 1$) Abdominal pain (n = 1)
Ang et al[24] (2007)	Transluminal	2	2/2	Pneumoperitoneum ($n = 1$)
Fujita et al[43] (2007)	Transluminal	1	1/1	None
Yamao et al[26,44] (2006, 2008)	Rendezvous	5	5/5	Pneumoperitoneum ($n = 1$)
Tarantino et al[45] (2008)	Transluminal and rendezvous	9	9/9	None
Itoi et al[46] (2008)	Transluminal	4	4/4	Bile peritonitis ($n = 1$)
Mangiavillano et al[47] (2008)	Rendezvous	1	1/1	None
Larghi et al[48] (2008)	Rendezvous	1	1/1	None
Brauer et al[49] (2009)	Rendezvous and transluminal	12	11/12	Peritonitis ($n = 1$) Cardiorespiratory failure ($n = 1$)

Based on an intention-to-treat analysis, clinical success occurred in 7 (78%) patients. Complications developed in 3 patients (21%), including biliary peritonitis (requiring percutaneous drainage), abdominal pain, and pneumoperitoneum. All complications were managed conservatively.

Patients were followed up for an average of 9 months (range, 1 to 51). For patients with benign disease, 1 to 7 repeat interventions were required with plastic stent exchange and eventual stent removal in 3 patients following resolution of the stricture. Although stent occlusion did not occur, the stents were electively replaced at an unstated interval. All patients with malignant disease were adequately palliated until death, except for a single patient who required conventional ERC with metal stent exchange. All 30 deaths were attributed to cancer disease progression.

EUS-GUIDED ACCESS AND THERAPY OF THE PANCREATIC DUCTAL SYSTEM (VIDEO 23.3)

EUS-guided pancreatography was first reported by Harada et al[29] in 1995 as a case report involving a patient requiring removal of an MPD stone following pancreaticoduodenectomy. Other reports soon followed.[18,30]

Indications

EUS-guided pancreatic duct access and therapy are most often attempted following failed ERP in patients with the following:

1. Chronic pancreatitis requiring decompression (secondary to strictures or stones)
2. Prior pancreaticoduodenectomy with suspected pancreaticojejunal anastomotic stenosis (manifested by recurrent pancreatitis, pain, steatorrhea, or evaluation of tumor recurrence)
3. Endoscopic snare ampullectomy (when prophylactic stent insertion failed)
4. MPD disruption

Technique

Most of the aforementioned technical aspects for performing EUS-guided biliary access and therapy also apply to pancreatic interventions. The optimal point of MPD access varies depending on the site of ductal obstruction and is located anywhere from the gastric cardia to the second portion of the duodenum. EUS-guided MPD access can be more difficult than in the biliary tree because of the tendency for guidewire passage into and through pancreatic duct side branches. Otherwise, similar to biliary access, the MPD is localized and punctured using EUS guidance. MPD access is confirmed by contrast injection and antegrade pancreatography. A guidewire is then advanced through the EUS FNA needle into the MPD and then the duodenum. As with biliary access, fluoroscopy is used to verify the echoendoscope position, to perform ductography, and to facilitate guidewire passage. Subsequent steps, including fistula enlargement and stent insertion, also proceed in the same manner as noted for the biliary tree. Stent insertion may then be achieved through a rendezvous procedure and retrograde stent placement (Fig. 23.6), by an antegrade route using endosonography alone (Fig. 23.7), or by transluminal stent drainage of the pancreatic duct to the gastric lumen (Fig. 23.8).

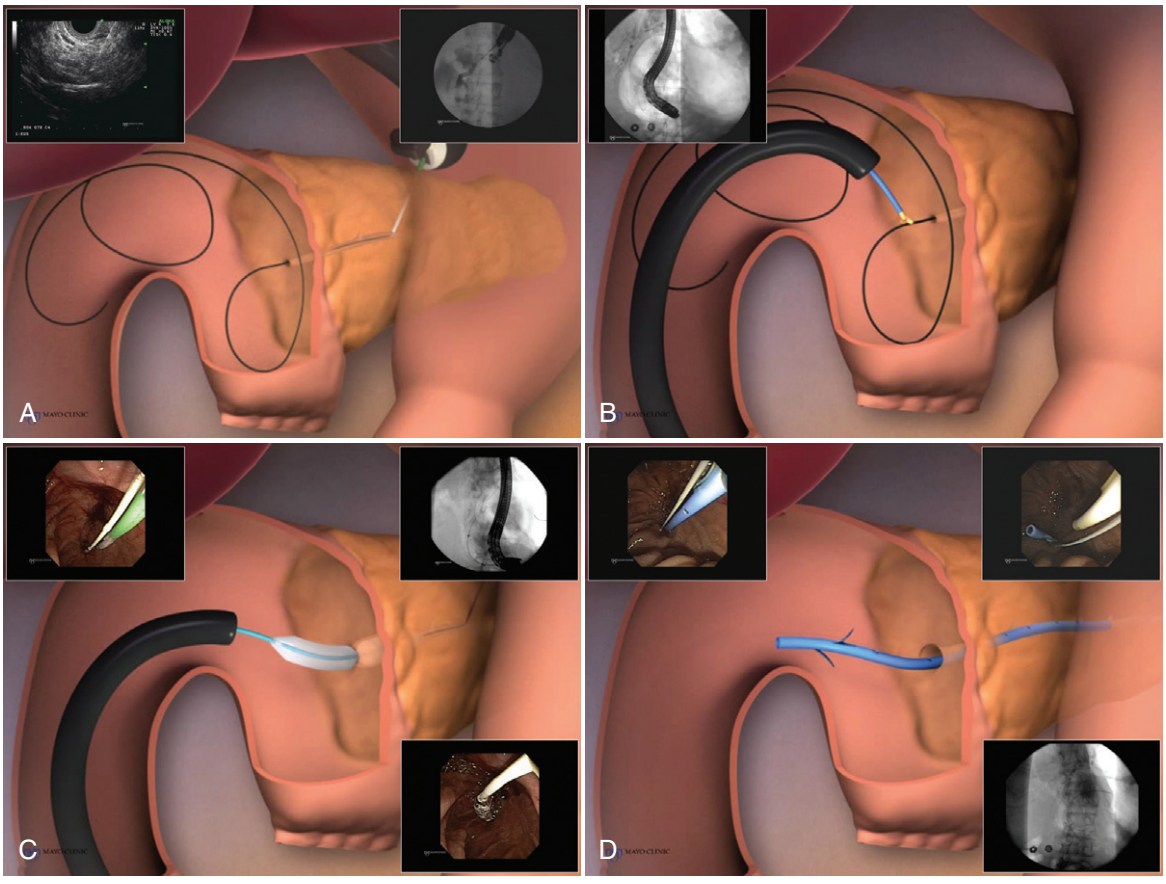


FIGURE 23.6 The technique for pancreatic duct access and transpapillary/transanastomotic drainage with retrograde stent insertion performed by a rendezvous procedure is demonstrated. A, EUS imaging reveals the main pancreatic duct with needle advancement, wire placement, and pancreatography. **B,** A side- or forward-viewing instrument is then passed to the small bowel to allow either biopsy cable or snare retraction of the guidewire. **C,** Standard techniques may be used to perform duct cannulation and balloon dilation in retrograde fashion. **D,** Standard techniques are also used for retrograde stent insertion.

The technique was highlighted in the post–snare ampullectomy setting, with a subsequently inaccessible pancreatic duct requiring stenting.[31] Tessier et al[32] suggested that a minimum MPD caliber of 6 mm is needed to achieve access. Although a larger duct caliber does facilitate access, Papachristou et al[33] reported MPD access in ducts as small as 1 mm. Several technical variations have been described for MPD drainage. The initial approach was reported by Bataille et al,[34] who created a pancreaticoenteric fistula with antegrade wire passage to facilitate the subsequent rendezvous with retrograde stent insertion. Subsequently, other investigators provided drainage by creation of a pancreaticogastric fistula with antegrade stent insertion (13 to 15 mm).[35–38]

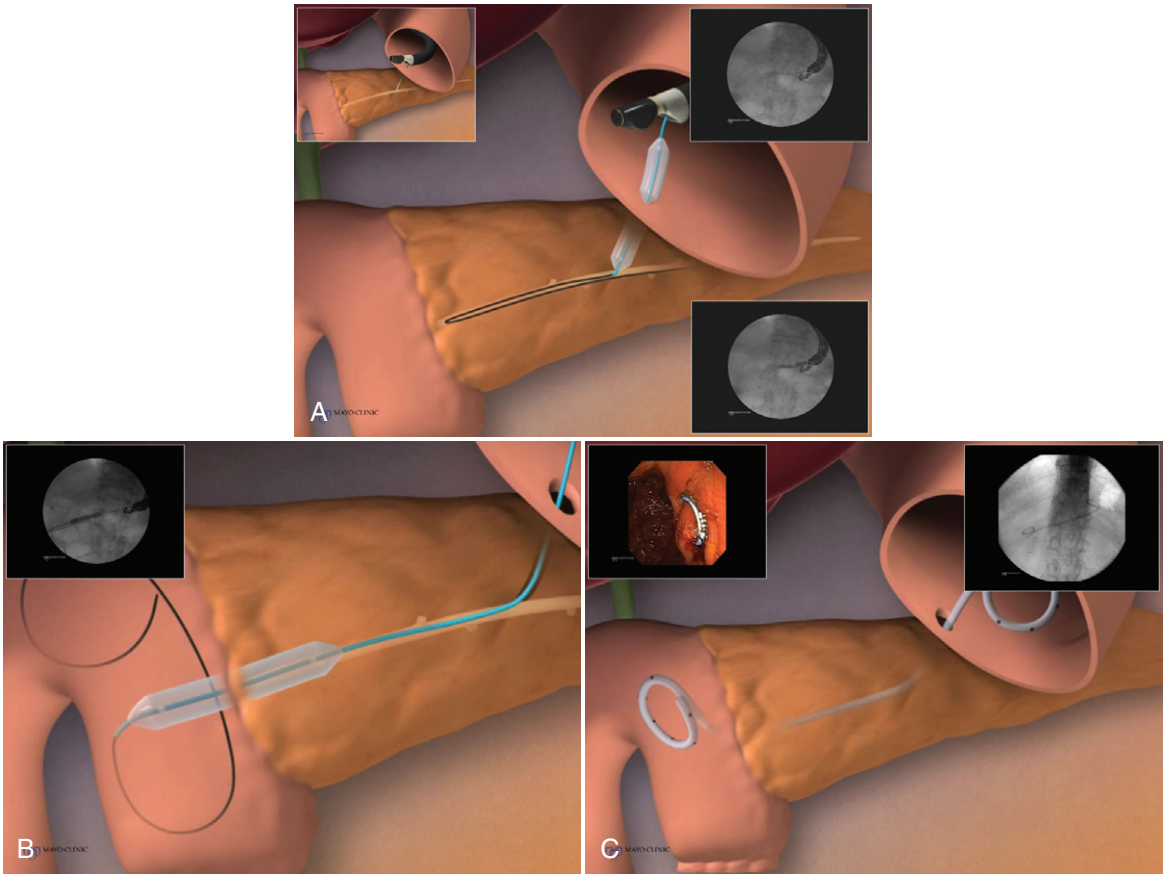


FIGURE 23.7 The technique for pancreatic duct access and transpapillary/transanastomotic drainage following antegrade stent insertion, performed entirely through an echoendoscope, is demonstrated. A, EUS imaging reveals the main pancreatic duct with needle advancement, wire placement, and pancreatography with balloon dilation of the gastric wall, pancreatic parenchyma, and pancreatic duct wall. **B,** A guidewire is passed through the site of obstruction or anastomosis, followed by balloon dilatation. **C,** A stent is advanced in an antegrade fashion from the gastric lumen, into the pancreatic duct, and through the site of obstruction.

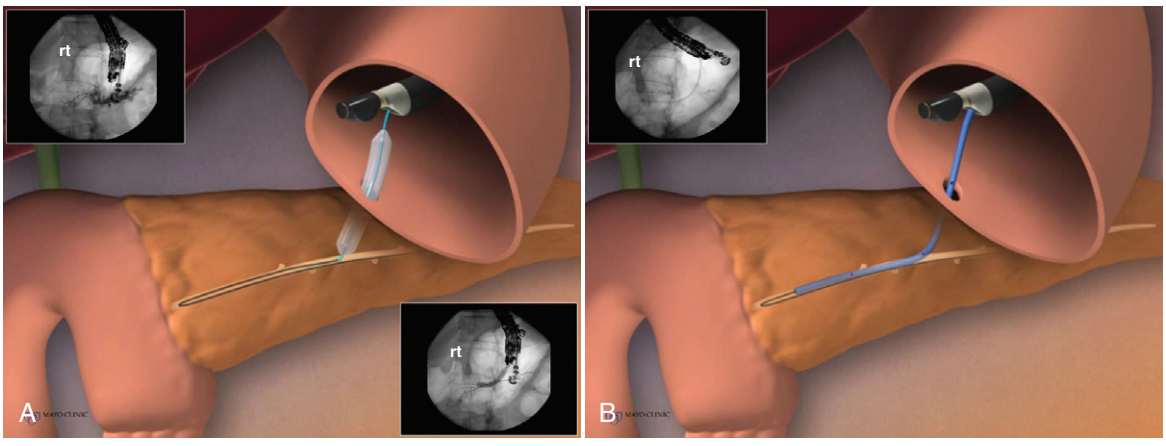


FIGURE 23.8 The technique for pancreatic duct access and transluminal drainage of the pancreatic duct to the gastric lumen following antegrade stent insertion, performed solely with an echoendoscope, is demonstrated. A, EUS imaging of the pancreas and main pancreatic duct allows guided needle insertion, wire placement, and pancreatography with balloon dilation of the gastric wall, pancreatic parenchyma, and pancreatic duct wall. **B,** Antegrade stent insertion is performed through the echoendoscope.

EUS-guided pancreaticoduodenostomy is a more recently described technique employed in patients with either acute or chronic pancreatitis and allows access to the MPD from the duodenal bulb. Săftoiu et al[39] reported combined EUS-assisted rendezvous stenting of the MPD with subsequent transpapillary stenting of the common bile duct for managing pancreatic fluid collections. Other variations have included access and drainage through the minor papilla.[40]

Technical Success, Outcomes, and Complications

Although the results of these studies are encouraging, they, too, suffer from methodologic shortcomings that limit the strength of the conclusions. Among the 91 reported patients, technical success of EUS-guided MPD intervention was noted in 74 (81%), and complications developed in 8 (9%) patients (Table 23.3). Complications included bleeding ($n = 3$) and perforation ($n = 2$), and one patient each developed fever, a hematoma requiring endoscopic drainage, and pancreatitis with pseudocyst formation requiring endoscopic drainage.

As for EUS-guided biliary interventions, the need and timing of reintervention and long-term clinical outcomes cannot be accurately determined based on published data. However, Will et al[50] noted that during the follow-up period that spanned 4 weeks to 3 years, 29% of patients required surgical intervention. Tessier et al[32] reported stent dysfunction in 55% (20/26) of patients that required a total of 29 repeat endoscopies. In two separate studies, François reported that at a mean of 10 months, more than 75% of patients with pancreatic duct disruption or chronic pancreatitis had pain relief and fistula closure.[35]

In the largest report to date, Tessier et al[32] reviewed their experience in patients undergoing attempted EUS-guided pancreatic duct access and therapy for chronic pancreatitis ($n = 20$) complicated by either complete obstruction (secondary to stenosis, a stone, or ductal rupture), an inaccessible papilla or failed cannulation, pancreaticojejunal anastomotic stenosis following pancreaticoduodenectomy ($n = 12$), or a completely disrupted MPD secondary to acute pancreatitis or trauma ($n = 4$). Technical success was achieved in 33 (92%). Major complications were reported in 2 patients including hematoma and severe acute pancreatitis. Another 3 patients developed unspecified complications, leading to an overall complication rate of 14%. The median follow-up was 14.5 months (range, 4 to 55), excluding 1 patient lost to follow-up. Based on an intent-to-treat analysis, pain relief was reported as complete ($n = 18$, 50%), partial ($n = 7$, 19%), or absent ($n = 11$, 31%). For patients initially experiencing a complete response, pain recurrence developed a median of 210 days (95% confidence interval, 42 to 377 days) following initial therapy. Among patients who did not experience any pain relief ($n = 11$, 31%), the lack of response was attributed to an underlying malignant disease ($n = 4$), stent migration with failed replacement ($n = 1$), urgent pancreatectomy secondary to pseudocyst formation ($n = 1$), and failed response to stenting ($n = 1$). Stent dysfunction occurred in 20 patients (55%) and required a total of 29 repeat endoscopies, with the median time of first stent exchange occurring at 195 days (range, 10 to 780 days).

TECHNICAL CHALLENGES AND TIPS

There are certain technical challenges that one may face during attempted EUS-guided pancreaticobiliary access and drainage and maneuvers that may help to overcome these difficulties. The risk of inadvertent parenchymal or vascular injection may be minor in volume or more severe, potentially hindering further interventions. Care should be taken to limit the volume and concentration of the contrast injected, in an attempt to reduce the risk and help maintain visualization of targeted areas.

The guidewire often inadvertently passes into ductal side branches. This is prone to occur when there is a nearly perpendicular orientation of the echoendoscope to the desired duct. This problem may be overcome by altering the needle angle of entry or by selecting an alternate wire, such as a glide wire or angled wire. These maneuvers, along with careful wire manipulation, usually allow access to the desired segment.

Guidewire passage across the papilla, anastomosis, or other site of obstruction may be difficult and may lead to wire buckling or inadvertent passage into undesired ducts or parenchyma. Although gradual retraction and readvancement may suffice, at times the wire will not traverse the site of obstruction despite repeated efforts. Fluoroscopic techniques such as the use of magnification can facilitate wire passage. In addition, it is ideal to use a fluoroscopic C-arm, if available, to allow imaging from multiple angles to display the anatomy in various orientations. One should also consider insertion of a catheter or balloon into the duct in close proximity to the site of obstruction. In this position, the catheter or balloon may serve to constrain the guidewire and allow delivery of greater longitudinal force to facilitate wire passage through the site of obstruction. It may also be helpful to select an alternate wire.

Even with a guidewire in place, it may be difficult to pass a catheter or balloon across the gastric or duodenal wall, site of anastomosis, or other site of obstruction. Prolonged pressure

TABLE 23.3

EUS-Guided Pancreatic Duct Access

Authors (yr)	Approach	Cases (*n*)	Technical Success (*n*)	Complications
Harada et al[29] (1995)	Opacification alone	1	1/1	None
Gress et al[30] (1996)	Opacification alone	1	1/1	None
François et al[35] (2002)	Rendezvous	4	4/4	None
Bataille et al[34] (2002)	Rendezvous	1	1/1	None
Mallery et al[17] (2004)	Rendezvous	4	1/4	Fever ($n = 1$)
Kahaleh et al[37]* (2007)	Transluminal	13	11/13	Bleeding ($n = 1$) Perforation ($n = 1$)
Will et al[50] (2007)	Rendezvous and transluminal	12	9/12	Bleeding ($n = 1$) Perforation ($n = 1$)
Tessier et al[32] (2007)	Transluminal	36	33/36	Severe pancreatitis ($n = 1$) Hematoma ($n = 1$) Unspecified mild complications ($n = 3$)
Keenan et al[31] (2007)	Rendezvous	1	1/1	None
Săftoiu et al[39] (2007)	Rendezvous	1	1/1	None
Kinney et al[51] (2009)	Rendezvous	9	4/9	Fever ($n = 1$)
Brauer et al[49] (2009)	Rendezvous and transluminal	8	7/8	None

*Prospective study.

may allow the device to pass suddenly. Initial dilatation with the needle sheath can aid passage as well. One may also consider selection of alternate devices that may traverse otherwise inaccessible strictures.

One must always be mindful of the risk of wire shaving that occurs when retracting the wire into the needle at an acute angle. The risk is minimized by avoiding acute angles during wire retraction and by gently retracting the guidewire. When resistance is felt and the wire cannot be removed, withdrawal of the wire and needle in unison allows safe removal.

When one is attempting to dilate the tract, the balloon may inadvertently pass between the gut wall and target organ. This situation may be suggested by difficulty when inserting subsequent devices. The risk may be minimized by careful observation using EUS and fluoroscopic guidance.

During biliary access, when one attempts to pass a guidewire from the left intrahepatic bile ducts to the extrahepatic bile duct, the wire is prone to pass into the right intrahepatic ducts instead. Fluoroscopy is useful for guiding wire passage. Similarly, use of an alternate guidewire may facilitate duct access, as may selection of a left intrahepatic duct that provided an opportune angle for wire passage.

Finally, there tends to be a loss of apposition between the stomach and the liver that predisposes to biliary leak during hepaticogastrostomy. Placement of a longer, pig-tail catheter may diminish this risk, as may the placement of transpapillary stents, which is preferred whenever possible.

PHYSICIAN EXPERIENCE AND TRAINING

EUS-guided pancreaticobiliary access and drainage procedures are likely the most technically complex and challenging to perform among all ERCP and EUS procedures. Endoscopists are well served by having a full skill set that includes advanced ERCP and EUS training, because the interventions performed include techniques that have been historically considered with either ERCP or EUS. Therefore, performing physicians will ideally receive dedicated training in both disciplines. These procedures may also be performed by teaming two endoscopists with separate EUS and ERCP skills, but doing so complicates scheduling, decreases room efficiency, and has financial impact. Because increasing numbers of advanced training programs provide dual training and are performing more of these procedures, the availability of adequately trained endoscopists will gradually increase. In the training program at the Mayo Clinic in Rochester, Minnesota, advanced fellows are introduced to these techniques during the first half of the year and then obtain hands-on experience in the second half of the year once they have gained reasonable technical skill, proficiency, and didactic experience. Because of the somewhat delayed exposure, procedural complexity, and the relative paucity of cases, few advanced endoscopy trainees will graduate with sufficient skills to allow independent performance of all aforementioned techniques. We encourage graduates to develop their practice in a stepwise manner that is influenced by a particular patient's health and clinical needs, by their particular skill set, and by their practice setting and available nonendoscopic expertise.

SUMMARY

EUS often allows access and drainage of the biliary and pancreatic ducts following failed ERCP and can obviate the need for percutaneous and surgical interventions. As a result of the complexity of these procedures, new techniques and equipment are needed. These procedures are likely to be aided by the development of shear-resistant guidewires and by the creation of multistep, combination devices that aid initial access, dilation, and stenting.

These procedures are technically challenging and time and personnel intensive. Caution must be exercised because complications are relatively common and can be severe. In addition, data are sparse, and current reports have methodologic limitations, thereby limiting our understanding of the utility and role of these techniques. Additional data are needed to define the risks and long-term outcomes more accurately before the role of these techniques can be clarified. Until then, EUS-guided intervention cannot be broadly advocated and must be performed in carefully selected patients managed by a multidisciplinary team of physicians.

REFERENCES

1. Kulesza P, Eltoum IA. Endoscopic ultrasound-guided fine-needle aspiration: sampling, pitfalls, and quality management. *Clin Gastroenterol Hepatol*. 2007;5(11):1248–1254.
2. Levy MJ, Wiersema MJ. EUS-guided trucut biopsy. *Gastrointest Endosc*. 2005;62(3):417–426.
3. Wiersema MJ, Wiersema LM. Endosonography-guided celiac plexus neurolysis. *Gastrointest Endosc*. 1996;44(6):656–662.
4. Levy MJ, Wiersema MJ. Endoscopic ultrasound-guided pain control for intra-abdominal cancer. *Gastroenterol Clin North Am*. 2006;35(1):153–165.
5. Levy MJ, Topazian MD, Wiersema MJ, et al. Initial evaluation of the efficacy and safety of endoscopic ultrasound-guided direct ganglia neurolysis and block. *Am J Gastroenterol*. 2008;103(1):98–103.
6. Lopes CV, Pesenti C, Bories E, et al. Endoscopic ultrasound-guided endoscopic transmural drainage of pancreatic pseudocysts. *Arq Gastroenterol*. 2008;45(1):17–21.
7. Norton ID, Clain JE, Wiersema MJ, et al. Utility of endoscopic ultrasonography in endoscopic drainage of pancreatic pseudocysts in selected patients. *Mayo Clin Proc*. 2001;76(8):794–798.
8. Kruger M, Schneider AS, Manns MP, et al. Endoscopic management of pancreatic pseudocysts or abscesses after an EUS-guided 1-step procedure for initial access. *Gastrointest Endosc*. 2006;63(3):409–416.
9. Seifert H, Dietrich C, Schmitt T, et al. Endoscopic ultrasound-guided one-step transmural drainage of cystic abdominal lesions with a large-channel echo endoscope. *Endoscopy*. 2000;32(3):255–259.
10. Kwan V, Elsendrath P, Antaki F, et al. EUS-guided cholecystenterostomy: a new technique (with videos). *Gastrointest Endosc*. 2007;66(3):582–586.
11. Chang KJ, Nguyen PT, Thompson JA, et al. Phase I clinical trial of allogeneic mixed lymphocyte culture (cytoimplant) delivered by endoscopic ultrasound-guided fine-needle injection in patients with advanced pancreatic carcinoma. *Cancer*. 2000;88(6):1325–1335.
12. Chang KJ. EUS-guided fine needle injection (FNI) and anti-tumor therapy. *Endoscopy*. 2006;38(suppl 1):S88–S93.
13. Erickson RA. EUS-guided pancreaticogastrostomy: invasive endosonography coming of age. *Gastrointest Endosc*. 2007;65(2):231–232.
14. Voegeli DR, Crummy AB, Weese JL. Percutaneous transhepatic cholangiography, drainage, and biopsy in patients with malignant biliary obstruction: an alternative to surgery. *Am J Surg*. 1985;150(2):243–247.
15. Oh HC, Lee SK, Lee TY, et al. Analysis of percutaneous transhepatic cholangioscopy-related complications and the risk factors for those complications. *Endoscopy*. 2007;39(8):731–736.
16. Kahaleh M, Hernandez AJ, Tokar J, et al. Interventional EUS-guided cholangiography: evaluation of a technique in evolution. *Gastrointest Endosc*. 2006;64(1):52–59.
17. Mallery S, Matlock J, Freeman ML. EUS-guided rendezvous drainage of obstructed biliary and pancreatic ducts: report of 6 cases. *Gastrointest Endosc*. 2004;59(1):100–107.
18. Wiersema MJ, Sandusky D, Carr R, et al. Endosonography-guided cholangiopancreatography. *Gastrointest Endosc*. 1996;43(2):102–106.
19. Sahai AV, Hoffman BJ, Hawes RH. Endoscopic ultrasound-guided hepaticogastrostomy to palliate obstructive jaundice: preliminary results in pigs [abstract]. *Gastrointest Endosc*. 1998;47:AB37.
20. Giovannini M, Moutardier V, Pesenti C, et al. Endoscopic ultrasound-guided bilioduodenal anastomosis: a new technique for biliary drainage. *Endoscopy*. 2001;33(10):898–900.
21. Burmester E, Niehaus J, Leineweber T, Huetteroth T. EUS-cholangiodrainage of the bile duct: report of 4 cases. *Gastrointest Endosc*. 2003;57(2):246–251.
22. Kahaleh M, Yoshida C, Kane L, Yeaton P. Interventional EUS cholangiography: a report of five cases. *Gastrointest Endosc*. 2004;60(1):138–142.
23. Kahaleh M, Wang P, Shami VM, et al. EUS-guided transhepatic cholangiography: report of 6 cases. *Gastrointest Endosc*. 2005;61(2):307–313.
24. Ang TL, Teo EK, Fock KM. EUS-guided transduodenal biliary drainage in unresectable pancreatic cancer with obstructive jaundice. *JOP*. 2007;8(4):438–443.

25. Lai R, Freeman ML. Endoscopic ultrasound-guided bile duct access for rendezvous ERCP drainage in the setting of intradiverticular papilla. *Endoscopy*. 2005;37(5):487–489.
26. Yamao K, Sawaki A, Takahashi K, et al. EUS-guided choledochoduodenostomy for palliative biliary drainage in case of papillary obstruction: report of 2 cases. *Gastrointest Endosc*. 2006;64(4):663–667.
27. Bories E, Pesenti C, Caillol F, et al. Transgastric endoscopic ultrasonography-guided biliary drainage: results of a pilot study. *Endoscopy*. 2007; 39(4):287–291.
28. Maranki J, Hernandez AJ, Arslan B, et al. Interventional endoscopic ultrasound-guided cholangiography: long-term experience of an emerging alternative to percutaneous transhepatic cholangiography. *Endoscopy*. 2009;41(6):532–538.
29. Harada N, Kouzu T, Arima M, et al. Endoscopic ultrasound-guided pancreatography: a case report. *Endoscopy*. 1995;27(8):612–615.
30. Gress F, Ikenberry S, Sherman S, Lehman G. Endoscopic ultrasound-directed pancreatography. *Gastrointest Endosc*. 1996;44(6):736–739.
31. Keenan J, Mallery S, Freeman ML. EUS rendezvous for pancreatic stent placement during endoscopic snare ampullectomy. *Gastrointest Endosc*. 2007;66(4):850–853.
32. Tessier G, Bories E, Arvanitakis M, et al. EUS-guided pancreatogastrostomy and pancreatobulbostomy for the treatment of pain in patients with pancreatic ductal dilatation inaccessible for transpapillary endoscopic therapy. *Gastrointest Endosc*. 2007;65(2):233–241.
33. Papachristou GI, Gleeson FC, Petersen BT, Levy MJ. Pancreatic endoscopic ultrasound-assisted rendezvous procedure to facilitate drainage of nondilated pancreatic ducts. *Endoscopy*. 2007;39(suppl 1):E324–E325.
34. Bataille L, Deprez P. A new application for therapeutic EUS: main pancreatic duct drainage with a "pancreatic rendezvous technique." *Gastrointest Endosc*. 2002;55(6):740–743.
35. François E, Kahaleh M, Giovannini M, et al. EUS-guided pancreaticogastrostomy. *Gastrointest Endosc*. 2002;56(1):128–133.
36. Kahaleh M, Yoshida C, Yeaton P. EUS antegrade pancreatography with gastropancreatic duct stent placement: review of two cases. *Gastrointest Endosc*. 2003;58(6):919–923.
37. Kahaleh M, Hernandez AJ, Tokar J, et al. EUS-guided pancreaticogastrostomy: analysis of its efficacy to drain inaccessible pancreatic ducts. *Gastrointest Endosc*. 2007;65(2):224–230.
38. Will U, Meyer F, Manger T, Wanzar I. Endoscopic ultrasound-assisted rendezvous maneuver to achieve pancreatic duct drainage in obstructive chronic pancreatitis. *Endoscopy*. 2005;37(2):171–173.
39. Săftoiu A, Dumitresco D, Stoica M, et al. EUS-assisted rendezvous stenting of the pancreatic duct for chronic calcifying pancreatitis with multiple pseudocysts. *Pancreatology*. 2007;7(1):74–79.
40. Gleeson FC, Pelaez MC, Petersen BT, Levy MJ. Drainage of an inaccessible main pancreatic duct via EUS-guided transgastric stenting through the minor papilla. *Endoscopy*. 2007;39(suppl 1):E313–E314.
41. Puspok A, Lomoschitz F, Dejaco C, et al. Endoscopic ultrasound guided therapy of benign and malignant biliary obstruction: a case series. *Am J Gastroenterol*. 2005;100(8):1743–1747.
42. Will U, Thieme A, Fueldner F, et al. Treatment of biliary obstruction in selected patients by endoscopic ultrasonography (EUS)-guided transluminal biliary drainage. *Endoscopy*. 2007;39(4):292–295.
43. Fujita N, Noda Y, Kobayashi G, et al. Histological changes at an endosonography-guided biliary drainage site: a case report. *World J Gastroenterol*. 2007;13(41):5512–5515.
44. Yamao K, Bhatia V, Mizuno N, et al. EUS-guided choledochoduodenostomy for palliative biliary drainage in patients with malignant biliary obstruction: results of long-term follow-up. *Endoscopy*. 2008;40(4): 340–342.
45. Tarantino I, Barresi L, Repici A, Traina M. EUS-guided biliary drainage: a case series. *Endoscopy*. 2008;40(4):336–339.
46. Itoi T, Itokawa F, Sofuni A, et al. Endoscopic ultrasound-guided choledochoduodenostomy in patients with failed endoscopic retrograde cholangiopancreatography. *World J Gastroenterol*. 2008;14(39):6078–6082.
47. Mangiavillano B, Arcidiancono PG, Carrara S, et al. EUS-guided rendezvous technique for difficult cannulation of an intradiverticular papilla. *Endoscopy*. 2008;40(suppl 2):E87–E88.
48. Larghi A, Lecca PG, Mutignani M, Costamagna G. EUS-directed transpapillary self-expandable metallic stent placement after successful interventional EUS-guided cholangiography. *Gastrointest Endosc*. 2008;67(6): 996–998.
49. Brauer BC, Chen YK, Fukami N, Shah RJ. Single-operator EUS-guided cholangiopancreatography for difficult pancreaticobiliary access (with video). *Gastrointest Endosc*. 2009;70(3):471–479.
50. Will U, Fueldner F, Thieme AK, et al. Transgastric pancreatography and EUS-guided drainage of the pancreatic duct. *J Hepatobiliary Pancreat Surg*. 2007;14(4):377–382.
51. Kinney TP, Li R, Gupta K, et al. Therapeutic pancreatic endoscopy after Whipple resection requires rendezvous access. *Endoscopy*. 2009;41(10): 898–901.

CHAPTER 24

EUS-Guided Ablation Therapy and Celiac Plexus Interventions

William R. Brugge

Key Points

In its simplest form, EUS-guided ablative therapy consists of injection of cytoxic agents into cystic cavities or ganglia to eliminate premalignant epithelium or to produce neurolysis.

Celiac plexus block or neurolysis is the most common EUS-guided intervention in current practice. Significant pain control is achieved with injection of ethanol in the setting of pancreatic cancer. More modest results are seen in patients with abdominal pain arising from chronic pancreatitis.

More advanced techniques include the use of photodynamic therapy, brachytherapy, and radiofrequency ablation. Although preliminary data are promising, most of these procedures are still experimental.

Although many of these EUS-based techniques are designed to be used to ablate or control pancreatic malignancies, some may facilitate the delivery of radiation therapy by placement of radiopaque markers into the tumor.

INTRODUCTION

EUS represents one of the major developments in endoscopy since 1990. Although endoscopic ultrasonography (EUS) was originally designed to assist the endoscopist in the imaging of gastrointestinal malignancies, the procedure has evolved into a means of guiding tissue acquisition from the gastrointestinal tract and adjacent organs. Using fine-needle aspiration (FNA) accessories, interventional EUS is often based on fine-needle injection (FNI) therapy. Developments in interventional EUS have also highlighted a broad range of therapies beyond FNI, including tissue ablation and cancer therapeutics.

INSTRUMENTATION

Therapeutic EUS is performed using a linear echoendoscope because of the ability of linear EUS to guide needle placement into structures adjacent to the gastrointestinal tract. Numerous EUS accessories have been introduced that make interventional EUS possible.[1]

The quality of linear instruments has steadily increased in terms of ultrasound image processing, flexibility, and shaft diameter. The availability of a 3.2-mm instrument channel has made it possible to use a broader range of accessories. The enhanced sensitivity of color and flow Doppler in real-time imaging has improved the ability of clinicians to detect small lesions and to avoid vascular structures during injection therapy.

RADIOFREQUENCY ABLATION AND BRACHYTHERAPY

The principle of radiofrequency ablation (RFA) is the induction of thermal injury to the target tissue through the use of electromagnetic energy. In monopolar RFA, the patient is part of a closed-loop circuit that includes an RF generator, an electrode needle, and a large dispersive electrode (ground pad). The delivery of electromagnetic energy in tissue results in rapid movement of ions in tissue. The agitation of ions produces frictional heat around an electrode. The tissue destruction depends on both the tissue temperature achieved and the duration of heating. At temperatures between 60° and 100°C, near immediate protein coagulation is induced. Cells experiencing this extent of thermal damage undergo coagulative necrosis over the course of several days.

The procedural technique used for RFA is based on the EUS guidance of a needle catheter into the target lesion. In RFA of liver and pancreatic lesions, this procedure requires placement of the needle across the gastric or duodenal walls. In contrast, the needle in traditional RFA is placed through the skin and into the liver by using ultrasound or computed tomography (CT) guidance. Because the RF catheter must be precisely directed into the target lesion, the lesion must visible by ultrasound or CT. Once the needle has been successfully placed into the tissue mass, the RF current is delivered. During heating of tissue, ultrasound monitoring demonstrates a hyperechoic "cloud" surrounding the tip of the needle.

TABLE 24.1

Examples of EUS-Guided Tumor Ablation Therapy

	Photodynamic Therapy	Radiofrequency Ablation	TNFerade	Cryotherm (Cool-Tipped RFA)	Ethanol Injection	Brachytherapy	Paclitaxel (Taxol) Injection
Device used	Light fiber	Needle prongs	FNA needle	Dedicated catheter	FNA needle	FNA needle	19-G needle
Animal model	Swine	Swine	N/A	Swine	Swine	Swine	Swine
Mechanism of action	Reactive oxygen release	Heat-induced necrosis	Radiation sensitizer	Heat-induced necrosis	Protein denaturation	DNA damage	Cytotoxic
Target lesion	Pancreatic cancer	Liver	Pancreatic cancer	Pancreas, liver, spleen	Neuroendocrine tumors, IPMN, celiac ganglia	Pancreatic adenocarcinoma	Cystic lesions
Human studies	Non-EUS studies	None	Yes	IRB protocols	Yes	Yes	Yes
Availability	Research	Research	Research	Clinical trials	Widely	Yes	Widely

FNA, fine-needle aspiration; IPMN, intraductal papillary mucinous neoplasia; IRB, institutional review board; N/A, not applicable; RFA, radiofrequency ablation.

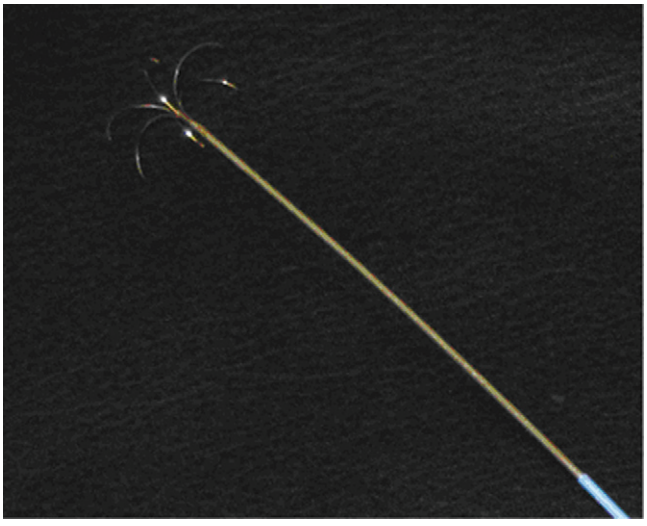


FIGURE 24.1 The tip of the EUS radiofrequency ablation needle revealing a multiprong catheter.

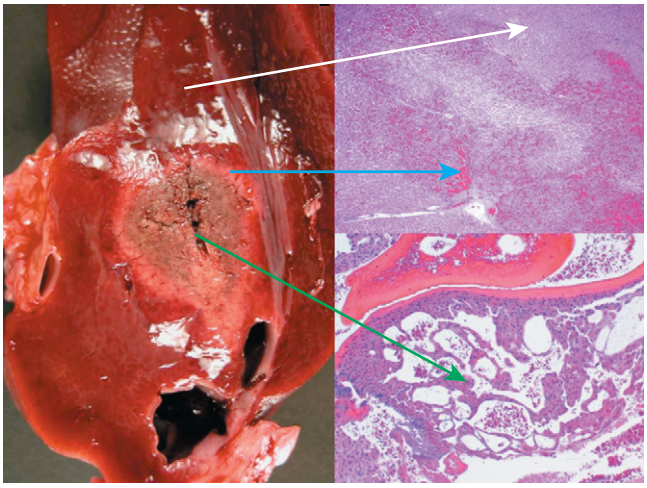


FIGURE 24.2 Focal hepatic tissue ablation using the multiprong needle catheter. The *white arrow* corresponds to unremarkable liver parenchyma as seen in the gross picture. The area immediately adjacent to the unremarkable liver parenchyma shows a zone of hyperemia. Histologically, this is seen as a zone of congested sinusoids with compression of adjacent hepatocytes *(cyan arrow).* The inner area *(green arrow)* reveals marked coagulative necrosis of the hepatocytes.

EUS-guided delivery of ablative energy to localized malignant tumors has become increasingly possible through the introduction of commercial devices. EUS-guided RFA was originally described using a modified EUS needle and a commercial RF catheter. RFA resulted in tissue necrosis of an area of 1 to 3 cm surrounding the RF needle catheter (Table 24.1). Focal tissue ablation was demonstrated using a single RFA 19-gauge (G) needle placed into the normal pancreas.[2] A large, multiprong needle assembly was used to induce a spherical area of complete coagulation necrosis (Figs. 24.1 and 24.2). A 200-watt generator with an impedance-based feedback system safely controlled the delivery of energy to the liver tissue.[3]

A commercial cool-tipped Cryotherm device was designed and tested in an animal model for pancreatic ablation[4] (Fig. 24.3). A flexible bipolar ablation probe combining RF and cryotechnology was used to induce foci of complete pancreatic ablation. The heated tip of the probe was cooled with simultaneous cryogenic carbon dioxide (650 psi). EUS-guided Cryotherm RFA was also successfully used in the liver and spleen.[5] The size of the tissue ablation was time dependent and correlated with the abnormal tissue echogenicity. Early results of a clinical trial in patients with pancreatic cancer indicated that the device can be safely used in large malignant pancreatic masses. Ultrasound-guided microwave and high-frequency ultrasound have also been used to ablate pancreatic tissue, but these techniques have not been reported with endoscopic ultrasound guidance.

Brachytherapy in the form of small seeds or beads can also be used for the local control of malignant disease. Solid gastrointestinal malignant tumors often respond to the local administration of radiation therapy, and the risk of recurrence is reduced.[6] Traditionally, radiation therapy was provided intraoperatively, but precise targeting is difficult. CT-guided placement of radiation beads and seeds adjacent to malignant gastrointestinal tumors is reportedly safe and somewhat effective.[7] EUS-guided brachytherapy was described in an animal model of pancreatic cancer.[8] Localized tissue necrosis and fibrosis were achieved in the pancreas, without significant complications. Through an 18-G EUS needle, multiple small radioactive seeds were placed into the pancreatic tissue to provide interstitial brachytherapy.

A pilot study in patients with unresectable stage III and stage IV pancreatic adenocarcinoma demonstrated the feasibility and safety of the procedure with a mean of 22 seeds per patient.[9]

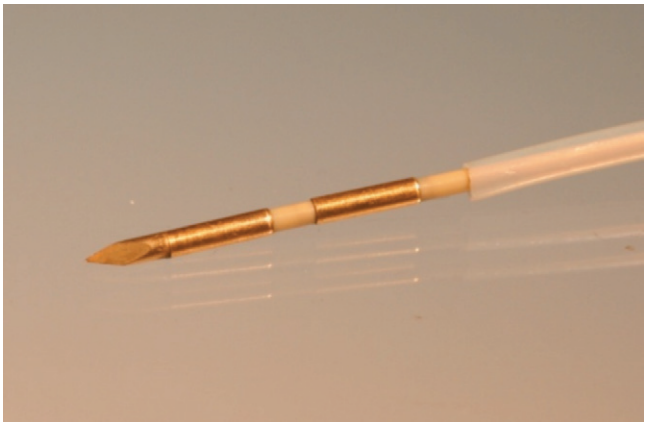


FIGURE 24.3 **Cool-tipped radiofrequency catheter designed for EUS.**

Although the tumor response to brachytherapy was modest (33% of the tumors were stabilized), there was a transient clinical benefit in patients (30%) who experienced a reduction in abdominal pain. The mean total implanted activity was 20 mCi, the minimum peripheral dose was 14,000 cGy, and the mean volume of implants was 52 cm^3. EUS-guided radioactive iodine-125 seed placement into pancreatic cancer was also reported to produce a transient decrease in abdominal pain.[10] In this trial of 22 patients, all patients were successfully implanted with iodine-125 seeds by EUS, with a median of 10 seeds and a maximum of 30 seeds per procedure. The estimated median survival time was 9.0 months. Partial remission was achieved in three patients (13.6%) during the 4-week period, and disease in 10 patients (45.5%) remained stable. Pain scores dropped from 5.1 to 1.7 ($P < .01$) 1 week after brachytherapy but increased again to 3.5 a month later ($P < .05$ versus baseline).

Another promising technique for tumor ablation is photodynamic therapy (PDT). This light-based tumor ablative technique is more selective than RFA and brachytherapy (see Table 24.1). The basis of PDT is the use of an intravenous tumor-sensitizing agent that is selectively concentrated by the tumor. There are large numbers of potential photosensitizers, but only a few have been used for the treatment of pancreatic cancer.[11] Animal models demonstrated necrosis of malignant tissue exposed to laser light (630 nm) after intravenous injection of 5-aminolevulinic acid.[12] EUS-guided PDT enables the placement of a small-gauge, flexible light catheter into the target through a large-gauge EUS needle. Once the needle has been placed into the target tissue, the needle is withdrawn, and the light catheter exposes the tissue to laser light for 5 to 15 minutes. The use of porfimer sodium as the sensitizer resulted in small foci of tissue ablation in the normal pancreatic tissue of the swine.[13] More recent studies demonstrated a dose-response relationship with the amount of light administered and resulting tissue necrosis. A maximum diameter of more than 3 cm of pancreatic tissue necrosis was achieved.[14] Combining PDT with intravenous gemcitabine in a xenograft mouse model of pancreatic cancer demonstrated a significant additive effect of PDT.[15]

FINE-NEEDLE INJECTION THERAPY

Along similar lines, EUS-guided ethanol injection has been used to ablate pancreatic tissue.[16] In animal studies, the concentration of ethanol injected into the pancreatic parenchyma was associated with a linear dose-response relationship with the amount of tissue ablation. Tissue ablation failed to take place with ethanol injection at concentrations of less than 40%, as well as with saline injection.[17] Another study also demonstrated that ethanol ablation of pancreatic tissue appears to be remarkably safe and resulted in well-controlled ablation, as evidenced by a decreased vascular perfusion.[18] It appears that the mechanism of action of ethanol injection therapy is localized tissue ischemia with subsequent necrosis but without widespread pancreatitis. Similar results were achieved with hot saline injection into the pancreas.[19]

EUS-guided ethanol injection therapy has been reported in only a few case studies in patients with a localized malignant tumor (see Table 24.1). For example, EUS-guided ethanol injection was used in a patient with an insulinoma.[20] Although the patient developed abdominal pain requiring hospitalization, there was evidence of successful and durable ablation of the insulinoma. A similar report demonstrated successful gastrointestinal stromal cell tumor ablation as a result of EUS-guided transgastric ethanol injection.[21] Localized ethanol injection was also successful at ablating an adrenal metastasis from lung cancer.[22]

The possibility of providing local control of pancreatic cancer with EUS therapy remains a major challenge. The original report of injection therapy into pancreatic malignancy used sensitized culture of lymphocytes and established the feasibility and safety of this therapy.[23] In a phase I clinical trial, eight patients with unresectable pancreatic adenocarcinoma underwent EUS-guided FNI of cytoimplants. Four patients had stage II disease, three had stage III cancer, and one had stage IV pancreatic cancer. Escalating doses of cytoimplants (3, 6, or 9 billion cells) were implanted using EUS guidance. The median survival was 13.2 months, with two partial responders and one minor response. Major complications including bone marrow toxicity and hemorrhagic, infectious, renal, or cardiopulmonary toxicity were absent. Low-grade fever was encountered in seven of the eight patients and was symptomatically treated with acetaminophen. Although the study demonstrated the safety of the injection therapy, no large-scale trials have been performed.

The technique of EUS-guided FNI has also been applied to deliver antitumor viral therapy.[24] ONYX-015 (dl1520) is an E1B-55-kDa gene-deleted replication-selective adenovirus that preferentially replicates in malignant cells and causes cell death. Twenty-one patients with locally advanced adenocarcinoma of the pancreas or with metastatic disease, but minimal or absent liver metastases, underwent eight sessions of ONYX-015 delivered by EUS injection into the primary pancreatic tumor over 8 weeks. The final four treatments were given in combination with intravenous gemcitabine (1000 mg/m^2). After combination therapy, 2 patients had partial regressions of the injected tumor, 2 had minor responses, 6 had stable disease, and 11 had progressive disease. No clinical pancreatitis occurred despite mild, transient elevations in lipase in a minority of patients. Two patients had sepsis before the institution of prophylactic oral antibiotics. Two patients had duodenal perforations from the rigid endoscope tip. No perforations occurred after the protocol was changed to transgastric injections only. No additional trials are ongoing.

TNFerade is the newest EUS-guided antitumor therapy that involves a novel gene injection.[25] The attractiveness of this approach is the potential to maximize local antitumor activity and minimize systemic toxicity. TNFerade was constructed as a second-generation (E1-, partial E3-, and E4-deleted) adenovector, expressing the cDNA encoding human tumor necrosis factor (TNF). To optimize local effectiveness and minimize systemic toxicity further, the radiation-inducible immediate response *Egr-1* (early growth response) promoter was placed upstream of the transcriptional start site of the human TNF cDNA. This vector was engineered to ensure that maximal gene expression and subsequent TNF secretion were constrained in space and time by radiation therapy. Thus, the synergistic "triple threat" is formulated: 5-fluorouracil chemotherapy is directly toxic to cancer cells and is also a radiosensitizer; external beam radiation destroys cancer cells and upregulates TNF production; and TNFerade causes cancer cell death and is itself a radiosensitizer.

TNFerade in combination with radiation therapy was studied in preclinical and early clinical (phase I) trials, with encouraging results.[26,27] The study design consisted of a 5-week treatment of weekly intratumoral injections of TNFerade (4×10^9, 4×10^{10}, and 4×10^{11} particle units in 2 mL). EUS-guided FNI was compared with percutaneous approaches (CT or ultrasound). TNFerade was combined with continuous intravenous 5-fluorouracil (200 mg/m^2/day × 5 days/week) and radiation (50.4 Gy). TNFerade was delivered with a single needle pass at a single site in the tumor for percutaneous approaches (PTAs), whereas up to four injections were given by EUS. The long-term results from a cohort of 50 patients showed that toxicities potentially related to TNFerade were mild and well tolerated. Compared with two lower-dose cohorts ($n = 30$), the higher-dose group ($n = 11$) was associated with greater locoregional control of treated tumors, longer progression-free survival, a greater proportion of patients with stable or decreasing levels of CA 19-9, a greater percentage (45%) of patients resected, and improved median survival (6.6, 8.8, 11.2, and 10.9 months, in the 4×10^9, 4×10^{10}, 4×10^{11} or 1×10^{12} particle units cohorts, respectively). At the 4×10^{11} dose, four out of five patients whose tumors became surgically resectable achieved pathologically negative margins, and three survived more than 24 months.

The experimental basis of EUS-guided chemotherapy injection into solid pancreatic malignant tumors was based on an investigation using a sustained-released chemotherapy gel.[28] More recently, EUS was used to guide the injection of a temperature-sensitive gel containing paclitaxel (Taxol) into a normal pig pancreas (Fig. 24.4). Therapeutic tissue levels of paclitaxel were demonstrated in the pancreatic tissue, as far away as 3 to 5 cm from the site of injection. The diffusion of the paclitaxel into the pancreatic tissue was not associated with evidence of pancreatitis or other toxicities. A similar report demonstrated the safety of EUS-guided injection of a biodegradable polymer containing 5-fluorouracil into the canine pancreas.[8]

EUS-GUIDED FIDUCIAL PLACEMENTS

Advances in radiation therapy have provided the opportunity for the real-time delivery of radiation using three-dimensional mapping and guided by radiopaque markers. Respiratory-dependent movement of the target lesions often results in inappropriate radiation exposure to surrounding tissue. The use of marking of focal malignancy allows the precise targeting of focused beams of radiation despite respiratory movements.

Although CT scanning is capable of guiding the placement of fiducials in and adjacent to pancreatic malignancy, EUS guidance is probably more precise.[29] These small radiopaque markers are placed into the periphery of a malignant lesion to facilitate better targeting of radiation therapy.

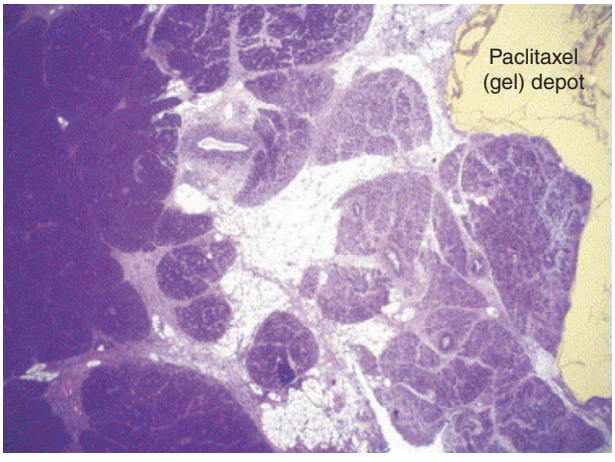


FIGURE 24.4 Histopathology of EUS-guided injection of a chemotherapeutic agent (paclitaxel [Taxol]) into the pancreas.

Procedural Technique (Video 24.1)

After identifying the tumor and excluding the presence of intervening vasculature, EUS-guided fiducial placement is undertaken using 19-G FNA needles. Commercially available sterilized gold fiducial markers 3 mm in length and 0.8 mm in diameter are preloaded into the needle by retracting the stylet and manually back-loading the fiducials into the tip of the needle. The tip of the needle is then sealed with bone wax to prevent accidental dislodgment of the fiducials. Smaller fiducials have been developed that enable deployment through 22-G FNA needles. After identifying a target lesion, the tumor is punctured, and the fiducial is deployed by advancing the stylet forward. Resistance can be encountered during deployment of fiducials if the tip of the echoendoscope is deflected. This resistance can be overcome by removing the stylet and applying hydrostatic pressure from a syringe containing sterile water attached to the needle to deposit the markers into the tumor. Depending on the size of the tumor, four to six fiducials should be deployed into the tumor to provide for ample separation of fiducials in distance, angulation, and plane. Both fluoroscopic and ultrasonographic visualization may be used to enable correct positioning of the fiducials within the tumor mass (Figs. 24.5 and 24.6). Although preliminary

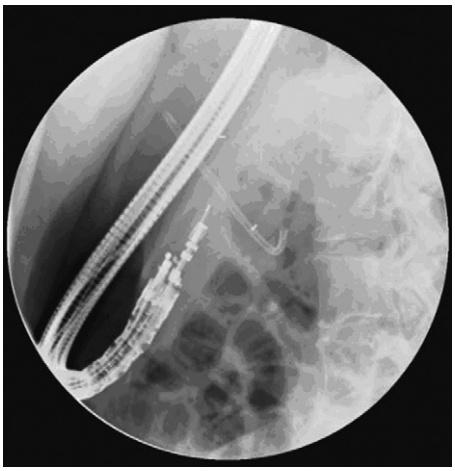


FIGURE 24.5 Fluoroscopy demonstrating fiducial placement within a pancreatic mass.

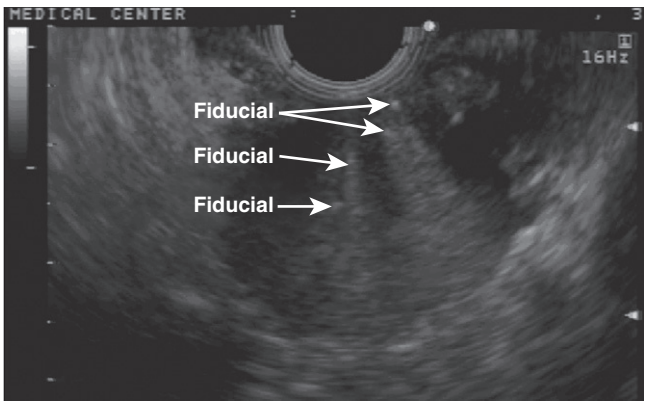


FIGURE 24.6 EUS image demonstrating fiducial placement within a pancreatic mass.

studies mainly focused on the role of EUS-guided fiducial placement in pancreatic cancer, fiducials can potentially be deployed into any intramural or extramural malignant tumor that can be accessed by EUS.[30]

In a study reported in 2006, fiducials were deployed under EUS guidance in 13 patients with mediastinal or intra-abdominal tumors.[29] All patients were scheduled to undergo Cyberknife stereotactic radiosurgery following fiducial placement. The EUS procedure was technically successful in 11 of 13 (84%) patients. Failures were caused by an inability to advance the echoendoscope into the duodenum in a patient with gastric outlet obstruction and by the presence of an intervening vasculature in another. The investigators used fiducials that were either 3 or 5 mm in length and reported difficulty with deployment of 5-mm fiducials when the tip of the echoendoscope was angulated. This technical difficulty was overcome either by straightening the tip of the echoendoscope during fiducial deployment or by placing 3-mm fiducials instead. The fiducials are readily seen with fluoroscopy as small radiopaque objects within the target tissue (Fig. 24.7). One patient in this study developed cholangitis 25 days following the procedure. The role of prophylactic antibiotics for this procedure and the impact of EUS-guided fiducial placement on patient survival or quality of life are unclear.

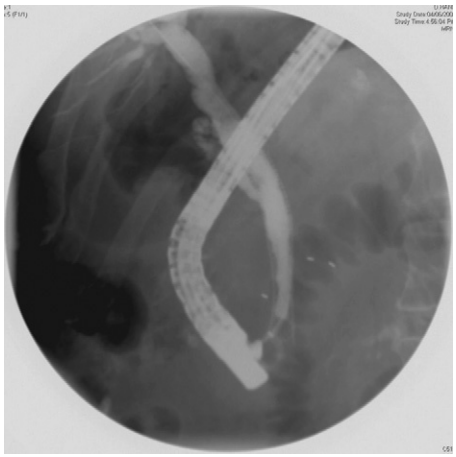


FIGURE 24.7 Multiple fiducials are seen within the tumor mass (with fluoroscopy during endoscopic retrograde cholangiopancreatography) after completion of placement.

EUS-GUIDED PANCREATIC CYST ABLATION

EUS-guided pancreatic cyst ablation is based on the principle that injection of a cytotoxic agent into a pancreatic cystic lesion will result in ablation of the cyst epithelium. The close contact between the injected agent and the epithelium results in both immediate and delayed tissue necrosis. The cytotoxic agent remains within the cyst cavity without extravasation into the parenchyma.

Procedural Technique (Video 24.2)

EUS-guided ethanol lavage of pancreatic cystic lesions employs techniques based on FNA of the pancreas. After prophylactic antibiotics are administered, a linear echoendoscope positioned in the duodenum, gastric body, or fundus provides access to pancreatic head, body, or tail, respectively, and guides the use of FNA. The injection of ablative agents into a cystic lesion requires the complete or partial evacuation of the fluid contents of the cyst. Although it may be difficult to aspirate the highly viscous fluid of mucinous cysts, it is necessary to provide room for the injected ablative agent. This principle of cyst injection therapy, coupled with a dead space of approximately 0.8 mL in the aspiration needle, limits target cysts to more than 10 mm in diameter. Once the needle is in place within the lumen of the cyst, the ablative agent is injected under ultrasound monitoring. Swirls of aerated liquid are readily observed with ultrasound, and the distribution can be easily determined during the procedure. In many cases, ablative therapy is provided with a lavage of the liquid, such as ethanol, in and out of the cyst over several minutes. Unilocular cysts with a diameter of 1 to 2 cm are easily treated in one or two sessions. Larger and more complex lesions require multiple lavage sessions. The end point of ethanol lavage is elimination of the cyst as evidenced by cross-sectional imaging.

Clinical Outcomes

EUS-guided ethanol injection into pancreatic cystic lesions was originally described using a variety of low concentrations of ethanol[31] (Table 24.2). In the initial studies, the safety of cyst injection therapy was established first using saline solution, followed by highly dilute ethanol. There was no evidence of clinical pancreatitis with injection of ethanol using concentrations up to 80%. Small numbers of lavaged cystic lesions were resected, and there was evidence of epithelial ablation with pancreatitis.[31] In a randomized, prospective, multicenter trial, ethanol lavage was found to provide greater rates of complete ablation as compared with saline lavage.[32] The overall CT-defined rate of complete pancreatic cyst ablation was 33.3%. The histology of four resected cysts demonstrated epithelial ablation ranging from 0% (saline solution alone) to 50% to 100% (one or two ethanol lavages). Although one patient developed transient pancreatitis,

TABLE 24.2

EUS-Guided Ablation of Pancreatic Cystic Lesions

Authors (yr)	Agent	Target	Results	Complications
Gan et al[31] (2005)	5%-80% ethanol (diluted with saline)	Pancreatic cystic lesions (EUS guidance)	Resolution of cystic lesion in 8/23 patients; resected patients had ablated epithelium	None
Oh et al[33] (2008)	80%-90% ethanol paclitaxel	Pancreatic cystic lesions (EUS guidance)	Resolution of cystic lesion in 11/14 patients	Episode of pancreatitis with a fluid collection
DeWitt et al[45] (2009)	80% ethanol compared with saline	Pancreatic cystic lesions (EUS guidance)	Resolution of cystic lesion in 12/36 patients	Abdominal pain; rare pancreatitis
Oh et al[34] (2009)	80%-90% ethanol paclitaxel	Septated pancreatic cystic lesions	Resolution in 6/10 patients	Episode of mild pancreatitus in one patient

approximately 20% of patients from both groups (ethanol and saline) experienced some abdominal pain the day after lavage.

Ethanol lavage was coupled with paclitaxel injection.[33] In a small number of patients with a variety of cystic lesions, the combination of ethanol and paclitaxel injection resulted in elimination of the cysts, as determined by CT scanning, in nearly 80% of patients (Fig. 24.8). However, the high viscosity of paclitaxel makes injection into the cyst difficult. In contrast, ethanol is easily injected and aspirated from the cyst and at times reduces the cyst fluid viscosity, thus aiding in cyst evacuation. The combination of ethanol and paclitaxel is also capable of ablating septated cystic lesions, a much more difficult target for EUS injection therapy.[34] Presumably, the surface area of a septated cyst is quite large, and it is difficult to be certain that the cytotoxic injectant comes in contact with all of the epithelium.

CELIAC PLEXUS INTERVENTIONS

The principle of celiac injection therapy is based on the ability of EUS to guide injection of cytotoxic agents into the retrogastric space containing the celiac ganglia (Fig. 24.9). Presumably, the injected agent, such as ethanol, comes into contact with the ganglia and disrupts the ascending sympathetic ganglia, Histologically, there is evidence of neuronal vacuolization in nerves injected with ethanol.[35] Because the efferent nerves from the pancreas travel with the sympathetic chain, interruption of the celiac ganglia should result in a decreased sense of pain within the pancreas. In the setting of pancreatic cancer, there is evidence of sensory nerve hyperplasia, and this may be the basis for the often observed chronic abdominal pain.

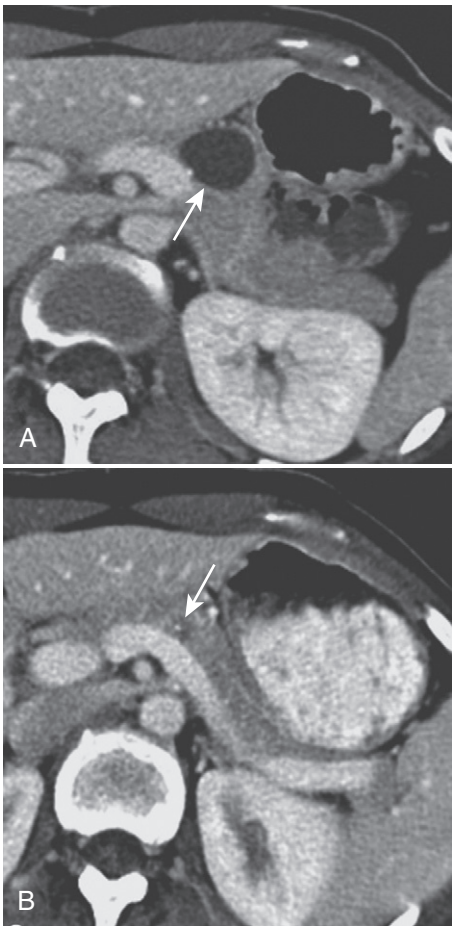


FIGURE 24.8 Pancreatic cyst lavage. Computed tomography scanning before (**A**) and after (**B**) ethanol-paclitaxel (Taxol) lavage of a pancreatic cyst *(arrows).*

Procedural Technique (Video 24.3)

The technique for EUS-guided celiac plexus neurolysis and block is identical; the only difference is in the substances injected. With a curvilinear array echoendoscope, the region of the celiac plexus is visualized from the lesser curve of the stomach by following the aorta to the origin of the main celiac artery and is traced, using counterclockwise rotation, to its bifurcation into splenic and hepatic arteries, with Doppler control if needed (Fig. 24.10). With careful inspection, it is often possible, by using slight rotational movements, even to visualize the celiac ganglia directly (Fig. 24.11).

A 22- or 19-G EUS FNA needle is usually used, but in some countries a dedicated 20-G spray needle with multiple side holes is available and allows solutions to spread over a greater area. The needle tip is placed slightly anterior and cephalad to the origin of the celiac artery or directly into the ganglia if these can be identified as discrete structures. Aspiration is first performed to ensure that vascular puncture has not occurred. Bupivacaine is injected first, followed by alcohol (or triamcinolone for block). One of two strategies can be used: injection of the entire solution into the area cephalad of the celiac trunk or injection into the right and left sides of the celiac artery. Patients should be observed for 2 to 4 hours with careful monitoring of pulse, blood pressure, temperature, and pain scores.

Clinical Outcomes

EUS injection therapy has been used clinically since the early 2000s in patients with pain associated with pancreatic diseases. Traditionally, EUS injection therapy was based on ethanol-induced celiac ganglion neurolysis for pain relief in pancreatic cancer.[36] The original prospective trial demonstrated a significant

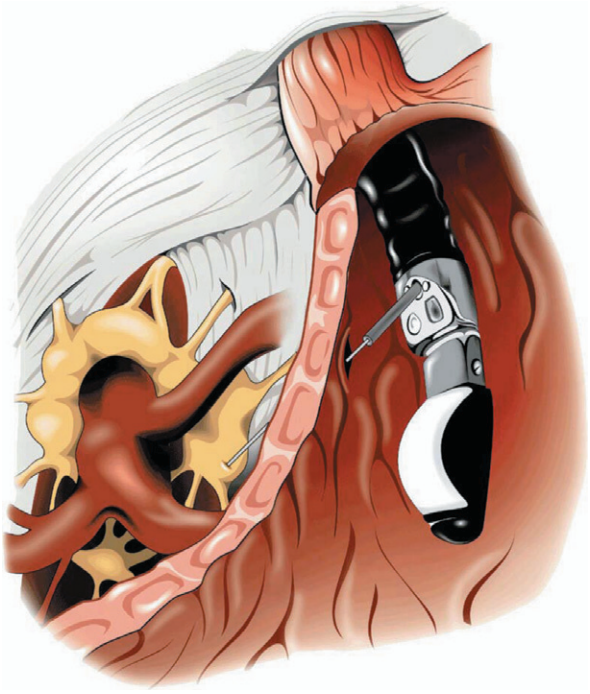


FIGURE 24.9 Illustration of an EUS-guided celiac ganglia injection.

reduction in pain scores 2 weeks after EUS celiac plexus injection, an effect that was sustained for 24 weeks when adjusted for morphine use and adjuvant therapy[37] (Table 24.3). Forty-five of the 58 patients (78%) experienced a decline in pain scores after EUS-guided celiac plexus neurolysis. The use of chemotherapy and radiation therapy also aided in the reduction in pain. A meta-analysis of the literature reported that EUS-guided celiac plexus neurolysis was 72.54% effective in managing pain resulting from pancreatic cancer and is a reasonable option for patients with tolerance to narcotic analgesics.[38]

A large retrospective study demonstrated that bilateral celiac neurolysis injection was more effective than central injection in terms of pain reduction.[39] More than 70.4% of patients reported a decrease in pain levels at 7 days, compared with 45.9% of patients receiving a single injection. The most common complication of celiac plexus neurolysis was postprocedural hypotension, at a rate of 3.2%.[40] Occasionally, patients complain of severe abdominal pain after ganglion injection, and the pain may persist.[40] The most serious complication was a single episode of injury to the adrenal artery.

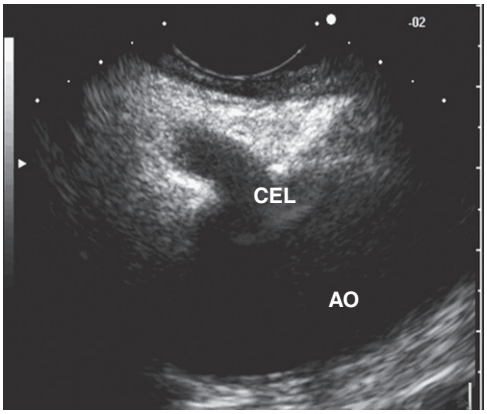


FIGURE 24.10 Celiac plexus neurolysis being undertaken at the space around the celiac artery (CEL). Note the needle at the base of the celiac artery. AO, aorta.

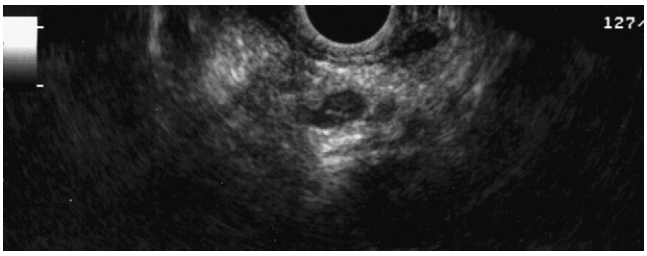


FIGURE 24.11 EUS imaging of a focal round, hypoechoic celiac ganglion.

Injection therapy in patients with pain associated with chronic pancreatitis has not been as successful as reported in pain control of pancreatic cancer.[41] The overall rate of response has been approximately 50%, and responses have been transient.[38] Ganglion blockade using local anesthetics rather than permanent chemical neurolysis has generally been the approach in pain control in chronic pancreatitis. LeBlanc et al,[42] in a prospective trial, determined that the average duration of effect of a ganglion block was 1 month, and one injection of bupivacaine and triamcinolone produced the same effect as two injections. Many investigators believe that short-term relief of pain may not be a clinically important effect in the long-term care of patients with chronic pancreatitis.

Developments have focused on the ability of EUS to target celiac ganglia specifically with needle injection therapy.[43] In a retrospective study, 33 patients underwent 36 direct celiac ganglia injections for unresectable pancreatic cancer ($n = 17$) or chronic pancreatitis ($n = 13$) with bupivacaine (0.25%) and alcohol (99%) for neurolysis or methylprednisolone (Depo-Medrol, 80 mg/2 mL) for nerve blockade. Nearly all patients with cancer (94%) reported pain relief. In contrast, patients with chronic pancreatitis experienced lower response rates (80% response rate with alcohol injection and 38% response rate with steroids).

In a large, prospective randomized trial, celiac neurolysis provided significant improvement (40% of patients) in severe abdominal pain (for 6 weeks) associated with pancreatic cancer, as compared with a response rate of 14% of patients taking opioids.[44] Despite these reported high rates of response to injection therapy, the large trial failed to demonstrate a significant improvement in quality of life and survival in patients with pancreatic cancer.

SUMMARY

EUS-guided injection therapy is based on the accurate placement of ablative agents into various gastrointestinal tissues, including celiac ganglia. Effective tissue ablation has been achieved in the pancreas, pancreatic cystic lesions, and ganglia. Excellent rates of pain control have been observed in patients with pancreatic cancer who were undergoing EUS-guided celiac neurolysis. In the future, local control of malignant tumors will be aided by injection therapy.

TABLE 24.3
Published Clinical Trials of EUS-Guided Celiac Injection Therapy

Authors (yr)	Patients (*n*)	Clinical Condition	Neurolysis or Block	Pain Score Change	Major Complications
Gunaratnam et al[37] (2001)	58	Pancreatic cancer	Neurolysis	78% improved	None
Gress et al[46] (1999)	18	Chronic pancreatitis	Block	50% improved (EUS)	None
Gress et al[47] (2001)	90	Chronic pancreatitis	Block	55% improved	1.1% abscess
Levy et al[43] (2008)	33	Pancreatic cancer and chronic pancreatitis	Block and Neurolysis	94% improved (cancer); 50% improved (chronic pancreatitis)	None

REFERENCES

1. Yusuf TE, Tsutaki S, Wagh MS, et al. The EUS hardware store: state of the art technical review of instruments and equipment (with videos). *Gastrointest Endosc*. 2007;66:131–143.
2. Goldberg SN, Mallery S, Gazelle GS, Brugge WR. EUS-guided radiofrequency ablation in the pancreas: results in a porcine model. *Gastrointest Endosc*. 1999;50:392–401.
3. Varadarajulu S, Jhala NC, Drelichman ER. EUS-guided radiofrequency ablation with a prototype electrode array system in an animal model (with video). *Gastrointest Endosc*. 2009;70:372–376.
4. Carrara S, Arcidiacono PG, Albarello L, et al. Endoscopic ultrasound-guided application of a new hybrid cryotherm probe in porcine pancreas: a preliminary study. *Endoscopy*. 2008;40:321–326.
5. Carrara S, Arcidiacono PG, Albarello L, et al. Endoscopic ultrasound-guided application of a new internally gas-cooled radiofrequency ablation probe in the liver and spleen of an animal model: a preliminary study. *Endoscopy*. 2008;40:759–763.
6. Skandarajah AR, Lynch AC, Mackay JR, et al. The role of intraoperative radiotherapy in solid tumors. *Ann Surg Oncol*. 2009;16:735–744.
7. Calvo FA, Meirino RM, Orecchia R. Intraoperative radiation therapy. Part 2: clinical results. *Crit Rev Oncol Hematol*. 2006;59:116–127.
8. Sun S, Wang S, Ge N, et al. Endoscopic ultrasound-guided interstitial chemotherapy in the pancreas: results in a canine model. *Endoscopy*. 2007;39:530–534.
9. Sun S, Xu H, Xin J, et al. Endoscopic ultrasound-guided interstitial brachytherapy of unresectable pancreatic cancer: results of a pilot trial. *Endoscopy*. 2006;38:399–403.
10. Jin Z, Du Y, Li Z, et al. Endoscopic ultrasonography-guided interstitial implantation of iodine 125-seeds combined with chemotherapy in the treatment of unresectable pancreatic carcinoma: a prospective pilot study. *Endoscopy*. 2008;40:314–320.
11. Fan BG, Andren-Sandberg A. Photodynamic therapy for pancreatic cancer. *Pancreas*. 2007;34:385–389.
12. Regula J, Ravi B, Bedwell J, et al. Photodynamic therapy using 5-aminolaevulinic acid for experimental pancreatic cancer: prolonged animal survival. *Br J Cancer*. 1994;70:248–254.
13. Chan HH, Nishioka NS, Mino M, et al. EUS-guided photodynamic therapy of the pancreas: a pilot study. *Gastrointest Endosc*. 2004;59:95–99.
14. Yusuf TE, Matthes K, Brugge WR. EUS-guided photodynamic therapy with verteporfin for ablation of normal pancreatic tissue: a pilot study in a porcine model (with video). *Gastrointest Endosc*. 2008;67:957–961.
15. Xie Q, Jia L, Liu YH, Wei CG. Synergetic anticancer effect of combined gemcitabine and photodynamic therapy on pancreatic cancer in vivo. *World J Gastroenterol*. 2009;15:737–741.
16. Aslanian H, Salem RR, Marginean C, et al. EUS-guided ethanol injection of normal porcine pancreas: a pilot study. *Gastrointest Endosc*. 2005;62:723–727.
17. Matthes K, Mino-Kenudson M, Sahani DV, et al. Concentration-dependent ablation of pancreatic tissue by EUS-guided ethanol injection. *Gastrointest Endosc*. 2007;65:272–277.
18. Giday SA, Magno P, Gabrielson KL, et al. The utility of contrast-enhanced endoscopic ultrasound in monitoring ethanol-induced pancreatic tissue ablation: a pilot study in a porcine model. *Endoscopy*. 2007;39:525–529.
19. Imazu H, Sumiyama K, Ikeda K, et al. A pilot study of EUS-guided hot saline injection for induction of pancreatic tissue necrosis. *Endoscopy*. 2009;41:598–602.
20. Jurgensen C, Schuppan D, Neser F, et al. EUS-guided alcohol ablation of an insulinoma. *Gastrointest Endosc*. 2006;63:1059–1062.
21. Gunter E, Lingenfelser T, Eitelbach F, et al. EUS-guided ethanol injection for treatment of a GI stromal tumor. *Gastrointest Endosc*. 2003;57:113–115.
22. Artifon EL, Lucon AM, Sakai P, et al. EUS-guided alcohol ablation of left adrenal metastasis from non–small-cell lung carcinoma. *Gastrointest Endosc*. 2007;66:1201–1205.
23. Chang KJ, Nguyen PT, Thompson JA, et al. Phase I clinical trial of allogeneic mixed lymphocyte culture (cytoimplant) delivered by endoscopic ultrasound-guided fine-needle injection in patients with advanced pancreatic carcinoma. *Cancer*. 2000;88:1325–1335.
24. Hecht JR, Bedford R, Abbruzzese JL, et al. A phase I/II trial of intratumoral endoscopic ultrasound injection of ONYX-015 with intravenous gemcitabine in unresectable pancreatic carcinoma. *Clin Cancer Res*. 2003;9:555–561.
25. Chang KJ, Lee JG, Holcombe RF, et al. Endoscopic ultrasound delivery of an antitumor agent to treat a case of pancreatic cancer. *Nat Clin Pract Gastroenterol Hepatol*. 2008;5:107–111.
26. Mundt AJ, Vijayakumar S, Nemunaitis J, et al. A Phase I trial of TNFerade biologic in patients with soft tissue sarcoma in the extremities. *Clin Cancer Res*. 2004;10:5747–5753.
27. McLoughlin JM, McCarty TM, Cunningham C, et al. TNFerade, an adenovector carrying the transgene for human tumor necrosis factor alpha, for patients with advanced solid tumors: surgical experience and long-term follow-up. *Ann Surg Oncol*. 2005;12:825–830.
28. Matthes K, Mino-Kenudson M, Sahani DV, et al. EUS-guided injection of paclitaxel (OncoGel) provides therapeutic drug concentrations in the porcine pancreas (with video). *Gastrointest Endosc*. 2007;65:448–453.
29. Pishvaian AC, Collins B, Gagnon G, et al. EUS-guided fiducial placement for CyberKnife radiotherapy of mediastinal and abdominal malignancies. *Gastrointest Endosc*. 2006;64:412–417.
30. Yang J, Abdel-Wahab M, Ribeiro A. EUS-guided fiducial placement before targeted radiation therapy for prostate cancer. *Gastrointest Endosc*. 2009;70:579–583.
31. Gan SI, Thompson CC, Lauwers GY, et al. Ethanol lavage of pancreatic cystic lesions: initial pilot study. *Gastrointest Endosc*. 2005;61:746–752.
32. DeWitt J, Al-Haddad M, Fogel E, et al. Endoscopic transduodenal drainage of an abscess arising after EUS-FNA of a duodenal GI stromal tumor. *Gastrointest Endosc*. 2009;70:185–188.
33. Oh HC, Seo DW, Lee TY, et al. New treatment for cystic tumors of the pancreas: EUS-guided ethanol lavage with paclitaxel injection. *Gastrointest Endosc*. 2008;67:636–642.
34. Oh HC, Seo DW, Kim SC, et al. Septated cystic tumors of the pancreas: is it possible to treat them by endoscopic ultrasonography-guided intervention? *Scand J Gastroenterol*. 2009;44:242–247.
35. Vranken JH, Zuurmond WW, Van Kemenade FJ, Dzoljic M. Neurohistopathologic findings after a neurolytic celiac plexus block with alcohol in patients with pancreatic cancer pain. *Acta Anaesthesiol Scand*. 2002;46:827–830.
36. Wiersema MJ, Wiersema LM. Endosonography-guided celiac plexus neurolysis. *Gastrointest Endosc*. 1996;44:656–662.
37. Gunaratnam NT, Sarma AV, Norton ID, Wiersema MJ. A prospective study of EUS-guided celiac plexus neurolysis for pancreatic cancer pain. *Gastrointest Endosc*. 2001;54:316–324.
38. Kaufman M, Singh G, Das S, et al. Efficacy of endoscopic ultrasound-guided celiac plexus block and celiac plexus neurolysis for managing abdominal pain associated with chronic pancreatitis and pancreatic cancer. *J Clin Gastroenterol*. 2010;44:127–134.
39. Sahai AV, Lemelin V, Lam E, Paquin SC. Central vs. bilateral endoscopic ultrasound-guided celiac plexus block or neurolysis: a comparative study of short-term effectiveness. *Am J Gastroenterol*. 2009;104:326–329.
40. O'Toole TM, Schmulewitz N. Complication rates of EUS-guided celiac plexus blockade and neurolysis: results of a large case series. *Endoscopy*. 2009;41:593–597.
41. Puli SR, Reddy JB, Bechtold ML, et al. EUS-guided celiac plexus neurolysis for pain due to chronic pancreatitis or pancreatic cancer pain: a meta-analysis and systematic review. *Dig Dis Sci*. 2009;54:2330–2337.
42. LeBlanc JK, DeWitt J, Johnson C, et al. A prospective randomized trial of 1 versus 2 injections during EUS-guided celiac plexus block for chronic pancreatitis pain. *Gastrointest Endosc*. 2009;69:835–842.
43. Levy MJ, Topazian MD, Wiersema MJ, et al. Initial evaluation of the efficacy and safety of endoscopic ultrasound-guided direct ganglia neurolysis and block. *Am J Gastroenterol*. 2008;103:98–103.
44. Wong GY, Schroeder DR, Carns PE, et al. Effect of neurolytic celiac plexus block on pain relief, quality of life, and survival in patients with unresectable pancreatic cancer: a randomized controlled trial. *JAMA*. 2004;291:1092–1099.
45. DeWitt J, McGreevy K, Schmidt CM, Brugge WR. EUS-guided ethanol versus saline solution lavage for pancreatic cysts: a randomized, double-blind study. *Gastrointest Endosc*. 2009;70:710–723.

CHAPTER 25

EUS-Guided Drainage of Pelvic Abscesses

Shyam Varadarajulu

Key Points

EUS enables drainage of pelvic fluid collections that are adjacent to the rectum or colonic lumen and are within the reach of an echoendoscope. Patients with unilocular fluid collections that measure 4 cm or larger are ideal candidates for the procedure.

The presence of a fluoroscopy unit, therapeutic echoendoscope, accessories such as 19-gauge needles, endoscopic retrograde cholangiopancreatography cannula or needle-knife catheters, 0.035-inch guidewires, balloon dilators, and double-pigtail stents or biliary drainage catheters are essential for the procedure.

Both transluminal stents and drainage catheters can be deployed at EUS, to allow quick resolution of the fluid collections. Most patients can be discharged home within 2 to 3 days following EUS-guided drainage.

The procedure is very safe and has a treatment success rate greater than 75%.

INTRODUCTION

Pelvic abscesses can occur after surgery or in patients with medical conditions such as Crohn's disease, diverticulitis, ischemic colitis, sexually transmitted diseases, or septic emboli from endocarditis. Management of a pelvic abscess can be technically challenging because of the need for navigation around the bony pelvis, bowel loops, bladder, reproductive organs in women, prostate in men, rectum, and other neurovascular structures. Historically, these collections necessitated surgery, ultrasound-guided transrectal or transvaginal intervention, or percutaneous drainage under computed tomography (CT) guidance. Advances in the field of interventional EUS have opened a new avenue for management of pelvic abscesses. This chapter focuses on the technique and outcomes of EUS-guided pelvic abscess drainage.

CURRENT TREATMENT OPTIONS

Ultrasound-Guided Drainage

Ultrasound guidance has typically been by the transvaginal or transrectal route.[1–6] Passage through the transvaginal route was used because of the close proximity of the vaginal fornices to the pelvic abscess. In this technique, a catheter is attached to an endoluminal ultrasound probe, which enables the passage of a needle for direct drainage. However, only those abscesses that are within the reach of an ultrasound probe can be drained using this technique. Moreover, transvaginal drainage is associated with significant pain that necessitates local infiltration with lidocaine. Transrectal ultrasound-guided drainage is an effective technique,[7] but once again it is limited by the length of the probe and the location of the abscess. Both techniques mandate the presence of an indwelling drainage catheter for prolonged periods. Such catheters cause physical discomfort and often restrict patient mobility.

Computed Tomography–Guided Drainage

CT-guided drainage of pelvic abscesses used a transgluteal approach if the abscess is posterior and a transabdominal approach if the location is anterior.[2] For collections smaller than 3 cm, simple aspiration usually suffices, and percutaneous drainage is not necessary. The transabdominal anterior approach is the preferred route secondary to technical ease, but it is not always practical because of the presence of overlying bowel loops. If the fluid collection cannot be accessed by the anterior or lateral approach, it may be accessed through the greater sciatic foramen by the transgluteal approach.[8] Success rates range from 27% to 93%, with variations owing to differing clinical characteristics, abscess location and morphology, and the presence or absence of a fistula.[8]

This procedure is associated with pain at the procedural site in up to 20% of patients and with limitations in ambulation and bed rest resulting from catheter protrusion through the buttocks in others.[9] Additional limitations include (1) possible injury to the inferior gluteal artery that may lead to hemorrhage or formation of a pseudoaneurysm in 2% of patients and (2) inability to identify an adequate window at CT for placement of a drainage catheter in some patients.[10,11]

Surgery

Many abscesses are a result of postsurgical complications. For this reason, the optimal treatment approach chosen should be the least invasive option for the patient. Therefore, surgical exploration and drainage are usually limited to those patients who are clinically unstable and have life-threatening infections. One study evaluated 500 patients with perirectal abscesses who were undergoing surgical drainage.[12] Of the 500 patients, 9.6% required reintervention, and 4 of these patients required a second reintervention after initial drainage. The most common reasons for repeat interventions were inadequate incision and premature closure of the abscess cavity.

WHY EUS-GUIDED DRAINAGE?

The ability to visualize extrinsic fluid collections up to the splenic flexure and to intervene in real time under sonographic guidance makes EUS an ideal treatment modality for management of patients with pelvic abscesses. Currently available evidence suggests that the procedure is technically easy, safe, and associated with excellent treatment outcomes.[10,11,13,14]

Preprocedural Assessment

All patients should undergo a dedicated CT or magnetic resonance imaging scan of the pelvis to define the anatomy and location of the abscess. Abscesses that are multiloculated, measure less than 4 cm, have immature walls (without a definitive rim), are located at the level of the dentate line, or are more than 2 cm from the EUS transducer should be managed by alternative techniques. It is recommended that patients be administered prophylactic antibiotics before the procedure. Patients should undergo local preparation with an enema to assist with optimal visualization and to minimize contamination. Laboratory parameters must be checked to ensure that patients are not coagulopathic or thrombocytopenic. It is essential that the procedure take place in a unit equipped with fluoroscopy to guide stent and drain placements within the abscess cavity. In addition, patients should either void before the procedure or have an indwelling Foley catheter to ensure that a distended bladder does not impair visualization of a small fluid collection or that it is not mistaken for an abscess.

Procedural Technique

The following procedural steps are undertaken in sequence:

1. First, the abscess must be located using a curved linear array echoendoscope (Video 25.1). Once it is located, intervening vasculature must be excluded using color Doppler. Under EUS guidance, a 19-gauge (G) fine-needle aspiration (FNA) needle is used to puncture the abscess cavity (Fig. 25.1A). The stylet is removed, and the needle is flushed with saline and aspirated to evacuate as much pus as possible. A sample of purulent material may be sent for Gram staining and culture.
2. A 0.035-inch guidewire is then passed through the needle and is coiled within the abscess cavity (see Fig. 25.1B). The needle is then exchanged over the guidewire for a 5-Fr endoscopic retrograde cholangiopancreatography (ERCP) cannula or a needle-knife catheter to dilate the tract between the rectum and the abscess cavity (see Fig. 25.1C). The tract is then further dilated using an 8-mm dilator over the wire biliary balloon dilator (see Fig. 25.1D).
3. Once the tract is dilated, one or two 7-Fr 4-cm double-pigtail transmural stents are deployed (see Fig. 25.1E). The decision to place one or more stents is based on the viscosity of the abscess contents: one if the fluid flowed smoothly and more if the contents were thicker.
4. In patients with abscesses that measure 8 cm or larger and in those abscesses that do not drain well despite placement of transmural stents, an additional transluminal drainage catheter is deployed (see Fig. 25.1F). The abscess cavity

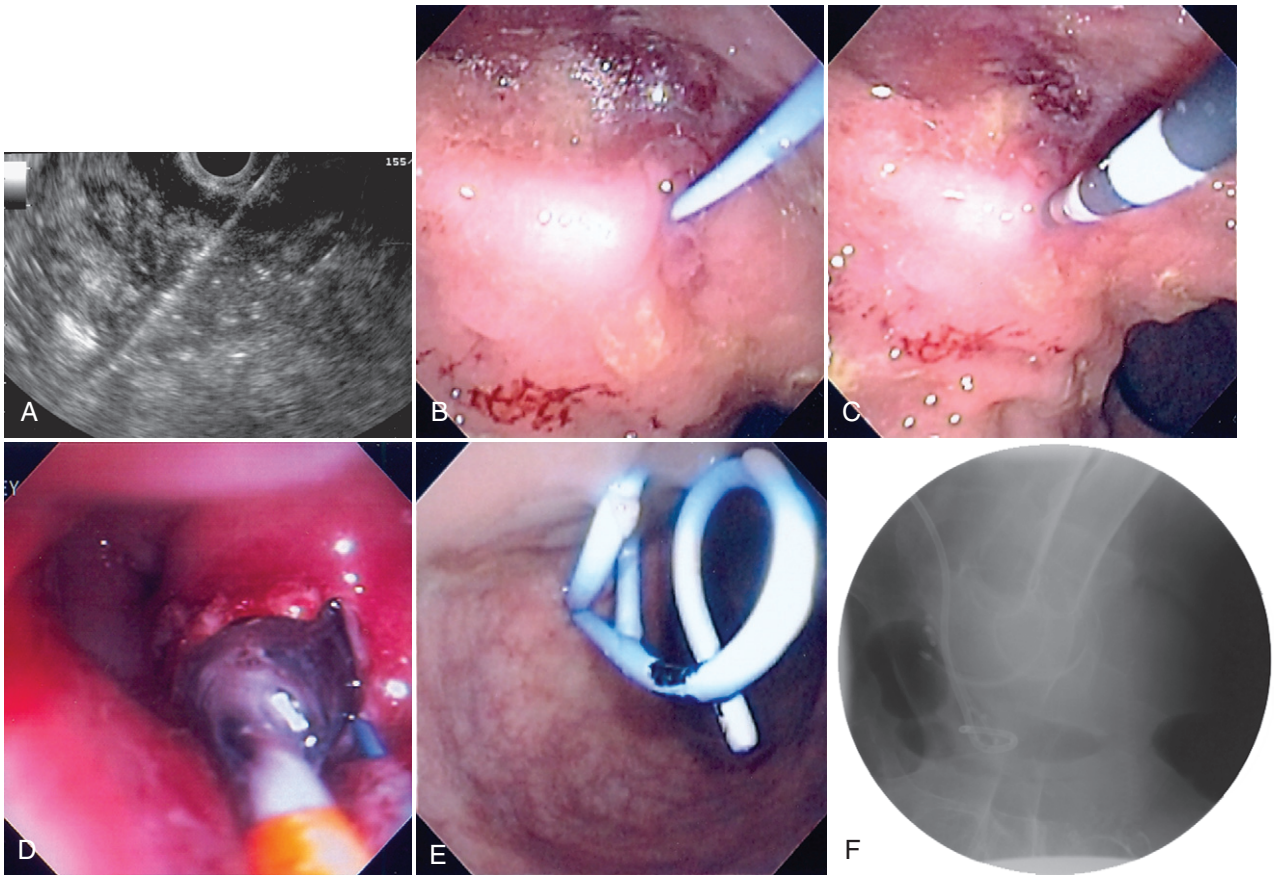


FIGURE 25.1 **A,** A fine-needle aspiration needle is passed into the pelvic abscess under EUS guidance. **B,** A 0.035-inch guidewire is then coiled within the abscess cavity. **C,** The transmural tract is dilated using a 5-Fr endoscopic retrograde cholangiopancreatography cannula. **D,** The transmural tract is then sequentially dilated using a 8-mm dilator. **E,** Two double-pigtail transrectal stents are deployed within the abscess cavity. **F,** A transrectal drainage catheter is seen within the pelvic abscess at fluoroscopy.

is accessed with a 5-Fr ERCP cannula to pass another 0.035-inch guidewire. A 10-Fr, 80-cm single-pigtail drain is then deployed over the guidewire. This drain will exit the anus and remain secured to the patient's gluteal region with tape. This drain is then flushed with 30 to 50 mL of normal saline every 4 hours until the aspirate is clear.

5. A follow-up CT scan should be obtained at 36 to 48 hours to ensure the fluid collection has decreased in size (Fig. 25.2). If there is a greater than 50% reduction in size of the abscess cavity, the drainage catheter can be removed, and the patient discharged home.
6. The remaining stents can continue to assist with drainage and can be removed in 2 weeks with sigmoidoscopy as long as a repeat CT scan of the pelvis shows complete abscess resolution.

Technical and Treatment Outcomes

Four studies (Table 25.1) evaluated the effectiveness of EUS for the treatment of pelvic abscesses.[10,11,13,14] The first study, from Europe, evaluated 12 patients by means of EUS-guided transrectal stents.[13] In this study, an 8.5- or 10-Fr transrectal stent was deployed for a period of 3 to 6 months and yielded a successful clinical outcome in 8 of 12 patients (75%). Treatment failures were more common in patients with large abscess that measured more than 8 cm. The limitation of transrectal stents is their potential to clog easily, particularly by fecal matter or pus. These stents, when left long term, can also cause perirectal pain or migrate spontaneously. In the second study, this limitation was overcome by placement of a transrectal drainage catheter in four patients.[10] Although the technical and treatment outcomes were successful, there was the potential for accidental dislodgment of the drainage catheter. Additionally, the need for periodic flushing and aspiration of the drainage catheter mandated a prolonged inpatient hospital stay (median days, 4) for most patients. Therefore, a combined technique that included EUS-guided placement of a transrectal drainage catheter and stent for drainage of the pelvic abscess was adapted.[11] The short-term (36 to 48 hours) drainage catheter provided access for continued evacuation of the abscess, whereas the medium-term (2 weeks) stent facilitated maintenance of a patent transmural tract for eventual abscess resolution. This combined therapy demonstrated favorable outcomes for resolution of the abscess in all patients and shortened the postprocedure length of stay to a median of 2 days.

The effectiveness of the foregoing combined approach was prospectively validated in a cohort of 25 patients with long-term follow-up. The abscesses were postsurgical in 68% of patients, and the origin was perforated diverticulitis or appendicitis in 20% and ischemic colitis, infective endocarditis, or trauma in the remaining 12%. Treatment using percutaneous catheter placements in 2 of the 25 patients had previously failed. The mean size of the abscesses was 68.5 mm (range, 40 to 96 mm). The investigators placed transrectal stents in all patients and an additional drainage catheter in 10 patients whose abscesses measured 8 cm or larger. The procedures were technically successful in all patients, the treatment success rate was 96%, and no complications were encountered. Seventy-six percent of the abscesses were drained by the transrectal route, and the others were drained through the left side of the colon. In this study, 2 of 25 patients who were critically ill in the intensive care unit underwent EUS-guided drainage at bedside. The mean and median procedural duration was 23 and 14 minutes, respectively. The median duration of post-procedure hospital stay was only 2 days.

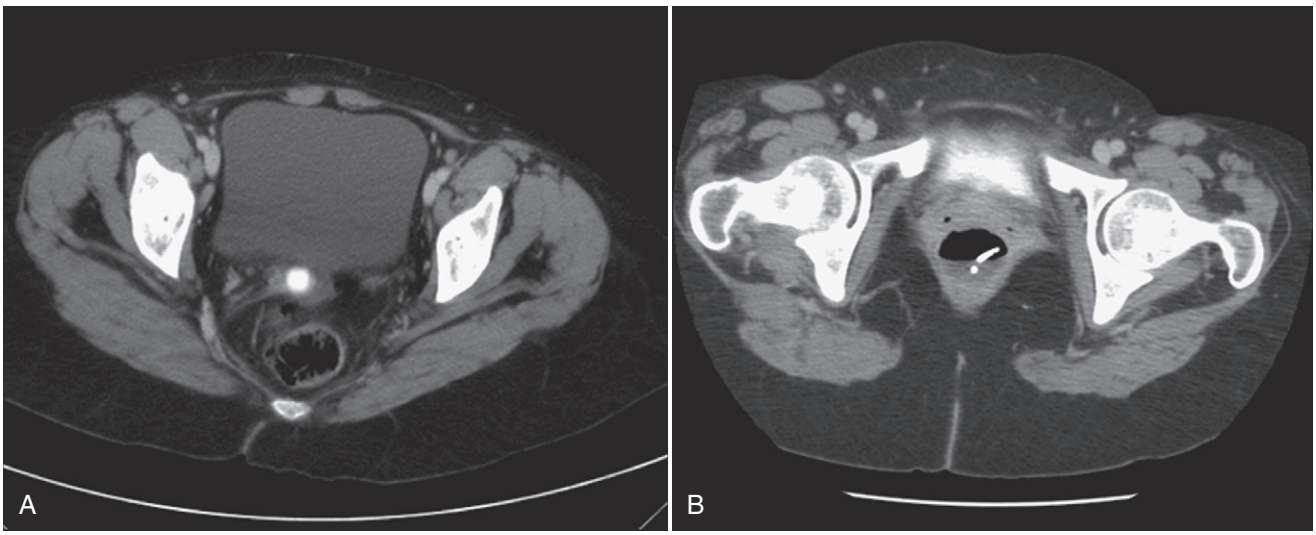


FIGURE 25.2 **A,** Computed tomography (CT) of the pelvis shows an abscess that measures 80 × 60 mm. **B,** After EUS-guided drainage, a follow-up CT scan at 36 hours demonstrates nearly complete resolution of the abscess.

TABLE 25.1

Studies Evaluating the Effectiveness of EUS-Guided Drainage of Pelvic Abscess

Authors (yr)	No. of Patients (*n*)	Mean size (mm)	Drainage Modality	Technical Success (%)	Treatment Success (%)
Giovannini et al[13] (2003)	12	48.9 × 43.4	Stent	100	88
Varadarajulu and Drelichman[10] (2007)	4	68 × 72	Drainage catheter	100	75*
Trevino et al[11] (2008)	4	93 × 61	Drainage catheter and stent	100	100
Varadarajulu and Drelichman[14] (2009)	25	68.5 × 52.4	Drainage catheter and stent	100	96

*One of four patients died of causes unrelated to the procedure.

Advantages of the EUS-Based Approach

Current data suggest that the time to resolution of pelvic abscess is approximately 8 days with percutaneous techniques. Unlike ultrasound or CT, EUS facilitates deployment of transluminal stents and thus enables early discharge of patients from the hospital, usually within 2 to 3 days, nor does it impair patient mobility. Moreover, the procedures can be performed within 30 minutes and yield optimal clinical outcome in most patients. Unlike percutaneous catheters, which can predispose to fistula formation, transluminal stenting does not seem to have long-term complications. The technique is effective not only for the management of postsurgical fluid collections, but also for those secondary to medical illnesses. Whereas most percutaneous procedures require transport to the radiology unit, EUS-guided drainage can be undertaken at bedside if the patient is critically ill. In addition, although most pelvic fluid collections are either inflammatory or infectious, some may represent another cause such as a perirectal cyst.

EUS can accurately establish an alternative diagnosis in these patients and can facilitate appropriate management.*14* Small abscesses that measure less than 4 cm do not require stenting. These fluid collections can be aspirated thoroughly using a 19-G FNA needle, and the abscess cavity can be evacuated of infectious contents.

Technical Limitations

Some limitations of the EUS-guided technique include the following:

1. If the fluid collection has multiple cavities, it will not respond well to EUS-guided drainage.
2. Transmural stenting may not be possible if an abscess is located more than 2 cm from the gastrointestinal lumen.
3. With the current limited maneuverability of the curvilinear array echoendoscopes, accessing abscesses that are located more proximally is not feasible.

SUMMARY

EUS-guided drainage is a minimally invasive, safe, and effective technique for management of patients with pelvic abscesses. Cost-effectiveness studies are required to compare this technique with other modalities such as CT and ultrasound. The role of EUS for drainage of pelvic abscesses secondary to inflammatory bowel disease is unclear and requires further investigation.

REFERENCES

1. Sudakoff GS, Lundeen SJ, Otterson MF. Transrectal and transvaginal sonographic intervention of infected pelvic fluid collections. *Ultrasound Q*. 2005;21:175–185.
2. Jaffe TA, Nelson RC, Delong DM, et al. Practice patterns in percutaneous image-guided intraabdominal abscess drainage: survey of academic and private practice centers. *Radiology*. 2004;233:750–756.
3. Wroblicka JT, Kuligowska E. One-step needle aspiration and lavage for the treatment of abdominal and pelvic abscesses. *AJR Am J Roentgenol*. 1998; 170(5):1197–1203.
4. Kuligowska E, Keller E, Ferrucci JT. Treatment of pelvic abscesses: value of one-step sonographically guided transrectal needle aspiration and lavage. *AJR Am J Roentgenol*. 1995;164:201–206.
5. Ryan RS, McGrath FP, Haslam PJ, et al. Ultrasound-guided endocavitary drainage of pelvic abscesses: technique, results and complications. *Clin Radiol*. 2003;58:75–79.
6. Varadarajulu S. EUS-guided drainage of pelvic abscess. *Tech Gastrointest Endosc*. 2007;9:51–54.
7. Nelson AL, Sinow RM, Olaik D. Transrectal ultrasonographically guided drainage of gynecologic pelvic abscesses. *Am J Obstet Gynecol*. 2000;6: 1382–1388.
8. Golfieri R, Cappelli A. Computed tomography-guided percutaneous abscess drainage in coloproctology: review of the literature. *Tech Coloproctol*. 2007; 11(3):197–208.
9. Harisinghani MG, Gervais DA, Maher MM, et al. Transgluteal approach for percutaneous drainage of deep pelvic abscesses: 154 cases. *Radiology*. 2003; 228:701–705.
10. Varadarajulu S, Drelichman ER. EUS-guided drainage of pelvic abscess. *Gastrointest Endosc*. 2007;66:372–376.
11. Trevino J, Drelichman ER, Varadarajulu S. Modified technique for EUS-guided drainage of pelvic abscess (with video). *Gastrointest Endosc*. 2008; 68(6):1215–1219.
12. Onaca N, Hirshberg A, Adar R. Early reoperation for perirectal abscess. *Dis Colon Rectum*. 2001;44:1469–1473.
13. Giovannini M, Bories E, Moutardier V, et al. Drainage of deep pelvic abscesses using therapeutic echo endoscopy. *Endoscopy*. 2003;35:511–514.
14. Varadarajulu S, Drelichman ER. Effectiveness of EUS in drainage of pelvic abscesses in 25 consecutive patients. *Gastrointest Endosc*. 2009;70: 1121–1127.

APPENDIX: VIDEOS

Chapter 5

Video 5.1: Examination of the esophagus using a high-frequency catheter probe passed through a dual-channel gastroscope with the condom technique.
Video 5.2: Examination of the mediastinum with a radial echoendoscope.
Video 5.3: Examination of the mediastinum with a curvilinear array echoendoscope.
Video 5.4: Evaluation of the left adrenal gland with a linear array echoendoscope.

Chapter 6

Video 6.1: Video demonstrating EUS-guided fine-needle aspiration of the subcarinal lymph node in a patient with non–small cell lung cancer.
Video 6.2: Video demonstrating EUS-guided fine-needle aspiration of the left adrenal gland in a patient with metastatic non–small cell lung cancer.
Video 6.3: Video demonstrating endobronchial ultrasound transbronchial needle aspiration in a patient with mediastinal adenopathy and non–small cell lung cancer.

Chapter 7

Video 7.1: Use of an esophageal high-frequency probe using the condom technique.
Video 7.2: EUS-guided fine-needle aspiration of a celiac lymph node with the curvilinear echoendoscope.
Video 7.3: Post-treatment EUS-guided fine-needle aspiration of a celiac lymph node with the curvilinear echoendoscope. The lymph nodes features are less reliable in this setting, and fine-needle aspiration is recommended because it alters management.
Video 7.4: Staging of esophageal cancer with the mechanical radial echoendoscope. The mass invaded the muscularis propria but not all the way through, hence T2. An elongated lymph node with a central scar was seen in the peritumoral area. This appears to be a benign lymph node but is not amenable to fine-needle aspiration.
Video 7.5: Staging of esophageal cancer with the mechanical radial echoendoscope. The esophageal tumor appears to invade the muscularis propria (T3). In addition, the mass invaded the azygous vein (T4). Multiple peritumoral lymph nodes were seen as well. The stage of this tumor is T4N1Mx.
Video 7.6: Staging of esophageal cancer with the mechanical radial echoendoscope. A circumferential hypoechoic tumor invaded the muscularis propria. Multiple peritumoral lymph nodes were seen. In addition, a very proximal lymph node was seen right below the upper sphincter around the proximal esophagus consistent with a T3N1M1b tumor.

Chapter 9

Video 9.1: Radial EUS, performed after instillation of water, reveals a T1 gastric cancer confined to the mucosal layer.
Video 9.2: EUS examination performed using a 20-MHz high-frequency mini-probe (water-filled technique) revealing a T1 gastric cancer confined to the mucosal region.

Chapter 11

Video 11.1: Radial EUS, performed after instillation of water, reveals a T1 gastric cancer confined to the mucosal layer.
Video 11.2: Radial EUS revealing a T3 gastric cancer that abuts the liver but without any invasion.
Video 11.3: EUS examination performed using a 20-MHz high-frequency mini-probe (water-fill technique) revealing a T1 gastric cancer confined to the mucosal region. The tumor is subsequently removed by injection-assisted polypectomy.

Chapter 12

Video 12.1: Evaluation of the body and tail of the pancreas with a radial echoendoscope.
Video 12.2: Evaluation of the body and tail of the pancreas with a curvilinear echoendoscope.
Video 12.3: Evaluation of the head of the pancreas with a radial echoendoscope.
Video 12.4: Evaluation of the head of the pancreas with a curvilinear echoendoscope.
Video 12.5: Evaluation of the papilla of Vater with a radial echoendoscope.
Video 12.6: Evaluation of the papilla of Vater with a curvilinear echoendoscope.
Video 12.7: Evaluation of the uncinate region of the pancreas with a radial echoendoscope.
Video 12.8: Evaluation of the uncinate region of the pancreas with a linear echoendoscope.
Video 12.9: Video demonstrating imaging of the liver from the duodenal bulb.
Video 12.10: Video demonstrating imaging of the left lobe of the liver from the gastric antrum.
Video 12.11: Video demonstrating imaging of the left lobe of the liver from the fundus of the stomach.

Chapter 13

Video 13.1: Video segment of EUS showing calcifications (shadowing hyperechoic foci).
Video 13.2: Video segment showing an example of "high-probability" noncalcific (so-called minimal change) chronic pancreatitis.
Video 13.3: Video segment illustrating pancreas divisum and its assessment on EUS.

Chapter 14

Video 14.1: EUS fine-needle aspiration of a 2-cm hypoechoic mass in the tail of the pancreas in a 56-year-old asymptomatic male patient with history of renal cell carcinoma resected 3 years earlier. Cytology findings were conclusive for metastatic renal cell carcinoma.

Chapter 15

Video 15.1: Video demonstrating the evaluation of a pancreatic cyst lesion at EUS. The large, unilocular, anechoic collection was a pseudocyst.
Video 15.2: Video demonstrating EUS examination of a cyst lesion in the pancreas with numerous small septations consistent with serous cystadenoma.

Video 15.3: Video demonstrating a solid component within a pancreatic cyst lesion consistent with cystadenocarcinoma.
Video 15.4: Video demonstrating EUS evaluation of the pancreas. A large cyst is seen in the pancreatic genu communicating with the main pancreatic duct. In addition, papillary projections are seen in the main pancreatic duct consistent with intraductal papillary mucinous neoplasia. The papillary projections are then aspirated to rule out carcinoma.
Video 15.5: Video demonstrating a solid component within a pancreatic cyst lesion. EUS-guided fine-needle aspiration of the solid component revealed adenocarcinoma.

Chapter 16

Video 16.1: EUS performed with a radial echoendoscope reveals common bile duct stones.
Video 16.2: EUS performed with a radial echoendoscope evaluates for gallstones.
Video 16.3: EUS performed with a radial echoendoscope reveals a common bile duct stricture consistent with cholangiocarcinoma. A stent is seen in the bile duct.
Video 16.4: EUS-guided fine-needle aspiration of an extrahepatic T1 bile duct tumor.
Video 16.5: Staging of an ampullary tumor with a radial echoendoscope.

Chapter 17

Video 17.1: Video demonstrating the technique for endosonographic examination of the rectum with a radial echoendoscope.

Chapter 18

Video 18.1: Evaluation of the rectum with a radial echoendoscope.
Video 18.2: Evaluation of rectal cancer, staged T3N1 by EUS.

Chapter 20

Video 20.1: Video demonstrating the technical difficulty of performing transduodenal EUS-guided fine-needle aspiration and tips to overcome this challenge.

Chapter 21

Video 21.1: Video demonstrating an EUS procedure with fine-needle aspiration of a pancreatic mass lesion. In addition, the methodology adopted for on-site interpretation by a cytopathologist is shown in this video. The endosonographer and the cytopathologist constantly interact as the case is in progress.

Chapter 22

Video 22.1: Video demonstrating the graded dilation technique for drainage of pancreatic fluid collections.
Video 22.2: Video demonstrating the needle-knife technique for drainage of pancreatic fluid collections.
Video 22.3: Video demonstrating the technique for simultaneous placement of multiple guidewires for stent deployment within the pancreatic fluid collection.

Chapter 23

Video 23.1: Video demonstrating choledochoduodenostomy.
Video 23.2: Video demonstrating hepaticogastrostomy.
Video 23.3: Video demonstrating pancreaticogastrostomy.

Chapter 24

Video 24.1: Video demonstrating the technique of EUS-guided fiducial placement in a patient with pancreatic cancer.
Video 24.2: Video demonstrating the technique of EUS-guided pancreatic cyst ablation using ethanol.
Video 24.3: Video demonstrating the technique of EUS-guided celiac plexus neurolysis.

Chapter 25

Video 25.1: Video demonstrating the technique for EUS-guided drainage of pelvic abscess.

INDEX

Note: Pagenumbers followed by *b* indicate boxes, *f* indicate figures and *t* indicate tables.