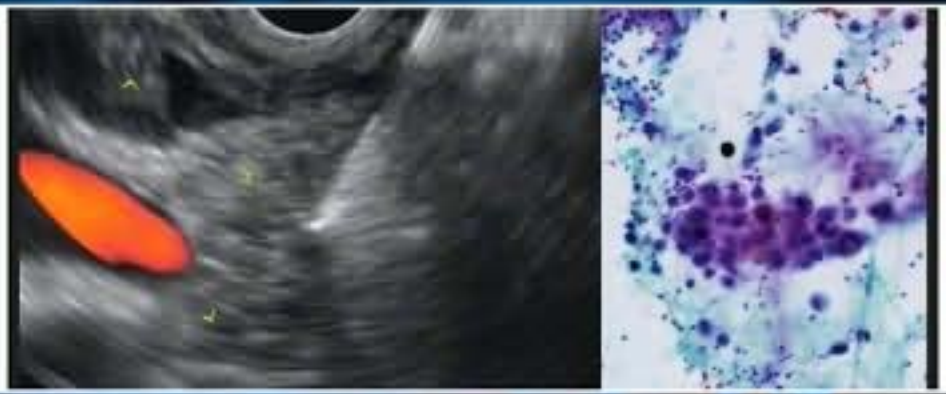
Endoscopic Ultrasonography

SECOND EDITION



EDITED BY
Frank Gress
Thomas Savides

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Many thanks to the faculty, trainees, and staff in the University of California at San Diego (UCSD) GI Division under the inspirational leadership of John Carethers, and the entire staff of assistants, technicians, and nurses at the UCSD GI Endoscopy Unit.

Preface

Endoscopic ultrasound (EUS) was first conceptualized almost 30 years ago during the early years of endoscopy and was developed in an attempt to improve ultrasound imaging of the pancreas. The first EUS prototype was designed and manufactured in the early 1980s. Since that first prototype, endoscopic ultrasound has evolved into an accepted and valuable endoscopic modality and subsequently, a therapeutic modality for the management of many gastrointestinal disorders. EUS is now entering a new era in which the procedure is leaving the confines of specialized tertiary referral centers and academic institutions, and becoming disseminated in community based hospitals throughout the world. Additionally, the technology is now progressing from that of diagnosis and staging, to a more interventional therapeutic role.

Our hope is that this 2nd Edition of *Endoscopic Ultrasonography* improves the training and dissemination of EUS by providing interested gastrointestinal endoscopists with an authoritative, yet practical, approach to the role of EUS in the management of specific digestive disorders. The primary purposes of this text are to first, allow a complete and thorough understanding of the current state of endoscopic ultrasonography and second, help guide the reader in learning both basic and advanced endoscopic ultrasound techniques. Both diagnostic and therapeutic applications of endoscopic ultrasonography are thoroughly reviewed.

The target audience for this text includes all gastroenterologists and trainees wishing to know more about endoscopic ultrasound and its role in managing digestive disorders. This work will also be of interest to gastrointestinal surgeons, surgical residents, medical housestaff and internists, pulmonary physicians, and oncologists who deal with gastrointestinal malignancies. For those interested in learning or training in endoscopic ultrasound, the text provides a technical "how to" approach to learning this advanced endoscopic procedure.

This 2nd edition brings many new and exciting changes and additions to the text including new chapters on the history of EUS, and several chapters on the emerging field of therapeutic EUS. We have also continued to emphasize a practical "how to" > approach to learning endoscopic ultrasound and have made great efforts to present each chapter in extensive detail. Each chapter individually discusses a specific aspect of EUS as it relates to a particular gastrointestinal disorder or organ system. The experts who have graciously contributed to the book have identified up to date current references in their chapters and more importantly, have purposefully included their own particular styles, practices, and opinions as to how EUS should be performed. This individualized approach provides a diverse introduction to the role of EUS in gastroenterology today without obscuring key concepts in both the theory and performance of this procedure.

Most of our contributors are either the "first-generation" pioneers of endosonograpy or "second-generation" protégés of those pioneers. They have contributed significantly to the field of gastrointestinal endosonography and have proven track records as clinicians, investigators, and educators. Their collective experience in applying endoscopic ultrasonography in the management of gastrointestinal diseases is unsurpassed. A tremendous amount of effort on the part of each individual author has led to this new 2nd edition. They are the true masters of gastrointestinal endoscopy. We are deeply grateful to them for their outstanding collaboration.

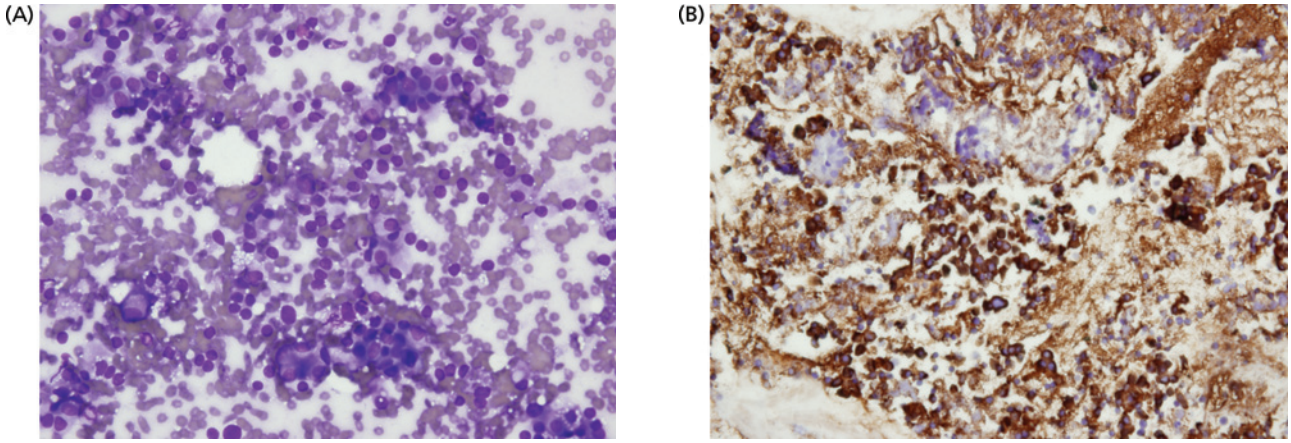

Plate 15.1 Pancreatic endocrine neoplasm. A well-circumscribed, 12 × 7 mm mass is seen within the pancreatic body between the callipers (see Fig. 15.08A). The mass is nearly identical in echogenicity to the surrounding pancreas (see Fig. 15.08B). Needle aspiration is performed using a 25-gauge needle. (A) Cytology returns relatively bland, uniform cells (DiffQuik stain) which show characteristic positive staining for chromogranin (B). All cytology images 400 × magnification.

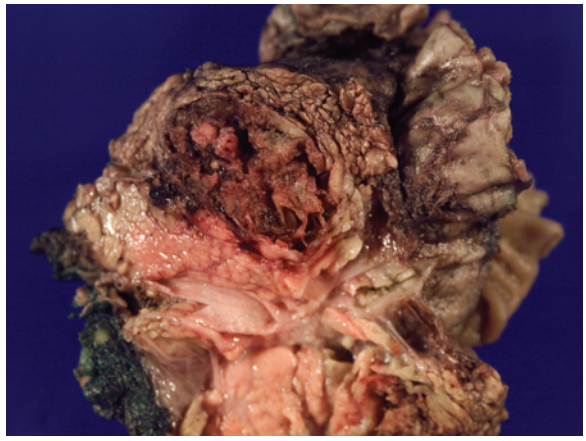

Plate 15.2 Solid pseudopapillary tumor of the pancreas. The lesion is a complex collection of irregularly-shaped cystic components of variable size (see Fig. 15.10A) and isoechoic/hypoechoic solid portions (see Fig. 15.10B). The lesion is encapsulated. Surgical pathology demonstrates an encapsulated lesion filled with papillary excrescences.

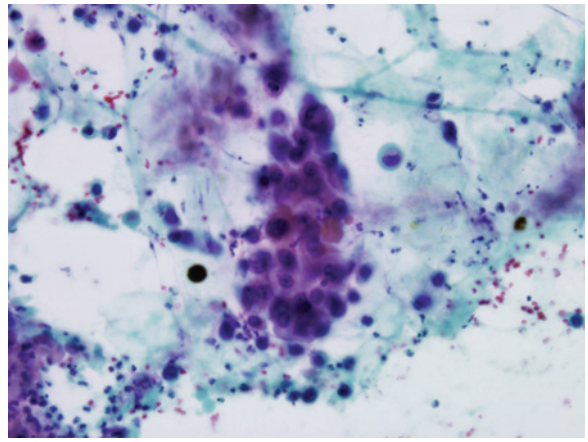

Plate 15.3 Metastatic squamous cell (lung primary) to the pancreas. A complex mass is seen in the pancreatic tail with cystic (see Fig. 15.11A) and solid (see Fig. 15.11B) components in a patient undergoing treatment for primary squamous cell carcinoma of the lung. Needle aspiration shows evidence of squamous cell carcinoma (400x mag.)

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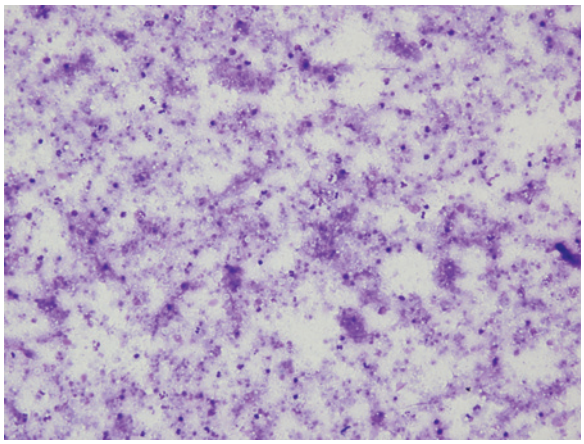

Plate 15.4 Calcific debris following acute pancreatitis. The patient had a well-circumscribed, hypodense pancreatic mass seen on CT interpreted as concerning for malignancy. There was a very remote history of acute pancreatitis managed at another institution. EUS demonstrated a 4.5 cm hypoechoic region which produced acoustic shadowing (see Fig. 15.13). Diagnostic needle aspiration returned pasty material with cytology showing necrotic, acellular debris with crystalline structures. Diff-Quik stain at 200x mag.

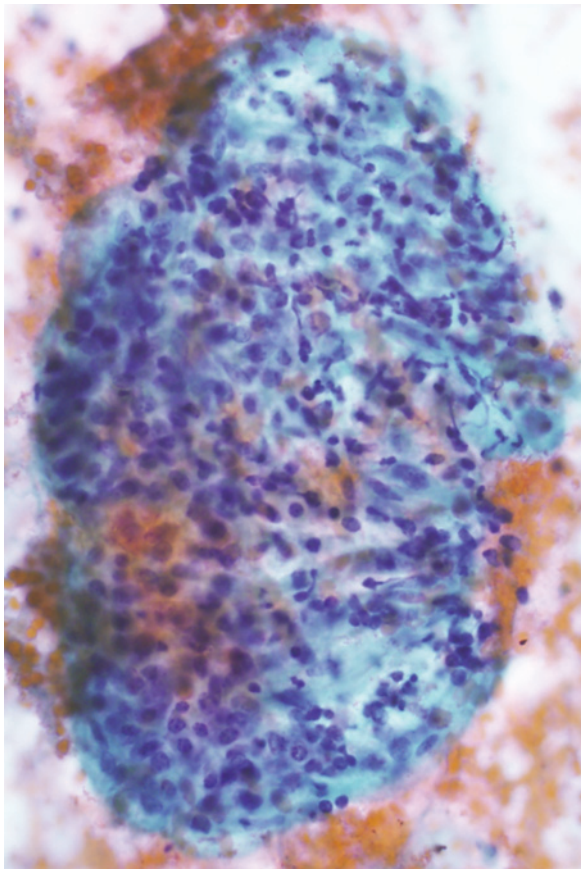

Plate 17.1 Cytology from EUS-FNA of chronic pancreatitis demonstrating monoculear chronic inflammatory cell infiltrate, reactive pancreative ductal cells and fibrosis (Papanicolaou stain; 200x).

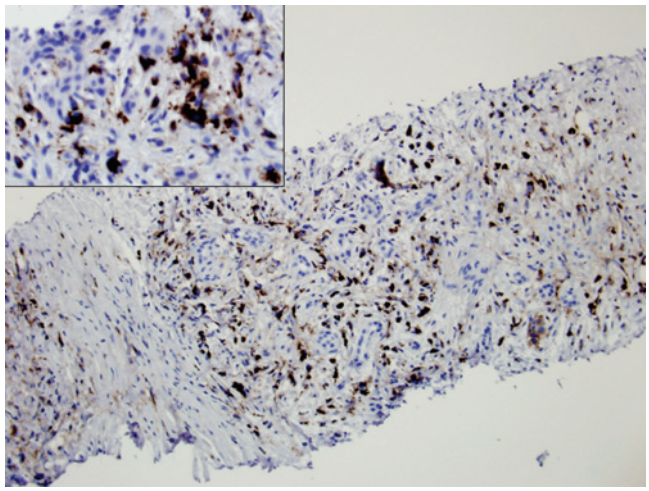

Plate 17.2 Photomicrograph of a histologic specimen from the pancreatic body in this patient following transgastric EUS-guided Trucut biospy. There is marked acinar atrophy, a mononuclear cell infilltrate with lymphocytes and plasma cells and marked fibrosis consistent with chronic pancreatitis. There are no ducts present. Plasma cells are stained positive by lgG4 (brown pigment) consistent with autoimmune pancreatitis.

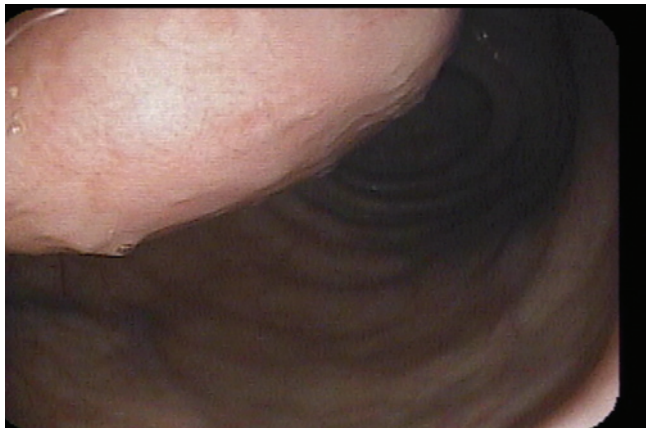

Plate 19.1 A subepithelial bulge in the rectum from a large intramural, subepithelial mass.

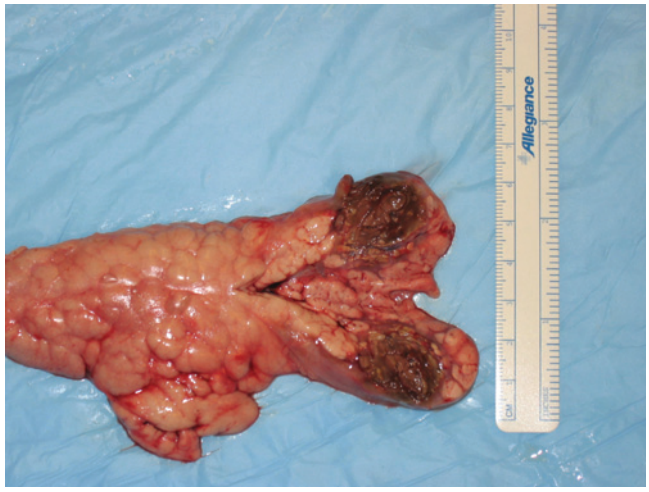

Plate 22.1 Example of pancreatic tissue ablation using EUS-guided ethanol injection.

1 Endoscopic Ultrasonography at the Beginning: a Personal History

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The first report of endoscopic ultrasonography (EUS), to my knowledge, is that of DiMagno et al. [1]. In their article, published in 1980, these investigators described a prototype echoendoscope assembled by attaching a transducer to a duodenoscope. Although images were obtained only in dogs, this work established the feasibility of EUS. As with nearly all seminal advances in endoscopy, EUS was basically an amalgamation of existing technologies. But in 1980, the potential of this hybrid technology was scarcely apparent to anyone – probably including these first endosonographers, who did not expand on their demonstration of the feasibility of EUS.

For practical purposes, the inception of EUS as a clinical entity in the United States can be traced to a meeting I had with Mr Hiroshi Ichikawa of the Olympus Optical Company. Neither of us can remember the exact date, but it was most likely 1981. Olympus was developing several new technologies, and Hiroshi offered me a choice between EUS and enteroscopy. The only other thing I recollect from that meeting is that, for some unknown reason, I did not ponder the choice very long before I selected EUS, largely because the idea of endosonography seemed especially intriguing; that it offered a greater challenge, but also a promise of a much wider range of prospective applications. I certainly gave little thought to, indeed did not appreciate, the formidable obstacles to the clinical realization of this potential, nor the investment of time and effort needed to reach this goal which was much more distant than I realized. Hiroshi did, in fact, lay emphasis on the obstacles, warning that the instrumentation was in the early stages of development (a euphemism for crude, barely usable). Because of the scope and difficulty of the project, Hiroshi advised that Olympus proposed to work with two investigators in the United States (actually the western hemisphere), the other being Dr Charles Lightdale in New York City, as well as a few individuals in other countries. I already knew Charlie, and thought him an excellent choice. As it turned out, this was the beginning of a long and rewarding professional association with Charlie, for which EUS became the basis. Thus, EUS in the United States began with me and Charlie Lightdale.

Given the technical sophistication of present-day EUS systems, it is important to recognize that during the early years the viability of endosonography was far from certain. Until about 1985, there was substantial skepticism concerning the future of EUS, even among those of us most closely involved with and committed to its development. The ample tribulations facing the very small cadre of nascent endosonographers became strikingly evident with the arrival of the first EUS system, a prototype in the truest sense. Despite the obvious problems, however, I do not believe that any of us were ever truly discouraged; the best description of our mindset during these formative years might be "doggedly enthusiastic."

I began by writing a simple, all-encompassing protocol that would allow me to use the instrument as an investigational device in patients. The protocol, essentially, had no hypothesis, other than the assertion that EUS was going to be a good thing. It listed almost every possible indication I could conceive, and minimized the risks, unknown in any case, to such a degree that I doubt it would be approved by any institutional research committee today.

The major problems that had to be addressed in the beginning divided into four categories: the technical limitations and deficiencies of the equipment, the development of efficient and safe techniques for use of the echoendoscope in patients, interpretation of the ultrasound images, and the need to define and establish indications for EUS in clinical practice. More issues, some even more complicated, became evident over time.

The prototype echoendoscope itself was, by modern standards, incredibly cumbersome. The electronic (video) endoscope had not been introduced into clinical practice, so that the prototype echoendoscope was a fiberoptic instrument; the optical (endoscopic) component consisted of an ocular lens and focusing ring coupled to a coherent fiberoptic bundle with another lens at the distal end of the insertion tube to focus an image on the bundle. The latter provided a limited, 80-degree field of view, oriented obliquely at an angle of 70 degrees to the insertion tube.

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Of these two parameters, the narrow field of view was more of a limitation than the oblique orientation, which was not especially problematic for endoscopists accustomed to the side-viewing duodenoscope.

The ultrasound component of early echoendoscopes consisted of a transducer coupled to a rotating acoustic mirror at the distal tip of the insertion tube. The mirror was turned by means of an electric motor within a motor housing situated between a standard design control section and the insertion tube; thus the designation, "mechanical, sector-scanning echoendoscope." Because the mirror turned around the long axis of the insertion tube, the ultrasound scanning plane was oriented perpendicular to the insertion tube. In retrospect, this was the best choice because it seemed to simplify the problems of image interpretation. But this arrangement also had its limitations, mainly that it was unsuitable for guiding a needle to a target. Needle aspiration was, in fact, attempted with the sector scanning instrument, albeit unsuccessfully because the width of the tissue within the circular scan was much too narrow.

Unfortunately, the ultrasound imaging sector provided by the first instruments was not a full 360 degrees, but only 180 degrees. To obtain a complete, circumferential sector scan of the surrounding tissue, a circumferential esophageal tumor for example, it was necessary to rotate the insertion tube 180 degrees while maintaining the same scanning plane. This was a considerable feat, especially with the instrument deeply inserted, for example in the third part of the duodenum. In truth, it was largely impossible because any application of torque to the insertion tube invariably altered the scanning plane. This was but one among many difficulties.

Owing to the mechanical components, principally the motor and its housing, the instrument was much heavier than a standard endoscope. I don't think I ever tried to weigh it, but it probably tipped the scale at more than one pound. Because EUS had no established clinical purpose, the first procedures can only be described as exploratory. Consequently, procedure length was determined largely by patient endurance, and with an especially tolerant patient, the weight of the instrument seemingly increased exponentially. After two or three examinations, often it was difficult (and painful) to straighten your left arm.

The combination of optical and acoustical components at the distal end of the insertion tube conferred other penalties including some potential hazards. The diameter of the insertion tube was 13 mm, i.e. substantially greater compared to the upper endoscopes of the time. To make matters worse, the distal end was rigid over a length of 4.5 cm, i.e. the distance from the tip to the bending section. Together with the limited field of view, this increased the difficulty of inserting the instrument through the mouth and pharynx and into the esophagus. Although we assumed that the risk of complications with EUS was no greater than that associated with upper endoscopy, and so informed our patients, in reality the risk of perforating the pyriform sinus was probably greater by comparison, a fact subsequently substantiated. Moreover, attempts at insertion of the large-diameter echoendoscope through a constricting tumor in the esophagus were no doubt associated with an appreciable risk of perforation.

In addition to developing technique for insertion of the echoendoscope safely, the learning curve for EUS imaging can only be described as long and steep, a line with a slope approaching straight up. According to Yogi Bera, "ninety percent of everything is half mental" and this was definitely true of EUS. The first quandary was the need to uncouple endoscopic imaging from ultrasonography. This related to the need for acoustic coupling; i.e. the creation of a suitable interface between the tissue and the transducer (in this case the acoustic mirror). We discovered in short order that ultrasound images can't be obtained through air. The obvious solution: remove the air. But this proved impractical for several reasons. The other alternative was to interpose water between tissue and "transducer," which can be accomplished in two ways: placing a balloon over the transducer section of the instrument and filling it with water, or by filling the gut with water. However, it was not simply a matter of choosing between these two options. Depending on circumstances, including location within the gastrointestinal tract, one or the other was usually a better choice. With the balloon method in particular, the endoscopic view was lost as the balloon was brought into contact with the gut wall, meaning that ultrasound imaging could only proceed by abandoning the endoscopic view. For technical reasons, therefore, EUS imaging was, of necessity, endoscopically blind. Although this decoupling might seem inconsequential today, it was a mental leap of faith in the early days, inasmuch as endoscopic dogma deemed "blind" use of an endoscope hazardous.

Use of the balloon with early model echoendoscopes was so exasperating that it deserves a digressive paragraph of its own. The latex material that constituted the balloon was not of uniform quality, which made it nearly impossible to place the balloon on the echoendoscope without tearing it. When expanded, the balloon had an asymmetric bulge, and according to the instructions the bulge was to be placed over the transducer on the same side as the optical component; this was never accomplished. Assuming that the balloon could be maneuvered intact into correct position, it was next necessary to tie it in place with small sutures. The design of the instrument was such that the proximal end of the balloon sometimes occluded the opening of the channel for air insufflation and water irrigation, which would not be evident until it was securely tied in place and tested. Subsequent attempts to nudge the balloon into proper position usually resulted in tearing. Since the objective was to create a water–tissue interface, it was necessary to remove all the air from the balloon (without breaking it). The balloon, if not placed exactly, could occlude the tiny diameter channel provided for this purpose. Once all of the delicate parameters were attained, and the balloon was in gloriously correct position and functioning properly, the most maddening occurrence was rupture of the ill-fated bag in the middle of an examination, usually at the most inopportune moment. I dealt with some of these frustrations by persuading a gentleman from the biomedical engineering department (designated the balloon man) to take on the task of balloon placement prior to each procedure.

During the examination, the balloon was filled with water via a Luer lock fitting located between the control section and the motor housing. Unfortunately, this design meant that the attached syringe protruded in perpendicular fashion. Accordingly, as the endosonographer moved his right hand from the control section to the insertion tube, he invariably broke the syringe. In order to fill the balloon, it was necessary to set a small lever on the motor housing to the balloon-filling position, clearly labeled as "B." The other choice was "G," which when selected channeled the water into the gut. Since it was not possible to see this lever, it was advisable to remember which position it was in. Otherwise, the balloon might be filled with water beyond its capacity.

One of the most gratifying aspects of endosonography, readily apparent at the very first examination, was the ability to obtain a structured image of the gut wall. Believe me, all of us knew intuitively and immediately that this was going to be very big. But the interpretation of these images was something else again. There was a natural tendency to assume, to hope, that the five-layer structure corresponded in exact fashion to the actual layers of the gut wall as seen microscopically in a histological section. This betrays a near total ignorance of the principles of ultrasound imaging, and over time, it became evident that the physical basis for the endosonographic representation of the bowel wall is much more complex. For reasons unknown to me, the main ultrasound frequency selected for the first EUS systems was 7.5 MHz, a frequency that happens, under the usual conditions, to render the wall structure of the stomach as five layers. I suspect that this choice of frequency was based on technical considerations rather than experimental data. In any case, it took some time to work out the actual physical basis for the ultrasound images of the gut wall.

One thing that occurred to me during my first discussion of EUS with Hiroshi Ichikawa, and probably influenced my choice of EUS as opposed to enteroscopy, was the possibility that EUS might have a positive impact on the problem of pancreatic cancer. By 1980 it was clear that ERCP could never alter the natural history of this disease, but perhaps EUS might provide an opportunity, under certain circumstances, for earlier detection and therefore improved survival. In retrospect, this was a worthy but naïve notion. Nevertheless, I resolved to pursue EUS of the pancreas. Charlie Lightdale, on the other hand, took a more sensible and practical path by studying the applications of EUS in staging esophageal cancer. Given the limitations of the first EUS systems, my focus on pancreatic imaging was not the wisest decision.

While my comprehension of the EUS image of the gut wall was next to zero, this knowledge was encyclopedic by comparison with my understanding of EUS of the pancreas. In truth, the only thing I could identify with certitude was a gallstone, and only if it was over 1 cm in diameter and solidly calcified. After a while, optimism becomes a poor substitute for know-how, and it was soon obvious that the only way to move forward was to seek the advice of a radiologist with expertise in ultrasonography. Many of the first endosonographers adopted a similar approach. And so, a radiologist by the name of Craig George came to my assistance. Our idea was that Craig would look over my shoulder during the EUS procedure and essentially interpret the images. By this time, we had a second-generation prototype EUS system. In contrast to the first prototype, the second system included an extremely bulky image processor with a tiny display screen, probably no more than 8 inches on the diagonal. Moreover, the quality of the image was poor, which made it necessary to get close to the screen to see anything. Furthermore, the screen was placed in the box such that it was only about 4 feet above the floor. So, Craig sat on a low stool in front of the box. But all of these limitations were inconsequential to me because Craig is a big guy with a correspondingly large head; most of the time the only thing I could see was the back of it. Somehow we evolved a set of hand signals to deal with this problem. It worked like this: if Craig (face pressed to the screen), saw something he recognized, he would make certain motions with his hand, either the left or right depending on the direction he wanted me to move the transducer, in an effort to obtain the best possible image (I always think of Craig whenever I watch a jet plane being guided to its parking place by the guy with the long, orange flashlights). When he got the image he wanted, Craig would hit the "freeze" button, quickly move his head out of the way so I could see it, and then place a camera in from of the screen to obtain a photograph (the permanent image in those days).

Although this arrangement was cumbersome, I learned most of what I know about pancreatic imaging, and the principles of ultrasonography, from Craig George. After about 6 months our partnership gradually dissolved, partly because it was difficult to coordinate our schedules, but mostly because I had acquired, so I thought, enough knowledge to proceed on my own.

Until June 1982, the struggle to develop EUS was a lonely one, i.e. only a handful of endoscopists had any practical experience with EUS and all were working essentially alone. This changed in June 1982 when Olympus sponsored the first "International Workshop on Endoscopic Ultrasonography" at the Grand Hotel in Stockholm, Sweden, a time and venue selected to coincide with the World Congress of Gastroenterology. We met in a very small room as there were, according to my notes, only about 15 active participants, including two invited guests with expertise in areas of digestive ultrasonography other than EUS, and excluding about a half dozen representatives from Olympus.

Keichi Kawai (Kyoto, Japan), who organized the meeting, asked me to speak on "Arrangement of Endoscopic Ultrasonography." I never did discover exactly what my assigned topic entailed. Nevertheless, compared to the many EUS meetings in which I participated in subsequent years, this first gathering was by far the most important. For by the time of the meeting, each participant had discovered many things about EUS, but none had a complete picture, whether of its limitations or true potential. Thus, there was a remarkable and exhilarating exchange of information and ideas that, in retrospect, amounted by aggregation to a significant advance. I led a long discussion on EUS of the pancreas that solidified the concept of stationed withdrawal of the echoendoscope from the duodenum. Essentially, we made a list of the organs and structures that should be imaged at each

station. But, most importantly, I think each of the dozen participants left the meeting with a revitalized sense of purpose as well as a stronger sense of confidence in the future of EUS.

Another aspect of EUS that was clarified by the 1982 meeting was the incredible value of cooperation in the effort to establish EUS as a clinically useful technology. In many ways, the meeting revealed more about what we didn't know and how much had to be done before EUS could be considered clinically relevant. Shortly thereafter, and I think in response to the lessons learned at the meeting, Mr Mark Donohue from Olympus asked me to help organize a small group of investigators that would meet two or three times each year. Our purpose was to grapple collectively with the problems of EUS and, in general, find ways to advance its development. In addition to myself, the original membership included Charlie Lightdale and Drs H. Worth Boyce and Lok Tio. Over the eight or so years of its existence, the membership changed somewhat, but it was always strictly limited to no more than six (usually five). Together with two or three people from Olympus, the total number attending each meeting was never more than eight or nine. Naturally, when the existence of this group became known, albeit not widely, Olympus was besieged by individuals who felt they had the qualifications for membership. But, to credit of Olympus, Mr Donohue resisted all requests in order to preserve the small group dynamic. Because we could never dream up a better name, we called ourselves the "EUS Users Group."

I used to make an agenda for each "Users" meeting, based on input from the members as well as Olympus. In retrospect, these lists of topics for discussion outline much of the developmental history of EUS from about 1982 to 1989. The subject matter divided into two major areas: technical development and the application of the technology to clinical practice, and training. During the earliest years, we did not recognize that there would be major issues and problems relating to the training of other endoscopists in EUS, or a need for the broader dissemination of information about EUS to the medical community at large. But as interest in EUS increased, it became glaringly evident that training constituted a most formidable problem, all the more so inasmuch as clinical relevance would never be achieved if EUS were performed by a small number of experts. This issue was further compounded by the high cost of the equipment (relative to that of standard endoscopes), and the absence of reimbursement. In those days, furthermore, echoendoscopes were fragile as well as expensive. The need for frequent maintenance and repair substantially increased the cost of operation. In the hands of an inexperienced operator, this fragility frequently pushed repair costs well beyond that normally anticipated by an endoscopy unit. All of these factors constituted a significant "cost barrier" to involvement with EUS.

There was a certain division within the "Users Group" as to the best approach to the problem of training. We were unanimous concerning the value of didactic teaching, and to this end we organized a number of short symposia. However, we fully recognized that this was no substitute for so-called "hands on" instruction. With respect to the latter, one viewpoint held that short periods of training, ranging from a few days for an accomplished endoscopist to 6 months for the less experienced, would be adequate to "get started." I and some others felt that a "quick and dirty" approach to training was doomed to failure; we advocated much more formal and prolonged training. The caveat of this approach, however, was that EUS might never become established. As late as 1988, the programs with the capability for training numbered only five, i.e. the members of the group. Even if we trained 10 endosonographers per year, it would take many years before EUS became widely available. In retrospect, I think I was right: it took better training and a lot more time than anyone expected.

It was fortunate that EUS was introduced during the decade of the 1980s, a period when endoscopists were under less pressure to be ultra efficient and financially productive. The commitment to screening colonoscopy, for example, had not yet arisen, even as a concept. Had the introduction of EUS been attempted 10 years later, the probability that it would become an established procedure would have been substantially reduced. In those earlier times, gastrointestinal endoscopy was less of a mass-produced commodity, and not something akin to a chest radiograph or complete blood count. It is true that we were somewhat mesmerized by technology, but this was always integral to the overriding desire to improve patient care.

The establishment of EUS as a clinical procedural entity stands as a tribute to the perseverance of a relatively small group of people, but as well to the resolve of the Olympus company. Although not generally known, EUS also constituted a substantial cost barrier for the company. I was never privy to the actual financial data, but Mr Donohue once told me that EUS was a financial loss for more than a decade. That any company would invest so much time and talent for so long a time, despite an uncertain prospect of financial gain, is remarkable. There is a story, which admittedly might be apocryphal, that Mr Ichizo Kawahara, then the director of the Medical Instrument Division of Olympus, was once asked why the company persisted in its efforts to develop EUS despite the obstacles and the uncertain chance for success. He is said to have replied, "Because the doctors want it." This, I believe, also reveals the different nature of those times.

I think I became fully convinced that EUS was here to stay with the introduction of the Olympus/Aloka UM2 system, which occurred around 1986. The GF-UM2 echoendoscope was still a fiberoptic instrument, but the EU-M2 display unit was markedly improved. In particular, it offered a 360-sector display, a gigantic improvement with respect to pancreatic imaging. This was followed by a gradual but steady flow of technical improvements. This, together with the continuing addition of more and better data solidified a lasting place for EUS in clinical practice. It took a lot longer than I had imagined, but it was gratifying to have played a part.

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2 Basic Principles and Fundamentals of EUS Imaging

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An understanding of the fundamental mechanisms of ultrasound (US) is useful to both the beginning and experienced endosonographer. It is not necessary to be a physicist or an engineer to appreciate some basic principles of ultrasound imaging and Doppler ultrasound. These principles can guide the endosonographer both in obtaining the best representation of a tissue structure with endoscopic ultrasound (EUS) and in interpreting the images. Knowing these fundamental concepts also aids in the recognition and avoidance of artifacts.

In this chapter the principles of ultrasound imaging will be reviewed. An emphasis will be placed on their practical application to endosonography rather than on the derivation of formulas and equations, which will soon be forgotten.

How ultrasound images are made

Sound is mechanical energy that is transmitted as a wave through a fluid or solid medium [1,2]. Unlike electromagnetic waves (e.g. radio, light and x-ray), sound waves cannot be transmitted through a vacuum. The energy must be transmitted via its impact on the molecules of the transmitting medium.

The periodicity or frequency of sound waves per unit of time varies widely and is measured in the number of cycles of the wave that are formed in one second, termed a *hertz* (Hz). Each wave cycle has both a positive and a negative pressure component. Sound higher in frequency than can be heard by the human ear is called ultrasound (Figure 2.1). The frequencies of waves commonly used in medical imaging are between 3.5 and 20 million Hz, usually abbreviated as 3.5 to 20 megahertz (MHz). Even higher-frequency waves can be used in microscopy to define tissue ultrastructure.

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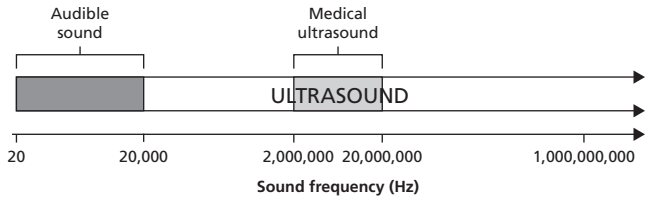

Figure 2.1 The frequencies of audible sound and ultrasound.

The high-frequency sound waves used in imaging have some interesting properties that affect how they are used. Unlike lower-frequency audible sound waves that travel well through air, high-frequency sound is more readily absorbed and attenuated by air and is strongly reflected at the boundary between tissue and air. This is why gas-filled lungs and bowel limit the use of transcutaneous ultrasound in imaging of mediastinal and retroperitoneal structures.

How ultrasound waves are made

Sound waves are made by applying an oscillating pressure to a medium. A radio speaker vibrates at variable speeds or frequencies to create sound waves in air, which we hear as sound. Higher-frequency ultrasound waves are made by crystals that vibrate to transmit an ultrasound pulse within a body fluid or tissue. These crystals are made from a special ceramic material because it can be made to vibrate at a high frequency when a high-frequency alternating polarity charge is applied to it. This property is termed *piezoelectric* and is also responsible for the crystal's ability to detect sound waves returning from the tissue and convert them back into an electrical signal.

Ultrasound transducers are composed of either one large crystal or, more commonly, multiple crystals aligned in an array. These transducers change an electrical signal to a sound wave and also receive the reflected sound wave back from the tissue. Ultrasound transducers typically emit a series of waves or a pulse, and then stop transmitting while they wait to detect the returning echo.

What happens when ultrasound waves encounter tissue

Ultrasound waves propagate through tissue at a speed that is determined by the physical properties of the tissue [3,4]. The speed of transmission is largely determined by the stiffness of the tissue: the stiffer the tissue, the faster the speed. For soft tissue, the variation in speed is only approximately 10%, ranging from 1460 meters per second in fat to 1630 meters per second in muscle [5–7].

Ultrasound waves are reflected back to the transducer when the sound wave encounters a tissue that is more difficult to pass through. For example, water easily transmits ultrasound, but air and bone do not. A sound wave that travels through a water-filled structure like the gallbladder is likely to reach the opposite gallbladder wall unless it encounters a gallstone that reflects the acoustic wave back to the transducer. Other solid tissues reflect sound waves to a variable extent depending on the tissue properties. Fat and collagen are more reflective to ultrasound than are muscle and lean solid organs. Sound waves are also reflected when they encounter a boundary or interface between two tissues with different acoustical properties (see following section).

How images are made from reflected ultrasound waves

Sound waves that are reflected by tissue components back to the transducer are detected by the same piezoelectric crystals that created them. These crystals then translate the waves back into electrical signals for processing into an image.

The transducer detects the returning echo as a function of the time that passed from when the sound pulse was emitted. The duration of time for an echo to return is a function of the speed of sound in the tissue and the distance from the transducer of the part of the tissue from which the sound wave is being returned. Because the speed of sound in lean tissue varies only by approximately 10%, the time between transmission of and return of an echo is a good marker for the distance the sound wave has traveled. Thus, for medical imaging, distance or location of a reflector within a tissue can be approximated by the delay observed in the return of an ultrasound pulse.

The returning waves or echoes can be displayed in a number of ways or modes. The simplest display plots the intensity or amplitude of echoes according to the time at which they are detected. This is termed A-mode and is infrequently used for medical imaging. If the amplitude of the returning signals is displayed as the brightness of a dot on the image, a *B-mode* image is created. If the transducer is moved across the tissue or if the transducer contains numerous crystals, a two-dimensional image is created out of the dots, which reflect echo amplitude; one dimension is the location or depth of the reflector causing the echo and the other dimension represents the span of tissue being imaged (Figure 2.2).

The precise time when a returning echo is detected is also a function of the orientation of the target tissue and the transducer. A more accurate representation of tissue structure is obtained when the ultrasound wave propagates in a direction that is perpendicular to the target. The reflected wave is then perpendicular to the transducer as well. If the ultrasound wave encounters the target from another angle or tangentially, then the returning wave is detected later and thus is displayed at a distance on the image that overestimates its actual position (see following section on artifacts).

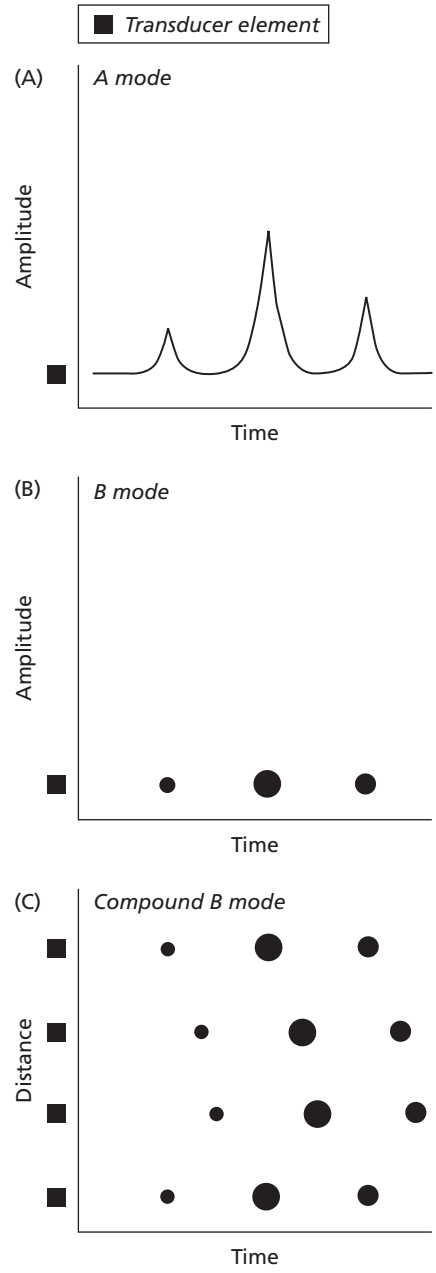

Figure 2.2 The basic types of ultrasound images. (A) A-mode image plots the amplitude of a returning echo versus the time when it returns relative to the transmitted ultrasound wave. Because the velocity of sound through soft tissue is relatively constant, the time of a returning echo can be converted into the distance or depth into the tissue from which the echo originated. (B) B-mode image displays the amplitude of an echo as the brightness of a dot. (C) When multiple transducers are used or when a single transducer is moved over an area, the multiple single-line B-mode images can be converted into a rectilinear or compound scan.

How transducer properties affect the image

Ultrasound frequency and axial resolution

When high ultrasound frequencies are used, more waves can be transmitted per unit of time and the duration of the pulse of ultrasound energy can be proportionately reduced. This allows the ultrasound transducer to receive returning echoes more often. The result is a better ability to discriminate between two points in the target tissue that are within the direction of the ultrasound beam. This distance between distinguishable points in the direction of the ultrasound beam is termed axial or range resolution (Figure 2.3). In general, the higher the ultrasound frequency, the better the axial resolution. Most endoscopic ultrasound systems have axial resolutions that are approximately 0.2 mm. However, tissue penetration is also reduced with higher ultrasound frequencies (Table 2.1).

Transducer size and lateral resolution

The lateral resolution makes it possible to distinguish between two points in the lateral dimension (see Figure 2.3). The magnitude of this resolution is dependent on the diameter of the transducer. In general, larger transducers have poorer lateral resolution. The lateral resolution is not constant but varies according to the distance of the target reflector from the transducer. The location of the best lateral resolution is often referred to as the focal zone of the transducer, and is the point at which the beam is focused and the lateral resolution is optimized. With most ultrasound endoscopes, this distance is between 2 and 3 cm from the transducer.

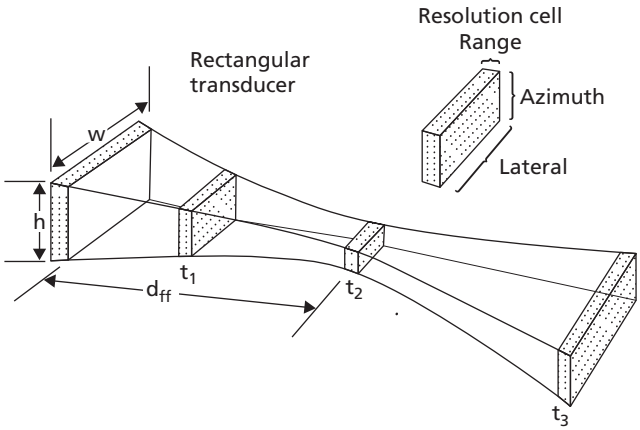

Figure 2.3 The resolution in three dimensions (resolution cell) for a pulse of ultrasound energy as it propagates from a rectangular-shaped transducer of defined width (w) and height (h). The duration of the pulse, defining the axial or range resolution, stays the same as the wave propagates and is illustrated at three times: t_1, t_2, and t_3. Changes in the beam pattern produce changes in the lateral and azimuthal resolutions at the three time points, however. The near-far field transition point (d_{ff}) is the point with the smallest resolution cell (in this case, illustrated at time t_2) and offers the best overall resolution. (Reproduced from Ref. 4 with permission from WB Saunders.)

Table 2.1 Effect of ultrasound frequency on axial resolution and tissue penetration

US frequency (MHz)	Axial resolution (mm)	Tissue penetration (cm)
5	0.8	8
10	0.4	4
20	0.2	2

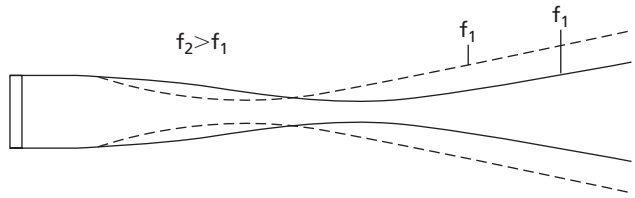

Figure 2.4 The effects of ultrasound frequency (f) on the beam pattern of a transducer. For the same size transducer, a beam (solid lines) with a higher ultrasound frequency (f_2) produces a near-far field transition point that is further from the transducer and also causes a narrower beam width in the far field. A beam (dashed lines) with a "lower frequency (f_1)" is illustrated for comparison. (Reproduced from Ref. 4 with permission from WB Saunders.)

The frequency of an ultrasound transducer also affects the lateral resolution. Small-diameter transducers used on catheter probes are especially vulnerable to this effect. With other variables being equal, higher-frequency small-diameter transducers have a narrower focal zone over a broader distance from the transducer than do lower-frequency transducers of the same diameter (Figure 2.4). This is the primary reason why catheter probes are made with higher-frequency (12 to 20 MHz) transducers.

Attenuation and tissue penetration

Attenuation refers to the loss of strength of the ultrasound beam over time or distance traveled. The degree of attenuation is dependent on the properties of both the ultrasound transducer and the tissue, but the most important factor is the ultrasound frequency. Higher ultrasound frequencies are maximally attenuated and hence do not penetrate as far into the tissue. Higher frequencies are also attenuated to a greater degree by specific tissue components, such as fat. For example, a lipoma within the gastrointestinal wall can attenuate a 12 or 20 MHz ultrasound beam so effectively that no ultrasound energy reaches the deep aspect of the lesion (Figure 2.5). The entire lipoma therefore may not be represented on the ultrasound image. In these situations, a lower-frequency ultrasound transducer might be preferable.

Since all tissue attenuates ultrasound to some degree, returning echoes from deeper tissue structures will have lower amplitude than those from more superficial structures. This is due to attenuation of both the transmitting ultrasound wave and the returning echo. Medical ultrasound imaging systems compensate for this effect by amplifying the echoes that return later to the transducer

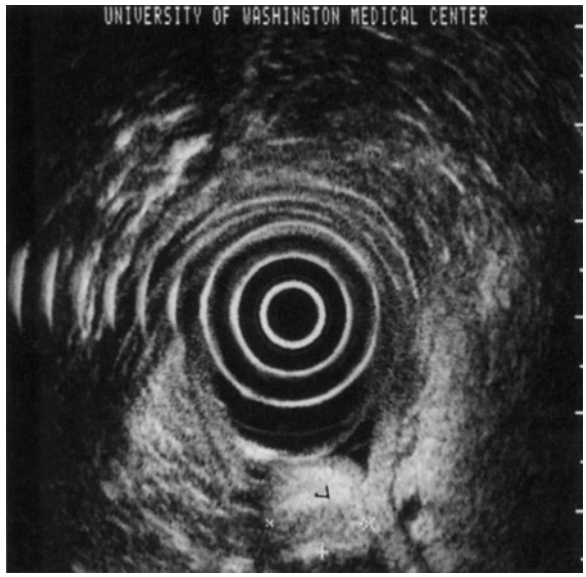

Figure 2.5 A duodenal lipoma (L) strongly attenuates the 12.5 MHz ultrasound beam producing an acoustic shadow (*arrows*) in the tissue deep to the lipoma.

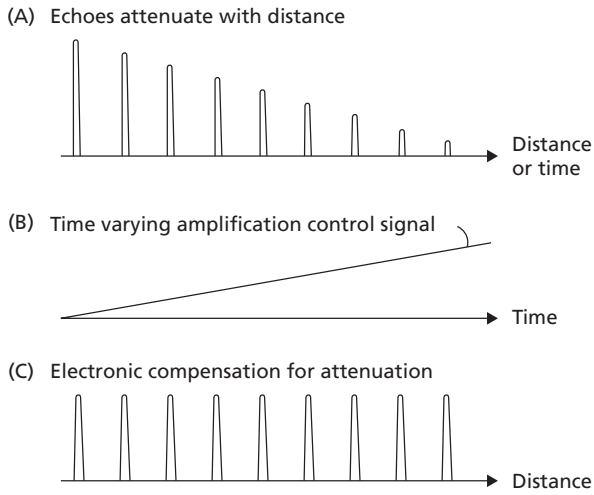

Figure 2.6 The concept of time varying gain (TVG) compensation is illustrated. The vertical axis represents the amplitude of the received echoes (A and C) and the control signal (B). (A) Ultrasound echoes with the same amplitude at the reflection site are received by the transducer as lower amplitude signals according to how far the reflector is from the transducer because of attenuation of both the transmitted and the reflected ultrasound waves. (B) The received echo can be electronically amplified according to when it is received, as shown by the linear increase in the exactly compensates for tissue attenuation, echoes from similar reflectors have the same amplitude at all distances from the transducer. (Reproduced from Ref. 4 with permission from WB Saunders.)

(Figure 2.6). Amplification of these echoes from deeper tissue structures is called time gain compensation (TGC). TGC can be controlled by the sonographer by changing settings on the ultrasound processor. The goal is to make similar tissue have the same ultrasound appearance irrespective of location within the tissue.

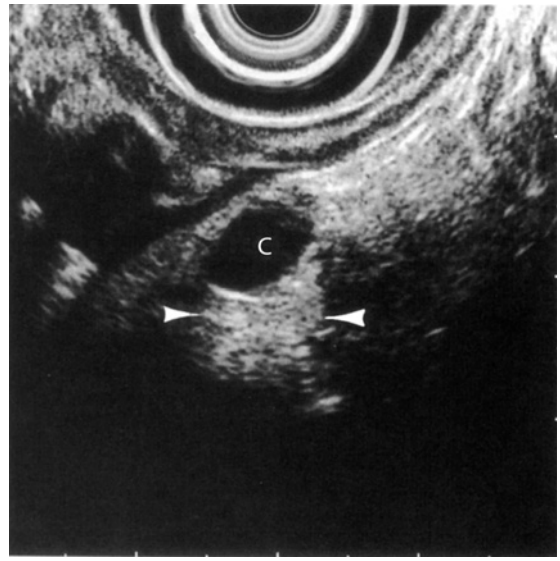

Figure 2.7 Fluid within this small pancreatic cyst (C) does not reflect much of the US beam, leading to more echoes being seen in the tissue deep to the cyst (*between arrows*). This is the through-transmission artifact.

Knowledge of attenuation can also be useful in image interpretation. Most body fluids (blood, urine and bile) attenuate an ultrasound beam very little. Thus, when imaging a fluid-filled structure, more ultrasound energy is transmitted to the tissue deep to the structure in comparison to the tissue deep to the adjacent solid tissue. There are then more returning echoes from the tissue deep to the fluid-containing structure, making this tissue brighter on the image. This through-transmission enhancement can be used to help distinguish between fluid-filled and solid structures. For example, images of a cyst will show brighter echoes in the area of tissue deep to the cyst (Figure 2.7).

How tissue properties affect images: the gastrointestinal wall

The composite image of a tissue depends on properties of the tissue as well as the ultrasound transducer and system used. Ultrasound imaging of the gastrointestinal tract wall is a good example of how these various factors interact.

Frequency dependence

Early reports of imaging of the gastrointestinal wall with transcutaneous ultrasound transducers described a three-layered structure. These layers represented luminal contents (echo rich), the wall itself (echo poor) and the surrounding tissues (echo rich). The axial resolution of these low-frequency (3 to 5 MHz) systems was too poor to detect the different components of the wall itself. With the development of endoscopic ultrasound systems with higher frequency (7.5 to 12 MHz) and better resolution transducers, the gastrointestinal wall was usually imaged as a five-layered structure, due to the different ultrasound properties of the mucosa,

submucosa, and muscularis propria [8]. Most recently, 20 MHz catheter-based EUS systems routinely image the gastrointestinal wall as a seven- or nine-layer structure due to better resolution, which allows the muscularis mucosae and the intermuscular connective tissue of the muscularis propria to be distinguished [9,10].

Higher ultrasound frequencies also produce brighter echoes from specular reflectors (see following section). This also contributes to the improved resolution seen with higher-frequency ultrasound systems.

Specular and nonspecular reflectors

Two types of tissue reflectors are sources of echoes on ultrasound images. These are termed nonspecular and specular reflectors. Echoes from nonspecular reflectors are produced by tissue components that scatter the ultrasound wave. Echoes from specular reflectors are produced when the ultrasound wave encounters two adjacent tissues with different acoustical properties. The ultrasound image is a composite of echoes from both types of reflectors. For example, the ultrasound image of a mixture of oil and water is homogeneous and echo rich. Echoes are reflected from nonspecular reflectors caused by the small oil droplets mixed in the water. After separation of the oil and water, however, only a thin echoic line is seen from the specular reflector at the interface between the oil and the water.

Nonspecular reflectors (scatterers)

Fat and collagen are the most reflective tissue components of the gastrointestinal wall. These tissue components are responsible for the bright layer seen in the center of the GI wall on EUS images. The submucosa is a dense network of collagen fibrils that provide structural support and allow for sliding of the overlying mucosa during motility. There is sometimes fat present in the submucosa as well. The other bright layer on EUS images of the bowel wall is from tissue just deep to the muscularis propria. In most areas of the body, this is from fat in the subserosa. In the esophagus, which is not covered by serosa, the bright layer is due to fat in the mediastinum. In the rectum, fat and collagen in the pelvis creates the bright layer.

Specular reflectors (interface echoes)

Early interpretations of ultrasound images of the gastrointestinal wall associated the echo-poor second layer with the muscularis mucosae. However, careful measurements later demonstrated that this ultrasound layer was much too thick to be the muscularis mucosae [8]. Further measurements also suggested that the central echoic layer was too thick to be the submucosa and the deep echo-poor, or fourth, layer was too thin to represent the muscularis propria. These observations were reconciled by considering the contribution to the image of specular reflectors produced at the interface between tissue layers of the bowel wall [8].

The thickness of an interface echo is determined by the pulse length or axial resolution of the ultrasound transducer. The beginning of an interface echo corresponds with the location of the interface so that the thickness of the interface echo itself will colocate with the most superficial aspect of the deeper tissue layer. Thus, an interface echo will add thickness to a more superficial echo-rich layer like the submucosa but subtract from the apparent thickness of a deeper echo-poor layer like the muscularis propria. When layer measurements are corrected for the presence of interface echoes, an accurate interpretation of the images is possible (Figure 2.8).

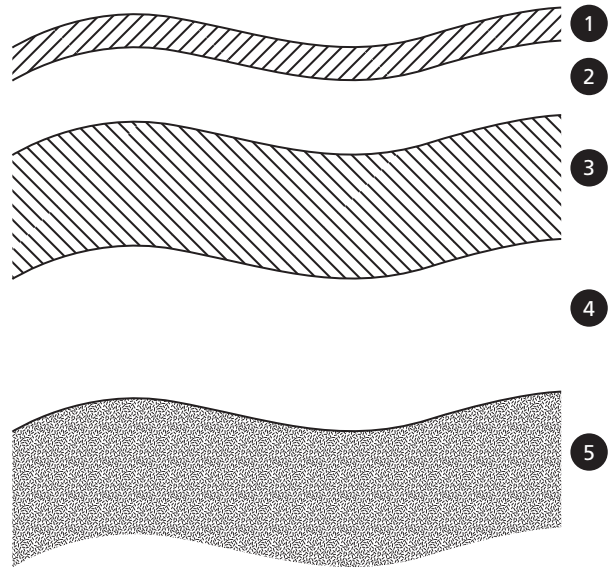

Figure 2.8 The five layers of the normal gastrointestinal wall as imaged with most endoscopic ultrasound equipment. From the mucosal surface at the top, layer 1 is produced by the interface between luminal fluid and the mucosal surface. Layer 2 is from the remainder of the mucosa. Layer 3 is from the submucosa and its interface with the muscularis propria. Layer 4 is the remainder of the muscularis propria. Layer 5 is from subserosal fat and connective tissue.

These principles can also be applied to the interpretation of seven- or nine-layered images of the gastrointestinal wall that are obtained with higher ultrasound frequencies. Better axial resolution and thinner interface echoes allow the muscularis mucosae to be visualized as a thin echo-poor layer superficial to the submucosa. The interface echo between the lamina propria and the muscularis mucosae divides the mucosa into four layers: an interface echo at the mucosal surface, the lamina propria, an interface echo between the lamina propria and muscularis mucosae, and the remainder of the muscularis mucosae that was not obscured by the interface echo [9,10]. The additional three layers in a nine-layered gastrointestinal wall are due to the division of the muscularis propria into inner circular and outer longitudinal components by a line of nonspecular echoes from a thin layer of connective tissue (Figure 2.9).

Detection of tissue movement: Doppler imaging

When an ultrasound wave encounters a moving object the ultrasound frequency is shifted. This frequency change is termed the

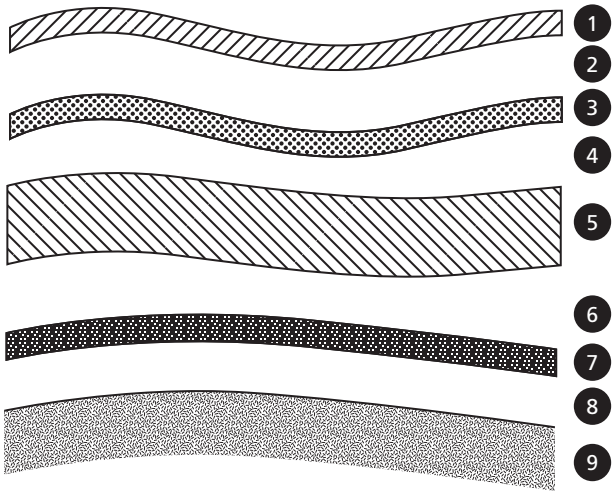

Figure 2.9 High-frequency ultrasound transducers may image the gastrointestinal wall as a nine-layered structure. From the mucosal surface at the top, layer 1 is produced by the interface between luminal fluid and the mucosal surface. Layer 2 is from the remainder of the lamina propria. Layer 3 is from the interface of the lamina propria and the muscularis mucosae. The remainder of the muscularis mucosae is visualized as a hypoechoic fourth layer only if the muscularis mucosae is thicker than the pulse length or axial resolution of the US transducer used. Layer 5 is from the submucosa and its interface with the muscularis propria. Layer 6 is the remainder of the inner circular component of the muscularis propria. The intermuscular connective tissue produces a thin echoic layer 7. The outer longitudinal component of the muscularis propria is responsible for layer 8. Layer 9 is from subserosal fat and connective tissue.

Doppler shift, and the use of this principle in detecting tissue movement is called Doppler *imaging*. Movement of red blood cells within blood vessels is the most common application of Doppler imaging. The direction of the frequency shift can also be used to determine the direction of the movement (i.e. toward or away from the transducer).

A few special principles of Doppler physics need to be recalled to optimize use of this technique. First, the Doppler frequency shift is maximal when the ultrasound wave encounters the moving objects at a tangential rather than a perpendicular angle. This is contrary to the principle of ultrasound imaging that tissue structure is reproduced most faithfully by an ultrasound wave that is perpendicular to the tissue. It is therefore often necessary to move the transducer in real time to simultaneously obtain optimal imaging and Doppler information.

There are two basic methods for performing Doppler measurements: pulsed Doppler and continuous-wave Doppler. Continuous-wave Doppler requires two transducers: a transmitting transducer and a receiving transducer. The transmitting transducer delivers a continuous fixed frequency ultrasound wave into the tissue. The receiving transducer then receives the signal. If there is movement in the tissue the transmitted and received signals will differ and when the two signals are summed together the result will be a waveform that contains a *beat frequency* that is equivalent to the Doppler shift frequency. Continuous-wave Doppler is unable to give information regarding the location that the Doppler shift is being detected; therefore, pulsed Doppler was developed to obtain depth information regarding where the motion causing the Doppler shift was occurring. In pulsed Doppler a single transducer is used to send an ultrasound pulse intermittently so detection of the returning Doppler wave is not limited by further transmitting waves. This leads to a more reliable detection of the depth of the moving object. For example, pulsed wave Doppler probes have been shown to reliably detect the location of blood vessels in the gastrointestinal wall [11].

Doppler information can be displayed in a number of ways. The Doppler shift of *moving* blood is approximately 15,000 Hz. Because this is within the range of human hearing, the signal can be amplified into an audible signal. The Doppler signal can also be superimposed on a B-mode scan so that the location of the moving objects can be determined by looking at the B-mode image. This is called *duplex scanning* and is commonly used in endoscopic ultrasound. The presence of a Doppler signal is good evidence that a cystic anechoic structure on B-mode imaging is a blood vessel. The direction of the Doppler shift can also be codified with color in a technique called *color Doppler*. Red is commonly used to represent flow toward the transducer and blue to represent flow away from the transducer. *Power Doppler* is the most recent advancement in Doppler ultrasound imaging and is the most sensitive method for detecting blood flow. For power Doppler imaging, pulsed Doppler is used to obtain the Doppler signal. However, power Doppler evaluates the strength of the Doppler signal and discards any information regarding the velocity or direction of motion.

New techniques in EUS imaging

Contrast-enhanced EUS imaging

Intravenous injection of an ultrasound contrast agent (UCA), gas-filled microbubbles that are 2 to 5 micrometers in diameter, results in enhancement of vascular structures on ultrasound imaging if an appropriate imaging technique and processing is used. This is a relatively well-developed imaging technology for cardiac imaging and transabdominal applications; however, the technology for EUS imaging is still in development [12]. The use of UCAs have enhanced the diagnostic capabilities of ultrasound imaging by improving the ability to image smaller caliber blood vessels, improved identification of tumors, and enhanced visualization of the cardiac wall [13–15]. Potential applications in EUS include evaluation of vascular invasion for tumor staging, differentiating benign and malignant lymph nodes [16], discriminating between focal pancreatitis and pancreatic carcinoma [17,18] and localizing vascular tumors such as insulinomas [19].

Elastography

Elastography is a method to assess the stiffness of tissue in response to compression by comparing the backscattered ultrasound signal from tissue in a compressed state and non-compressed state [20]. This method is being evaluated for use

in diagnosing disease processes that cause the stiffness of tissue to change such as cirrhosis, inflammation or malignancy. This method is analogous to the physical examination technique of palpation. For example, malignant tumors are often firm when palpated on physical examination. Elastography is a form of palpation using ultrasound to detect the regions that have different stiffness relative to the surrounding tissue. By externally compressing the tissue the ultrasound signal that is received from the region of interest will be different than the signal received when the region of interest is not compressed. The two signals are compared using image processing algorithms to produce an *elastogram*. For external imaging applications the ultrasound transducer can be used to apply compression to the region of interest, typically in a repetitive motion (compression-relaxation). For endoscopic applications it can be difficult to apply compression to a region of interest using the EUS transducer; therefore, the compressions to the region of interest can be from vascular pulsation or respiratory motion. EUS elastography should improve the diagnostic capabilities of EUS and help to improve localization of lesions and diagnostic yields on biopsy [21].

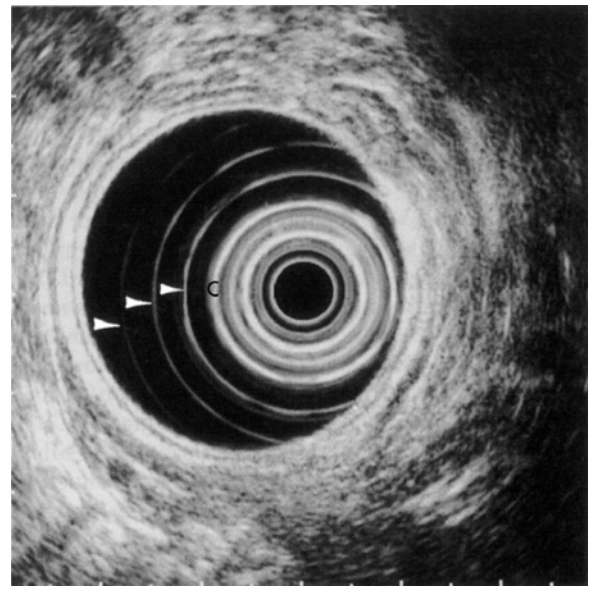

Figure 2.10 The plastic casing (C) around the ultrasound transducer produces a strong reverberation of the ultrasound beam between the transducer and the casing. This results in a series of circular rings (*arrows*) of equal spacing and diminishing amplitude around the transducer.

Imaging artifacts

A number of artifacts should be recognized when performing endoscopic ultrasound imaging. Artifacts are echoes seen on an image that do not reliably reproduce the actual tissue structure. Failure to recognize artifacts can lead to image misinterpretation and errors in patient management. This section will highlight some common artifacts and discuss how to recognize or, if possible, avoid them.

Reverberation artifacts

Strong echoes are produced when an ultrasound wave encounters solid nontissue objects. The most common example of this is reverberation of the ultrasound beam from the casing of the transducer. This produces a characteristic series of echoes at equal intervals radiating out from the transducer: the ring artifact (Figure 2.10). It is seen more commonly with the radial scanning echoendoscope than the curvilinear array instrument, and in some situations can interfere with the near-field image. Reducing overall and near-field gain helps to minimize this artifact. Moving the transducer away from the area of interest by filling the balloon or bowel lumen with water may also help move the artifact away from the area of interest.

Another problem created by reverberation is the mirror image artifact [22]. In this situation, ultrasound waves bounce off of an interface between water and air (Figure 2.11). This is typically seen when imaging within a partially water-filled organ such as the stomach or rectum. The ultrasound waves bounce back and forth between the transducer and the air–water interface, creating a mirror image of the transducer on the opposite side of the air–water interface (Figure 2.12). This effect is similar to observing a mountain and its inverted reflection in a lake. The artifact

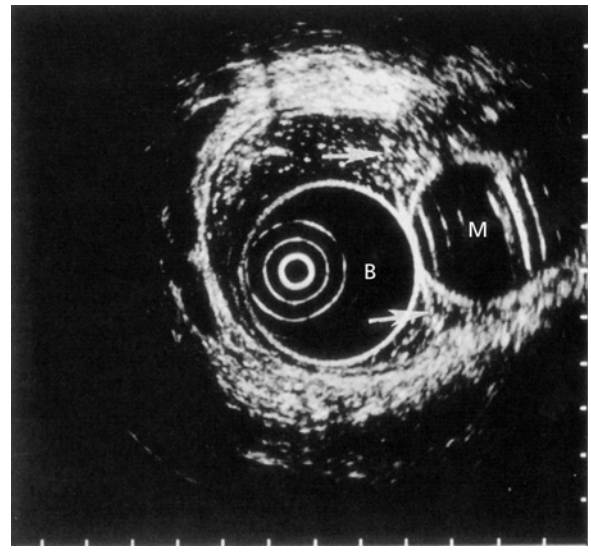

Figure 2.11 A mirror image (M) of the ultrasound transducer and water-filled balloon (B) is produced by reverberation between the transducer and the interface (*arrow*) between water and air within the gastric lumen.

is easily recognized and can be avoided by removing air and adding more water into the lumen.

Tangential scanning

As previously discussed, distances and therefore tissue thickness are most accurate when the ultrasound wave is perpendicular to the area of interest. When the ultrasound wave is tangential, tissue layers appear artificially thickened (Figure 2.13). This artifact can result in tumor "overstaging," especially in the esophagus

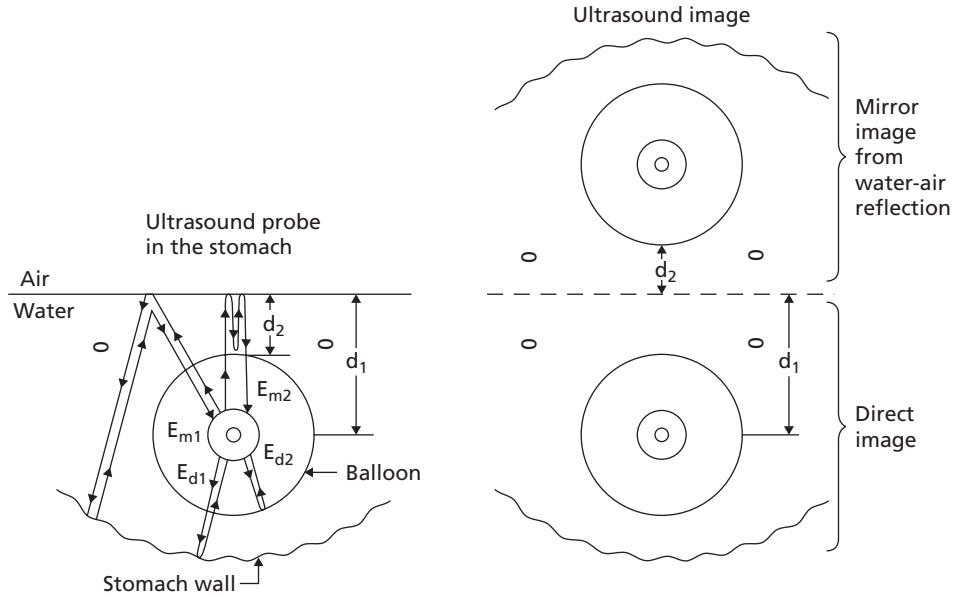

Figure 2.12 How reverberation of echoes from a water–air interface produces a mirror image artifact. The water–air interface reflects so strongly that ultrasound energy is redirected back to the transducer like a mirror redirects light. In the illustration at the left, the echoes E_{m1} and E_{m2} result from a double reflection, one from the water–air interface and one from a reflection from the stomach wall or balloon (or transducer case), respectively. The ultrasound processor records the position of the echo according to the time it receives the signal; the double reflection path takes longer and therefore causes the echo to appear further away from the transducer as if it were a reflection in a mirror (diagram at left). The echoes received by the transducer directly (for example, E_{d1} and *Ed2*) are displayed on the image in the expected location. The distance from the transducer to the water–air interface (d) and the distance from the balloon or transducer case to the interface (d_2) also are illustrated. (Reproduced from Ref. 4 with permission from WB Saunders.)

and gastroesophageal junction, and particularly when the radial scanning ultrasound endoscope is used (Figure 2.14). To avoid the problem, the endoscope should be carefully maneuvered so that the ultrasound wave is perpendicular to the tissue. The normal wall layers should appear symmetric and of uniform thickness. When imaging abnormal tissue, care must be taken that the findings are reproducible and not altered by small deflections of the endoscope tip.

Attenuation artifacts

Other artifacts are caused by attenuation of the ultrasound wave, but attenuation artifacts facilitate image interpretation in some cases. For example, lack of transmission of ultrasound through a gallstone or pancreatic duct stone is a key feature of cholelithiasis, choledocholithiasis and pancreaticolithiasis. Soft tissue can also attenuate the ultrasound waves, making it difficult to image deep into the tissue, especially when high-frequency transducers such as those on catheter probes are used. This can limit the ability to image the deep aspects of tissue masses.

Another common artifact is due to attenuation by air bubbles. Bubbles develop in several unwanted locations, including the oil surrounding the transducer within the transducer housing, the water in the balloon on the outside of the transducer housing, in water placed into the gastrointestinal lumen, and air within the lumen itself. The transducer casing should be inspected for air bubbles prior to each procedure; removing these bubbles requires a minor repair by the manufacturer. Air bubbles in the balloon can be avoided by using degassed water and by repetitive filling and suctioning of the balloon prior to use. Air in water placed into the lumen can be avoided by using degassed water and by having the patient drink a simethicone "cocktail" before the procedure [23].

Side lobe artifacts

These artifacts are characterized as nonshadowing echoes within an otherwise anechoic or fluid-filled structure [24]. They can be confused with biliary sludge in the gallbladder or a mass within a pancreatic cyst (Figure 2.15). Side lobe artifacts are caused by low-amplitude components of the transmitted ultrasound beam that are not perpendicular to the target. If these echoes are reflected by solid tissue outside the fluid-containing target, they may be displayed by the ultrasound processor as having come from the fluid-filled structure. When imaging solid tissue, low-amplitude side lobe echoes are obscured by the echoes from the solid tissue and do not pose a problem in image interpretation. However, when an anechoic structure is being imaged, these echoes become visible and can artifactually suggest the presence of a solid component. They are easily recognized because they disappear with transducer movement and are eliminated by scanning from other angles.

Doppler artifacts

Artifacts associated with Doppler imaging can lead to signals being detected when no flow is present and, conversely, a lack of signal when flow is present. Flow can be artifactually seen when the Doppler gain is set too high. Under those conditions,

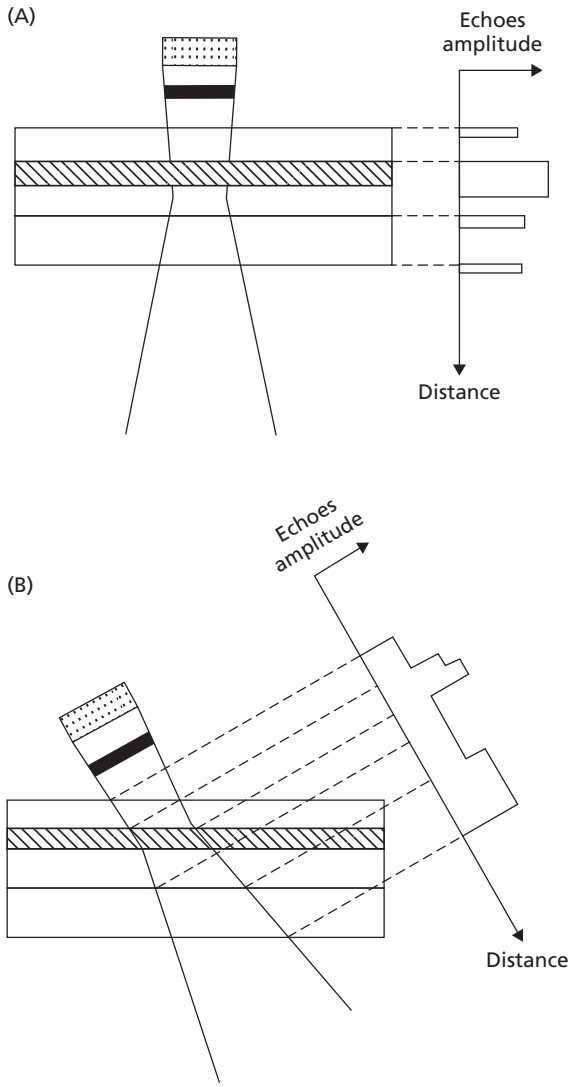

Figure 2.13 Why artifactual layer thickness increases with tangential scanning. (A) The amplitude and spatial duration of the echoes from the interfaces and specular reflectors in the normal gastrointestinal wall are shown in the case when the ultrasound beam is at right angles to the wall. The diagonally-hatched region represents a tissue type with nonspecular echoes (for example, the submucosa); the remaining echoes are produced by interfaces between tissue layers (specular echoes). The duration of the interface echoes is the same as the duration of the ultrasound pulse or the range resolution of the system (illustrated as a black rectangle in the beam). The echoes (displayed at the right) are spatially separated and distinguishable from each other. (B) When the ultrasound beam is not perpendicular to the wall, both the lateral and range resolution affect the duration of the echoes from each layer. In the extreme situation illustrated here, echoes from each layer overlap and cannot be distinguished individually. (Reproduced from Ref. 4 with permission from WB Saunders.)

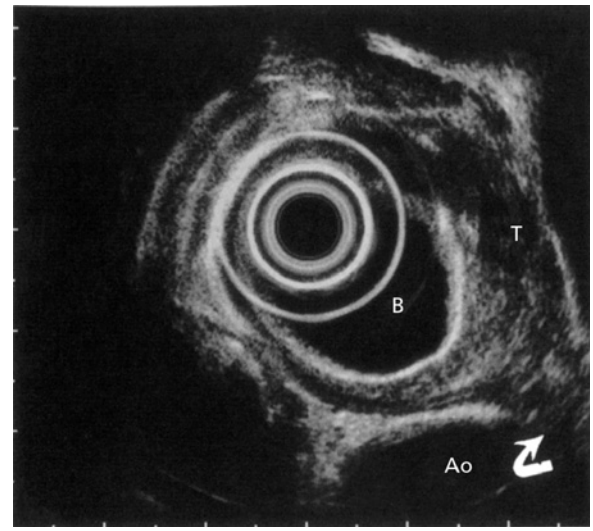

Figure 2.14 This EUS image of an esophageal cancer (T) appears to show invasion of the descending aorta (Ao) at the arrow. This is an artifact caused by nonperpendicular or tangential scanning; a clue to this is the located water-filled balloon (B). The transducer and balloon should be positioned in the center of the esophagus with the transducer in the center of the balloon to avoid this artifact and avoid tumor overstaging.

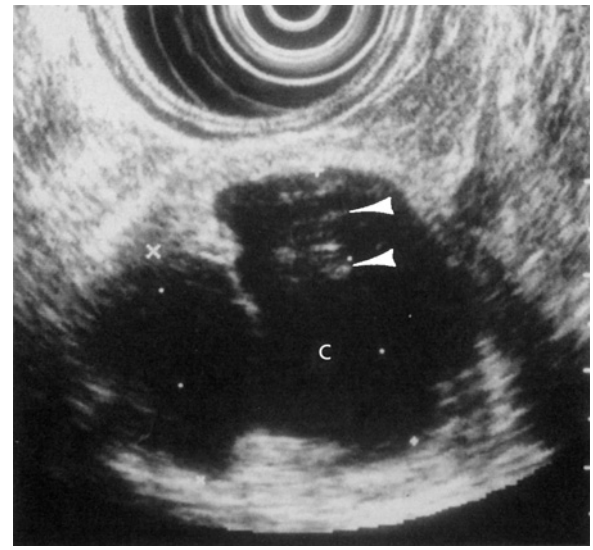

Figure 2.15 This pancreatic cyst (C) appears to have echoes within it (*arrows*) suggesting a solid component. These echoes are caused by side lobe artifacts and are recognized because they are not consistently imaged when the transducer is maneuvered into another imaging plane.

bowel wall and transmitted cardiac and respiratory motion can be amplified and give the appearance of flow. However, this false signal is usually easy to recognize because the Doppler signal is diffuse and not localized to a specific structure.

False negative Doppler signals can occur if the ultrasound beam is perpendicular to the target. Doppler shift is best detected with an ultrasound beam that is less than 60 degrees incident to the target. Doppler can also miss low levels of venous flow if the ultrasound processor's wall filter is improperly set. This filter is meant to reduce noise from vessel wall motion but can sometimes indiscriminately delete clinically important low-frequency echoes.

Table 2.2 Using ultrasound principles to optimize image quality

Principle	Practice
US frequency affects penetration depth	Use lower US frequency for distant targets
US frequency affects axial resolution	Use highest US frequency that provides adequate penetration
Lateral resolution varies with distance from the transducer	Position transducer so target is in the optimal focal zone
Attenuation is greater with higher US frequencies	Use lower frequency for fatty and fibrous structures
The same tissue type should appear the same throughout the US image	Adjust the time gain compensation on the US processor
Air transmits high-frequency US poorly	Eliminate air bubbles in the water-filled balloon and in the lumen
Images are more reliable if the US beam is perpendicular to the tissue	Recognize and avoid tangential scanning artifacts
Doppler shift is greatest with a tangential US beam	Adjust the transducer position to optimize Doppler signal

Using ultrasound principles to obtain better images

The principles of ultrasound that have been discussed can be used to facilitate better endosonographic scanning and produce images that more accurately reproduce tissue structure. The importance of a standardized preprocedure checklist and consistent procedure technique cannot be overemphasized. The basic steps in achieving an optimal examination, based on the principles discussed in this chapter, are summarized in Table 2.2.

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3 EUS Instruments, Room Setup and Assistants

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Introduction

Endoscopic ultrasound (EUS), like ERCP, utilizes specialized instruments and accessories. Furthermore, just as an endosonographer has obtained additional endoscopic training to ensure competency in EUS, nurses and other assistants will also acquire a specialized skill set. Attention to these issues is important when establishing an EUS practice. This chapter will review the equipment required to perform EUS, provide tips for setting up an EUS examination room, and address aspects about the assistants who will be helping you with EUS. Spending some extra time thinking about what equipment you'll truly need, where and how to set up that equipment, and how to build an EUS team will make procedures run more efficiently, and help you to provide the best possible care for your patients.

EUS instruments and other equipment

There are essentially two forms of echoendoscope, denoted as radial or linear, based upon the arrangement of the piezoelectric crystals that generate the EUS image. In a linear array echoendoscope, the crystals are arranged along one side of the endoscope's tip, generating an image parallel to the long axis of the instrument (Figure 3.1). In an *electronic* radial array echoendoscope (sometimes referred to as a transverse array echoendoscope), these crystals are arranged in a band around the shaft of the endoscope perpendicular to the long axis of the instrument, generating a cross-sectional image (Figure 3.1). In a *mechanical* radial echoendoscope, a small transducer literally rotates perpendicularly to the long axis of the instrument, again to generate a cross-sectional image. Only the linear array echoendoscope can be used to guide a needle for fine needle aspiration (FNA). A needle viewed with a radial array echoendoscope would be seen in cross section, and therefore would appear only as a dot in the image, making it impossible to guide safely for fine needle aspiration.

The relatively new electronic radial array echoendoscopes will likely replace the older, mechanical radial instruments over the next few years. The new instruments have no rotating parts, making electronic radial array echoendoscopes less prone to mechanical breakdown. Another key feature of electronic radial echoendoscopes is the addition of Doppler capabilities similar to what has been available with linear instruments. In addition, some electronic radial and linear instruments can use the same processor, potentially cutting start-up costs. The earlier mechanical radial instruments are still available for purchase from Olympus, while Pentax offers only electronic instruments. However, should you consider purchasing a mechanical radial echoendoscope, be sure you

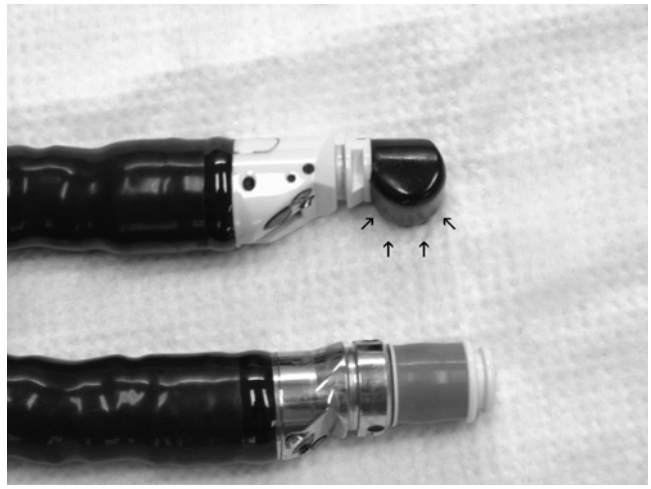

Figure 3.1 A linear array echoendoscope (*top*) and an electronic radial array (also called transverse array) echoendoscope (*bottom*). The piezoelectric crystals on the linear array echoendoscope are arranged along a single curved surface (*arrows*). On the electronic radial array echoendoscope the crystals are arranged as a band around the side of the instrument's tip.

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discuss the costs of repair contracts with your sales representative as this may impact on your overall equipment purchasing costs.

Deciding about appropriate equipment for an EUS practice requires consideration of several factors. What types of echoendoscopes are you familiar with from your training? If you've trained only using radial echoendoscopes, and have no experience with fine needle aspiration, a linear echoendoscope may not necessarily be one of your initial purchases. In some cases, you may have trained predominantly with linear echoendoscopes, in which case you may feel a radial echoendoscope is not necessary. Studies have demonstrated that radial and linear echoendoscopes perform similarly in appropriate hands for the staging of upper gastrointestinal malignancies, although radial array instruments may detect more lymph nodes per patient [1,2]. Therefore, your choice of radial versus linear echoendoscopes will not be an evidenced-based decision so much as one based on your familiarity with the instruments. Most people will have used both types of echoendoscopes in their training and will therefore be familiar with the benefits and shortcomings of each.

Table 3.1 lists the instruments currently available for purchase and technical details about each system. Currently Pentax and Olympus each offer both radial and linear echoendoscopes, while Fujinon intends to bring both types of echoendoscope to market in the near future. There are minor differences between the different manufacturers' echoendoscopes. For example, the Olympus instruments have an oblique viewing angle as the video camera lens is located behind the ultrasound transducer. The Pentax radial instruments have the camera lens in the endoscope's tip, similar to standard forward-viewing endoscopes. Additionally, depending on your choice of echoendoscope, you will need the appropriate processor as detailed in Table 3.1.

When making the decision about the ratio of radial to linear instruments to purchase (e.g. one of each, or two radial and one linear, etc.) it is prudent to first understand the nature of the anticipated EUS practice. Will there be many referrals for cancer diagnoses and staging? If so, what forms of cancer are most likely to be seen? Esophageal and rectal cancers will often present with malignant adenopathy. There is strong evidence demonstrating that endosongraphic criteria alone are unreliable, necessitating the use of fine needle aspiration for optimum accuracy [3,4]. Pancreatic cancers often require fine needle aspiration for diagnosis at the time of staging EUS. If you anticipate a fair number of pancreatic cystic neoplasms for fine needle aspiration and/or a large number of lung cancer cases with mediastinal lymphadenopathy, consider one linear echoendoscope for each radial echoendoscope you purchase. In fact, for some of these cases such as pancreatic cystic lesions or mediastinal masses, you may find yourself reaching exclusively for a linear echoendoscope.

The next decision is the total number of echoendoscopes to purchase. To answer this question there are several factors to consider. How many procedures do you expect to perform in a given year? Will that number grow rapidly once you introduce EUS into your practice? How rapidly can your endoscopes be appropriately disinfected and processed between procedures? How many physicians in your practice will be performing EUS?

If you plan to perform an EUS case here and there, sandwiched between screening colonoscopies and routine upper endoscopies, you should purchase one radial and one linear echoendoscope. If you prefer to cluster several EUS cases into a single half-day or full-day session, you will need at least two instruments, and ideally four (two radial and two linear). One large academic practice that performs 800 EUS cases a year uses two radial and two linear echoendoscopes. Another practice that performs 1,700 cases a year gets by with two radial and three linear echoendoscopes.

What about high-resolution ultrasound miniprobes? These fragile probes are unmatched for evaluating small subepithelial lesions in the esophagus, stomach and rectum. They are even more important for staging of early cancers, such as a T1 esophageal cancer [5]. Probes can also be used to image biliary and pancreatic duct strictures, particularly if you purchase a wire-guided system for passage during ERCP [6]. Probes are available in a range of frequencies, enabling the endosonographer to choose between greater depth of imaging (the lower frequencies) and greater image resolution (the higher frequencies) when selecting a probe for a particular case. If you don't anticipate staging a large number of early cancers, you may get by without these. If you do purchase the probes, be aware of their compatible probe drivers and processors. Table 3.2 includes information about the available catheter probe systems offered by both Olympus and Fujinon. Pentax does not offer a probe system.

Echoendoscopes are disinfected and reprocessed using similar equipment to other endoscope reprocessing devices. However, there may be important considerations based upon the equipment you purchase. For instance, if you have other endoscope equipment made by Fujinon, and choose to buy EUS equipment from Olympus, you must be sure to have a reprocessor that will accommodate the Olympus echoendoscopes. In addition, some echoendoscopes cannot be reprocessed in a Steris® device. Be sure to address this issue with your sales representatives when formulating a purchase plan.

Finally give some thought to the other accessories and equipment you will use during EUS. For example, there are two types of needle currently available for use during EUS. One is a hollow bore needle with a stylet used to obtain material for cytological analysis. The other type extends a sharp tray into the target tissue while a cutting sheath is then deployed over the tray to cut a core biopsy for histological analysis. Both types of needle have proven useful, and appear at times to offer complementary information [7,8]. The core biopsy needle is more difficult to deploy when the echoendoscope is contorted, and is best used for masses reached with a straight-scope configuration. You will certainly need fewer core biopsy needles than standard needles. In addition, give consideration to the size of needles you want to stock. Most fine needle aspiration is done with 22- or 25-gauge needles, but you may occasionally want a 19-gauge needle for draining large fluid collections or obtaining cellular material from stromal tumors. Sales representatives are generally eager to help keep you abreast of recent

Table 3.1 Echoendoscopes currently available

Manufacturer	Model	Ultrasound type and orientation	Ultrasound frequencies (MHz)	Ultrasound field of view (degrees)	Insertion tube length (mm)/diameter (mm)/ accessory channel diameter (mm)	Angulation up/down right/left	Video image viewing orientation (degrees) and angle (degrees)	Compatible processor
Pentax	EG-3670URK	Electronic Radial	5/7.5/10	360	1,250/12.1/2.4	130/60 60/60	Forward Viewing, 140	Hitachi EUB 5500 and 8500
	EG-3630UR	Electronic Radial	5/7.5/10	270	1,250/12.1/2.4	130/60 60/60	Forward Viewing, 120	Hitachi EUB 6000 and 525
	EG-3870UTK	Electronic Linear	5/7.5/10	120	1,250/12.8/3.8	130/130 120/120	Oblique Viewing (50), 120	EUB 5500
	EG-3830UT	Electronic Linear	5/7.5/10	120	1,250/12.8/3.8	130/130 120/120	Oblique Viewing (50), 120	EUB 6500, 6000, and 525
Olympus	GF-UE160-AL5	Electronic Radial	5/6/7.5/10	360	1,250/11.8/2.2	130/90 90/90	Oblique Viewing (55), 100	Aloka SSD-Alpha 5 and SSD-5000*
	GF-UM160	Mechanical Radial	5/7.5/12/20	360	1,250/10.5/2.2	130/90 90/90	Oblique Viewing (50), 100	Olympus EU-M60
	GF-UM130	Mechanical Radial	7.5/12	360	1,250/10.5/2.2	130/90 90/90	Oblique Viewing (50), 100	Olympus EU-M60 and EU-M30
	GF-UMQ130	Mechanical Radial	7.5/20	360	1,250/10.5/2.2	130/90 90/90	Oblique Viewing (50), 100	Olympus EU-M60 and EU-M30
	MH-908	Mechanical Radial	7.5	360	700/7.9/NA	130/90 90/90	Non-viewing (wire-guided)	Olympus EU-M60 and EU-M30
	GF-UC140P-AL5	Electronic Linear	5/6/7.5/10	180	1,250/11.8/2.8	130/90 90/90	Oblique Viewing (55), 100	Aloka SSD-Alpha 5 and SSD-5000*
	GF-UCT140P-AL5	Electronic Linear	5/6/7.5/10	180	1,250/12.6/3.7	130/90 90/90	Oblique Viewing (55), 100	Aloka SSD-Alpha 5 and SSD-5000*
	GF-UC160P-OL5	Electronic Linear	7.5	150	1,250/11.8/2.8	130/90 90/90	Oblique Viewing (55), 100	Olympus EU-C60
	GF-UC160P-OL5	Electronic Linear	7.5	150	1,250/12.6/3.7	130/90 90/90	Oblique Viewing (55), 100	Olympus EU-C60

*The Aloka SSD-5000 requires an upgrade kit for compatibility with the GF-UE160-AL5.

Table 3.2 Ultrasound catheter probes currently available

Manufacturer	Model	Frequency (MHz)	Working Length (mm)	Diameter (mm)	Probe driver/processor	Comments
Fujinon	P2625	25	2200	2.6	SP-702	
	P2620	20	2200	2.6	SP-702	
	P2615	15	2200	2.6	SP-702	
	P2612	12	2200	2.6	SP-702	
	PL2226-7.5	7.5	2200	2.6	SP-702	Requires an additional probe adapter
	P2025	25	2200	2.0	SP-702	
	P2020	20	2200	2.0	SP-702	
	P2015	15	2200	2.0	SP-702	
	P2012	12	2200	2.0	SP-702	
Olympus	UM-2R	12	2050	2.5	MAJ-935/EU-M60 or MAJ-682/EU-M30S or MAJ-682/EU-M60	
	UM-3R	20	2050	2.5	As above	
	UM-S20-20R	20	2050	2.0	As above	
	UM-S30-20R	30	2050	2.0	As above	
	UM-S30-25R	30	2050	2.4	As above	
	UM-BS20-26R	20	2050	2.6	As above	Must be used with a balloon sheath (MAJ-643R)
	UM-G20-29R	20	2050	2.9	As above	Wire-guided for use within ductal structures
	RU-75M-R1	7.5	150	12	As above	Rigid rectal probe
	RU-12M-R1	12	150	12	As above	Rigid rectal probe
	UM-DP12-25R	12	2200	2.5	MAJ-935/EU-M60 only	Permits dual-plane reconstruction (linear and radial plane imaging)
	UM-DP20-25R	20	2200	2.5	MAJ-935/EU-M60 only	Permits dual-plane reconstruction (linear and radial plane imaging)

advances in equipment and accessories, so check in periodically with these vendors either locally or at national meetings.

Other accessories to have on hand during EUS, besides balloons for acoustic coupling and photo paper, are cytology supplies, tubes for sending pancreatic cyst fluid for chemical analyses, and esophageal dilators. The latter are particularly important if you plan to stage esophageal cancers as a malignant stenosis precluding passage of the echoendoscope is encountered in approximately 30% of cases [5]. Both Savary-type dilators and through-the-scope (TTS) balloon dilators have been shown to be safe and effective in this setting [5,9].

If you anticipate having a cytopathologist available for in-room cytopathological evaluation, consider purchasing a microscope to keep in the EUS room. Otherwise, the cytopathologist will have to bring one with her each time she is called to assist in a case, a potential disincentive for voluntary participation. If you are purchasing a microscope for this purpose, it is highly worthwhile to obtain a video microscope. In this case the microscopic image can be displayed on a video monitor in the EUS room for others to view. This video output can also be captured with recording equipment either for incorporation of still images into a report, or for brief video clips used for teaching purposes.

Room setup

There are several things to consider when setting up a room for EUS. First, unlike standard endoscopy which may be performed in several rooms within a single endoscopy unit, EUS requires at least one additional processor that you will probably not want to move from room to room. Therefore, if you have several rooms in your endoscopy unit, you must first determine which will be dedicated to EUS. This is not to say other endoscopic procedures can't take place in the room; rather you are simply "setting up shop" in one location to permit centralization of various EUS equipment and accessories.

The ideal EUS room would be large enough to house both standard endoscopic equipment and the EUS processor(s). Additional space for a small worktable and microscope permits easy processing of samples during on-site cytopathological evaluation. In addition to cabinets for housing typical endoscopy needs (e.g. gloves, oxygen tubing), you may want extra space for storing FNA needles, EUS balloons, paper for an EUS image printer, and perhaps even the echoendoscopes themselves. If you have EUS catheter probes and a probe driver, consider keeping these in the

Figure 3.2 A wall-mounted storage system works well for organizing small EUS-related supplies such as air and suction buttons, balloons, and balloon applicators.

EUS examination room as well. Given the delicate nature of EUS catheter probes, having them corralled in one safe place protects them from unwanted contact with heavier equipment and curious hands. Finally, the air and suction buttons for echoendoscopes are different from those used in standard endoscopy. You may find it helpful to store these buttons in the EUS room and not mixed with standard buttons in a clean equipment area. This permits rapid access to the proper buttons when preparing for a procedure, and lets you easily monitor your inventory (Figure 3.2).

If your endoscopy unit has a dedicated fluoroscopy room, such as for ERCP, there are reasons both for and against using this same room for EUS. Fluoroscopy is generally required for intraductal EUS when catheter probes are passed into the biliary or pancreatic ducts [6]. In addition, EUS is often used to assist with, or as the primary instrument for, endoscopic pancreatic pseudocyst drainage, requiring fluoroscopic guidance [10]. In the case of an obstructing esophageal cancer, many endosonographers dilate the stricture with wire-guided bougienage dilators. This requires fluoroscopic guidance for placement of the guidewire. Finally, patients who present with obstructive jaundice will often require both ERCP for biliary stent placement and EUS for fine needle aspiration and staging. It is very convenient for patients to have these procedures performed "back to back" during the same endoscopy session.

However, some of these benefits for locating EUS within the fluoroscopy room can also be addressed in other ways. For example, if you anticipate performing frequent intraductal cases, consider purchasing a separate catheter probe unit specifically for use in the fluoroscopy room. For patients with stenotic esophageal cancer, dilation can also be accomplished with through-the-scope dilating balloons without the need for fluoroscopy [9]. Finally, for patients who require both EUS and ERCP in the same session, or pseudocyst drainage, remember EUS processors are mobile and, though this is not ideal, can be wheeled into the fluoroscopy room when needed.

There are several reasons not to perform all your EUS cases in a fluoroscopy room. First and foremost, the fluoroscopy unit generally consumes a large amount of space, making it difficult to accommodate all the requirements for EUS. With EUS separated from fluoroscopy, an endoscopy unit can accommodate both ERCP cases and EUS cases simultaneously, providing more scheduling freedom for providers in a multi-person practice. In addition, while most ERCPs can be accomplished in a reasonable amount of time, the occasional procedure may run quite long for technical reasons (e.g. a difficult bile duct cannulation; multiple large stones). Likewise, fluoroscopy may be suddenly required for an unanticipated emergent ERCP. These situations can dramatically hamper your ability to provide timely service for scheduled EUS cases as you wait for your room to become available. Another consideration relates to mobility within the room. During EUS-FNA, a procedural assistant may need to perform several functions, including removal of the needle's stylet and collection of aspirates into cytology fixative. These functions may best be performed with the assistant situated in various locations around the patient's stretcher. A fluoroscopy table can severely limit the assistant's ability to navigate freely for these tasks.

Placement of the EUS processor within the endoscopy room also requires some thought. Unlike standard endoscopy, you will need easy access to the processor's keyboard and instrument panel during the procedure. For standard endoscopy, the processor is usually located behind the endoscopist. During EUS, it is very helpful to have the processor placed to the right of the endoscopist, keeping his right hand within easy reach of the instrument's keypads. Left-handed endoscopists may want to modify this arrangement.

The imaging monitor for EUS may be incorporated into the processor, such as with the Aloka SSD or Hitachi 5500. In this case you may also want to connect the processor's video output to your standard endoscopy monitor which is typically on the opposite side of the patient from where you are positioned. This is desirable for two reasons: (1) others in the room (e.g. nurses, fellows, residents) may be able to see the EUS images when the EUS processor's monitor is obscured by your body; and (2) positioning your body for an optimal FNA approach may require some contortions that take the EUS processor's monitor out of your field of view. In these cases, the standard monitor may be easier to see. Most monitors have auxiliary input jacks in S-video, RGB, or RCA formats that accommodate EUS processor outputs. The EUS image can then be shown on the standard monitor by selecting the auxiliary input mode (Figure 3.3).

In our EUS room we have a cytology workstation with a video microscope and dedicated overhead lighting (Figure 3.4). The microscope's video output also connects to the main room monitor via a switcher box, permitting the endosonographer to choose between viewing the EUS image or the microscopic image (Figure 3.5). Such switcher boxes are available at most electronics stores. As the endosonographer can view the microscopic image at the same time as the cytopathologist, there can be more informed discussion about specimen adequacy and a possible diagnosis. Over time, the endosonographer can also learn the appearance of malignant cells and develop a sense of when an aspirate is likely inadequate. The endosonographer thus

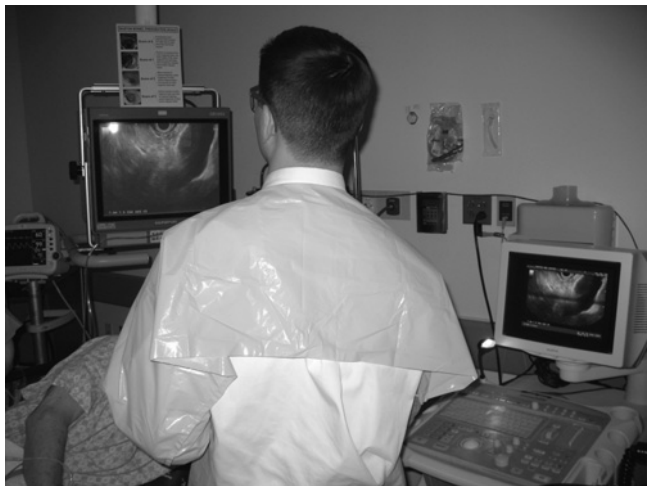

Figure 3.3 The EUS image is fed from the processor to the room's primary monitor to increase options for viewing. Note that the EUS processor is to the right of the endosonographer to improve access to the instrument panel and keyboard.

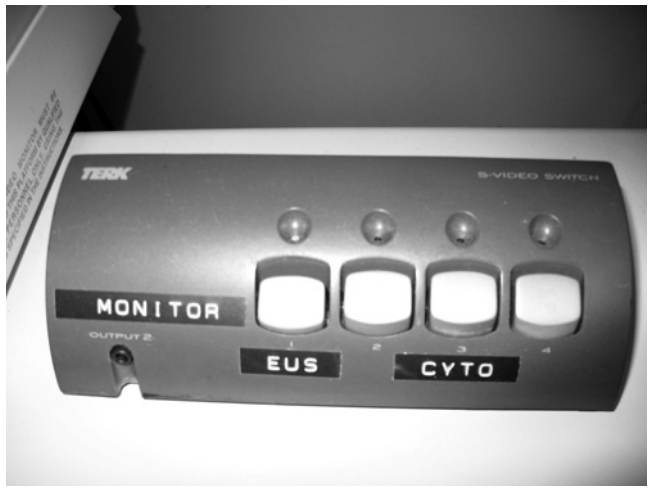

Figure 3.5 The endosonographer can maintain control over the image displayed on the room's primary monitor using a switcher box. In this case, the box receives input from both the EUS processor and a video microscope.

Figure 3.4 A small worktable in the EUS room provides dedicated workspace for processing cytology samples. Keeping a microscope and cytology reagents in the EUS room makes it easier for a cytopathologist to simply stop in to help with a case.

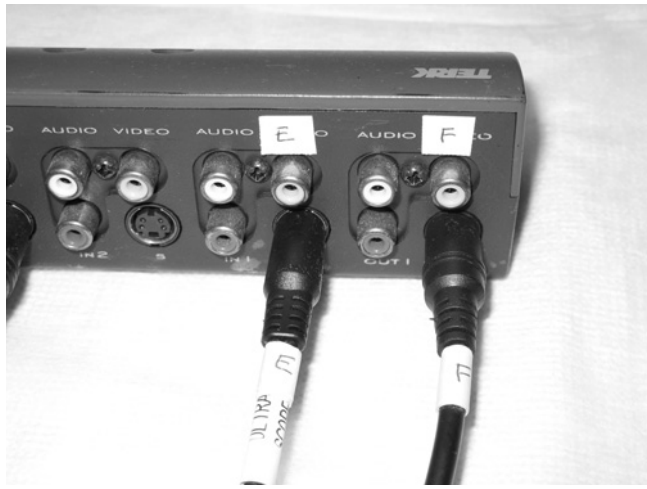

Figure 3.6 Keeping both wires and their receptacles clearly labeled helps ensure quick and accurate hook-ups after equipment is moved for room cleaning.

becomes more efficient as he can decide fairly quickly on his own that another FNA pass will be required, even before hearing it from the cytopathologist.

Like a home stereo system, the well-equipped EUS room may contain a complex network of wiring. As mentioned, the EUS processor and a microscope may both connect to the room's primary monitor. You may have a single printer connected to two different EUS processors. You'll be faced with even more wires if you have a device for recording video, such as a digital video recorder (DVR). Keep in mind these wires may be fragile and easily crushed under the wheels of heavy endoscopy carts. It is best to run wires along the wall, protected by conduits such as CordMate®, available at most home centers. In addition, as endoscopy rooms are cleaned regularly, cords may end up disconnected from equipment that needs to be rolled out of the way. It is therefore a good idea to clearly label both your wires and their intended receptacles, so endoscopy unit staff can reconnect all your equipment quickly and accurately (Figure 3.6).

EUS assistants

Like any complicated endoscopic procedure, EUS is best viewed as a team effort with the endosonographer providing clear, concise instructions to assistants who help complete the procedure

safely and efficiently. The endosonographer, for example, will be holding the echoendoscope during fine needle aspiration, relying on assistants to prepare the needle and syringe, remove the stylet when appropriate, collect the cytological material from the needle after the aspiration, and perhaps even help a cytopathologist prepare slides for preliminary review. This means additional efforts on your part to prepare endoscopy personnel for the tasks required during EUS. Some units may find it more efficient to train only a few nurses among a larger staff to assist with EUS, ensuring frequent exposure to the techniques used. This would be especially helpful if you will performing EUS infrequently. Otherwise, any individual nurse or assistant among a large group may not have sufficient practice to keep his or her skills honed. Many national and international EUS courses are held each year, and some of these have sessions devoted specifically to nursing roles. These courses often have a "hands on" component that enables nurses or other EUS assistants to practice using certain needles, and to handle echoendoscopes properly. Remember, unless you are going to prepare your own echoendoscopes for use, someone else will need to know how to affix a balloon to the tip and perhaps clear air bubbles from the balloon prior to use.

Beyond the specialized technical skills required of your EUS nurses, there are other patient care aspects that should be reviewed as you introduce EUS into your practice. EUS nurses should be aware that patients are often much more anxious about their EUS than standard endoscopic procedures. This is because many are aware of a newly diagnosed cancer or suspected cancer and know that the EUS will be providing information about that cancer's diagnosis and stage. Many patients have already had an endoscopy or colonoscopy that has led to the EUS, and therefore may have fewer concerns about the technical aspects about what they are about to undergo. Rather, they may be looking to the nurses for information about cancer management and prognosis, or just for someone to help them feel less frightened during a harrowing time. Likewise, as nurses complete the necessary intake questions, there are often anxious family members present who may have cancer-related questions and concerns. Nurses should be prepared for these issues, and have appropriate responses to questions that may arise. Nurses should also be reminded to check for latex allergies as the detachable balloons used on the tips of echoendoscopes are made of natural rubber latex and can result in severe allergic reactions in susceptible patients.

Other important members of the EUS team are those assistants who clean and process your equipment. The fragility of EUS instruments, especially catheter probes, must be stressed to ensure safe handling and maximum instrument life. These assistants must also know how to carefully remove balloons from the echoendoscope tip and about any cleaning steps that may be particular to your specialized instruments. At the same time, the endosonographer with back-to-back cases must also be attentive to turnover demands placed on these assistants by all physicians performing endoscopy simultaneously in a busy unit. It is helpful to communicate with endoscope reprocessing personnel when a particular instrument will be needed in short order. For example, if you know your next case will require the use of an instrument you just used, you should have a mechanism in place for moving that echoendoscope to the "head of the line" for cleaning.

Those persons who schedule your EUS cases should also be considered part of your team. EUS, particularly when done for cancer diagnosis or staging, should be scheduled in a timely manner. Patients and referring physicians should not wait more than a few weeks at most. Therefore schedulers need to know the importance of accommodating these cases. However, when fine needle aspiration or dilation may be part of the procedure, schedulers must pay careful attention to any anticoagulation issues, especially when cases are booked within only a few days of referral. For example, patients should have enough time to discontinue warfarin therapy if necessary. As many EUS referrals can come from outside your institution, your EUS schedulers may also be the ones who request and assemble pertinent patient information such as office notes and imaging reports from referring physicians. In this case schedulers will need guidance about what information, including copies of CT or MRI images, you require prior to the patient's EUS appointment. You may also want to establish guidelines about who can "direct book" an EUS with you, or what types of EUS procedure can be arranged without your prior consideration. For example, you may be comfortable with direct booking an EUS for anal sphincter evaluation in the setting of incontinence, but may want to personally review the case of someone referred for pancreatic head "fullness" on CT prior to scheduling an EUS.

A discussion of EUS assistants would not be complete without mention of our cytopathology colleagues. First, if you are purchasing a microscope, you may want to seek their advice about what to buy. In addition, if you want someone to help with onsite evaluation of fine needle aspiration samples, it is important to discuss this with your pathology department and find out exactly what services are possible [11]. For instance, your pathology department may make a cytopathology fellow available to assist with slide preparation and assessment for sample adequacy, but may not provide an attending cytopathologist for a preliminary interpretation of results during the procedure. Likewise, you must establish a system for notifying cytology personnel when their assistance will be needed. Some cytopathologists may want to be "booked" days in advance; others may be able to respond to a page shortly before your case begins. This will undoubtedly depend on specific factors within your institution and may require some negotiations on your part.

Cytopathologists interpreting EUS-FNA samples may not be accustomed to evaluating this type of material. If EUS is new to your institution, it is a good idea to make a formal presentation about EUS to your pathology colleagues. Without your clarification of the technical aspects of the procedure, they may not necessarily understand why columnar mucosa is present in your pancreatic aspirates or why squamous cells appear in your mediastinal lymph node aspirates. Review the special stains available to you such as when looking for glycogen-rich cells or mucin in pancreatic cyst aspirates. Your cytopathologists may also help

arrange for flow cytometry when aspirating lymph nodes suspected of involvement by non-Hodgkin lymphoma.

Conclusion

EUS is one of the most important advances in gastrointestinal endoscopy to date and often yields fascinating findings. But establishing an EUS practice requires careful decision making about what equipment to purchase, how to set up an endoscopy room for efficient EUS, and even how to assemble a specialized team to help perform safe and accurate procedures. Hopefully this chapter has provided some insight into that decision-making process. The instruments and accessories available for EUS may change from year to year, so this chapter should serve as a starting point, but not necessarily a comprehensive source. Other places to look for information about new EUS devices, techniques and technology include endoscopy-oriented journals, your local endoscope equipment vendors, and national and international endoscopy societies. The American Society for Gastrointestinal Endoscopy, for instance, has a special interest group devoted specifically to endoscopic ultrasound. Also, never be shy about asking colleagues in the field for advice. As you build or expand your EUS practice, it is attention to this initial foundation that will provide your biggest return on investment.

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4 EUS Procedure: Consent and Sedation

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There are specific issues related to potential complications and sedation with endoscopic ultrasound (EUS) and EUS-guided fine needle aspiration (EUS-FNA) compared to regular upper endoscopic procedures. This chapter will review the consent process and sedation involved with performing EUS.

Consent

The consent process is a continuum of the patient's understanding of the disease and pathological process that they have or are suspected of harboring. It is important that patients scheduled for an EUS examination understand the indications for the procedure and also be aware of the alternatives, if any exist. The possibility of complications and potential adverse outcomes needs to be discussed at the time of consent. Complications that are specific to or are more frequent with EUS will be discussed below.

Infection

There does not appear to be an increased risk of infection after EUS or EUS-FNA of solid upper gastrointestinal tract lesions when compared to regular diagnostic upper endoscopy. Three prospective studies to date addressing this issue have reported a 0% to 5.8% incidence of bacteremia after EUS-FNA; none of the patients with bacteremia had clinical signs of illness [1–3]. This is in comparison to bacteremia rates of 12% to 22% and up to 31% after esophageal dilation and esophageal variceal sclerotherapy, which are not associated with an increased risk of clinical infection in the absence of other risk factors [4–7].

Infection, bacteremia and sepsis after EUS-FNA of mediastinal and pancreatic cystic lesions have been reported in the literature [3,8–11]. Despite the administration of prophylactic antibiotics, a case of streptococcal sepsis was reported after EUS-FNA of a pancreatic cystadenoma, which resolved with additional antibiotic therapy [11]. Wildi et al. reported infection of a mediastinal cyst with beta-hemolytic *Streptococcus* C after EUS-FNA was performed without prior antibiotic administration; in contrast, infection was not reported in the three other patients in this series who received antibiotics prior to EUS-FNA of mediastinal cysts as well as after the procedure [8]. Candidal infection has also been described after EUS-FNA of a mediastinal foregut cyst [9].

No cases of infectious complications after EUS or EUS-FNA of the lower gastrointestinal tract have been reported in the literature to date. We have had experience with a febrile episode after FNA of a perirectal cyst, which resolved with 7 days of oral antibiotics.

The American Society of Gastrointestinal Endoscopy (ASGE) recommends the administration of prophylactic antibiotics prior to EUS-FNA of pancreatic cystic lesions, although there have been no randomized controlled trials that have supported this approach [12]. The recommended antibiotics for endocarditis prophylaxis in this setting are amoxicillin 2 g by mouth 1 hour prior to the procedure or ampicillin 2 g intravenously or intramuscularly within 30 minutes of the procedure. For penicillin-allergic patients, cephalexin or cefadroxil 2 g by mouth, azithromycin or clarithromycin 500 mg by mouth, or clindamycin 600 mg by mouth 1 hour prior to the procedure can be substituted. Clindamycin 600 mg intravenously, cefazolin 1 g intravenously or intramuscularly, or vancomycin 1 g intravenously within 30 minutes of the procedure can also be used. In a more recent summary statement, the ASGE suggests that antibiotic prophylaxis before EUS-FNA of mediastinal cysts is also warranted [13].

Bleeding

There have been few reports of bleeding after EUS-FNA. Mild intraluminal bleeding occurred in 4% of cases in one study and another reported a 1.3% rate of extraluminal bleeding after EUS-FNA of various lesions [14,15]. In both studies, no clinically significant symptoms were noted when bleeding occurred. However, serious intraluminal and extraluminal bleeding has been reported with one resulting death [16]. We tend not to perform EUS-FNA

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in patients with acute pancreatitis because there appears to be an increased risk of hemorrhage in this setting.

Perforation

There is limited data regarding perforation during EUS. Duodenal perforation has been reported in the literature and anecdotally in other instances [17]. It appears that distorted anatomy due to pancreaticobiliary malignancy or prior surgery may be predisposing factors. It has been suggested that partially inflating the balloon may facilitate passage of the echoendoscope and lessen the likelihood of perforation [18]. One retrospective analysis and one published survey reported a 0.03% to 0.07% rate of perforation during EUS [19,20]. Interestingly, it appears that perforation occurs prior to introduction of the echoendoscope into the esophagus and rarely within the gastrointestinal lumen proper. Based on these data, perforation appears to occur at a similar rate compared to upper endoscopy, which has a 0.03% perforation rate [21].

Esophageal dilation for facilitation of EUS evaluation

Compromise of the esophageal lumen from esophageal cancer may prevent advancement of the echoendoscope through the lesion into the stomach, which also precludes visualization of the celiac axis and distant lymph nodes. Early studies reported esophageal perforation rates of up to 24% with aggressive dilation of high-grade malignant strictures to allow passage of the echoendoscope [22,23]. However, more recent studies have shown that less aggressive dilation is safe and effective [24,25]. Pfau et al. reported no perforations after dilation of malignant esophageal strictures using three 1 mm sequentially larger balloon or Savary dilators above which resistance was first encountered; using this technique, the echoendoscope was able to cross the stricture in 85% of patients studied [24].

Pancreatitis

There is a risk of pancreatitis if EUS-FNA of the pancreas is performed. Scant data exists and almost all is retrospective, which most likely underestimates the overall risk. The rates of pancreatitis after pancreatic EUS-FNA have ranged from 0% to 2% [11,16,26–28]. In a recent survey of centers offering training in EUS, pancreatitis was reported in 0.29% of cases (range 0% to 2.35%) after EUS-FNA of solid pancreatic masses [29]. Anecdotally it appears that the risk is increased in those who have normal pancreatic tissue traversed to sample benign lesions or neuroendocrine tumors.

Bile peritonitis

Bile peritonitis is a rare complication of EUS-FNA, though it is difficult to confidently estimate its true incidence. It has been reported in case series after inadvertent perforation of the common bile duct after EUS-FNA of a pancreatic head mass or after puncture of the gallbladder in an attempt to identify patients with microlithiasis [30,31]. However, a small study reported no complications after EUS-FNA of gallbladder masses [32].

Specific issues related to celiac plexus neurolysis

Celiac plexus neurolysis (CPN) can be performed for palliation of pain in pancreatic cancer patients by injecting absolute alcohol and a local anesthetic through an FNA needle under EUS guidance. Percutaneous and surgical CPN for pain control have been associated with serious complications such as lower extremity weakness, paresthesia and paraplegia [33,34]. One prospective study in patients with inoperable pancreatic cancer undergoing transgastric EUS-guided CPN reported minor complications such as postural hypotension (20%), diarrhea (17%) and exacerbation of pain (9%) [35]. Intravenous volume loading and pharmacological therapy appear to decrease the incidence.

Sedation

Sedation plays an important role in the performance of EUS, as it does in regular endoscopic procedures. The possible adverse effects of sedation need to be discussed with the patient at the time of consent, since this accounts for nearly half of all endoscopic complications [36].

The most commonly used sedatives for EUS are a benzodiazepine with or without an opiate, which constitutes moderate sedation. Adjunctive medications such as diphenhydramine, droperidol, ketamine and promethazine have also been utilized. More recently, propofol has also been used for deep sedation during EUS. Regardless of what type of sedation is used, a greater amount of medication may be required for EUS due to the often increased length of the procedure.

Preprocedure assessment

The goal of the preprocedure assessment is to identify aspects of the patient's medical history and physical examination that could have a deleterious impact on the outcome after administering sedation. The presence of conditions such as neurological disorders and cardiopulmonary diseases including sleep apnea, chronic obstructive pulmonary disease or coronary artery disease should be noted as part of this assessment. Prior adverse reactions to anesthesia, medication allergies, and a history of drug or alcohol abuse should also be ascertained. In addition, each patient should be risk stratified based on the American Society of Anesthesiologists (ASA) physical status classification system. Consideration should be made for employing anesthesia assistance in sedating ASA class IV or V patients, those who have previously failed conscious sedation, or patients who have had an adverse reaction to sedation.

Benzodiazepines

Benzodiazepines bind to the gamma-aminobutyric acid ($GABA_A$) receptor within the cerebral cortex. They have several pharmacological effects, including sedation, amnesia and anxiolysis. Side effects of benzodiazepines are generally dose dependent and include respiratory depression and hypopnea that may lead to apnea and hypoxia, hypotension and paradoxical reactions such as agitation.

Midazolam is the currently the preferred benzodiazepine for sedation during endoscopic procedures because of its short onset and duration of action. It undergoes both hepatic and renal metabolism. The typical starting dose is 1 mg intravenously over 1 to 2 minutes. Additional doses of 1 to 2 mg can be given every 2 minutes until adequate sedation is achieved. Lower doses of midazolam may be necessary with concurrent opioid use due to the synergistic interaction between both medications.

Diazepam, which is available in intravenous and oral forms, undergoes hepatic metabolism to a metabolite with slow clearance. This accounts for its longer duration of effect compared to midazolam. The initial dose is 5 to 10 mg given over 1 minute. Additional doses can be given at 5-minute intervals. Injection site discomfort is common after intravenous diazepam administration; this along with its slower onset of action and longer duration of effect makes it less preferable when compared to midazolam.

Flumazenil, a $GABA_A$ receptor blocker, reverses the central effects of benzodiazepines and should be used in cases of oversedation. It is less effective in reversing benzodiazepine-induced respiratory depression. Flumazenil is effective when administered as incremental intravenous boluses of 0.1 to 0.3 mg, but can also be given as an infusion of 0.3 to 0.5 mg per hour if prolonged usage is anticipated. The occurence of resedation should be carefully looked for, since the duration of the effects of midazolam may be longer than that of flumazenil, which has a half-life of approximately 1 hour.

Opiates

Meperidine and fentanyl are the most commonly used opioids for endoscopic procedures. Both bind to opioid receptors in the central nervous system, thereby altering pain perception. Both opiates can lead to sedation and respiratory depression if given in larger amounts.

Meperidine is an opioid that is converted by the liver to normeperidine, a metabolite that is several times more potent. Meperidine has an onset of action of 3 to 6 minutes and is administered in doses of 25 to 50 mg slowly over 1 to 2 minutes. The combination of meperidine and monoamine oxidase inhibitors should be avoided due to the increased risk of developing serotonin syndrome, which can manifest as mental status changes, autonomic instability and neuromuscular hyperactivity. Meperidine should also be prescribed with caution in patients with renal insufficiency due to the accumulation of metabolites that are associated with seizures.

Fentanyl is an entirely synthetic opioid that is structurally similar to meperidine. Allergic reactions and cross-reactivity with reactions to the other opiates should not occur. The initial dose given for endoscopic procedures is 50 to 100 μg; supplemental doses of 25 μg can be given every 2 to 5 minutes until the desired effect is achieved. Large doses of fentanyl have been reported to cause chest wall rigidity from skeletal muscle hypertonicity. Fentanyl is considered the preferred opiate for conscious sedation, given its rapid onset of action and lack of potential for development of toxic metabolites.

Naloxone is an opioid antagonist that can be given to reverse the central nervous system effects of opiate overdose, including respiratory depression and analgesia. It has an onset of action in 1 to 2 minutes and a half-life of 30 to 45 minutes. The recommended dose of naloxone is 0.2 mg to 0.4 mg intravenously every 2 to 3 minutes as needed. Additional doses may be necessary since both meperidine and fentanyl have a longer half-life than does naloxone.

Adjuncts to benzodiazepines and opiates

Several agents have been studied to potentiate the effects of benzodiazepines and opiates. Diphenhydramine, a histamine-1 antagonist, has central nervous system depressive effects at higher doses, theoretically making it a useful adjunct to benzodiazepines and opiates. Although it has not been formally studied in the setting of EUS, one trial using 50 mg of diphenhydramine intravenously or placebo in addition to midazolam and meperidine for colonoscopy showed improved patient sedation and amnesia in the diphenhydramine group [37].

Droperidol is a butyrophenone neuroleptic with antiemetic and anti-anxiety effects that can be used for conscious sedation in addition to benzodiazepines and opioids. It has been shown to be a useful adjunct in difficult-to-sedate patients [38]. However, its use has been tempered more recently by reports of cardiac events, specifically QT prolongation and torsades de pointes [39].

Ketamine is a phencyclidine derivative that inhibits the N-methyl D-aspartate (NMDA) receptor. It possesses both analgesic and sedative properties and generally does not result in cardiovascular or respiratory depression. Ketamine has a very short onset of action of less than 1 minute and short duration of action of 15 to 30 minutes [40]. A dose-dependent stimulation of the sympathetic nervous system manifesting as elevated heart rate and blood pressure is seen with ketamine. An emergence reaction, consisting of dreams, hallucinations and delirium, can occur in adults. The use of ketamine in adults is limited and most studies using this agent for endoscopic sedation have been in the pediatric population.

Promethazine is a phenothiazine that is often used for its antiemetic effects. It has α-adrenergic inhibitory effects and competitively inhibits the histamine-1 receptor. Promethazine has been studied to a limited extent as a possible adjunct for sedation in endoscopic procedures [41]. Its onset of action is typically around 5 minutes and has as half-life of 9 to 16 hours. The typical dose given is 12.5 to 25 mg intravenously. Side effects with promethazine include hypotension, respiratory depression, neuroleptic malignant syndrome and extrapyramidal effects.

Propofol

There has been increased interest recently in the use of propofol, an ultrashort-acting hypnotic and amnestic agent with minimal analgesic properties. Although published studies in the use of propofol for standard upper and lower endoscopic procedures have not consistently demonstrated clinical benefits, propofol has been shown to be beneficial in prolonged procedures such as endoscopic retrograde cholangiopancreatography or EUS. One study that included

patients undergoing EUS found that, compared to midazolam and meperidine, patients who received propofol had significantly shorter recovery times and good quality of sedation [42].

Procedural monitoring

All patients receiving sedation for EUS must have monitoring of vital signs throughout the procedure. Blood pressure, oxygen saturation, pulse and respiratory rate should be followed during the procedure and recovery period. Capnography, used to monitor end tidal carbon dioxide, can be employed as a superior way of evaluating respiration, although improved outcomes with its routine use have not yet been reported. Bispectral index monitoring, which quantifies the depth of sedation by measuring electroencephalographic waveforms, has been used in some centers but does not appear to correlate well with mixed analgesic and sedative regimens.

Post-procedural monitoring

Sedated patients need to be observed after the EUS for adverse effects from the sedation or the procedure itself. Blood pressure, oxygenation, pain and level of consciousness need to be assessed at regular intervals during the recovery period. Patients receiving naloxone or flumazenil should be monitored for an extended period in the event that resedation develops, since the half-life of these reversal agents is shorter than opioids and benzodiazepines. Several systems have been described to assess the patient's suitability for discharge. One example is the Aldrete scoring system, which evaluates the patient's activity, respiration, oxygen saturation, blood pressure and level of consciousness [43]. Patients should be instructed not to drive, operate heavy machinery or sign important documents.

Conclusions

The use of FNA and injection techniques has expanded the armamentarium of diagnostic and therapeutic EUS. As a result, the role of EUS has expanded for both gastrointestinal and non-gastrointestinal disease processes. The consent for EUS is a multistep process, similar in nature to that of other endoscopic procedures, with FNA and therapeutic EUS potentially carrying additional risks to the patient. FNA may increase the risk of bleeding, infection and pancreatitis, and when the performance of injection therapy or drainage procedures are anticipated, there are specific additional risks that merit discussion with the patient before the procedure.

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5 The EUS Report

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Reports form the essential link in medical practice. They are used by healthcare providers as a tool to convey patient information. Clear and accurate reporting is essential for providing appropriate care and minimizing medico-legal risk. A report is considered a document: "*an original or official paper relied on as the basis, proof, or support of something*" [1] used to report: "*to give a formal or official account or statement of; to return or present a matter referred for consideration with conclusions or recommendation*" [1]. While these terms and the intent of the report are clear, they are often overlooked, rendering reports inadequate in terms of clarity, detail or completeness. Professional societies are recognizing the increasing importance of establishing minimal reporting standards including the American Society for Gastrointestinal Endoscopy (ASGE), which published their recommendations for the minimal elements that an endoscopy report should include (Table 5.1). While alternate versions exist, most follow a similar structure that conveys the same general information.

Table 5.1 ASGE recommendations for elements of an endoscopy report. Reproduced from Ref. 2 with permission

1. Date of procedure
2. Patient identification data
3. Endoscopist(s)
4. Assistant(s)
5. Documentation of relevant patient history and physical examination
6. Indication of informed consent
7. Endoscopic procedure
8. Indication(s)
9. Types of endoscopic instrument
10. Medication (anesthesia, analgesia, sedation)
11. Anatomic extent of examination
12. Limitation(s) of examination
13. Tissue or fluid samples obtained
14. Findings
15. Diagnostic impression
16. Results of therapeutic intervention (if any)
17. Complications (if any)
18. Disposition
19. Recommendations for subsequent care

Roles of the endoscopic report

While the main function of the report is to serve as a clinical decision-making tool, it plays other roles in healthcare. This document is often used to assess quality control efforts, to facilitate clinical research, and for administrative and legal purposes. Accordingly, various aspects of the report have different significance depending on the particular interest of the reviewer.

Clinical care

When considering which details to include in an EUS report, one must be mindful of the medical specialists and subspecialists who are likely to participate in the patient's care. While certain information is germane to all providers, there are specific details that may have variable importance depending on one's area of expertise; whether primary care physician, gastroenterologist, surgeon or oncologist.

Quality control

Quality is measured in a number of ways. Patient-derived measures include: quality of life, cost-effectiveness, patient satisfaction, morbidity and mortality. Some of these data are derived directly from the information contained in reports and related databases. In this setting, details pertaining to outcomes, such as procedure-related morbidity, might be more important than patient demographics or findings. Specific quality indicators for EUS have been established and rely heavily on proper reporting. Procedure findings that are used as quality indicators vary based on the specific context and goals of the examination; for instance identification of key structures such as celiac lymph nodes during esophageal cancer staging [2].

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Clinical research

Clinical research largely depends on information contained within reports. Accurate and detailed reporting is necessary, but demands additional time and dedication on the part of the person completing the report. Prospectively conducted studies allow for complete and accurate reporting and avoid the need for subjective interpretation of findings. For example, when reporting the T stage for an esophageal cancer, one may cite uncertainty whether the tumor is T2 or T3 and make no clear designation. As such, retrospectively collected data from established databases may be incomplete or inaccurate. Prospective study and reporting usually requires specific designation of the T stage, thereby facilitating data retrieval. In essence, information obtained from a database is only as good as the information contained in the reports.

Administrative and legal issues

Administrative and management decisions are frequently guided by data derived from reports. Among other activities, patient, personnel and procedure scheduling as well as supply purchasing and planned instrument repairs are impacted by key elements in the report. Patient demographics, instruments used, and procedure type and duration are only a few of the features that are considered in this regard.

From a legal perspective, a detailed and comprehensive procedure report is a vital risk management tool that may be used to defend or prosecute a malpractice suit. The legal system takes the stance that "If it isn't documented it didn't happen" and "If it is documented then it must have happened." Detailed, precise, and accurate reporting is necessary to document the finding and events and to avoid misrepresentation. It is imperative that the report not be modified, whether written or dictated, unless typing or clerical errors are noted. Reporting software should stamp the date and time the report is initially prepared, edited and signed.

Evolution of the medical report

Medical reports, including endoscopic reports, have evolved from a somewhat anecdotal account of events to an objective set of data. Handwritten reports have given way to dictated notes and, more recently, to computer software-generated electronic reports. However, as recently as 1999, a survey discovered that 80% of gastroenterologists in the United States were still using handwritten or dictated reports [3]. In 2001, an international survey of distinguished endoscopists from Latin America, the Middle East, Asia, Africa and Europe found that most still write or dictate reports, or utilize custom software adapted from commercial databases (e.g. Excel or Access) and maintain their data in local databases [4].

Standard terminology and structured reporting

Radiologists and pathologists were pioneers in the use of standardized terminology and structured reporting. SNOMED® (Systematized Nomenclature of Medicine) is one such system that is used worldwide in a variety of settings including language associated with Health Level 7 (HL7) and DICOM (Digital Imaging and Communications in Medicine) standards commonly used in gastroenterology. Currently, this system provides insufficient detail to be used for EUS reporting.

The first dedicated effort to design a universally accepted language for gastrointestinal endoscopy emerged from Europe in 1989 and was published as the OMED (Organization Mundial D'Endoscopie Digestif) terminology [5]. Their idea was to create a widely accepted list of terms having broad applicability in reporting the majority (present in $\geqslant 1\%$ of endoscopic examinations). Terminology was arranged in hierarchical order: headings, terms, attributes, values and sites. Preliminary use of the OMED system showed that it applied to 95% of routine upper endoscopies, colonoscopies and cholangiopancreatographies [6]. In a retrospective analysis of $>10{,}000$ cases from six European centers, this system accurately described 87% of procedure indications, 94% of findings and 91% of diagnoses [7]. The remaining findings required use of free text. After further revision, the Minimal Standard Terminology (MST) system was validated [8] but, despite some use in Europe, it has not gained wide acceptance in the United States. However, newer software systems are using modifications of MST including one recently validated for use with capsule endoscopy.

Standard terminology in endosonography

Most of the findings and descriptors associated with EUS differ from the ones used in other endoscopic procedures. Therefore, a similar effort to introduce MST for EUS (MST EUS Version 1.0) was initiated in 1997 by a panel of expert endosonographers from Europe, Japan and the United States [9] met. Their first step was to identify widely accepted terms that allow accurate description of most EUS examinations. This was achieved by reviewing 350 EUS reports from the Medical University of South Carolina. A goal was to avoid excessive detail and seldom used terms. The EUS MST was divided based on reasons for performing EUS (with qualifiers), equipment, EUS anatomic terms (with modifiers), findings (with attributes and attribute value options), interventions and diagnoses (with qualifiers). After several reiterations, the EUS MST was published as part of the OMED terminology. Although development of this system was an important initial step, use has been modest. Within the upcoming year, the OMED terminology is scheduled for review and modification (L. Aabakken-personal communication).

Structured reporting

Although use of structured reporting may limit expressivity, it offers advantages over free text by reducing error, suppressing duplication and minimizing oversight. In addition, structured reporting along with use of MST forms the skeleton for automation of electronic reports. Other potential advantages of structured reporting include speed and completeness in reporting.

Speed

Structured reports can often be completed more quickly than dictated or transcribed notes. In one study [10], while ~30% of routine upper endoscopies were normal allowing use of the phrase "normal findings," only ~10% required extensive and detailed reporting. The remaining ~60% of reports could be completed with structured reporting. It is likely that the percentage of normal or negative EUS examinations is much lower since most are performed to assess known pathology.

However, faster reporting may not always be realized when using systems that incorporate too many variables and choices, which can lead to confusion and becoming lost within the network of options. Similarly, delays may occur when attempting to locate a variable within the MST framework because of the lack of similarity or accuracy for describing the finding. Furthermore, dissimilarity between the sequence of data acquisition and data entry may slow reporting and lead to inaccuracy.

Completeness through memory recall

When structured systems are used for reporting, a reminder effect has been noted. Studies show that use of electronic reporting software leads to more complete and accurate reporting. In contrast, studies comparing free text to a desired list of reported items have commonly found relevant information to be missing. In a series of colonoscopies performed in patients with ulcerative colitis, important details were absent in the majority of reports and individual endoscopic signs of inflammation were mentioned in only 27% to 77% of reports [11].

Acceptance of MST systems requires a careful balance of sufficient structure and function to allow thorough and accurate reporting, while not providing so many as to slow the process and to restrict effective expression of findings. Limitations of restrictive formats may be partially overcome by allowing use of free text entry.

Free text and conventional reports

Reporting is optimized by systems that allow addition of free text to explain terms or items that are vague or insufficiently detailed. However, when used for clinical (and other scientific) purposes it is often inadequate. Terms such as: "likely," "possible" and "probable" have different meanings and carry different weight for patients and physicians [12,13]. Other limitations of free text include omission of findings, redundancy and use of different styles and terminology for expressing the same finding. For instance, review of chest radiography reports in 8426 Medicare patients with cardiac disease found as many as 23 terms to report a single finding [14]. One can only speculate about the finding of a similar study reviewing EUS reports. In addition, free text does not lend itself to systematic computer searches, thereby hampering research efforts. Finally, use of conventional reporting requires transcription that is associated with additional cost, delays in report availability, and reporting inaccuracy due to errors of communication and typing. A study of 4871 radiology reports from the Brigham and Women's Hospital found that 33.8% of reports required editing by the radiologists and nearly 6% were substantive leading to unnecessary treatment or testing [15]. Optimized free text capability also requires sufficient space, copy and paste text capability, and ability to customize text features including font size, type and color.

Databases

One of the most important advantages of electronic versus handwritten or dictated reports is the ability to construct databases. A database is defined as: "*a usually large collection of data, organized especially for rapid search and retrieval*" [1]. Database construction requires use of a common language and "structured reporting" using fields distinguished by clear headings with pulldown menus that incorporate preset terms derived from a standard language. Data are incorporated and organized by several models including *hierarchical, network* and *relational* models [16]. The most suitable structure depends on the application, transaction rate, number of inquiries made, and advantages and limitations unique to each model.

Hierarchical

With this model data are entered into a network or tree (parent) with main branches that give rise to smaller branches (children) and so forth. Data entry must follow a strict order requiring all information within a given branch to be entered before inserting data into a parallel branch. Use is limited by the difficulty in adding new terms and in searching for information located "deep" into or within a distal branch. This model was often used by older databases.

Relational

In this model, each term or attribute is chosen from a list that is independent of prior and subsequent lists. Advantages include the ease of adding new terms, and enhanced search function at all levels of data entry. This is the most common design used currently in most commercially available databases. In gastrointestinal endoscopy, the CORI (Clinical Outcomes Research Initiative) database is an excellent example. Now in its version 3.2 and soon to follow version 4, the CORI project began in 1995 under the auspices of the ASGE as the National Endoscopy Database. In 2005, the repository was receiving 21,000 reports monthly from 107 practice sites and more than 750 physicians in the United States [17]. More than one and a half million reports exist in the database, including EUS procedures (Judith Logan MD, personal communication).

Network

Whereas hierarchical models structure data as a tree of records, with each record having one parent record and many children, the network model allows each record to have multiple parent

and child records, forming a lattice structure. This structure facilitates rapid simultaneous data retrieval. This model can be useful when input comes from different sources to form one body, such as the final report. However, this model lacks flexibility and is no longer employed in medical record keeping.

Commercial software for EUS reporting

There are a few practical points to consider when purchasing a commercial software product. A list of the websites of some of the commercial software companies that offer EUS reporting capabilities is provided (Table 5.2). When selecting software, the needs of a particular EUS department should be identified (administrative, research, clinical) as well as the interface potential and available budget. Most hospital-based information management systems (administrative, billing) are HL-7 (health level 7) standard compatible. Automatic labeling of CPT codes is a possibility that should be sought, as is ICD-9 coding. Some also provide for coding using SNOMED. Minimal hardware requirements should be clear, although most current commercial software products can be used with the average personal computer and are compatible with Windows 98 or higher.

It is important to know whether the report format can be customized and to what degree. For instance, does the system allow modification, addition and deletion of fields and/or terms within a specified field? Use is greatly aided by the ability to insert free text. Use of the database for research purposes requires search capabilities using any of the terms and fields. Some provision for secure access should also be available and the software should be HIPAA compliant.

Depending on preference or institutional practice, images can be incorporated within the report. One should verify compatible formats and number of images that can be added. The method of doing this is also important, as a simple cut-and-paste option works best, but is not always available. Commonly used image formats include .jpg and .tif. Although some support the addition of video clips this feature is not essential. Other nonessential features include bar code reading and voice recognition capabilities. Instrument tracking, automated coding and billing are other features that are available. Finally, software products should be scalable to meet growth demands as EUS volumes increase.

Table 5.2 List of commercially available software for endoscopic reporting

www.endosoft.com
www.pentaxmedical.com
www.gmed.com
www.meditrac.com
www.endoworks.com
www.provationmedical.com
www.md-reports.com
www.cori.org

The EUS report

No universally accepted set of criteria has been published concerning essential data or findings that should be included in an EUS report. In the absence of a consensus, we offer opinion regarding the key elements that most EUS reports should contain. Our recommendations are not intended to represent a formal mandate of what the EUS report should include. This may instead serve as a template for one's practice with modifications based on the procedure indications and goals. Similarly, the extent, detail and granularity of EUS reports should be tailored to a particular practice setting. Although certain information should be standard in all settings, specific details may have lesser or greater importance based on clinical and research activities within a particular center.

In addition, our recommendations do not address which procedures or techniques should be employed at the time of EUS. Instead, we offer opinion as to the need to document the various findings, procedures and techniques when performed. The same is true when findings or procedures are not performed, which is relevant, because omission of a particular finding may indicate that the finding was not present or that no effort was made to search for this finding.

Non-EUS information

Key non-EUS information should be documented in most patients undergoing EUS that may appear in the referring physician, nurse, cytopathology or EUS report. The information includes relevant personal history, physical examination findings, names of healthcare providers participating in the procedure, and verification that informed consent has been obtained. An increasing number of centers are performing a "pre-procedure pause" for the purpose of verifying the correct patient, procedure site, and procedure intent and goals. This process should be documented.

The procedure date, time and location, as well as patient identifying information such as name and medical record number, should be specified. It may be necessary to substitute a de-identifying code in place of the patient's name in order to comply with HIPAA regulations. The report should include the title and IRB number of EUS studies that the patient is participating in. It is important to clearly and accurately list the primary and secondary procedure indications in order to provide a framework that the examination should logically follow, set the key elements that the report should contain, and facilitate data retrieval for research and administrative purposes.

The names and dosages of all medications administered should be specified including those employed for inducing and reversing sedation, inhibiting motility, and as part of EUS guided therapy. It often helps to document patient tolerance along with advice regarding the need of anesthesia support during subsequent examinations. The report should include information regarding prophylactic administration of oxygen and flow rate versus use following desaturation. Vital signs must be recorded during and following the procedure. As appropriate, the physician

should convey to the staff and document the need for prolonged post-procedure observation (e.g. following celiac plexus neurolysis), guidelines for patient discharge whenever they differ from standard practice, instructions for dietary restriction, and patient education regarding alarm symptoms and measures to take in the event of their occurrence.

General EUS information

It is important to list all EUS equipment used (radial, linear, probes) and their serial numbers. We also recommend that the findings for each instrument be noted separately, given the various advantages and limitations of each instrument. This provides greater perspective in terms of the findings, complications, and in guiding instrument selection for future examinations.

While the technique of performing EUS varies, most recommend that a structured and uniform approach be adopted in order to assure a complete and thorough examination. The same is true when documenting EUS findings. We suggest describing pertinent positive, negative and incidental findings. Key elements of the report are likely to evolve over time based on future research (e.g. whether one should report an esophageal tumor as T3 or to specify "superficial" versus "deep" T3 as emerging data suggest a difference in prognosis and outcomes) [18].

It is important to note the precise location of all pathology as well as the anatomic extent of the examination. This can be achieved by relating the findings to key anatomic landmarks (for example, stating that a 6.0 × 5.0 mm pancreatic islet cell tumor is located in the caudal aspect of the pancreatic neck 1.0 cm from portal vein confluence). This level of detail is necessary to guide screening and plan therapeutic intervention. One should also note factors that limited the completeness of the examination including retained gastric contents, an obstructing tumor, presence of a stent, air and/or shadowing stones within the bile duct or gallbladder, inadequate sedation, or poor colon preparation, etc. Incomplete examination may result in failure to identify pathology, reduce staging accuracy, and impact billing and reimbursement.

EUS interventions (diagnostic and therapeutic)

Whenever tissue sampling is performed via fine needle aspiration (FNA) or Trucut biopsy (TCB) one should note the site, number of passes and needle gauge. Although we discourage obtaining biopsies that require traversal of the primary luminal cancer, this should be noted when doing so. Reasons for failed or difficult tissue sampling should be noted. When performing therapeutic interventions it is important to indicate the instruments and accessories used and to outline key technical aspects of the procedure. Other pertinent information varies based on the specific procedure, but may include the medications administered as a part of EUS therapy along with the dose and route of injection. The specific site of intervention and short-term effect should also be noted.

Complications

It is important to carefully document all complications and to specify whether they developed secondary to sedation, during routine imaging, or as a result of therapeutic intervention. Include details regarding intra-procedural monitoring and efforts to manage complications. Consider providing initial guidance to those reading the note as to the suggested post-procedure management, although most aspects of patient care following a complication will be conveyed within the hospital chart and through immediate and direct physician communication.

Procedure summary

It is important to summarize the findings, to provide perspective as to the significance, and to suggest a differential diagnosis. Some measure of certainty or confidence in one's findings is often helpful. In addition, the need and a suggested approach for further evaluation, monitoring and/or therapeutic management, based on information acquired during the EUS examination, may assist referring and consulting physicians. This should be done in a general and qualified manner so as not to force or mandate a particular course of action with potential legal implications when suggestions are not acted on. The report should state which medications to administer (e.g. antibiotics following cyst aspiration) after the procedure with suggestions regarding the specific antibiotic, dose and duration of therapy. The need and timing for resumption of long-term medications, such as anticoagulants, should also be addressed. When these issues are handled by the endosonographer, then the report may serve as a means of documenting your care, rather than as a means of suggesting a course of action to other physicians.

Disease-specific information

Luminal cancer (esophageal, gastric, rectal)

An upper endoscopy or flexible sigmoidoscopy is usually performed to asses the tumor site, traversibility and need to dilate, and to acquire mucosal biopsies. The proximal and distal tumor extent should be measured relative to landmarks including the incisors and gastroesophageal junction for esophageal and gastric cancer, versus the anal verge for rectal cancer. The report should include details concerning dilatation, when performed, and number and sites of mucosal biopsies. The morphology (exophytic, ulcerated or sessile) and degree of circumferential involvement should be reported. The presence or absence of a hiatal hernia, Barrett's esophagus and esophagitis should be mentioned for patients with esophageal or gastric cancer. Tumor mobility (fixed or tethered) should be noted for rectal cancers.

Current treatment protocols are guided by TNM staging as part of the American Joint Committee on Cancer staging criteria. A primary aim of EUS is to establish the tumor (T) stage, nodal (N) stage, and when possible to detect metastasis (M stage). The specific T stage should be noted, and for patients with a T4 tumor, the report should specify which tissue is infiltrated that signifies this advanced stage. Consider recording the greatest depth of primary tumor extension as this finding roughly correlates with T stage. One should indicate whether the N stage was determined by imaging characteristic alone or by onsite FNA results. It is necessary to document the exact location

of nodal metastasis given the impact on prognosis and therapy. For example, one should separately note the presence of celiac, perigastric and mediastinal lymphadenopathy for patients with esophageal cancer [19]. Similarly, in patients with rectal cancer, it is important to distinguish iliac nodes (M1) from rectal nodes (N1) [20]. Consider listing each nodal feature (size, echodensity, shape and border). The site of distant (M stage) metastasis when present should be reported, including the sites examined to make this determination. Mention of ascites, omental thickening, and/or a pleural effusion should be included. In addition, one should specify whether the EUS is performed at the time of initial diagnosis, after chemoradiation, or to evaluate recurrent disease.

Subepithelial lesions

Findings of initial endoscopy that should be included in the EUS report include the lesion site, size, color, presence of a pillow sign, and whether the lesion is mobile or fixed. The aim of EUS is to characterize the lesion and often to obtain a tissue diagnosis. Since a tentative diagnosis is based on the layer of origin, this is essential information to include. Other important features include lesion size, echogenicity, homogeneity, presence or absence of calcification, cystic spaces, necrosis, and border appearance. Some of these features have been variably mentioned as predictors of malignancy for certain types of subepithelial lesions [21]. Similarly, the presence or absence of direct infiltration of surrounding structures and malignant lymphadenopathy should be reported. Presence of internal blood vessels or proximity to the papilla and other key structures should be noted as these features may influence the surgical approach.

Solid pancreatic tumor

Endoscopic evidence of tumor infiltration into the duodenum, papilla or stomach should be reported as should presence of an obstructing mass. The role of EUS in this context is to identify or exclude the presence of a suspected mass not otherwise seen, establish resectability, and often to obtain a tissue diagnosis. The report should describe the primary lesion in terms of the echodensity, homogeneity, border features, presence of cystic spaces and the number of lesions as these features often correlate with the underlying pathology.

As for luminal cancer, current treatment protocols for patients with pancreatic cancer are guided by the TNM stage. T4 tumors are considered locally unresectable via involvement of major vascular structures such as the celiac trunk, hepatic artery and/or superior mesenteric artery. Involvement of these vessels should be noted in the EUS report. Additionally, while T1 to T3 tumors are generally deemed resectable, patients with significant involvement of the portal and/or superior mesenteric vein are often not taken to surgery. Therefore, the report should indicate the perceived extent of involvement. Use of terms and criteria, such as infiltration, abutment, invasion, percent encasement, length of involvement, tumor thrombus, and presence of collateral vessels varies among centers. However, their use is encouraged, as appropriate, even though they have only moderate sensitivity and specificity and interobserver variability [22].

Although tumor size influences T stage (T1 $\leqslant$ 2 cm vs. T2 $>$ 2.0 cm), distinction of T1 and T2 does not influence therapy. Omental thickening and ascites should be reported as these findings may suggest omental seeding. While the presence of regional nodes does not alter therapy, distant lymphadenopathy and evidence of metastatic disease (M1) should be reported along with the specific site(s). Findings suggestive of acute and/or chronic pancreatitis should be noted as their presence may explain the failure to discern an underlying malignancy, and impact the timing of repeat imaging. In addition, consider reporting additional information such as bile duct caliber, presence of sludge or stones, and post-obstructive pancreatic features.

Pancreatic cystic lesions

The goals of EUS in this context are to further characterize the cystic lesion(s), in order to narrow the differential, and to search for malignant transformation. The EUS report should describe the appearance of the papilla and specify the location, number and size of the cysts. The report should also mention the presence or absence of internal echogenic material, a wall (presence, thickness, regularity), septations (presence, thickness, regularity), a focal solid component or evidence of local invasion. The report should note whether the cyst communicates, abuts and/or deforms the pancreatic duct, as well as characterize the main pancreatic duct. The presence of an associated solid pancreatic mass or chronic pancreatitis should be reported. For patients with a large and complex cyst, it is important to note each feature for the cyst as a whole as well as the smaller cystic components.

Details of cyst fluid aspiration should include the needle used, fluid appearance, viscosity, volume and completeness of aspiration, and string sign results. One should also indicate which tests were ordered for cystic fluid analysis, such as carcinoembryonic antigen, amylase, cytology, etc. The report should specify the desired sequence of testing based on perceived priority and volume aspirated. The antibiotic, dose and route of administration should be included as well as the need for therapy following the examination.

Pancreatitis

While pancreatitis is typically thought of as acute (AP), acute recurrent (ARP), chronic (CP), or autoimmune (AIP), there is frequent overlap of clinical and imaging findings. For the purpose of the EUS note they are considered together, since we favor reporting each feature regardless of the presumed "state" of pancreatitis. The presence and location of all established ductal and parenchymal features that suggest chronic pancreatitis should each be specified individually. Also, for the benefit of those reading the report, in particular non-gastroenterologists, we suggest an interpretive comment as some may mistake the presence of any feature as diagnostic of chronic pancreatitis. In addition, findings that suggest pancreatic or peri-pancreatic acute inflammation should be reported. Finally, EUS findings that may

suggest the underlying pathology or an alternate diagnosis should be recorded including evidence of microlithiasis, bile duct stones, pancreas divisum, anomalous pancreatobiliary junction, or a benign or malignant tumor.

Summary

Key elements to include within an EUS report vary based on many factors including the procedure indications and goals and the particular practice setting. However, there is increasing recognition as to the importance of providing clarity, detail and completeness in reporting. While our suggested minimal criteria may not be ideal for all settings, they can serve as a template for one's practice with modifications as needed.

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6 Radial EUS: Normal Anatomy

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Introduction

Radial endoscopic ultrasound (EUS) is one of two basic methods for studying the gastrointestinal tract, including staging gastrointestinal cancers. Radial EUS scopes use a 360-degree ultrasound probe at the tip of an endoscope to image wall lesions and organs adjacent to the gastrointestinal tract. Images are displayed in a cross-sectional orientation in a circle perpendicular to the axis of the endoscope tip. The quality of the radial EUS images has improved over the years with the advent of newer processors and particularly with electronic solid state transducers. Radial EUS remains a very important in staging gastrointestinal cancers. However, The only major limitation of radial endosonoscopes is the inability to guide fine needle aspirations and other therapeutic procedures.

From a technical standpoint, the oblique viewing radial echoendoscope is handled in a similar manner to the side-viewing scope. Unlike the situation with transabdominal ultrasound, the exact position of the transducer remains relatively unknown due to the constant mobility of the gut wall by peristalsis or respiratory motion. Thus, it remains of paramount importance to the EUS learner to be familiar with the normal endosonographic views of the different organs from different viewing "windows." There is an infinite number of potential windows based on the location of the transducer, the location of the scope within the gastrointestinal tract and the angle/distance from the gut wall. To facilitate learning, it is very helpful to perform the examination systematically each time to provide a complete and reliable evaluation of each organ. The "station" technique will be discussed in this context. Each station has a standard starting point and set of conventional landmarks which are used to locate and interpret pathological findings while reducing operator dependent error to a minimum. The same techniques can generally be applied to radial or linear echoendoscopes; the only difference being the orientation of the image.

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In this chapter, we suggest a detailed station approach to EUS examination. The areas to be discussed in detail include:

1. Normal gastric and esophageal wall layers
2. Mediastinum
3. Pancreaticobiliary examination stations
   Station 1: views from the stomach
   Station 2: duodenal apical view
   Station 3: duodenal sweep views (C-sweep)
4. Rectum (male and female)

Gastric and esophageal wall

Normal gut wall anatomy

Similar to the rest of the gastrointestinal tract, there are five alternating hyperechoic and hypoechoic layers seen in the gastric and esophageal wall from an ultrasonographic perspective. The inner hyperechoic layer corresponds to the fluid–mucosa interface. The inner hypoechoic layer represents the mucosa. The submucosa is the following hyperchoic layer moving outward. The fourth hypoechoic layer corresponds to the muscularis propria, and the final outer hyperechoic layer corresponds to the serosa/subserosa in the case of the stomach, small and large bowel, and the adventitia in the case of the esophagus (Figure 6.1). The normal gastric wall is 4 to 6 mm thick compared to the thinner esophageal wall (2 to 3 mm). The individual layers are usually discretely visible, especially if the higher frequency (12 MHz) is used rather than lower frequencies.

Examination technique

Although the same examination principles discussed here apply to any radial EUS examination, there are a few points that are specific for gut wall evaluation. The patient is usually placed in the left lateral position. After intubation of the esophagus, the radial echoendoscope is advanced under direct endoscopic guidance to the distal antrum. For optimum visualization of the stomach, it should be empty of fluid and gastric juices and then filled with 200 to 500 ml de-aerated (distilled) water. Utilizing a

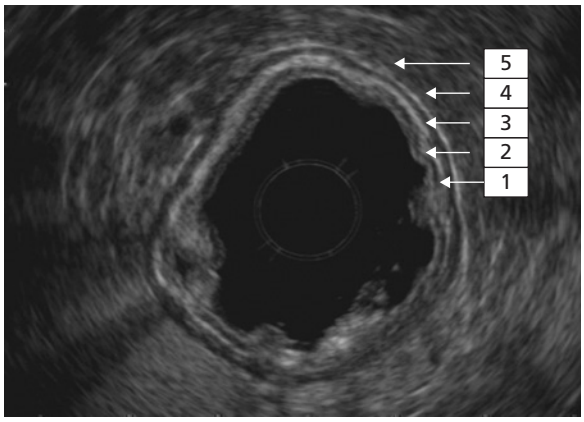

Figure 6.1 Radial EUS examination of a normal stomach. The five distinct echogenic layers described in the text are apparent and labeled 1–5.

dedicated endoscopic water pump saves time and delivers large amounts of water, thus improving echogenic coupling. The stomach should be filled until the rugal folds are separated one from another. We typically elevate the head of the bed and angle the entire bed head-up to reduce the risk of aspiration. Small bubbles should be eliminated as much as possible by use of suction and thick mucus and debris should be aspirated in the usual fashion. We generally avoid simethicone solutions since insoluble particles in the commercial solutions cause hyper-echogenic artifacts. Use of the balloon is still helpful in the antrum where water filling of the lumen is difficult in a left lateral decubitus position.

Examination is undertaken during slow withdrawal of the echoendoscope. The most important rule in imaging the stomach wall is to have the transducer perpendicular to the wall and to have the stomach wall within the focal point of the transducer. If imaging at 7.5 MHz, the transducer should be 1.5 to 2.5 cm from the gut wall. If using a 12 MHz (miniprobe), the transducer should be positioned 1 to 1.5 cm from the gut wall. This is easily accomplished in the gastric body but may be more difficult in the antrum as the endoscope is pressed against the greater curvature. In this case, overinflating the water balloon to move the transducer off the wall is helpful. Certain areas of the stomach are difficult to visualize well even when following the recommendations above (for example, the antrum, due to suboptimal immersion with water). In these cases, repositioning the patient may be of help. For small mucosal and submucosal tumors in the antrum, we find it easier to use a two-channel endoscope (one to fill water and evacuate air) with an ultrasound miniprobe. After water filling to submerge the lesion, the miniprobe can be placed under direct endoscopic vision over (but not in direct contact with) the tumor.

Duodenal and rectal wall examination utilizes the same water submersion principle with the balloon maximally inflated. The esophageal wall layers are similar to those of the stomach but may be more difficult to visualize given that it is a narrow diameter tubular structure. The main concern with the esophagus is the risk of aspiration with water filling. There are several options for dealing with this. For larger tumors (e.g. esophageal carcinomas), the standard echoendoscope is best and can be passed through the tumor after adequate dilation. The balloon is slightly inflated to come in contact with, but not artificially flatten, the esophageal mucosa. The highest possible frequency should be used to image the wall. At 12 MHz, the wall and mediastinum can both be visualized well. The echoendoscope should be pulled (not pushed) from distal to proximal since the endoscopic view will be obscured.

For small esophageal tumors and submucosal tumors, a miniprobe provides the best examination. We find that instillation of a small volume of water (either with a syringe or using the water from the endoscope's water bottle) and evacuation of all luminal air works best. Other more sophisticated techniques include use of a water-filled condom or miniprobe balloons.

Mediastinum

Radial EUS allows for complete "surveillance" of the mediastinum. This examination starts at the gastroesophageal junction (although in lung cancer, the left adrenal and liver should also be evaluated). The balloon is inflated modestly and then, using the electronic rotation function, the aorta is placed at the 5 o'clock position. The zoom function should be zoomed out to at least 6 to 9 cm. In this orientation, the top of the screen is anterior, the bottom posterior, the right screen is the patient's left and the left screen is the patient's right (the same as if viewing a chest computed tomography). The echoendoscope is then slowly withdrawn. The first anatomical landmark to look for is the left atrium. This usually occurs around 30 to 33 cm from the incisors. With the aorta at the 5 o'clock position, the left atrium will appear at the 12 o'clock position. The mitral valve should be seen in the anterior portion of the left atrium. The spine is easily visible at the 7 o'clock position as a bright "arc" with a shadow behind. The azygous vein also comes into view at this level, which appears just left (screen left) of the spine. From this position, small amounts of pericardial fluid can be seen and often there are small retrocardiac nodes between the esophageal wall and the left atrium. Around 32 cm from the incisors, two structures can be identified in close proximity to the aorta and spine (5 and 7 o'clock respectively): the larger one being the azygous vein and the smaller one the thoracic duct (Figure 6.2). With further withdrawal, as the left atrium disappears, one begins to enter the subcarinal space, which is located at the twelve o'clock position (Figure 6.3). One can now identify small lymph nodes very close to the esophageal wall in this space. The subcarinal lymph node is present in almost everyone and has a "draping" shape like a mustache over the "mouth" of the esophagus and often a central bright echo due to fat. Further withdrawal reveals the left and right mainstem bronchi at the 2 o'clock and 10 o'clock positions respectively, usually identified by strong mixed echoes due to ultrasound artifacts created by the air-filled lumens. This position typically is present at 27 to 29 cm from

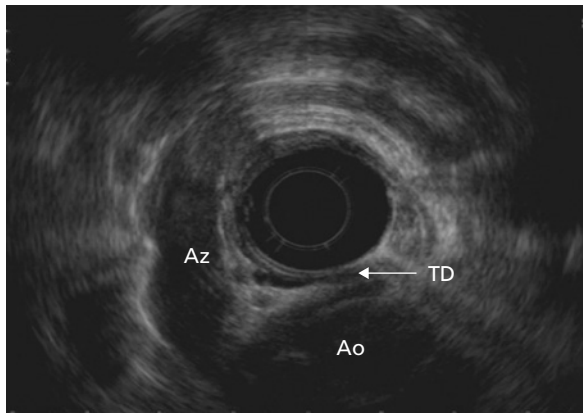

Figure 6.2 The aorta, azygos vein and the thoracic duct all appear from this mediastinal window at the lower esophagus.

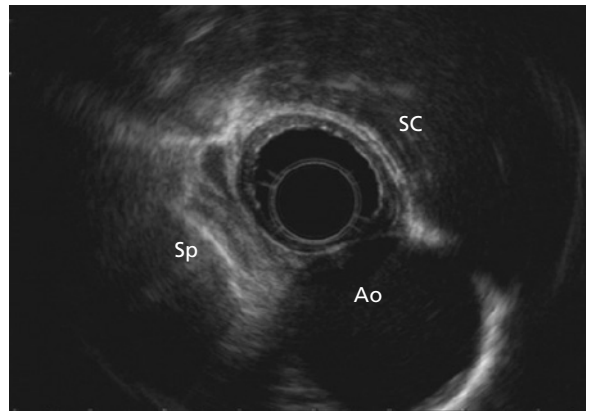

Figure 6.3 Mid mediastinal views showing the aorta (Ao) and the spine (Sp) at the lower half of the field and a benign appearing node in the subcarinal window (SC).

the incisors. With further withdrawal, three anatomic "events" happen:

1. The azygous vein will be seen to move anteriorly to join the superior vena cava.

2. The left and right mainstem bronchus come together to form the trachea.

3. The aorta elongates to form the aortic arch.

Once the aortic arch is identified, if one advances by pushing the scope 2 to 3 cm until it assumes the cross-sectional position, one will be at the level of the aorta pulmonary window (Figure 6.4). This will typically be at the three o'clock position and is a very important area for pathological lymph nodes. This space is located just below the aortic arch. The pulmonary artery can occasionally be seen at the 2 to 3 o'clock position but is not as clear as the aorta.

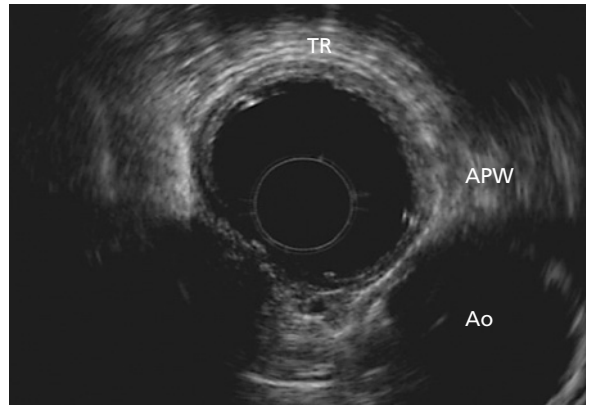

Figure 6.4 Aortopulmonary window (APW) visible just distal to the aortic arch as seen in a cross section. Trachea appears anteriorly as alternating hyperchogenic rings.

Pancreaticobiliary stations

Station 1: views from the stomach

The endoscopic landmark for this station is the gastroesophageal junction. Attention should be paid to endoscopic location and the distance from the incisors, and also for the presence of a hiatal hernia which can make visualization difficult (see below). The balloon is inflated, the lumen is collapsed and the echoendoscope is advanced forward while looking for the usual ultrasonographic landmarks. The following structures are usually readily seen from this station.

Liver and gall bladder

The left lobe of the liver is usually seen at the gastroesophageal junction and should be electronically rotated to the top left of the screen. Also seen anteriorly are the gallbladder body and lesser gastric curve. Lower frequency (5 MHz) allows deeper penetration of the liver. Complete inspection of the liver, particularly the superior, lateral segments (6, 7 and 8) is not possible at 7.5 to 12 MHz due to incomplete penetration. The medial and left lobes (segments 2, 3 and 4) of the liver are seen in the upper left portion of the screen as the scope is advanced inwards. The right lobe (segment 5) of the liver is best seen during the C-sweep maneuver. The gallbladder is best seen from either the antrum, with the echoendoscope pushed inwards into a "long" position, or from the proximal duodenal bulb.

Pancreatic body and tail

This position is begun with the transducer at the gastroesophageal junction. The balloon is slightly inflated and the electronic rotation function is used to position the aorta at the 5 to 6 o'clock position. The scope is then slowly advanced while maintaining the aorta perfectly in cross-sectional orientation. With insertion, one will eventually see the celiac artery coming off the aorta usually from the 10 o'clock position. The first branch to come off the celiac is the left gastric artery seen at the 1 o'clock position, although this is not always seen (Figure 6.5). The axis continues and bifurcates into the hepatic artery (branching towards the left upper screen towards the liver) and the splenic

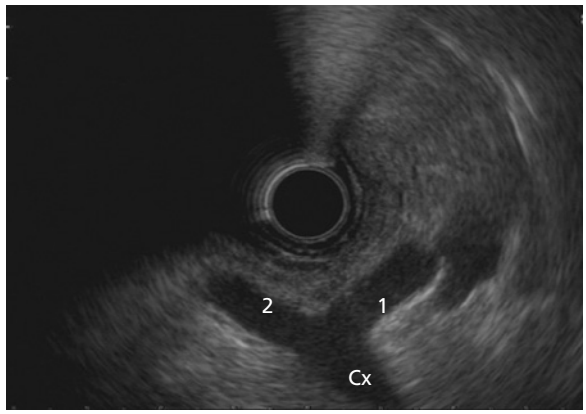

Figure 6.5 Celiac artery (Cx) is seen giving origin to the left gastric artery (1) and splenic artery (2).

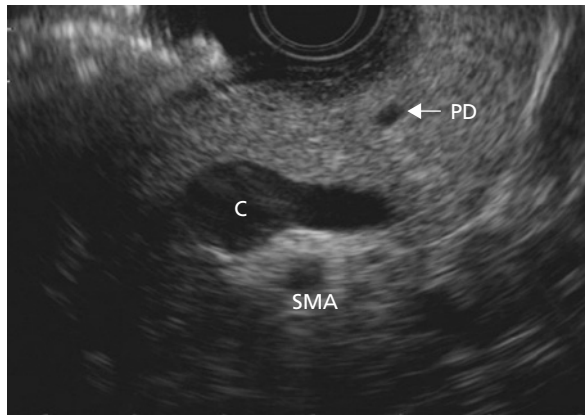

Figure 6.6 Radial view of pancreatic body, tail and duct. The black splenic vein and portal confluence make up the "clubhead" view. The superior mesenteric artery (SMA) is seen in cross section underneath the clubhead.

artery which extends anteriorly towards the top of the screen, then curves abruptly towards the right screen and spleen, often in a circuitous route. Once this is identified, a further 1 to 2 cm of insertion will show the confluence of the superior mesenteric vein and splenic vein to form the portal vein and the superior mesenteric artery; the pancreas will be seen to lie above the structures. The splenic vein and portal vein confluence are seen in long axis and for a view resembling a golfclub driver (with the portal vein as the club head and the splenic vein represented by the "shaft"), termed the "clubhead" view (Figure 6.6). The splenic artery is usually seen closer to the probe and has a thicker hyperechogenic wall. The transducer should be slowly moved in and out until the small pancreatic duct is seen in the center of the parenchyma in a long axis orientation (Figure 6.7). From this position, rightward torque and withdrawing the scope will demonstrate the tail of the pancreas and left kidney and left torque in advancing the scope will demonstrate the genu. These movements should be adjusted for each individual's anatomy with the aim to follow the pancreatic duct throughout its course. In the

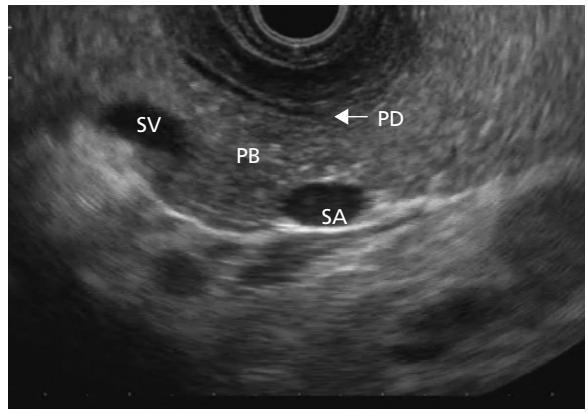

Figure 6.7 Station 1 views: pancreatic duct (PD) is seen coursing through the pancreatic body. Splenic artery (SA) and splenic vein (SV) are seen in cross section close to the pancreatic parenchyma.

presence of a hiatal hernia, it may be necessary to advance the scope under optical visualization past the pancreas (into the mid body of the stomach, approximately 50 cm from the incisors) and perform the examination in reverse (i.e. pulling back). The liver is identified and positioned at the top of the screen. The scope is slowly pulled back, looking for the pancreas and "clubhead" view at 6 o'clock. It is then further pulled back to the celiac artery around the gastroesophageal junction.

Adrenal gland

The left adrenal gland can be routinely identified with EUS; however the right is much more difficult and inconsistent due to its location far from the gastrointestinal lumen. To locate the left adrenal gland, begin at the gastroesophageal junction to identify the aorta and follow it to the celiac artery as described above for the pancreas body and tail. When the celiac artery is seen, the adrenal gland is typically seen 1 to 2 cm to the right screen. It has a classic "gullwing" or "long-horn" shape and hypoechoic appearance (Figure 6.8). The left kidney can be readily identified by advancing the echoendoscope forward. In challenging cases, it may be easier to first find the left kidney (see pancreas body section above) then pull upwards to just above the superior pole to identify the adrenal. The right adrenal, if seen, is best identified from the third portion of the duodenum located between the superior pole of the right kidney and the liver.

Station 2: duodenal apical view

This maneuver is begun with the echoendoscope in the stomach. The echoendoscope is advanced along the greater curve of the stomach until the pylorus is identified. The scope is then advanced past the pylorus and once the pylorus is cleared, air is insufflated to extend the duodenal bulb and the tip of the echoendoscope is deflected inferiorly slightly in order to make visual contact with the distal, narrowed portion, the "apex" of the duodenal bulb. The balloon is inflated until it occludes the apex

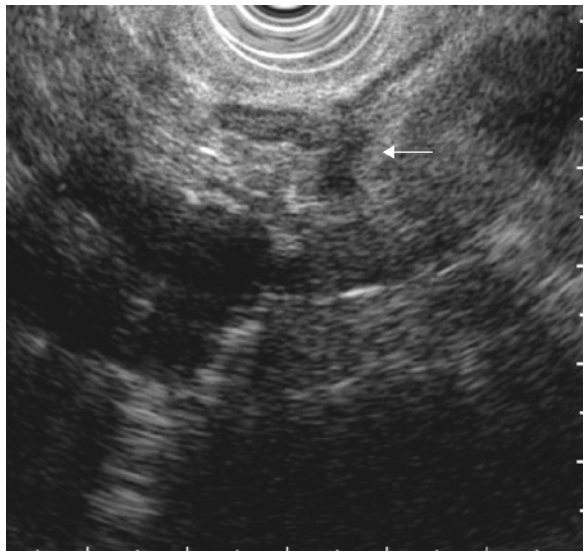

Figure 6.8 Radial view of left adrenal with classic "gullwing" shape.

approximately at the level of the first circular fold of the duodenum. It is helpful to look for the liver and, once it is identified, the electronic rotation function should be used in order to position the liver in the upper left-hand corner of the screen. From this point, any one of several movements may be required to obtain optimal imaging. This can include going right or left, up or down, advancing the scope in or withdrawing it. Most commonly, the endoscope is pushed inwards into a "long" position with slight rightward torque and right-up dial (simulating the maneuver to pass a standard endoscope around the C-sweep). These maneuvers are made in an attempt to visualize the bile duct, which will be a tubular, anechoic triple-layered structure coming down from the liver extending to the 6 o'clock position. Once identified in cross section, the scope tip is further maneuvered in order to produce a long axis image of the bile duct, sweeping from the 10 o'clock position to the 6 o'clock position. Deep to the bile duct, the pancreatic duct can usually be visualized. In the lower left-hand portion of the screen, the portal vein will appear. Once the structure is identified, fine movements of tip deflection will allow careful examination of these structures. The landmark view is the echoendoscopic "stack sign" (Figure 6.9) which refers to positioning the common bile duct (CBD), pancreatic duct (PD) and portal vein (PV) all in parallel alignment with the pancreatic head. The distalmost aspect of the bile and pancreatic duct can be imaged by filling the duodenal lumen with water to see the interface between ducts and lumen (at the ampulla). The duodenal lumen should be seen curving away and right from the transducer at approximately 6 o'clock.

Station 3: duodenal sweep views (C-sweep)

After completing the above steps from the stomach, the radial echoendoscope is advanced deeply into the duodenum, similarly to the duodenal intubation and shortening methods used during ERCP. Once the tip of the endoscope is past the papilla, the

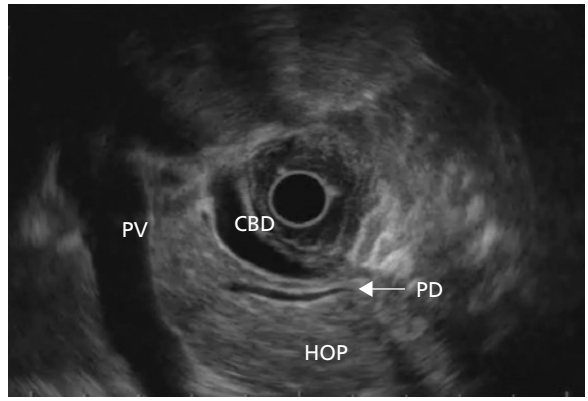

Figure 6.9 Apical views of the pancreatic head from the duodenal bulb: the pancreatic duct (PD), common bile duct (CBD) and portal vein are all seen in alignment with the pancreatic head surrounding the CBD and PD (stack sign).

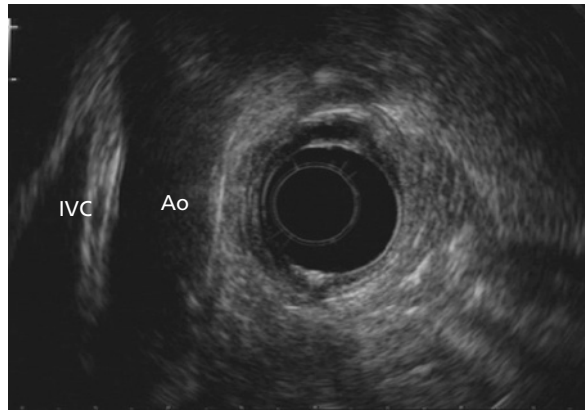

Figure 6.10 Aorta (Ao) and inferior vena cava (IVC) examined from the second portion of the duodenum.

balloon is inflated; the right/left knob is locked in the slightly rightward position and the up/down dial is maintained (but not locked) in the maximum "upward" position while the echoendoscope is slowly withdrawn. Using torque to further manipulate the tip, the aorta and inferior vena cava should be sought. The aorta typically has a less echogenic lumen with brighter, thicker walls and is seen on the left side of the screen (Figure 6.10). Relative to the aorta, the IVC is found by rotating left (counterclockwise) approximately 30 degrees.

Once the aorta is identified, it is electronically rotated to position just left of the transducer running from 11 o'clock to 7 o'clock on the screen. The scope is then slowly withdrawn. As the scope pulls around the duodenal sweep, keeping the aorta in view the entire time, the uncinate process and head of the pancreas will start to appear on the right side of the aorta at the 6 o'clock position on the screen. Simultaneously, the aorta goes from a long axis view to a cross-sectional view. As the instrument is further withdrawn, one can usually identify the superior mesenteric artery (SMA) and superior mesenteric vein (SMV) deep to the head of the pancreas, typically seen in long axis from 2 o'clock to 6 o'clock. The SMV runs closer to the pancreas and

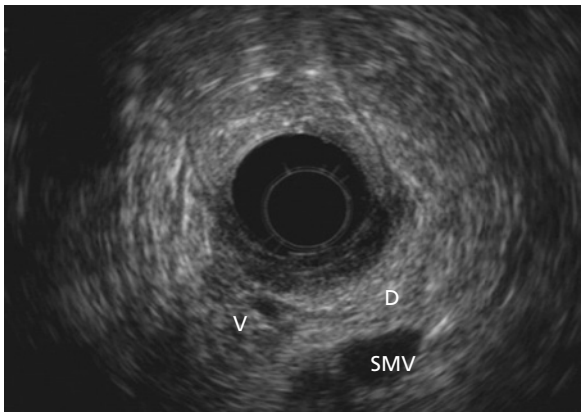

Figure 6.11 Radial view of uncinate process. Ventral (V) and dorsal (D) pancreas are seen with different echogenicities, along with the superior mesenteric vein (SMV).

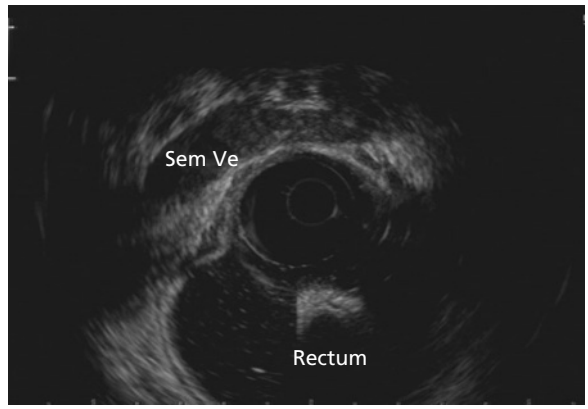

Figure 6.12 Seminal vesicles appear anterior to the EUS probe. Note the normal rectal wall layers seen at the lower half of the screen.

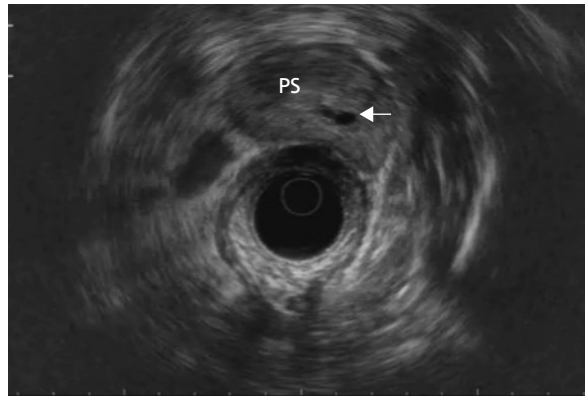

Figure 6.13 Radial EUS views of a normal prostate gland (PS) above the EUS probe in a male approximately 5 cm above the anal verge. The urethra appears as an anechoic tubular structure in the middle of the gland (*arrow*).

the SMA further away. The head of the pancreas itself is usually seen as a crescent-shaped structure. When the transducer is withdrawn to the level of the papilla, the bile duct and pancreatic duct can often be seen as two round anechoic circles commonly called "snake eyes." A difference in pancreatic echo texture is also seen in this location with the less fatty, ventral pancreas appearing darker, and the dorsal pancreas appearing brighter (Figure 6.11). This maneuver is continued until the balloon surrounding the transducer comes to rest against the pylorus. As the scope pulls back against the pylorus, it is not uncommon to visualize the body of the pancreas in a typical "clubhead" view since the echoendoscope and the inflated balloon everts the pylorus back into the stomach. If visualization is suboptimal, this maneuver can then be repeated.

From this station, the right adrenal gland can occasionally be seen from the third portion of the duodenum. The right kidney is identified adjacent to the aorta and IVC. Instead of rotating rightward to the pancreas, turning leftward by 30 to 60 degrees can help identify the right kidney. Pulling upwards to the superior pole of the kidney brings the gullwing-shaped adrenal gland into view. However, the right adrenal gland is identifiable in only 10 to 20% of cases.

Rectum

Rectal radial EUS is frequently employed for rectal cancer staging and restaging. The usual five alternating echoic layers discussed above are noted in the rectum as well. When performed for cancer staging purposes, it is important to inspect for lymph nodes along the left ileac vessels (the right ileac vessels are typically not seen via EUS). To do this, the scope is advanced to approximately 25 cm in the sigmoid. The air is removed and the balloon inflated with water to fill the sigmoid lumen. The ileac vessels are usually two, large (8 to 10 mm) caliber vessels running parallel at 20 to 25 cm from the anal verge. Occasionally, the ileac vessels can be traced to the aorta and IVC but varies depending on the position of the sigmoid colon. The echoendoscope is further withdrawn until the bladder is seen as an anechoic round structure, depending on the filling of the bladder (a full bladder is better visualized). This should be positioned at 12 o'clock. As the scope is slowly withdrawn, the anatomy of the pelvic organs comes into view.

In a male, the seminal vesicles are seen first as lobular, hypoechoic structures extending from 10 o'clock to 2 o'clock (Figure 6.12). Care should be taken not to confuse those with perirectal lymphadenopathy. With further withdrawal, the prostate with a central, hyperechoic urethra is usually seen, followed by the urethra only (Figure 6.13).

In a female, the uterus (if present) is seen just below the bladder, followed by the more flat vagina, often with a hyperechoic line in the center due to the presence of air (Figure 6.14). Finally, the urethra is seen as a hollow anechoeic structure.

In both genders, the muscles of defecation are seen below the pelvic organs. The levator ani muscle extends to form a hypoechoic "V" just below the pelvic organs. As the scope is pulled into the anal canal, a clear, hypoechoic ring is seen closest to the transducer representing the internal anal sphincter (IAS). Outside this

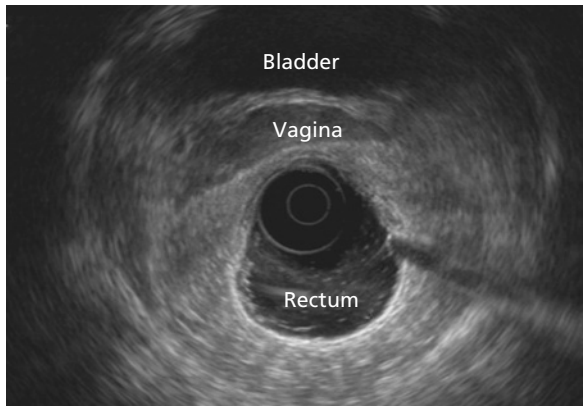

Figure 6.14 Views of the normal vagina and urinary bladder from the rectum.

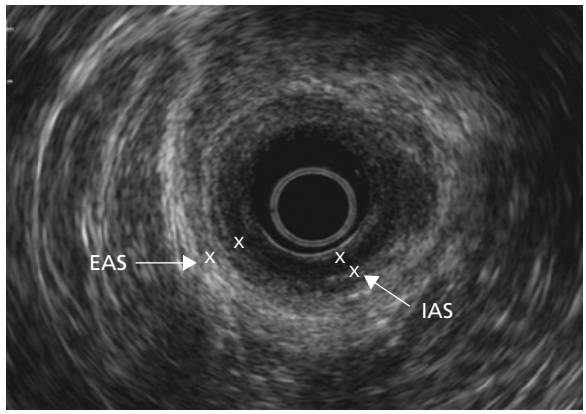

Figure 6.15 Hyperechogenic external anal sphincter (EAS) and the hyoechoic internal anal sphincter (IAS), seen between the X marks in a normal female.

ring is a more hyperechoic ring, less clear than the IAS, representing the external anal sphincter (Figure 6.15). Visualization of the anal sphincters is best accomplished with either the rigid rectal ultrasound probe, or the flexible EUS scope.

Conclusion

A good baseline knowledge of the normal anatomy in EUS is essential before identification of various pathologies is possible. This is of particular significance for beginners. We believe that a systematic EUS examination of the upper gastrointestinal tract using the above described stations and maneuvers is important and potentially reproducible in each case. It is not uncommon to have to return to a familiar station and begin examination of that area over again when unsure about the location or views.

Suggested reading

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7 Linear Array EUS: Normal Anatomy

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Introduction

With the advent of interventional endosonography, led by EUS-guided fine needle aspiration, there has been a rapidly growing interest in linear endosonography. The essentials for learning both radial and linear endoscopic ultrasound have been well described [1,2]. A thorough review of mediastinal, upper abdominal and pelvic anatomy is essential. It is also important to understand the normal major anatomic variations. Thus a well-illustrated anatomic atlas(es) is foundational to any endosonographic library. Radiology texts on computerized tomography or magnetic resonance imaging can be very helpful for understanding the normal, anatomic variations and pathological appearances of the mediastinum, abdomen and pelvis in transverse, sagittal and coronal planes. Next, the basic principles of ultrasound need to be mastered, including ultrasound physics, instrumentation and artifacts (see Chapters 2 and 3). The specific resources for training in endoscopic ultrasonography are fortunately now very extensive; including a large body of medical literature, many excellent monographs and textbooks and multiple online learning videos and DVDs on EUS available from such organizations as the the American Socieity for Gastrointestinal Endoscopy (http://www.asge.org). A variety of monographs, atlases, CD-ROM or DVD-based learning tools are available from endoscopic industrial educational resources. Institutionally based Internet learning tools are also rapidly growing such as those from the Medical University of South Carolina (http://www.ddc.musc.edu/ddc_pro/index.htm) and the Harvard Medical School DAVE (Digital Atlas of Video Education) Project at http://dave1.mgh.harvard.edu/index.cfm. The *Visible Human Journal of Endosonography* from the Center for Human Simulation at the University of Colorado Health Sciences Center (http://www.vhjoe.org) deserves special recognition as a remarkably useful tool for understanding EUS anatomy.

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 ISBN: 978-1-405-15722-3

Performing the examination

Soon after linear instruments became available, it was demonstrated that a complete upper and lower endosonographic examination could be just as easily done using linear or radial instrumentation [3]. The current instrumentation available for performing linear EUS is reviewed in Chapter 3. Most endosonographers, equally experienced in both techniques, find a linear examination a little more cumbersome for rapid survey of the mostly radially oriented gut; however, multiple studies have demonstrated that diagnostic EUS for almost all indications can be performed equally well with either radial or linear instrumentation in the hands of an experienced endosonographer.

There are four basic approaches to performing a complete upper endosonographic linear examination. The first and probably most common approach involves using radial endosonography as the primary diagnostic modality and then, if pathology needing endosonographic intervention is found (e.g. a mass for fine needle aspiration), one proceeds directly on to a focused linear endosonographic examination. With this approach, the endosonographer has the unique challenge of being able to rapidly relocate any pathology noted on the radial examination with the following linear study. This actually requires a very thorough understanding of normal linear anatomy, especially being able place lesions relative to the surrounding vascular structures and organs so as to find those same anatomic structures with the linear echoendoscope.

In the last three approaches, the linear echoendoscope is used for the whole examination. In the first of these, the scope is placed deep into the duodenum and then the organs around the duodenum, stomach and esophagus are systematically examined on withdrawal. This approach is especially practical when using a videoechoendoscope to also perform a visual endoscopic examination prior to endosonography. Once the endoscopic portion is completed in the duodenum, then the endosonographic examination can proceed on withdrawal from there.

Another approach at complete linear endosonographic examination is to systematically interrogate sections as the scope is

passed from the esophagus to the stomach and finishing in the duodenum. The final approach is to begin the endosonographic examination by focusing on the area of clinical interest and then examine other structures after the primary pathology has been interrogated. This approach may optimize time usage, but runs the risk of missing unexpected pathology if one forgets to examine all anatomic areas in the excitement of finding significant pathology at one location. The first and the last two approaches may or may not be preceded by a survey upper endoscopy examination using a standard endoscope. Personally, I often use the final approach because it allows me to most efficiently plan out the remainder of the procedure. For example, if one is examining a patient with a potential mass that may need fine needle aspiration, by proceeding directly to the anatomic area of interest, I can then quickly decide whether a fine needle aspiration is going to be needed and get the appropriate equipment set up and personnel mobilized from cytopathology while I finish up the diagnostic examination of the remaining endosonographic stations. Alternatively, if I am ruling out a common duct stone, and one is found, then the appropriate facilities and time for a subsequent ERCP under the same sedation can be arranged while finishing the examination. Any of these approaches are reasonable as long as the examination consistently covers all the structures accessible to routine endosonographic interrogation so that unexpected pathology is not missed.

An essential key to not missing pathology is including all the anatomic stations to be sure all anatomy areas are interrogated. The specific stations used in linear endosonography and their numbering have not been standardized and vary from author to author and institution to institution. Although the numbering and sequences may vary, the stations uniformly include viewing from deep duodenum, the mid duodenum and duodenal bulb, the mid-stomach, gastric cardia, and mid and distal esophagus.

Another helpful concept which is somewhat similar to anatomic stations is that of "home base" views. Home base views are locations that can be easily found in the major anatomic regions (esophagus, stomach, duodenum and rectum) where the anatomy varies little and the endosonographic structures are usually obvious and similar from patient to patient. Then, whenever one gets lost (which happens even to the most experienced endosonographer), the scope can be quickly repositioned to the easily found and anatomically uniform home base structure for that region. From there, uncertain structures can then be systematically located or followed to determine their identification. The linear home base locations and structures for the esophagus, stomach, duodenum and rectum are detailed in Table 7.1.

In displaying linear endoscopic images, there is a variation in conventions around the world. The agreed-on convention in radiology is to display longitudinal images with cranial to the left and caudal to the right. However, most endosonographers in the United States, the United Kingdom and France display linear endosonographic images with the scope tip oriented to the left of the image which is usually caudal with an upper endosonographic examination. Images from Japan and Germany typically display the tip of the echoendoscope, usually caudal, to the right of their images. For this chapter, I will follow the former convention of displaying the tip of the endoscope to the left. Orientation on the tip location makes more sense than whether the scope is viewing in a cranial or caudal orientation, since this can change rapidly when passing the scope beyond the proximal stomach.

Table 7.1 Home base structures linear endosonographic anatomy

Esophagus	Descending aorta at 30–35 cm (Figure 7.1A)
Stomach	Abdominal aorta just below gastroesophageal junction (Figure 7.5A)
Duodenum	Endoscopic and endosonographic ampulla (Figure 7.8A)
Rectum	Male: prostate at 7–9 cm (Figure 7.10B) Female: vagina at 6–9 cm (Figure 7.10D)

Like many experienced endosonographers, I do not usually use a balloon on the tip of a linear array echoendoscope as they are not needed to get excellent imaging. Balloons can occasionally be useful when trying to "lock" the scope in position in the second portion of the duodenum.

The linear esophagus

On initial deep intubation of the esophagus, i.e. 30 to 35 cm from the incisors (Figure 7.1A), the linear echoendoscope most naturally orients pointing down towards the patient's left anterior region. The home base structure throughout the esophagus is the descending aorta which is located by rotating the shaft of the echoendoscope a little to the right (clockwise) or left (counterclockwise). Rotation of the echoendoscope shaft is done by either grabbing the shaft with your hand and rotating and/or rotating your body toward the right, producing clockwise rotation, or left, producing counterclockwise rotation. The descending aorta is easily recognized as a large, echolucent, longitudinal structure with a very bright deep wall secondary to the air interface from the adjacent left lung. From the descending aorta, rotating the shaft of the echoendoscope about 90 degrees clockwise will bring into view the easily identified left atrium (Figure 7.1B). The left atrium will appear as a contracting, thin-walled echolucent chamber with the mitral valve opening into the deeper left ventricle. With a little further clockwise rotation and withdrawal (Figure 7.1C) the aortic outflow tract, aortic valve and ascending aorta can be visualized through the left atrium. Further withdrawal of the echoendoscope will follow the ascending aorta proximally and bring into view the right pulmonary artery. This is a very important view for localizing subcarinal lymph nodes (thoracic nodal station 7 – Figure 7.2) for fine needle aspiration. Further rightward (clockwise) rotation at this level will reveal the superior vena cava which can be followed distally to where it drains into the right atrium (Figure 7.1D). The inferior vena cava also may be seen draining into the

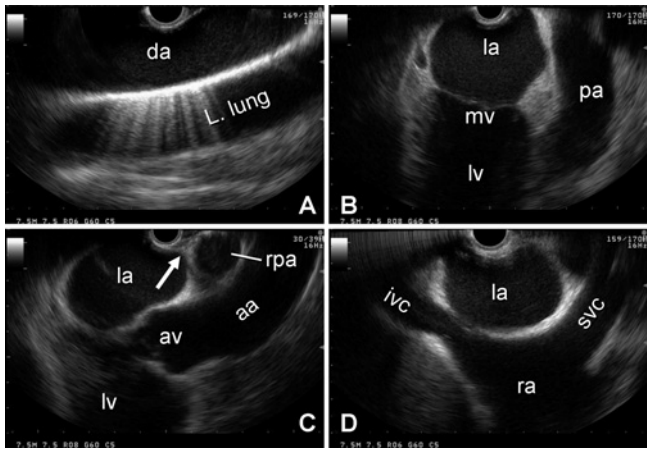

Figure 7.1 (A) "Home base" view of the descending aorta (da) in the mid-esophagus. (B) View of the left atrium (la) with the deeper mitral valve (mv) and left ventricle and the main pulmonary artery (pa). (C) View of the subcarinal region (*arrow*) with the deeper right pulmonary artery (rpa), ascending aorta (aa) and aortic valve (av). (D) View of the right atrium (ra) with the inferior vena cava (ivc) and superior vena cava (svc) running into it. Unless otherwise stated, all endosonographic images are done using the Olympus GF-UC240P-AL5 ultrasound gastrovideoscope using an Aloka ProSound Alpha 5 ultrasound processor at 7.5 MHz.

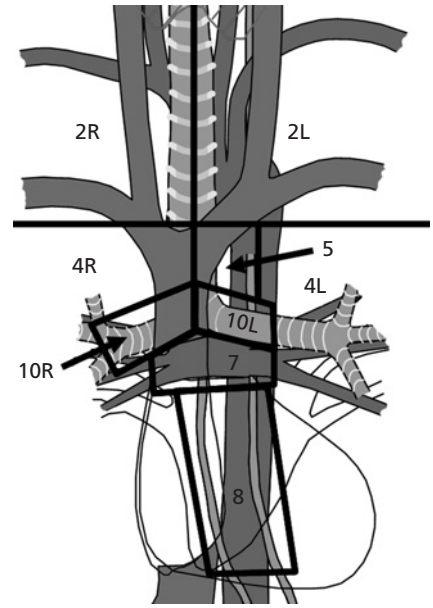

Figure 7.2 Locations of thoracic nodal groups used in lung cancer staging.

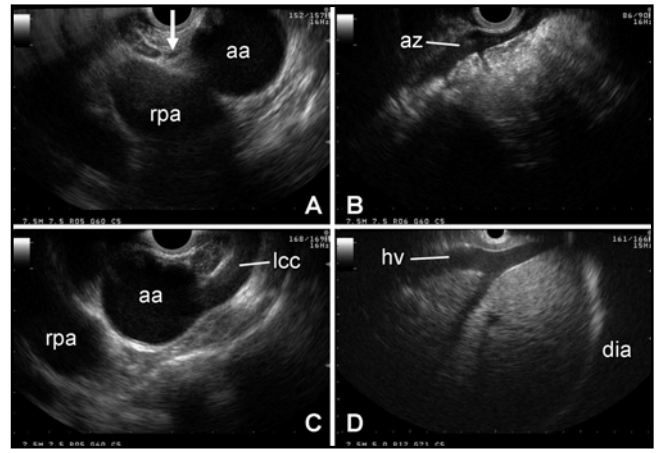

Figure 7.3 (A) View of the aortopulmonary window, thoracic nodal station 5A nestled between cross-sectional views of the arch of the aorta (aa) and right pulmonary artery (rpa). (B) View of the azygous vein (az) from the mid-esophagus level. (C) View of the left common carotid artery (lcc) arising out of the arch of the aorta. (D) View of the hepatic veins (hv) draining into the inferior vena cava at the dome of the diaphragm (dia).

right atrium. Further withdrawal of the echoendoscope from the subcarinal view will result in a blind spot as the scope is pulled over the air-filled left mainstem bronchus. Just proximal to the bronchus-caused blind spot and with some minor left-right rotation, the arch of the aorta comes into view as a large circular structure adjacent to the esophagus (Figure 7.3A). Just distal to the arch is the cross-sectional view of the right pulmonary artery. Between the aortic arch and the right pulmonary artery is the aorto-pulmonary window, the medial portion of thoracic nodal station 5 (Figure 7.2) which is another important area for fine needle aspiration of pathological mediastinal lymph nodes. By rotating the scope slightly right and left and withdrawing, the takeoffs of the left common carotid and more rarely the subclavian arteries can be seen (Figure 7.3C). Deep to the arch is the occasionally visible left innominate (brachiocephalic) vein. Along the path of the left common carotid is thoracic nodal station 2L (Figure 7.2). On withdrawing the echoendoscope into the neck, the esophagus is wedged between the impenetrable air-filled trachea anteriorly and spine posteriorly. Rotating further clockwise from the left common carotid in the very proximal esophagus may reveal views of the right common carotid artery and the deeper internal jugular veins along which is thoracic nodal station 2R (Figure 7.2).

Returning back to the linear esophageal home base of the distal esophageal descending aorta (Figure 7.1A), rotation to the left (counterclockwise) from the descending aorta for most of the distal half of the esophagus will promptly bring the azygous vein into view as a thin, longitudinal echolucency close to the wall of the esophagus (Figure 7.3B). Withdrawing the scope while following the azygous vein will bring the arch of the azygous into view as it courses into the deeper superior vena cava. Rotation of the echoendoscope leftward from the aorta at the level of the gastroesophageal junction will usually show the liver with its hepatic veins draining into the inferior vena cava which itself runs into the right atrium (Figure 7.3D).

The linear stomach

Like the radial examination, home base in the linear stomach is the abdominal aorta at the level of the gastroesophageal junction

(Figure 7.4 position 1). This posterior structure is always easy to locate by positioning the echoendoscope at the gastroesophageal junction and rotating it right or left until the aorta comes into view. Since the retroperitoneal structures are all posterior to the stomach, clockwise (rightward) rotation of the echoendoscope will point the echoendoscope towards the patient's left and counterclockwise (leftward) rotation towards their right side (Figure 7.4). Unlike the descending aorta in the mediastinum, the abdominal aorta at the level of the gastroesophageal junction will have the crus of the diaphragm interposed between the gastric wall and the aorta. The crus can occasionally appear quite mass-like, especially in muscular individuals and on radial viewing. It can be mistaken by novices for a celiac node or the left adrenal. From the gastroesophageal junction, rotating the echoendoscope slightly to the right (clockwise) with a few centimeters of insertion will bring the left adrenal into view (Figure 7.5B) with its echolucent cortex and more echogenic medullary portion. However, the linear left adrenal tends to be a more longitudinally flat organ and can be more difficult to identify than by radial EUS. Rotating left (counterclockwise) from the abdominal aorta at the gastroesophageal junction brings into view the liver, the dome of the diaphragm and the hepatic veins draining into the inferior vena cava (Figure 7.3D). Further rotation points the ultrasonic view anteriorly where the left lobe of the liver can be systematically interrogated. With the patient lying on their left side, this is a region where it is often easy to find and aspirate small amounts of ascites by EUS-guided fine needle aspiration. From the stomach home base at the abdominal aorta near the gastroesophageal junction, the echoendoscope is then inserted deeper into the stomach, following the course of the aorta (Figure 7.4 position 2). Soon the takeoff of the celiac artery is visible (Figure 7.5C). Usually, the more oblique takeoff of the superior mesenteric artery is apparent just distal to this. This view is important because it localizes the celiac axis region for EUS-guided fine needle aspiration of celiac nodes and for celiac plexus neurolysis. To view the celiac, the scope tip may need to be bent downward with the control knobs as the aorta appears to be moving deep, away from the posterior wall of the stomach as the scope is inserted. It is actually the stomach moving anteriorly that causes this effect. From the celiac artery, the scope is inserted a little more (Figure 7.4 position 3) bringing the pancreas neck or body into view within the triangle made by the celiac and superior mesenteric arteries and the gastric wall (Figure 7.5D). Note that the splenic artery can course tortuously in and out of the pancreas, but the splenic vein usually has a straight course and is the larger and deeper of the two vessels. Both vessels tend to appear at the caudad border of the pancreas neck, body and tail. The pancreas is interrogated from the neck to the body (Figure 7.6A) and tail through the stomach at this level by rotating the echoendoscope to the right (clockwise) with slight withdrawal (Figure 7.4 position 5) which follows the splenic vein and splenic artery as they run into the hilum of the spleen (Figure 7.6D). The pancreas neck, body and tail will appear between the splenic vein and the posterior gastric wall. The pancreatic duct is usually seen

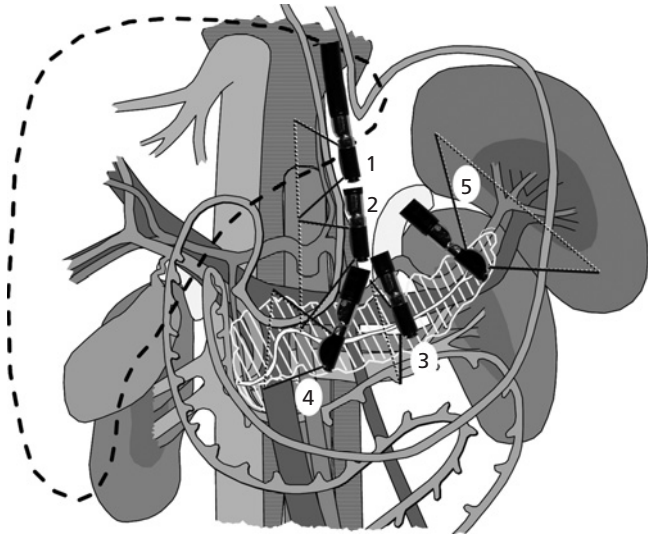

Figure 7.4 Endosonographic stations in the stomach.

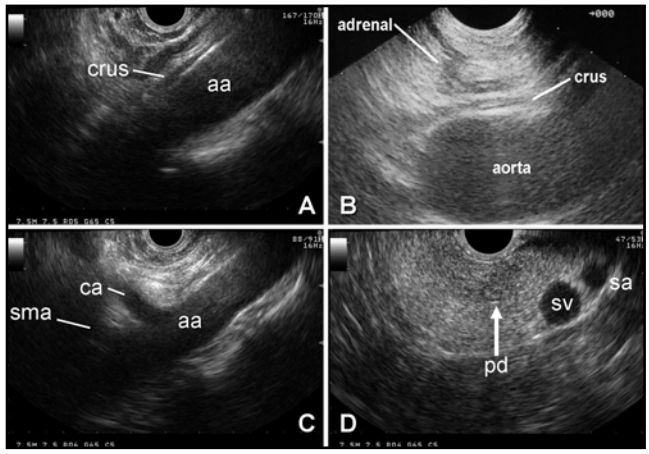

Figure 7.5 (A) "Home base" view for the stomach (station 1 Figure 7.4) with the abdominal aorta (aa) seen in longitudinal section with the crus of the left diaphragm overlying it. (B) View of the left adrenal using the Pentax FG36-UX echoendoscope with a Hitachi EUB-525 processor also at 7.5 MHz. (C) View of the celiac artery (ca) arising from the abdominal aorta with the more distal and oblique superior mesenteric artery (sma) (station 2 Figure 7.4). (D) View of the pancreas body in cross-section with the splenic artery (sa) and vein (sv) typically seen caudad to it (station 3 Figure 7.4). Note the very small normal pancreatic duct (pd) seen also in cross-section.

in cross section using linear EUS through the stomach; thus, it will normally appear as just a small, sometimes difficult-to-see, echolucent dot in the middle of the pancreatic parenchyma. Rotation to the left at the level of the celiac axis and body of the pancreas (Figure 7.4 position 4) brings into view the pancreatic neck with the portal vein confluence deep to it (Figure 7.6B). The splenic vein merges into the confluence from the patient's left and the superior mesenteric vein runs caudad from the portal vein confluence. Although it may take a little fine positioning

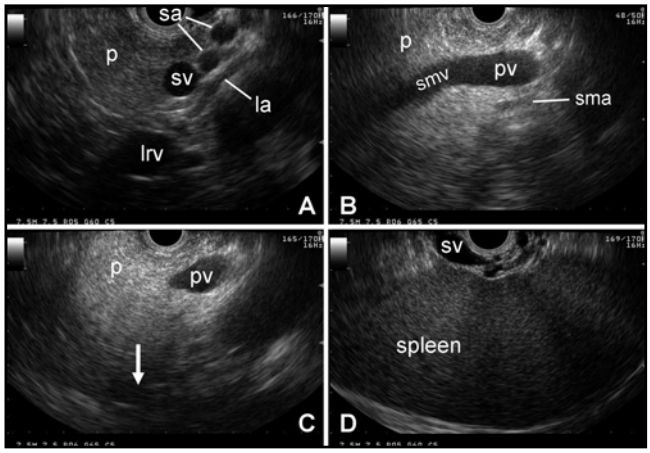

Figure 7.6 (A) Linear view across the mid body of pancreas (p) (station 3 Figure 7.4) showing the splenic artery (sa) weaving around the pancreas with the larger and straighter splenic vein (sv) deep to it. Also in view is the left adrenal (la) and left renal vein (lrv). (B) View of the neck of the pancreas at the level of the portal vein (pv) confluence (station 4 Figure 7.4). The superior mesenteric vein (smv) merges into the portal vein with glimpses of the superior mesenteric artery (sma) deep to this. (C) View of the right lateral margin of the pancreatic neck looking down towards the pancreatic head (*arrow*). (D) View of the spleen and its hilar vessels (station 5 Figure 7.4).

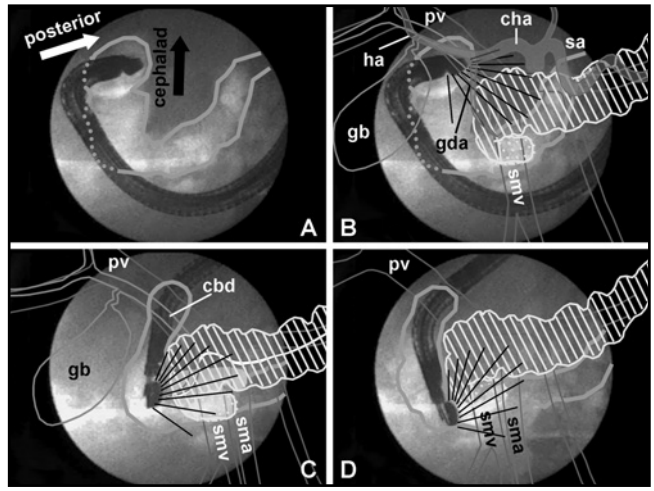

Figure 7.7 Fluoroscopic views of a linear echoendoscope maneuvering around the duodenum. (A) On first entering into the duodenal bulb, the scope is typically in a long position with the tip pointing posteriorly and caudad. (B) View from this first duodenal station looks down onto the pancreatic head intercepting gastroduodenal artery (gda), bile duct, hepatic artery (ha), portal vein (pv) and superior mesenteric vein confluence (smv). Also shown are the gallbladder (gb), common hepatic artery (cha) and splenic artery (sa). (C) Second duodenal station which is also the "home base" location of the echoendoscope over the ampulla in a short position. Here the common bile duct (cbd) and pancreatic duct appear within the pancreatic head with the smv and superior mesenteric artery deep to them. (D) In the third station of the duodenum, the echoendoscope is deep at the junction between the second and third portions looking up towards the ventral pancreas and mesenteric root vessels.

of the echoendoscope tip, portions of the superior mesenteric artery can usually be seen deep to the portal vein confluence. A little further leftward rotation of the echoendoscope may produce views of the right border of the pancreatic neck looking down towards the pancreatic head (Figure 7.6C). Sometimes, longitudinal views of the pancreatic duct can be obtained from this view. Further leftward rotation brings the left lobe of the liver back into view. Liver metastases are most easily aspirated between this level and the gastroesophageal junction. On moving the echoendoscope into the antrum, usually little more than surrounding bowel, liver and omentum are seen; however, some of the structures of the porta hepatis such as the gallbladder can be viewed through the prepyloric antrum.

The linear duodenum

As with radial endosonography, the linear duodenum presents the endosonographer with the most variability in endosonographic anatomical relationships of vessels, ducts and periduodenal organs. In addition there is a confusing array of linear structures very close to each other where just slight changes in orientation of the echoendoscope tip produces totally new views (Figure 7.7). Finally, there is a marked transition in the direction of the scope tip and therefore anatomic views between entering the duodenal bulb in a "long position" (Figure 7.7A, B) where the scope tip is pointing cephalad and posterior and a "short position" when withdrawing from the second portion of the duodenum (Figure 7.7C,D) where the scope tip is pointing caudad.

Adding to this complexity, an endosonographic home base is not as easily defined as for the linear esophagus or stomach or for the radial duodenum for that matter. I find that the most reliable starting point is to place the echoendoscope in a short position in the second portion of the duodenum, then endoscopically visualize the region of the ampulla of Vater with the partially side-viewing optics characteristic of all linear echoendoscopes. Then the tip is deflected, air is sucked from the duodenum and/or water is put in the duodenum (or balloon if one is used) to allow direct endosonographic evaluation of the region directly over the ampulla itself (Figure 7.8A). On slightly rotating the scope right or left with very gentle withdrawal the echoendoscope, usually the pancreatic duct will be seen first traveling relatively perpendicularly away from the transducer (Figure 7.8B). The common bile duct will be seen to originate from the ampulla between the duodenal lumen and the pancreatic duct. Like the pancreatic duct in the stomach, the common bile duct in the duodenum will be seen primarily in cross section by this maneuver. Although a markedly dilated common bile duct is easy to identify, this cross-sectional view means that a normal, 2 to 3-mm common bile duct will be just a black dot nestled within the pancreatic parenchyma (Figure 7.8B). Use of color flow Doppler can be very helpful in this region to differentiate vascular from ductal structures. The pancreatic parenchyma seen at the level of the

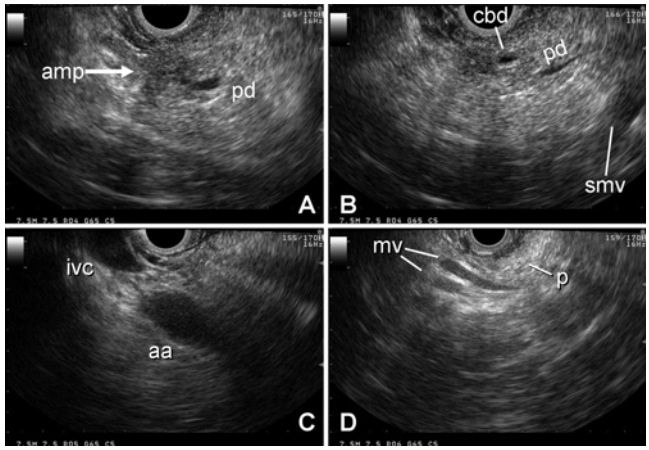

Figure 7.8 (A) Linear view from the second duodenal station (Figure 7.7C) where the echoendoscope is placed directly over the ampulla (amp) and usually the pancreatic duct (pd) is seen first at this level. (B) A little more caudad view from above with the common bile duct (cbd) now seen between the duodenal wall and pancreatic duct. (C) In the third duodenal station (Figure 7.7D), the abdominal aorta (aa) and inferior vena cava (ivc) come into view either in cross section or longitudinally. (D) View of mesenteric root vessels (mv) from the proximal third portion of the duodenum (third duodenal station Figure 7.7D) showing some uncinate pancreatic tissue (p).

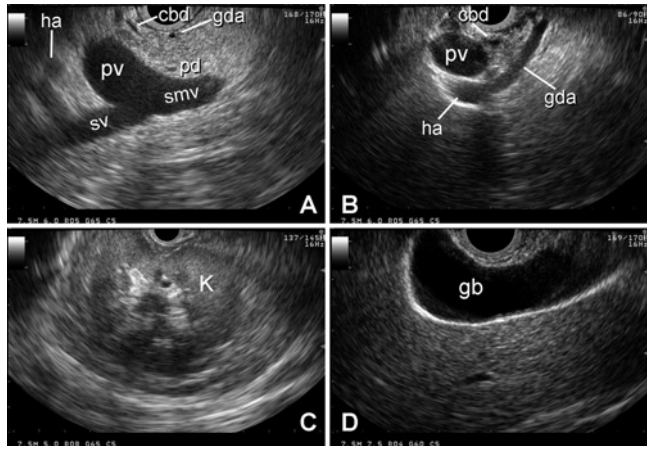

Figure 7.9 (A) Linear view from the first duodenal station (Figure 7.7A,B) where the echoendoscope is in a long position inserted deep into the duodenal bulb. From here the bulk of the pancreatic head is visible with the pancreatic duct (pd) running deep towards the neck. The common bile duct (cbd) is seen in cross-section as is the potentially confusing gastroduodenal artery (gda). The portal vein (pv), superior mesenteric vein (smv), splenic vein (sv) confluence is the prominent deep structure. Deep to the portal vein is the hepatic artery (ha). (B) More counterclockwise rotation from above brings the porta hepatis into view with the triad of the portal vein, common bile duct and hepatic artery in cross-section. Notice the large gastroduodenal artery coming off the hepatic artery which can be mistaken for the common bile duct. (C) Anywhere in the second portion of the duodenum, the right kidney (K) may be seen. (D) Rotation 180 degrees in the duodenal bulb or antrum usually will result in views of the gallbladder (gb).

ampulla represents primarily the ventral pancreas. The echolucency of the ventral anlage commonly seen by radial endosonography [4] may be less apparent by linear EUS (Figure 7.8B). At this level, if vessels are seen deep to the pancreatic head they are usually the superior mesenteric vein and artery. If the echoendoscope is placed deeper into the duodenum, a linear view of the aorta or inferior vena cava may appear in either transverse section as seen radially (Figure 7.8C) or longitudinally. If one inserts the echoendoscope into the third portion of the duodenum, one may see the uncinate portion of the pancreas nestled among the vessels of the mesenteric root (Figure 7.8D). Because this is a difficult view to get with a radial instrument, the same view using a linear instrument is sometimes the only way in which deep uncinate tumors may be seen. Anywhere in the second portion of the duodenum, views of the right kidney may appear. It is usually easy to pick out because of the characteristic appearance of the kidney (Figure 7.9C); however, sometimes the right renal vein or artery may be confused for a mesenteric vessel or duct. If there is any doubt, this can be resolved by following the vessel to its origin in the renal hilum or using pulse Doppler to determine that the structures are systemic veins or arteries.

From the home base of the ampullary region, further gradual withdrawal and rotation to the left (counterclockwise) will follow the course of the tubular structures of the porta hepatis (Figure 7.9B). The largest structure seen in cross section will usually be the portal vein which can be followed arising smoothly from the superior mesenteric vein. Sometimes, the splenic vein will be seen coursing into the portal vein/superior mesenteric vein from deep to these vessels (Figure 7.9A). This view is usually easier to obtain when the scope is first inserted into the duodenal bulb where the scope tip is oriented more cephalad (Figure 7.7B). Again, color flow Doppler or pulse wave analysis can help clear up any confusion about this. The pancreatic head can also be viewed at this level as the tissue between the superior mesenteric vein/portal vein and the duodenal wall.

Further leftward rotation and withdrawal into the duodenal bulb (Figure 7.9B) follows the course of the common bile duct up to the level of the common hepatic duct. The common bile duct will be seen between the duodenal wall and the portal vein but can sometimes be difficult to distinguish from vascular structures such as the gastroduodenal artery. As the echoendoscope is rotated up and down the porta hepatis, the hepatic artery (ha) will usually be seen above or deep to the portal vein. The gastroduodenal artery comes off the hepatic artery then travels towards the duodenal wall where it can run near the common bile duct. Rotation of the linear array echoendoscope almost 180 degrees counterclockwise from the pancreas in the duodenum or duodenal bulb should produce images of the gallbladder (Figure 7.9D). The right adrenal may also be seen from the bulb deep to the inferior vena cava or near the upper pole of the right kidney.

The linear rectum

Male

Linear evaluation of the rectum is usually reserved for therapeutic purposes such as EUS-guided fine needle aspiration. I find that negotiating the tortuous rectosigmoid is much easier to accomplish with a radial echoendoscope under ultrasonic guidance than with a linear echoendoscope. As with the radial rectal examination, the echoendoscope is usually inserted to the mid-sigmoid colon and then withdrawn. The first structures to come into view in both sexes will be cross-sectional images of the iliac vessels. These can be seen anywhere from 15 to 25 cm from the anus, depending on the orientation of the sigmoid colon. Withdrawal of the echoendoscope to approximately 7 to 11 cm in the rectum, with rotation to the right or left, will bring into view the easily identified home base structure in the male rectum, the prostate (Figure 7.10A). Just proximal to the prostate lie the seminal vesicles arising to the right and left of the prostate with the bladder seen more proximally and deep to the seminal vesicles. In older men the prostate often contains bright echoes from small calcifications. Withdrawal of the echoendoscope distally from the prostate reveals a short portion of the membranous urethra diving away from the lumen of the rectum toward the root of the penis (Figure 7.10B). The muscular peroneal membrane may also be visible distal to the membranous urethra.

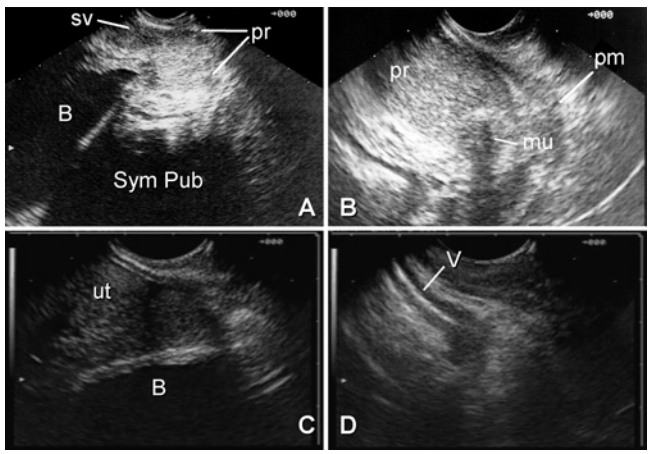

Figure 7.10 (A) Linear view of the male rectum at about 9 cm from the anal verge. The seminal vesicles (sv) are caudad to the prostate (pr). Deep to this is the bladder (B). (B) At the distal end of the prostate, the membranous urethra (mu) and perineal membrane (pm) mark the end of the male pelvis. (C) Linear view of the female rectum at about 9 cm showing the uterus (ut) and the deeper bladder. (D) At 5 to 9 cm from the anal verge, the vagina (V) is easy to detect because of the small amount of air within it producing a bright stripe.

Female

In females, withdrawal of the echoendoscope from the sigmoid colon will bring the uterus into view with the deeper bladder (Figure 7.10C). Sometimes the left adnexal structures can also be seen on deep insertion near the pelvic rim vessels. Withdrawal from the level of the uterus will show a home base view of the air stripe of the vagina anteriorly, with portions of the urethra seen deep to it (Figure 7.10D). The anal sphincters are more difficult to assess with linear than by radial endosonography and most anal sphincter studies are done using radial systems. If linear endosonography is used, the internal sphincter is seen as an echolucent layer just deep to the bright anal mucosal layer. Deep to the internal sphincter, the external sphincter blends into the other muscle layers of the levator ani complex.

Conclusion

Although most endosonographers look at linear EUS anatomy as more difficult than radial, it can be mastered through dedicated focus on the anatomic relationships of the organs and vessels around the gut. Once those relationships become "second nature", then remembering the ever changing direction of the tip of the linear echoendoscope in various locations will allow the endosonographer to put those anatomic relationships into clinical practice.

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8 Fundamentals of EUS-FNA

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Endoscopic ultrasound (EUS)-guided fine needle aspiration biopsy (EUS-FNA) has extended the application of EUS. Through this procedure, pathological examination of abnormalities discovered on imaging studies can be made. EUS-FNA has become an important diagnostic tool as it permits sampling of lesions not amenable to percutaneous biopsy or which are too small to be identified by other imaging modalities. This chapter focuses primarily on the fundamentals of performing EUS-FNA and is not intended to be a comprehensive literature review on EUS-FNA.

The safety and accuracy of EUS-FNA has been elucidated in a large number of studies involving thousands of patients [1–5]. Although diagnostic accuracy and risk are biopsy site dependent, most series report sensitivity for detection of malignancy ranging from 85% to 100% with rare complications [1,2]. The addition of EUS-guided Trucut biopsy (Quick-Core, Wilson-Cook, Winston-Salem, NC) can further enhance diagnostic accuracy in certain situations, such as stromal and hematopoietic tumors and cystic neoplasms of the pancreas [6–9].

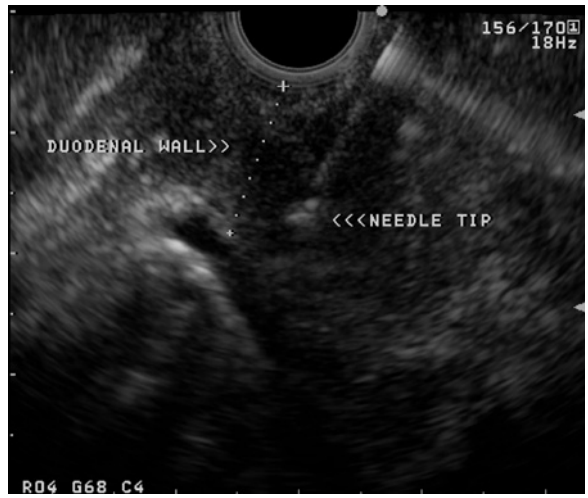

Figure 8.1 Fine needle aspiration of duodenal wall infiltration in a patient with lymphoma who presented with extensive lymphadenopathy.

Indications for EUS-FNA

EUS-FNA of intramural (Figure 8.1) and peri-intestinal (Figure 8.2) structures can be readily accomplished from different sites of the digestive tract. These sites afford an acoustic window to peri-intestinal and mediastinal structures thus obviating the need for more invasive sampling techniques such as mediastinoscopy. (Figure 8.3). In the hands of a skilled endosonographer, the pancreas (Figure 8.4), liver (Figure 8.5), kidneys, adrenal glands, biliary tree, as well as pleural or peritoneal based fluid collections can be successfully biopsied or aspirated [10–14]. Although thyroid and pericolonic lesions are accessible via EUS-FNA, experience in these settings has been limited [15]. Recently, celiac ganglion sampling to determine extrapancreatic neural invasion in patients with pancreatic cancer has been described [16].

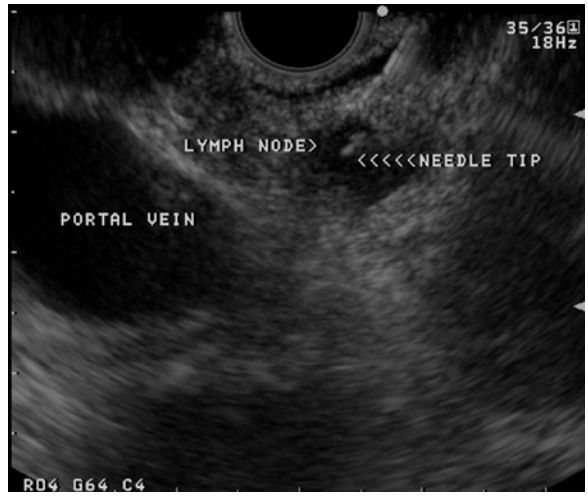

Figure 8.2 Fine needle aspiration of a portal hilar lymph node measuring 0.85 cm in a patient with pancreatic adenocarcinoma.

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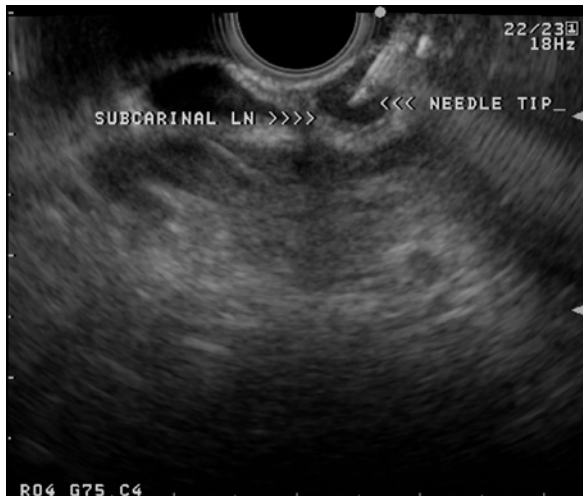

Figure 8.3 Fine needle aspiration of a subcarinal lymph node in a patient with a pancreatic mass.

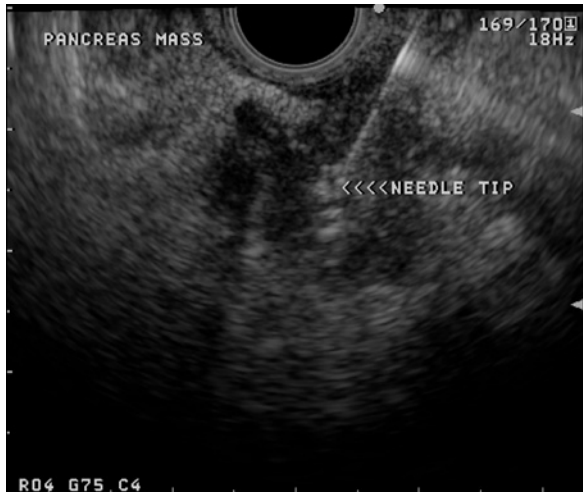

Figure 8.4 Fine needle aspiration of a pancreatic mass.

At present, the established indications for EUS-FNA are:

1. Primary diagnosis of parenchymal and intramural lesions of the gastrointestinal tract, including peri-intestinal organ systems.
2. Staging of digestive and pulmonary malignancies (Figure 8.3).
3. Evaluation of unexplained mediastinal, retroperitoneal and/or abdominal lymphadenopathy (Figures 8.2 and 8.3).
4. Sampling of peritoneal and pleural fluid for diagnostic purposes.
5. Prior nondiagnostic biopsy procedures for above described conditions.

Absolute contraindications

1. Uncorrectable coagulopathy with INR $>$ 1.5.
2. Uncorrectable thrombocytopenia with platelet count $<$ 50,000/μL.

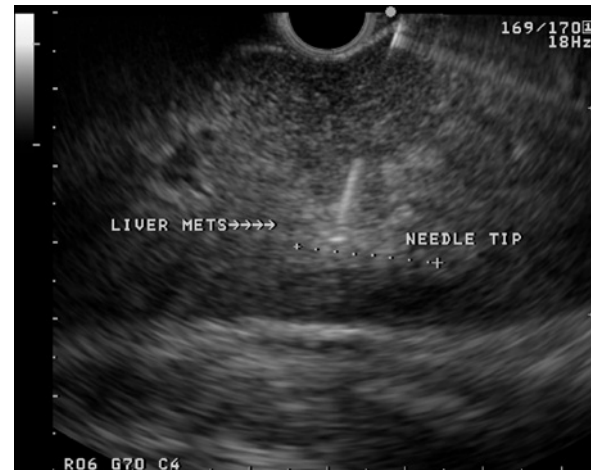

Figure 8.5 Fine needle aspiration of liver metastases in a patient with pancreatic adenocarcinoma.

Relative contraindications

1. Biliary obstruction without prior decompression.
2. Bronchogenic duplication cyst.
3. Mesenteric venous collaterals obstructing the needle trajectory.
4. Luminal stenosis requiring dilatation.
5. Biopsy of suspected malignant structures which may lead to clinically significant spread via the needle tract.

Prophylactic antibiotics

The risk of bacteremia related to EUS-FNA of solid lesions in the upper intestinal tract is rare and similar to diagnostic endoscopy. Therefore, biopsy of these lesions does not require antibiotics [17,18]. However, the biopsy of cystic lesions has been associated with serious infectious complications [2]. All patients undergoing aspiration of a cystic lesion or sampling of any fluid compartment should receive prophylactic antibiotics that are active against enteric organisms. Fluoroquinolone antibiotics or amoxicillin–clavulanic acid are acceptable and should be given pre-procedure and continued for 48 hours afterwards. This is to prevent local infectious complications rather than the systemic sequelae of bacteremia. Similar to solid lesions in the upper intestinal tract, the risk of bacteremia secondary to EUS-FNA of solid lesions in the lower gastrointestinal tract has also been reported to be clinically insignificant and prophylactic antibiotics are not recommended [19].

Equipment

The curvilinear echoendoscope permits continuous visualization of the needle as it is advanced beyond the biopsy channel. Most

instruments are equipped with an elevator that facilitates targeting of biopsy sites. EUS-FNA needles are available in several sizes from several manufacturers, with the most common being needles 22 gauge in diameter. A significant advantage between 19, 22, or 25 gauge needles has not been demonstrated in the sampling of pancreatic masses with regard to yield or safety [20]. All needles come with central stylets which may be beveled or ball-tipped. A 19 gauge Trucut core needle biopsy system (QuickCore, Wilson-Cook, Winston-Salem, NC) is now available [6]. The stiffness of the Trucut device limits biopsies to sites requiring minimal angulation of the echoendoscope tip. Due to the expense, stiffness of the device, and associated potential complications, its use is reserved for patients in whom FNA sampling and cytology is non diagnostic or when core specimens are mandatory for diagnosis.

The presence of an onsite cytopathologist can be extremely useful and has been show to improve diagnostic sensitivity by approximately 10% to 20%. In addition to confirming the adequacy of the biopsy sample, the cytopathologist can also direct additional testing depending on the preliminary findings.

In an ideal setting, two assistants are required to perform an EUS examination efficiently. The nurse monitors the patient's response to sedation while the technician facilitates the equipment needs of the endosonographer. With the addition of FNA, a third assistant, preferably a cytotechnician, may be needed to assist with slide preparation. The biopsy specimens are either reviewed by an onsite cytopathologist for a preliminary interpretation or sent to the pathology department to be examined at a later date. Patients scheduled for FNA will typically require deeper sedation than for conventional endoscopy to prevent potential complications. The presence of an anesthesiologist for monitoring and administering sedation enhances patient comfort and can potentially decrease the risk of complications.

Procedure

Patients scheduled for an examination of the upper gastrointestinal tract require an overnight fast and those undergoing examination of the lower gastrointestinal tract require a complete colonoscopy preparation. At the outset, certain basic key principles are worth emphasizing. The learning curve for EUS is very steep and complete confidence in identifying structures with linear imaging is imperative to avoid serious and potentially life-threatening complications.

1. Consider performing upper endoscopy with a forward-viewing or side-viewing instrument depending on the area of the upper gastrointestinal tract to be examined. One should identify luminal abnormalities and note their location relative to anatomic landmarks. This is of utmost importance in patients with luminal narrowing secondary to esophageal cancer or pancreatic masses which compress or deform the lumen, as passage of a larger diameter echoendoscope with its limited endoscopic field of view may lead to inadvertent perforation.

2. When appropriate, initially perform a radial EUS examination to identify intramural and periluminal abnormalities. This may be unnecessary in patients with pancreatic pathology as the imaging plane with the linear echoendoscope should provide complete visualization of the pancreas. If a malignancy is being evaluated, a complete diagnostic EUS should be performed initially to allow adequate staging. The site selected for EUS-FNA should represent that which would provide the most advanced stage disease if malignancy is ultimately identified.

3. The targeted lesion is placed in the projected plane of the needle path. Tubular structures between the transducer and target should be avoided as they may represent vascular structures. Doppler should be utilized to detect vascular structures. In patients with portal hypertension, particular care must be taken in that compression of the lumen may mask interposed varices.

4. The needle catheter device with the stylet in place is advanced through the biopsy channel after removing the rubber valve. The elevator should be in the down or fully released position to facilitate mounting of the device. The device is secured to the Luer lock on the biopsy port. Prior to inserting the needle device through the biopsy channel, the needle should be locked in a fully withdrawn position to avoid damaging the channel of the echoendoscope.

5. The optimal degree of balloon inflation that should be present when performing EUS-FNA will be gleaned from experience and personal preference but is generally less than for the radial examination. The balloon is typically left inflated with the up/down ratchet turned 'up' to displace the balloon behind the transducer. This is done to decrease the risk of balloon puncture while the needle is being advanced. Within the esophagus, duodenum and colon, balloon inflation can also help stabilize the position of the echoendoscope tip. With the needle sheath protruding from the biopsy channel a small pocket of air is potentially created which diminishes acoustic coupling and impairs imaging. This can be overcome by periodically or continuously applying suction.

6. The EUS image typically is oriented so that the needle enters the ultrasound view from the right side of the screen and courses toward the bottom left corner of the image. When utilizing Olympus echoendoscopes, the targeted lesion should be at the 6 o'clock position in the center of the ultrasound image field. Optimal position when using Pentax echoendoscopes is slightly to the left. As one is gaining experience with the technique, the distance from the transducer to the center of the targeted lesion can be measured and the depth stop set at this distance to avoid over-advancement of the needle. Under real-time imaging, the needle is then advanced into the target. Occasionally the stylet must be withdrawn slightly to make the needle sufficiently pointed to traverse the gut wall or enter the lesion.

7. Once in the target, the stylet is removed and negative pressure is applied with a 10 mL syringe. The degree of negative pressure may be important. In vascular tumors or lymphoid structures, limited or no negative pressure results in a less bloody aspirate that may allow for easier cytological interpretation. In general, the degree of negative pressure should be increased if the initial

biopsies are suboptimal and decreased following bloody aspirates. One study suggested that the cellularity of the sample was increased with suction during the sampling of lymph nodes, but did not improve the likelihood of a correct diagnosis [21]. The location of the aspiration within the lymph node did not influence the accuracy of the findings. Several manufacturers' needles are equipped with a locking syringe, thereby simplifying this task. Since echoendoscopes from different manufacturers having different lengths, some needle manufacturers have developed an adjustable sheath length or spacers to accommodate the variation. Our preference is to use a needle that is made specifically for the length of the instrument we use and thereby avoid the potential for inadvertent biopsy channel puncture by misjudging the proper sheath length.

8. With negative pressure applied, five to ten gradual to-and-fro movements are made within the lesion. One should maintain the position of the needle within the target, avoiding accidental withdrawal into the lumen when negative pressure is applied. If this occurs, the specimen may become contaminated with the lumenal contents and epithelium. Prior to removing the needle, the negative pressure is released by gradually releasing the syringe plunger, and not forcing it back to its neutral position. With the needle fully withdrawn and the stop secured, the device is unscrewed and removed from the biopsy channel.

9. Slide preparation:

- Slides and glass tubes for specimen collection should be labeled individually with the patient identification and pass number.
- The material is sprayed onto glass slides with subsequent fixation as determined by the type of specimen being examined.
- A saline wash through the needle is collected for a cell block. Each pass should be collected in a separate glass tube. The stylet is cleaned with a gauze to remove any remaining blood. The needle is purged of residual saline with air and the stylet is reinserted.
- If the needle is obstructed, the stylet should be used to clear the device.
- Material for culture and special studies can be collected in preservative media as recommended by a pathologist.
- For cystic lesions, the entire specimen can be left in a syringe. The specimen should not be diluted if biochemical analysis is planned. When the cyst volume is limited, the laboratory tests should be prioritized in case all the requested studies cannot be performed.

10. If a cytotechnologist or a cytopathologist is unavailable to evaluate the sample, three passes in lymph nodes and five to six passes in pancreatic lesions typically ensures adequate cellularity in $>90\%$ of cases [22–24].

Modifications of technique

Several special circumstances may arise that require modification of the above technique.

The muscularis propria of the stomach can be difficult to penetrate. The needle can usually be advanced through the intestinal wall by using the elevator to produce a more orthogonal angle of needle entry and by using a swift jabbing motion during puncture. In this setting, securing the needle stop to a specified depth may minimize the potential for overextension. If using an instrument without an elevator, advancing the echoendoscope after engaging the needle in the gastric wall may change the angle of entry to a more perpendicular orientation. Occasionally one may withdraw the stylet slightly to enhance the sharpness of the needle tip.

When performing EUS-FNA of small lesions <5 mm, maximal magnification of the EUS image will facilitate targeting and confirmation of entry into the lesion. Care should be taken not to overextend the needle while the image is magnified.

Small lesions that are firm may appear to deflect the needle or may be considerably difficult to enter. A needle trajectory that is close to perpendicular to the surface of the lesion is ideal. Similar to lesions in the muscularis propria, a rapid jabbing motion may facilitate needle entry. In some circumstances an adjustment in the needle direction may be needed once the intestinal wall has been traversed.

Occasionally the stylet can no longer be used after multiple biopsies have been obtained secondary to deformation during its use in areas of extreme tip angulation. Advancing the needle into lymph nodes and cystic pancreatic lesions is best done with a stylet in place to avoid contamination by luminal epithelial cells. For solid pancreas lesions and liver masses, this may not be a concern.

After several passes, the needle will develop a curve that can result in a needle trajectory outside of the plane of imaging. When this occurs, the echoendoscope should be rotated in the direction opposite to the curve to compensate. If the above fails, the entire needle apparatus should be replaced.

Bloody aspirates can arise from vascular lesions despite discontinuation of anticoagulant/antiplatelet agents for several days. As mentioned above, reduction of the negative pressure may reduce contamination with blood. Additionally, targeting the edge of the lesion may improve the diagnostic yield.

Hypocellular specimens typically reflect errors in targeting, insufficient negative pressure, and/or desmoplastic lesions.

If blood is visualized in the aspirating syringe during EUS-FNA, the entire specimen should be placed in a glass tube, as little of the material contained within the needle will be of the intended target.

Occasionally an echo-poor expanding region will arise around the biopsied lesion or within a cyst after FNA (Figure 8.6). This represents hemorrhage [25,26]. If intramural hemorrhage is suspected, we typically apply pressure with the echoendoscope transducer at the biopsy site and observe the area for 10 to 15 minutes to ensure that hemostasis is achieved. Most cases of bleeding are self-limited unless the patient is anticoagulated or on potent antiplatelet medications such as clopidogrel. When the bleeding is limited and identified in patients with normal hemostatic parameters, this does not appear to be clinically significant and does not necessitate an alteration in post-procedure care.

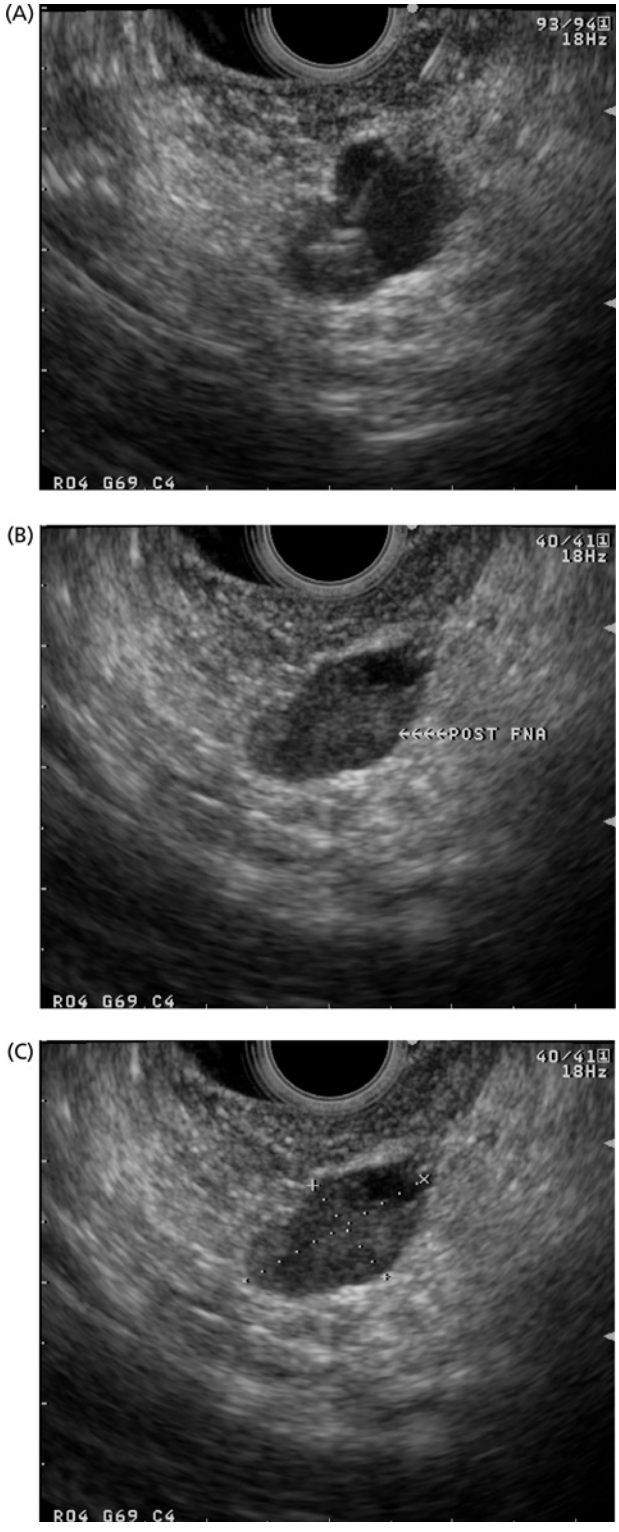

Figure 8.6 (A) Fine needle aspiration of a pancreatic cyst with intracystic solid component. The needle tip is located in the intracystic solid component. (B) Intracystic blood seen after fine needle aspiration. (C) Intracystic blood seen after fine needle aspiration.

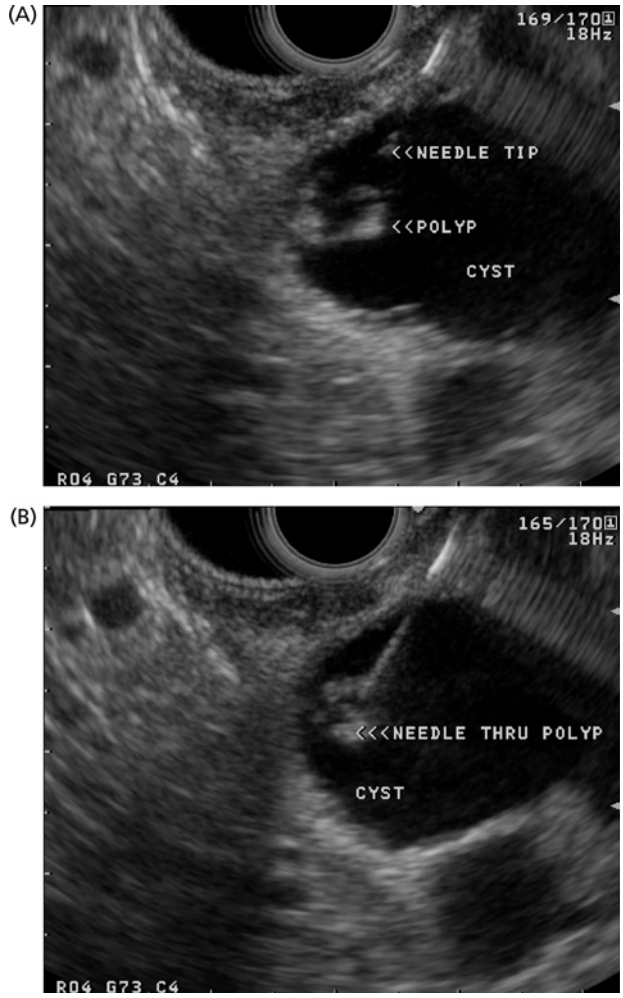

Figure 8.7 (A) Fine needle aspiration of a pancreatic cyst with intracystic solid component. (B) Fine needle aspiration of the polyp within the cyst.

Some other practical technical details that are helpful for the endosonographer are outlined below.

1. Applying torque in a straight scope position with the left hand transmits the torque to the scope tip much more effectively. This maneuver is essential, as continuous visualization and monitoring of the needle tip during FNA is imperative. This also aids in modifying the force being applied during biopsy as some of the targeted structures are firm in consistency. One example of a lesion that is potentially firm in consistency is a solid pancreatic mass (Figure 8.7A). Constant visualization of the needle path ensures that the needle actually traverses the structure rather than anchoring it and moving the whole target during the needle strokes. The force and the extent of the stroke should be constantly adjusted, as FNA represents a dynamic process and the targeted lesion may change in appearance during aspiration (Figures 8.6, 8.7).

2. The use of the elevator during FNA offers both advantages and disadvantages. Forceful use of an elevator can bend the needle

tip so that subsequent passes are almost impossible as the needle fails to traverse the target lesion because of tip deformation. In contrast, gentle use of the elevator can be helpful when a change in trajectory is needed to obtain samples from different regions of the target. This is illustrated in Figure 8.7A,B. These figures demonstrate the aspiration of a pancreatic cyst and subsequent change in trajectory of the needle to sample the intracystic solid component.

3. Increasing the distance between the endosonographer and the patient and using the body or thigh to stabilize the scope position can both facilitate performing FNA. The endosonographer is typically facing the ultrasound console located to the left of the patient's head, and the assistant can be situated across from the patient or on the same side depending on the echoendoscope position.

4. Ideally, the procedure room should be equipped with multiple monitors. One monitor can be positioned on the same side of the patient as the endoscopist. This monitor should have interchangeable endoscopic and microscope views so that the endoscopist can easily visualize both the real-time ultrasound and microscopic FNA samples as they are being examined by the pathologist.

5. The number of passes needed to obtain a successful sample is inversely proportional to the experience of the endosonographer. The presence of an onsite cytopathologist or cytotechnician also helps limit FNA attempts by obviating the need for multiple unnecessary passes required to secure the diagnosis.

6. Doppler of the intended target and the surrounding structures is helpful to identify any potential vascular structures in the needle path and should be used whenever vascular structures are in question. If no better window for performing EUS-FNA is available, careful navigation between vascular structures using the elevator should be attempted.

After the procedure

Patients are monitored in a recovery area with discharge criteria equivalent to standard endoscopic procedures. We advise patients who undergo pancreatic EUS-FNA to consume clear liquids on the day of the procedure and to contact us immediately if there are any signs of a complication. In patients who undergo prolonged procedures or require large doses of analgesia, we provide 500 to 1000 mL of intravenous normal saline and consider a single dose of an antiemetic during the recovery period. Patients undergoing liver biopsy are observed for 2 hours with adherence to bed rest and are advised to minimize activity for 24 hours. Those patients who undergo aspiration of a fluid compartment such as a cyst are provided a prescription for an oral antibiotic to be taken for 48 hours.

Training

Standardizing EUS training and credentialing will improve patient care. This topic is addressed in Chapter 21. The American Society for Gastrointestinal Endoscopy has published guidelines for achieving competence in EUS and EUS-FNA. These guidelines represent a minimum number of procedures necessary to gauge competency and may serve as a resource for practitioners interested in acquiring these skills [27,28]. A general consensus by EUS experts concluded that luminal (GI) EUS requires at least 3 to 6 months of intensive training to establish competency, whereas pancreatobiliary EUS and FNA may require 12 months [29,30]. EUS-FNA training should begin with readily accessible lesions followed by more difficult lesions once a sufficient degree of comfort has been obtained. Attending EUS courses taught by expert endosonographers and hands-on training in live animal laboratories or simulators is another option if participation in a formal training program is not feasible. Simple models for training for EUS-FNA have been presented [31,32]. Training on live pigs has also been described [33,34]. The value of all of these models is complementary rather than competitive and will shorten the learning curve during training.

Safety

Overall EUS-FNA is a safe technique if performed by a well-trained endoscopist in the appropriate clinical setting. Aside from the complications that are attendant with endoscopy there are certain unique complications that the endoscopist should be aware of during and after the procedure. The literature describes thousands of patients who have safely undergone the procedure. Their follow-up has revealed infrequent complications thus assuring the safety of this technique and validating its increasing use.

In a multicenter prospective evaluation, EUS-FNA was performed in 457 patients with 554 lesions. Five nonfatal complications occurred at a rate of 0.5% in solid lesions vs. 14% in cystic lesions [2].

In a single-center study, a total of 355 consecutive patients with a solid pancreatic mass underwent EUS-FNA. Major complications were encountered in nine patients (2.54%). Acute pancreatitis occurred in three of 355 (0.85%); two patients were hospitalized and one patient recovered with outpatient analgesics. Three patients were admitted for severe pain after the procedure; all were treated with analgesics and subsequently discharged with no sequelae. Two patients (0.56%) developed fever and were admitted for intravenous antibiotics; one patient recovered with intravenous antibiotics and the other required surgical debridement for necrosis. One patient required the use of reversal medication. Overall, 1.97% of patients were hospitalized for complications. None of the patients experienced clinically significant hemorrhage, perforation or death, and no clear predisposing risk factors were identified [5].

The incidence of acute pancreatitis after EUS-FNA of solid pancreatic masses was evaluated in a multicenter analysis with a total of 4909 EUS-FNA procedures performed over a 4-year period. Pancreatitis occurred after 14 (0.29%) procedures.

At two centers in which data on complications were prospectively collected, the frequency of acute pancreatitis was 0.64%, suggesting that the frequency of pancreatitis in the retrospective cohort (0.26%) was under-reported ($P = 0.22$). The median duration of hospitalization for treatment of pancreatitis was 3 days. Pancreatitis was classified as mild in ten cases, moderate in three, and severe in one; one death occurred after the development of pancreatitis in a patient with multiple comorbid conditions [35].

Acute intracystic hemorrhage during EUS-FNA (Figure 8.6) is a relatively rare complication and should be recognized as an echo-poor expanding lesion in the cyst, and further attempts at FNA should be avoided [26].

Pneumoperitoneum has been reported when endoscopy closely followed EUS-FNA, suggesting that intestinal insufflation should be minimized or avoided for a short period (e.g. 2 days) after EUS-FNA [36]. Same-day ERCP following EUS-FNA should be avoided [37].

The risk of bacteremia appears to be very low [17–19,38]. However, as noted above, antibiotic prophylaxis has been recommended before FNA of cystic lesions. Complication rates after biopsy of pancreatic cystic lesions appear to be similar to those observed after biopsy of solid lesions. In a study involving two centers with a total of 603 patients with 651 pancreatic cysts, complications occurred in 13 patients (2.2%): six patients had pancreatitis, four patients had abdominal pain, one patient had a retroperitoneal bleed, one patient had an infection, and one patient had bradycardia. Twelve patients required hospitalization, with an average length of stay of 3.8 days. The type of cyst, size, presence of septations or mass, and same-day ERCP were not predictors of complications [39].

A learning curve exists for EUS-FNA, which may have bearing on the likelihood of complications as shown in evaluation of a single endosonographer whose complication rate was prospectively evaluated in 300 consecutive EUS-FNA of solid pancreatic masses performed over a 3-year period. The endosonographer had undergone a third-tier EUS fellowship and had performed 45 supervised pancreatic EUS-FNAs during his training. The median number of passes was lower and there was less likelihood of encountering complications in the third year involving the last 100 cases [40].

In summary, EUS-FNA represents a versatile and safe technique with a very low complication rate when performed by a well-trained gastroenterologist in the appropriate clinical setting. The indications are ever expanding as it represents a relatively noninvasive technique which is performed on an outpatient basis with associated decreased costs and morbidity.

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9 EUS-FNA Cytology: Material Preparation and Interpretation

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Introduction

EUS has developed into a leading modality for obtaining tissue from submucosal lesions in the gastrointestinal tract or from organs near the gastrointestinal tract such as pancreas, lung and lymph nodes. A pathologist represents an important member of the patient care team, since microscopic evaluation is a key in determining the nature of the sampled lesion. This chapter outlines issues in the preparation and interpretation of tissue samples obtained via EUS guidance with the goal of improved diagnostic yield. This chapter is divided into three sections which relate pathology and EUS: the technical quality of the material, the quality of the pathological interpretation and the integration of pathological and clinical data.

The goal of the pathologist is to contribute to a successful EUS service by providing accurate and precise diagnostic information. Although EUS guided sampling is a relatively newer way of obtaining tissue, the means of preparing the cells or tissue are well developed and standard procedure in most cytology/anatomic pathology laboratories. In this chapter, the term "biopsy" will refer to any tissue sample obtained via EUS guidance. A "biopsy" could be a fine needle aspirate (FNA) representing cells obtained through a small needle and dispersed onto slides, or a core, representing an intact piece of tissue. The advantages and disadvantages of each type of biopsy will be discussed later.

Technical quality of EUS biopsy material

There are a number of techniques and strategies which can optimize the technical quality of EUS biopsy material.

Personnel

Before developing an EUS service, it is important to involve a pathologist or cytotechnologist in planning for specimen handling. Selection of pathological evaluation performed on material depends on the personnel and laboratory resources available. Use of a liquid-based cytological preparation, direct smears, core biopsy or some combination of these methods depends on the lesion, pathologist and endoscopist preference, staffing, location of the endoscopy suite in relation to the laboratory, and the relative sensitivity, specificity and diagnostic accuracy of the various technical choices.

Staff personnel issues are critically important in planning for an EUS service. For example, at some institutions, the laboratory is physically close to the endoscopy suite and a laboratory technologist travels to the site to prepare aspirate smears, while in other practices the gastrointestinal endoscopy staff is trained to make slides. If laboratory personnel help prepare specimens, the scheduling of procedures should be done in consideration of the laboratory schedule and any ancillary tests such as flow cytometry which might require special processing.

Biopsy type: aspirate or core?

There are two ways of obtaining biopsy material from a lesion. One is to cut out a small piece of the lesion with a cutting needle and the other is to aspirate individual cells and small fragments of tissue. Core biopsies provide tissue architecture, that is, the relationship of the lesional cells and their surrounding stroma are maintained. In core biopsies, vascular and duct structures usually remain intact. In an aspirate sample, the cells are dispersed although some microarchitecture remains.

Tissue obtained with a core biopsy is typically fixed in formalin, processed and embedded in a paraffin block from which 3 to 5 μm sections are cut and stained. The procedure is essentially identical to the way in which mucosal biopsies from the gastrointestinal tract are processed. These are the blue and pink hematoxylin and eosin stained slides with which all pathologists and gastroenterologists are familiar.

An aspirate biopsy is usually obtained with a "fine" needle which is 22 gauge or smaller [1]. In this type of biopsy, the material flows or is actively aspirated into the needle and then dispersed onto a slide or placed directly into a preservative or fixative for

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processing. Smears are prepared in a manner similar to that used in making blood smears. A small drop of the aspirate is placed on one end of the slides and then carefully pulled along the slide to make a dispersed layer of individual and small groups of cells. The features of the cells appear somewhat different in smears than in tissue sections and also depend on the type of smear preparation and staining. In many pathology laboratories, aspirate smears are prepared as both air-dried and alcohol-fixed smears.

Different criteria are used in interpreting tissue sections and cytology smears. In the tissue sections, preservation of the architecture allows observation of features such as the shape of glands, quality of the surrounding stroma, presence of vasculitis and others. In a cytological preparation, the diagnostic features of a lesion are based on fine detail of nuclear and cytoplasmic membranes of individual cells.

While examination of tissue sections is the core practice of pathologists, not all pathologists practice cytopathology and, in general, more pathologists are comfortable interpreting tissue sections [2]. For this reason and others, some believe that a tissue core is a better choice. The issue of core vs. aspirate can be debated, however, the two methods are complementary. Various strategies of "dual sampling" or sequential sampling, that is, using FNA when the core is macroscopically inadequate, have been examined [3]. For some situations, such as autoimmune pancreatitis, a core biopsy may provide better diagnostic material [4]. The tissue architecture of a core biopsy may be useful for traditional diagnostic criteria for lymphomas, and can help distinguish invasive and in situ malignancies or very well-differentiated malignancies such as some pancreatic carcinomas. In addition, core biopsy may require fewer needle passes for diagnostic material [5]. EUS-guided core biopsies are a recent technical development and have not been studied as completely as EUS-FNA, so the true diagnostic accuracy remains to be determined [6,7].

A potential advantage of core biopsy is that tissue remains in the paraffin block and is available for special stains or other studies as needed. Core biopsy may lead to a more confident benign diagnosis when used in combination with FNA for mediastinal lesions [8] but may be less sensitive in the pancreas [9]. Potential disadvantages to core biopsy include more tissue damage [7,10]. Deployment of a Trucut or other needle for core biopsy may also depend on characteristics and location of the lesion as well as clinical and imaging differential diagnosis [12].

Cell block

Preparation of a cell block from aspirate material can preserve material for special studies in a manner similar to a core biopsy. A cell block is made by placing the aspirate in a preservative medium such as RPMI, centrifuging the media to create a cell pellet, fixing the cells in formalin and then processing the pellet as a tissue biopsy [13].

A cell block has some but not all attributes of a biopsy. While the sections may seem more familiar to pathologists, formalin fixation and paraffin embedding is not optimal for preserving cytological detail [14] and cell block is not usually a "stand-alone" preparation. Cell blocks are however useful as a repository of lesional tissue on which special stains can be performed [15].

At some institutions a cell block is made from leftover material rinsed from the needle and may not contain cells from the lesion [16]. One way to ensure that the cell block contains useful material is to aliquot drops of material to the cell block medium at the same time as the slides are made. This procedure is discussed below.

A new method is that of brush cytology performed through the FNA needle. In a preliminary study, this method showed promise for cystic pancreatic lesions because it yielded more cellular specimens, but will require more testing and validation [17].

Needle size

The choice of needle size can influence the cytology preparation. Needles as small as 25 gauge have been shown to produce adequate numbers of cells for diagnosis. Furthermore, small needle sizes theoretically produce less tissue injury and less bleeding, decreasing the risk that diagnostic cells will be obscured by blood [18,19]. Smaller needle size may also be beneficial in patients with coagulopathy to reduce the risk of bleeding, in organs where air or fluid leak may occur, or in organs where tissue trauma could increase complications. Larger gauge needles can be used where a larger volume of cells is needed such as a workup for lymphoma [18].

Needle preparation

Heparin may be used in aspirate procedures to decrease clot formation in the needle lumen [20]. Typically, the stylet is completely removed from the needle and then the needle flushed with heparin. Air is then flushed through the needle to expel the excess heparin. The stylet is then replaced and the needle is ready for use. Use of heparin may have particular application to EUS aspirates in which the needle is extremely long. Clotting can interfere with the preparation of aspirate smears, and lead to artifacts such as clumping of cells. Too much heparin however can also distort the cells and thus flushing excess heparin from the needle with air is a necessary step in the procedure. If clots do form, the material trapped inside can be salvaged by gentle microdissection or by scraping the clotted material from the slide and placing it in medium for the cell block.

Suction

Application of suction during fine needle biopsy serves to hold the tissue against the cutting edge of the needle [20]. This may increase the number of cells which are sampled for some lesions. Before withdrawing the needle, however, suction should be released to prevent air drying of cells when air rushes in to the needle as it is removed and also to prevent the theoretical risk of contamination of the needle tract [21,22]. Not all studies document an increased diagnostic yield when suction is used, however, and for vascular organs, use of suction may increase blood contamination of the specimen [23–26]. In addition to increasing the blood in a specimen, suction can induce cytological artifact

[27,28]. This is rarely a problem in practice and, in general, fewer insufficient specimens are obtained when suction is used [29–31].

Slide preparation and staining

Technical aspects of slide preparation can influence specimen quality and ultimately its adequacy. The manner in which material is expressed onto the slide helps ensure optimal slide preparations. A trained technical assistant (nurse, laboratory technician or other person) holds the tip of the catheter needle over the end of a labeled glass slide while the needle is advanced approximately 1 cm from the catheter by another assistant (often the endoscopy technician). The stylet is slowly advanced into the needle. This causes a very controlled passage of single drops of material out of the tip. Alternate drops of the material are placed onto a slide and into RPMI-1640 medium. The optimal distribution of the material for both cell block and smears is ensured by this technique but it requires a very controlled expulsion of the material from the needle to avoid large "globs" of material on the slides. If there is too much material on a slide, the diagnostic cells could be obscured or, worse, drip off the slide. After several slides are prepared the remaining material is placed into medium for cell block. After the slides are prepared the remaining material is rinsed from the needle with a few mL of saline and then air to expel any remaining material into the RPMI. RPMI-1640 is a cell culture medium that is used as transport medium to preserve the cells until they are made into a cell block or sent for flow cytometry or other special study.

Usually between two and six slides are prepared from each pass, depending on the amount of material obtained. More than six slides usually add little to the diagnostic yield and make the cytotechnologist and pathologist unhappy since screening and then reviewing many slides containing only one or two cells of interest is quite time consuming and inefficient.

After the material is placed onto the slides, the drops of aspirated material are quickly spread downward onto the slides using another clean glass slide. This method is identical to that used to prepare a blood smear and requires practice. Too much pressure destroys the cells, while too little causes the cells to remain clumped or to be obscured by blood or mucus. Ideally, half of the slides are air dried and the remainder immediately immersed in 95% ethyl alcohol for later Papanicolaou staining. The air-dried slides can be stained with a DiffQuik™ stain for immediate cytological evaluation by the pathologist, if available. Immediate cytological evaluation is discussed below. When the procedure is finished the alcohol-fixed slides and RPMI-cell suspension are transported to the laboratory for standard Papanicolaou staining and cell block preparation respectively. To prepare a cell block, thrombin is added to the material in RPMI and the mixture centrifuged into a pellet. The pellet is resuspended and then the resulting clot removed, wrapped in lens paper, placed in a tissue cassette, fixed in formalin and routinely processed for paraffin embedding and hematoxylin/eosin or immunostaining. If indicated, material for flow cytometric immunophenotyping or other studies is removed from the RPMI before adding the thrombin.

Although the preparing of both air-dried and alcohol-fixed slides may seem like extra work, the two preparations are complementary and are used to demonstrate different cytological features of lesions. Air-dried smears are stained using a modified Romanowsky stain, such as DiffQuik™. As the cells dry, they spread over the glass and there is an exaggeration of pleomorphism if present. Air-dried smears also highlight intracytoplasmic material, and extracellular substances such as mucin. Air-dried, Diff-Quik-stained smears are also ideal for evaluating lymphoid lesions.

Alcohol fixation preserves nuclear features. Alcohol-fixed slides can be stained with hematoxylin/eosin or Papanicolaou (Pap) stains. The Pap stain highlights nuclear detail, chromatin quality and, if present, keratinization of squamous cells.

Liquid-based preparations

Liquid-based cytology is becoming a common means of preparing many cytology samples, and has been especially successful in gynecological practice. Its use for other samples including those derived from EUS-FNA is increasing. In this method, the zsample is placed into a proprietary fixative and slides prepared by an automated process. The automated sampling and slide preparation is designed to minimize technical problems associated with manual preparation of smears. Two methods are FDA approved. The first is produced by Cytyc Co. Marlborough MA (ThinPrep) and the second by TriPath Inc, Burlington, NC (SurePath™). The advantages of a liquid-based preparation are very consistent and high quality preservation of the cells and improved screening, since the cells are dispersed in a monolayer and confined to a smaller area of the slide than conventional smears. Another advantage is the decreased technical effort involved in slide preparation. Smears do not have to be made at the time of aspiration because the aspirate material is placed entirely into the fixative and transported to the laboratory. This method is especially appealing if the laboratory or pathologist are located at a distance from the endoscopy suite [32].

Liquid-based cytology is more expensive due to the use of proprietary media for fixation, however, and the method causes some alterations in cytological detail that need to be considered in interpretation. For example, the procedure decreases the mucin in a specimen. Although for some specimens, this is a desirable effect, mucin can be a helpful background feature in the interpretation of mucinous pancreatic neoplasms. The liquid-based preparation techniques may also cause disaggregation of cells and loss of microarchitecture. Finally, because the fixative is alcohol based, there may be some degradation of antigens, making immunohistochemistry less reliable.

Quality of the pathological interpretation

Pathologists are becoming more familiar with EUS-obtained material; however, most have limited experience with these specimens. Fortunately, there are a number of courses pertaining to

EUS-FNA which can serve to educate pathologist or endoscopist about pathology issues [33].

Just as the endoscopist's ability to perform EUS-FNA rises on a steep learning curve, so does the pathologist's ability to interpret the material obtained via EUS biopsy [34,35]. EUS-guided biopsies provide access to material, organs and tissues which were previously uncommonly sampled and, therefore, the pathologist may have little experience in interpreting these specimens. There are some peculiarities of samples obtained via EUS such as "noise" or contaminating cells from the digestive system which need to be distinguished from lesional cells.

Review of cytological diagnosis of mediastinal lymph nodes obtained from EUS-FNA shows good reproducibility between pathologists [35]. Performance is better for pathologists with more experience [36].

At centers with experience, false negative and false positive diagnoses are rare [37]. In general, a false negative result occurs when the lesion is not sampled, while false positive results are due to the pathologist's interpretive error. Adherence to criteria for diagnosis of malignancy and basic cytological principles can minimize the possibility of false positive diagnoses, although in published studies, false positive diagnoses are minimal [37,38].

Integration of pathological and clinical information

Rapid cytological evaluation

In an ideal situation, a rapid cytological evaluation is performed during the procedure to assess the adequacy of each pass and to determine whether other studies are needed. During immediate cytological evaluation, a pathologist microscopically examines the air-dried DiffQuik™-stained slides prepared at the site. If the material is adequate for diagnosis, then the procedure is stopped. If there is necrosis or no material, then the endoscopist can redirect the needle to another part of the lesion. The goal of rapid evaluation is to optimize the procedure by reducing the number of unsatisfactory or atypical diagnoses as well as reduce the overall number of passes [39–41]. Rapid evaluation may provide a preliminary diagnosis [41] and reduces the number of false negative procedures due to inadequate sampling.

The literature supports a role for rapid evaluation in optimizing EUS-FNA, however the practice is variable among institutions. Although rapid evaluation improves diagnostic yield, some pathologists are reluctant to provide rapid due to inadequate reimbursement [42] for the increased amount of pathologist time. On an institutional level, however, there may be significant cost savings by reducing the number of repeat procedure due to inadequate specimens [39,43]. Ways to minimize cost include calling the pathologist after several passes have been prepared instead of having them present for the whole procedure, using a cytotechnologist to assess adequacy instead of a pathologist, having the slides transported to the pathologist in real time, or making a gross assessment of the slides without microscopic evaluation.

The ability to redirect the needle during an EUS procedure is one of the chief advantages of EUS-FNA with rapid evaluation over a single needle core. The real-time image of EUS-FNA allows the needle to be placed directly in the tissue of interest [44]. For some tumors, it may be useful to target the edge of the lesion in order to avoid a necrotic center, while for other lesions the center may have a better yield of tumor cells. For example, an aspirate at the edge of a pancreatic cancer may yield only chronic pancreatitis. While precise direction of the needle is not always necessary, a thoughtful approach coupled with rapid interpretation may increase yield in difficult lesions.

Role of the laboratory in EUS

It is important for the pathologist to understand that, in many instances, the EUS procedure is intended to be a diagnostic test rather than a screening test.

Education of the pathologist and laboratory about the direct role they play in the EUS procedure and the patient care algorithm will help ensure the success of the EUS biopsy service [45]. The indications for the procedure and pertinent clinical and imaging details for each patient should be discussed. It is important to know if the procedure is performed for screening, diagnosis or to obtain material for culture, flow cytometry of genetic testing.

Archiving of slides, reports and creation of a database containing pathology and EUS information should be considered as part of a quality assurance and competency program. Records of clinical information, EUS features of a lesion, diagnosis and other data can allow assessment of individual practitioner competency (endosonographer and pathologist), diagnostic accuracy of the service and the utility of various techniques such as immediate cytological evaluation.

Pathologists and their staff should understand the limitations of EUS biopsy, know the technical aspects of their part of the process and be well trained. Laboratory services in the United States are regulated at state and national levels by the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88), the Laboratory Accreditation Program of the College of American Pathologists (CAP) and others. A high quality laboratory provides the best possible service to the patient [46]. Specific details of practice guidelines and other standards are available from the College of American Pathologists and American Society of Cytopathology.

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10 High-Frequency Ultrasound Probes

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Endoscopic ultrasound (EUS) has been developed to use radial and linear array to evaluate the luminal wall and adjacent tissues in the gastrointestinal tract. One of the most important roles of EUS has been the evaluation and local staging of gastrointestinal malignancies [1]. Standard echoendoscopes operate with frequencies between 5 and 20 MHz; the higher the frequency, the better the resolution of the image but the lower the penetration of the ultrasound [2].

High-frequency ultrasonography

The high-frequency ultrasound (HFUS) device is a small-caliber ultrasound probe (less than 2.6 mm) first introduced in 1989 [3] (Figure 10.1). These probes operate with higher frequencies (12 to 30 MHz), obtaining a significant higher resolution than conventional EUS [4,5]. Compared to the standard endoscopic ultrasonography, the high-frequency ultrasound probe is inserted into the accessory channel of an endoscope, allowing its use combined with standard upper or lower endoscopy. The higher resolution of the high-frequency ultrasound probe provides a better definition of the gastrointestinal wall layers, and therefore it yields a better accuracy in the study of small or superficial lesions of the gastrointestinal tract [4]. Another potential benefit of high-frequency ultrasound probes is their ability to pass through tight strictures.

Technical features

High-frequency ultrasound probes are divided into mechanical and electronic types. The mechanical type is based on a single ultrasound transducer in the tip of the probe, rotated by a central wire and thus producing a 360-degree image perpendicular to the axis of the probe. The transducer cap is filled with oil, which serves as an acoustic interface. The electronic type consists of fixed transducers, and it is mainly used in cardiovascular procedures [6].

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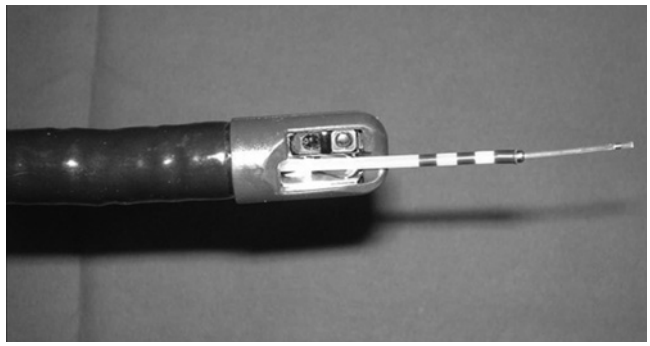

Figure 10.1 High-frequency ultrasound probe through the working channel of a side-view endoscope.

Standard high-frequency ultrasound mechanical probes are available in different diameters (2 to 2.9 mm), different frequencies (12 to 30 MHz) and lengths (1700 to 2200 mm) [6,7] (Table 10.1). Reportedly, the mean imaging depths based on the 12 MHz, 20 MHz and 30 MHz probes are 29 mm, 18 mm and 10 mm, respectively [4,8]. Currently available high-frequency ultrasound probes generate high-resolution radial images, and they can be used with upper endoscopy, enteroscopy, sigmoidoscopy, colonoscopy and ERCP. Prior to procedure, the tip of the high-frequency ultrasound probe should be rotated outside the body to allow even distribution of the immersion oil around the tip, while assessing the image quality. During the preparation the patient may be given intravenous glucagon or atropine to decrease peristalsis and facilitate the procedure. Some endoscopists advocate the administration of mucolytics to remove superficial mucus and thus enhance the quality of images. If a biopsy of the lesion is needed, it is highly recommended to perform it after the high-frequency ultrasound probe is used, to prevent artifact imaging. Once the tip of the endoscope is placed near the target lesion, the inactivated probe is passed through the biopsy channel and set out approximately 1 cm from the endoscope tip, close to the lesion. Useful hints to improve acoustic coupling between probe and tissue include: careful aspiration

of the air in the lumen; instilling water into the lumen (taking precautions to reduced the risk of aspiration); or applying jelly transuding medium. Some reports have shown that a condom or a balloon sheath may be affixed over the tip of the endoscope to improve acoustic coupling, particularly when using the high-frequency ultrasound probe in the esophagus and rectum [9,10]. Some endosonographers have utilized submucosal injection below a lesion to enhance the image of esophageal and colorectal lesions to improve accuracy when staging the depth of tumor invasion [11]. When a high-frequency ultrasound probe is used in the bile duct, the bile itself reduces the need for additional balloon or water immersion.

Anatomical correlation

The image obtained with a high-frequency ultrasound probe is smaller than the standard EUS, due to the higher frequency applied. The depth of penetration is limited to 2 to 3 cm. On the other hand, the superior definition provides an ultrasonographic image of the wall structure layers resembling those seen on histology [12]. Whereas conventional EUS is able to discern only five layers of the wall structure, the high-frequency ultrasound probe (20 to 30 MHz) imaging has been able to identify nine to eleven layers in the stomach and five layers in the colon [11,13].

The normal stomach wall anatomy under high-frequency ultrasonography may include nine layers (Figure 10.2):

- The first (hyperechoic) and second (hypoechoic) layers correspond to the interface with the probe surface and the mucosa.
- The third (hyperechoic) layer corresponds to the muscularis mucosae.
- The fourth (hypoechoic) layer corresponds to the interface between mucosa and submucosa.
- The fifth layer (hyperechoic) layer represents the submucosa.
- The sixth (hypoechoic) layer corresponds to the inner circular muscle layer, the seventh (hyperechoic) to the intermuscular connective tissue interface and the eighth (hypoechoic) to the outer longitudinal muscle layer.
- The final ninth layer (hyperechoic) represents the subserosal and serosal.

In the colon, the three layers of the muscularis propria may also be visualized:

- Inner hypoechoic = circular muscle.
- Middle hyperechoic interface = connective tissue.
- Outer hypoechoic longitudinal = muscle layer.

The superior resolution yield of the high-frequency ultrasound probe allows a detailed evaluation of the muscularis mucosa and muscularis propria. This capability is very useful in the diagnosis of motility disorders and local evaluation of early cancers prior to endoscopic mucosal/submucosal resection.

Applications of high-frequency ultrasonography

High-frequency ultrasound probes can be used in tumor staging in nonbulky lesions and depth evaluation of superficial early cancer prior to endoscopic therapy [14]. The accuracy of staging superficial tumors of the esophagus, stomach and colon may be as high as 60 to 90% [8,15–20]. However, due to the inability to correctly discern inflammation and malignancy on

Table 10.1 High-frequency ultrasound probes

Model	Designer company	Diameter (mm)	Length (mm)	Mode	Frequency (MHz)
PL 2220	Fujinon®	2.0	2200	Radial/Linear	12-15-20
PL 1726–1926		2.6	1700–1900	Radial/Linear	12-15-20
PL 2226		2.6	2200	Radial/Linear	7.5
UM-S20-20R	Olympus®	2.0	2140	Radial	20
UM-S30-20R		2.0	2140	Radial	30
UM-2R		2.5	2140	Radial	12
UM-3R		2.5	2140	Radial	20
UM-S30-25R		2.5	2140	Radial	30
UM-DP12-25R		2.5	2200	Radial/Linear	12
UM-DP20-25R		2.5	2200	Radial/Linear	20
UM-BS20-26R-3		2.6	2140	Radial	20
UM-G20-29R		2.9	2140	Radial	20

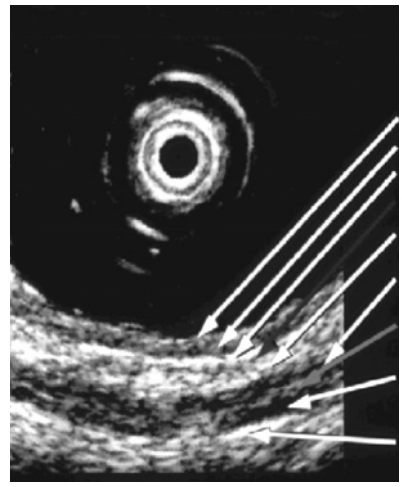

Figure 10.2 Sonographic correlation with wall structure of the gastric wall (HFUS 20 MHz).

ultrasonographic imaging, some limitations have been observed [19]. Moreover, the reduced visualization of distant lymph nodes due to the high frequency may prevent complete TNM staging.

Esophagus

Esophageal cancer: In comparison to the standard EUS, T-staging accuracy of esophageal cancer with high-frequency ultrasonography may be superior due to both improved resolution and the ability of the probe to traverse past tight strictures [8], reaching an accuracy up to 85% [15,21–23] (Table 10.2). This characteristic makes it particularly useful in the evaluation of superficial or early carcinomas eligible for endoscopic resection [21]. One of the main limitations of high-frequency ultrasonography is regional node staging, which should be attempted with standard EUS [15].

Barrett esophagus: The high-frequency ultrasound probe has limited accuracy in identifying invasive cancer in patients found to have high grade dysplasia or intramucosal carcinoma, even in the setting of Barrett esophagus with endoscopically visible lesions [13].

Other indications: High-frequency ultrasonography could be used in the evaluation of *esophageal varices*, measuring variceal radius and wall thickness [28–30]. The probe has the advantages of not requiring passage of the entire scope to the level of variceal lesions and not resulting in variceal compression. In *achalasia*, a high-frequency ultrasound probe has been used to identify the lower esophageal sphincter to properly localize the injection site of botulinum toxin [31], and to help in the evaluation of esophageal motor and sensory function. Hypertrophy or incoordination of the circular and longitudinal muscle layers could appear in achalasia, diffuse esophageal spasm, or nutcracker esophagus [32,33]. High-frequency ultrasonography may allow early identification and diagnosis of *eosinophilic esophagitis* by identifying significant expansion of the esophageal wall and individual tissue layers (mucosa, submucosa, and muscularis propria) [34].

Stomach

Early gastric cancer: High-frequency ultrasonography can be quite accurate for T-staging, which seems to be facilitated when the gastric cancer lesions are elevated and well differentiated [16,35,36]. Accuracy has been described as up to 80% compared with 63% for conventional EUS [23,24,26,27,36]. One of the main concerns in the use of high-frequency ultrasound is the risk of overstaging, related to local inflammation, edema, or fibrosis may [36]. On the other hand, the T-staging accuracy of high-frequency ultrasonography decreases when the lesions invade deeper than 10 mm [25]. Even with these limitations, high-frequency ultrasound can be very useful in decision making for EMR therapy of superficial/early gastric carcinoma [37,38].

Other indications: Reports have shown high-frequency ultrasound probes aid in the diagnosis of *gastric lymphoma*, *linitis plastica*, *Menetrier gastropathy* and *gastric varices* [39]. Lymphoma may appear to have thickened mucosa or submucosa with hypertrophic folds. Linitis plastica may present with marked thickening of the mucosa, submucosa and muscularis propria. Sonogoraphically, Menetrier gastropathy may appear to have mucosal thickening with cyst formation.

Table 10.2 Results of high-frequency ultrasound in esophageal carcinoma staging

Series	N	T-stage accuracy	N-stage accuracy
Yanai et al. [24]	52	71%	—
Akahoshi et al. [25]	78	67%	80%
Hunerbein et al. [26]	30	82%	80%
Kida et al. [27]	302	79%	—

Small bowel and colon

Colorectal cancer: The high-frequency ultrasound probe has the ability to be used through a standard colonoscope, thus allowing easy access from the colon to the cecum. T-staging accuracy appears to be similar to standard EUS [17,18]. The ideal target for the high-frequency ultrasound probe may be flat and superficial invasive tumors, where it can reach nearly 100% accuracy for small lesions [7]. High-frequency ultrasonography has also been compared with magnification colonoscopy for T-staging, obtaining superior results [20,40].

Other applications: The high-frequency ultrasound probe has been used to aid in the preoperative diagnosis of bowel tumors including *leiomyoma*, *leiomyosarcoma*, *lipoma, lymphoma* and *neuroendocrine tumors*. Studies have also shown the usefulness of the high-frequency ultrasound probe in active *inflammatory bowel disease* in measuring the colonic wall thickness and layer structure to identify lesions and try to determine the severity of the disease [41,42].

Intraductal ultrasonography

The development of intraductal ultrasononography (IDUS) based on special miniprobes has advanced the study of the pancreatico-biliary tree and the duodenal ampulla. These wire-guided miniprobes (5 to 10 F in diameter, with frequencies ranging from 12.5 to 30 MHz) can be advanced through the biliary and pancreatic ducts in a transampullary fashion, either by free cannulation or over a wire-guide. Intraductal ultrasonography creates radial images from within the duct lumen centering on the scanner unit; the tubular anatomy and the presence of bile or pancreatic fluid facilitates the acquisition of high-resolution images. These miniprobes can be used through a standard side-viewing endoscope or percutaneously.

Technical features

The technique of probe insertion is similar to that used with the stiffer occlusion balloon catheter (Figure 10.3). Cannulation with the miniprobe can be difficult without sphincterotomy or the use of a guide-wire. Although most probes are semi-flexible, excessive elevator use during cannulation of the miniprobe can result

in damage to the transducer. Some probes of small diameter and long length may be advanced to the distal main hepatic ducts. The exploration of the pancreatic duct may be especially tricky if it is not dilated or the anatomical duct is tortuous.

Anatomical correlation

Under intraductal ultrasound the sphincter of Oddi will appear as a hypoechoic circular thickening within the duodenal wall. The bile duct appears to have two or three layers: an inner hyperechoic layer corresponding to the interface between the duct mucosa and bile; a middle discontinuous hypoechoic liner correlate with the fibromuscular layer; and the outer hyperechoic layer that corresponds to the subserosal fat tissue layer (Figure 10.4). When the intraductal ultrasound miniprobe is placed in the intrahepatic duct, some vascular structures such as the portal vein or the right hepatic artery can be identified, although with significant limitation due to the higher frequencies.

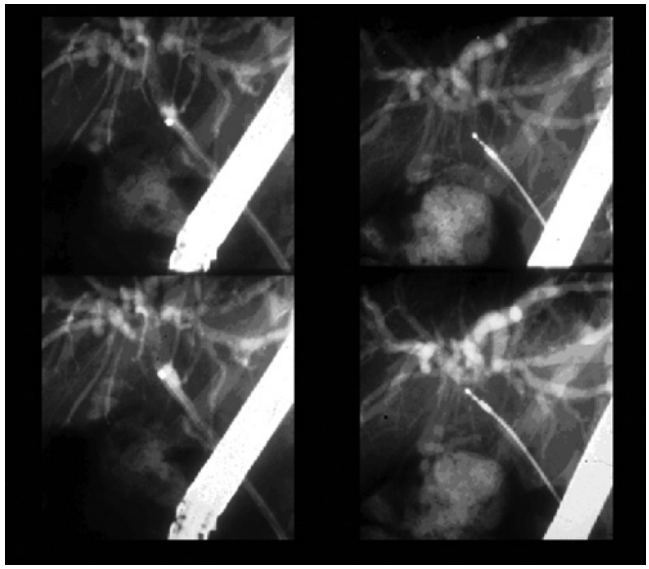

Figure 10.3 Radiologic images of intraductal ultrasound probe in the common bile duct during ERCP.

The pancreas, with its usual homogenous echogenicity, can be best viewed when within the intrapancreatic common bile duct. The main pancreatic duct can be seen traveling alongside the distal common bile duct. The inferior vena cava may also be visualized posterior to the pancreas.

Applications of intraductal ultrasonography

Choledocholithiasis: Several studies have demonstrated that IDUS is superior to ERCP or EUS alone in identifying stones [43,44]. A study by Ohashi et al. showed that IDUS was able to detect up to 33% of small stones not seen on ERCP [45]. Despite these advantages, its use is still limited due to the cost and reduced data to date.

Bile duct strictures: Various preliminary studies suggested that an hypoechoic mass, heterogeneity of the internal echo, irregular surface and wall thickening or disruption of the normal bile duct stricture can indicate underlying malignancy [46–48]. One retrospective study reported that the intraductal ultrasonographic images were able to correctly identify benign from malignant strictures with up to 90% accuracy [47]. Similar studies have shown that IDUS could be more accurate than EUS or ECRP in determining the nature and potential resectability of bile duct strictures [49,50]. An additional study found that high-frequency ultrasound probes used in conjunction with ERCP could increase the accuracy of characterizing bile duct strictures from 58% to 90% [51].

Cholangiocarcinoma: Management of cholangiocarcinoma depends largely on the location of the tumor, tumor stage (TNM) and resectability. Preliminary data on IDUS indicate that it is useful in assessing the extension of bile duct carcinoma into the portal vein and right hepatic artery. IDUS is significantly superior to conventional EUS for T-staging (77% vs. 54%) with a reported accuracy and sensitivity of 89% vs. 76% and 91% vs. 76% respectively [52–54]. The IDUS miniprobe allows further access to proximal cholangiocarcinomas at the hilum compared with standard EUS [52]. IDUS has also been shown to be more accurate than cholangiography in assessing for intraductal spread (86% vs. 43%) [52,55]. This modality proved useful for the differential diagnosis between (under) stage III and (over) stage IVA, as well as in assessing portal as well as right hepatic artery involvement [56].

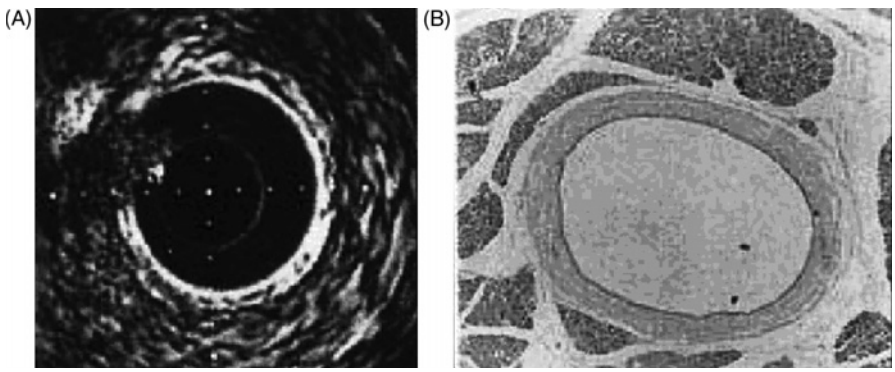

Figure 10.4 High-frequency ultrasound of normal pancreas (A) and correspondent histopathology (B).

IDUS has also been used in the assessment of response to radiation therapy by measuring the bile duct thickness before and after treatment, proving its usefulness for predicting patency of metallic stents in bile duct cancer [57]. Drawbacks included inability to demonstrate lymph node involvement, distant metastases or vessel invasion beyond the hepatoduodenal ligament.

Ampullary tumors: Some studies have found that IDUS probes were superior to standard EUS and computed tomography for visualization and diagnosis of ampullary tumors [50,58].

Pancreatic adenocarcinoma and pancreatic strictures: IDUS has been used in detection of pancreatic tumors in early stages [59,60] and evaluation of pancreatic strictures [46,47,61]. An echo-rich area surrounded by an echo-poor margin should be considered characteristic for pancreatic cancer [59]. On the other hand, a ring-like echolucent band surrounded by a fine reticular pattern is distinctive of chronic pancreatitis, and the degree of heterogenicity is considered to be in proportion to the degree of fibrosis [46,47].

Mucin-producing tumors: IDUS has been helpful in evaluation of mucin-producing pancreatic tumors where clear images of the cystic lesions and surface changes of the pancreatic duct may be identified.

Complications

To date, there have been no serious complications reported with the use of ultrasound probes, and no increased risks when compared with standard EUS have been described. Caution should be maintained when lumen irrigation is required, above all in the esophagus, due to the risk of aspiration. When using intraductal ultrasonography, the usual risks of pancreatic and biliary instrumentation apply, including the risk of pancreatitis, with an incidence between 0.4 and 1.5% [49,62,63].

The future

Some endoscopy manufacturers are developing three-dimensional scanning probes capable of obtaining up to 120 slices of radial images per minute and then producing 3-D figures by computer processing (Figure 10.5). Some preliminary studies in 3-D EUS have shown a promising accuracy in evaluation of tumor volume and accurate diagnosis of local invasion, with a good explorer agreement and low interobserver variability [64–67].

Recent reports of new 3D-IDUS suggest this technology might be better at assessing the extension of bile duct tumors and their relationship with surrounding organs [68,69]. Tamada et al. compared 3-D IDUS to 2-D imaging in assessing tumor extension of bile duct carcinoma. 3-D reconstructions of the primary tumor and its relationship to surrounding structures allowed for better recognition of tumor involvement into the pancreas and portal vein as compared to 2-D IDUS [68].

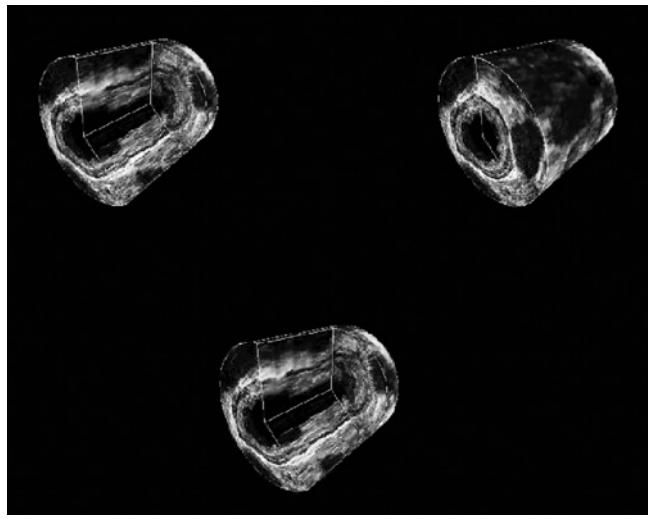

Figure 10.5 High-frequency ultrasound 3D imaging: reconstructed images.

Summary

High-frequency ultrasonography is a new technology that provides detailed imaging of the gastrointestinal wall for the evaluation and staging of mucosal and submucosal lesions of the gastrointestinal tract and pancreatic biliary tree. It operates at higher frequency than standard EUS, resulting in higher resolution images with limited depth penetration. High-frequency ultrasonography is relatively easy to perform by inserting the probe through an upper or lower standard endoscope (or side-view scope in the case of IDUS). The accuracy of high-frequency ultrasound for superficial gastrointestinal neoplasms (early carcinoma confined to mucosa or submucosa layers) exceeds conventional EUS in T-staging, providing useful information that alters therapeutic strategies in patients with superficial lesions. One of the main limitations is the poor lymph node staging due to the lower ultrasound penetration. IDUS is the modality applied in bilio-pancreatic diseases, can be safely performed during ERCP and can achieve accurate evaluation of bile and pancreatic stenosis, local staging of carcinoma and diagnosis of choledocolithiasis. Growing developments will continue to expand probe ultrasound technology and therapeutic capability.

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11 EUS: Applications in the Mediastinum

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Transesophageal endoscopic ultrasound (EUS) of the mediastinum is among the most informative, noninvasive and cost-effective techniques for evaluating the mediastinum. The explosion of interest in mediastinal EUS is driven primarily by the intense demand for precise staging of non-small cell lung carcinoma (NSCLC). EUS of the mediastinum is a well-described approach to posterior mediastinal adenopathy and undiagnosed masses. Since the differential diagnosis for hilar and mediastinal disease is broad, and includes both benign and malignant etiologies, tissue acquisition by fine-needle aspiration (EUS-FNA) is essential.

Benign entities include tuberculosis, granulomatous disease, sarcoidosis, histoplasmosis [1]. Metastatic disease to the mediastinum originates from primary carcinoma of the lung and esophagus, as well as from extrathoracic sites such as head and neck cancer, breast cancer, melanoma, and sub-diaphragmatic sites such as renal, gastric and pancreatic cancer [2,3]. This chapter reviews the expanding applications of EUS in the mediastinum and will focus on the critical role it plays in evaluating patients with known or suspected lung cancer.

Mediastinal cysts

EUS can accurately differentiate cystic lesions (bronchogenic or duplication cysts) from solid mediastinal masses. Equally important is its use in sampling primary lung masses not otherwise amenable to percutaneous or surgical approaches or in cases in which a less invasive approach is paramount.

Foregut duplication cysts account for 6 to 15% of primary mediastinal masses. Bronchogenic cysts usually reveal one of two echogenic patterns: anechoic and simple (the majority) or anechoic admixed with solid debris [4]. Clear liquid can often be aspirated from simple anechoic cysts.

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Mediastinal cyst aspiration or not: that is the question!

We do not advocate aspirating simple cysts since they have a classic appearance by EUS and are accurately classified by computed tomography (CT) [4]. The approach to heterogeneous cysts is not as straightforward. These cysts are usually filled with thick echogenic and tenacious debris; occasionally hyperechoic reflectors can be seen. Proper aspiration technique usually results in a frothy, brownish fluid. The high viscosity can sharply limit the yield to just a few drops for interpretation. These cysts are often incorrectly interpreted as solid masses by cross-sectional imaging (CT or MRI). The main indication to aspirate such lesions is to rule out a cystic metastasis. Prophylactic antibiotics should be given [5] as there have been case reports of infection of mediastinal cysts without antibiotic coverage [6,7]. Unlike pancreatic cyst aspiration, the absence of gastric acid in the esophagus and the high oral bacterial load may promote mediastinal cyst superinfection.

The second important indication for EUS in evaluating mediastinal lesions is sampling primary lung masses, particularly when the lesion is close to the esophagus. This approach has been shown to provide tissue diagnosis of primary lung masses when other modalities have failed and when neoadjuvant therapy is planned for borderline or unresectable masses. It can be helpful in obviating surgery in non-small cell lung cancer (Figures 11.3, 11.4). We have not encountered complications of pneumothorax in sampling primary lung masses [8].

Lung cancer

Non-small cell lung carcinoma (NSCLC) is an oncologic epidemic and the number one cause of cancer death worldwide. Despite remarkable advances elucidating molecular pathogenesis, high-resolution anatomical and functional imaging, and targeted therapies, its mortality rate and incidence are virtually identical. For the vast majority of patients, surgery with or without neoadjuvant therapy is the only hope for cure. Yet for all but the earliest stage tumors, the likelihood of cure after surgery remains poor [9].

Whether due to inaccurate preoperative or operative staging (mediastinoscopy), the inexorable progression of disease is most certainly driven by unrecognized metastases. The demand for accurate minimally invasive mediastinal staging is a tremendous opportunity for the motivated endosonographer.

Rationale for EUS

Precise mediastinal staging of non-small cell lung cancer is critical as mediastinal lymph node metastases are common (up to one third of patients) and generally indicate unresectable disease. Ipsilateral or subcarinal mediastinal nodal metastases (N2) or contralateral mediastinal lymph node involvement (N3, stage IIIB) generally obviates surgical resection [10]. Surgery alone is reserved for patients without nodal and/or distant metastases (stage I–II) [9].

Accurate staging is critical to minimize unnecessary surgery, provides prognosis and determines eligibility for clinical trials. While there is an increasing variety of competitive and complementary staging techniques, there is no consensus on how best to stage patients with the greatest accuracy and least morbidity [36]. Reliance on chest computed tomography (CT) and integrated positron emission tomography (PET) scanning alone to stage and evaluate surgical candidacy is plagued by false positive results. Pathological confirmation of enlarged or "hot by PET" lymph nodes findings should be pursued before surgical resection.

Patients with newly diagnosed NSCLC face a daunting array of varyingly invasive staging options. No modality is perfect or universally available. Mediastinoscopy (MS) and transbronchial fine-needle aspiration (TBNA) are widely established but imperfect modalities, primarily limited respectively by increased invasiveness and modest negative predictive value. EUS-FNA has emerged as a diagnostic and staging tool because of its safety, accuracy and patient convenience. Integration of EUS into institutional clinical pathways is best achieved by participation in a multidisciplinary thoracic tumor board.

Before you start

EUS for lung cancer staging requires a thorough understanding of the widely utilized tumor, node and metastasis (TNM) classification system and lymph node stations (see Figure 11.1) [11,12]. The lower posterior mediastinum is ideally suited to EUS. As a general rule, the reach of EUS includes the lower paratracheal (station L), the subcarina (station 7), distal para-esophageal nodes (station 8), the pulmonary ligament (station 9), and varyingly the AP window (station 5). An exquisite advantage of EUS is its ability to identify and sample celiac, left adrenal and hepatic metastases otherwise missed by cross-sectional imaging [13].

Evaluation of the anterior and right-sided mediastinum is limited by intervening tracheal and proximal bronchial air (stations 2 and 4R). Such lesions should be considered for bronchoscopic sampling, particularly with the advent of endobronchial ultrasound (EBUS).

Whenever possible it is advisable to review prior radiographs before embarking upon EUS. A recent summary of 13 prospective studies underscores the high accuracy of EUS [14].

Cross-sectional and functional imaging: How does EUS stack up?

Computed tomography is the most common initial staging modality due to its widespread availability. While excellent for distant metastatic staging, the performance of CT in evaluating the mediastinum is not optimal [15]. A recent meta-analysis

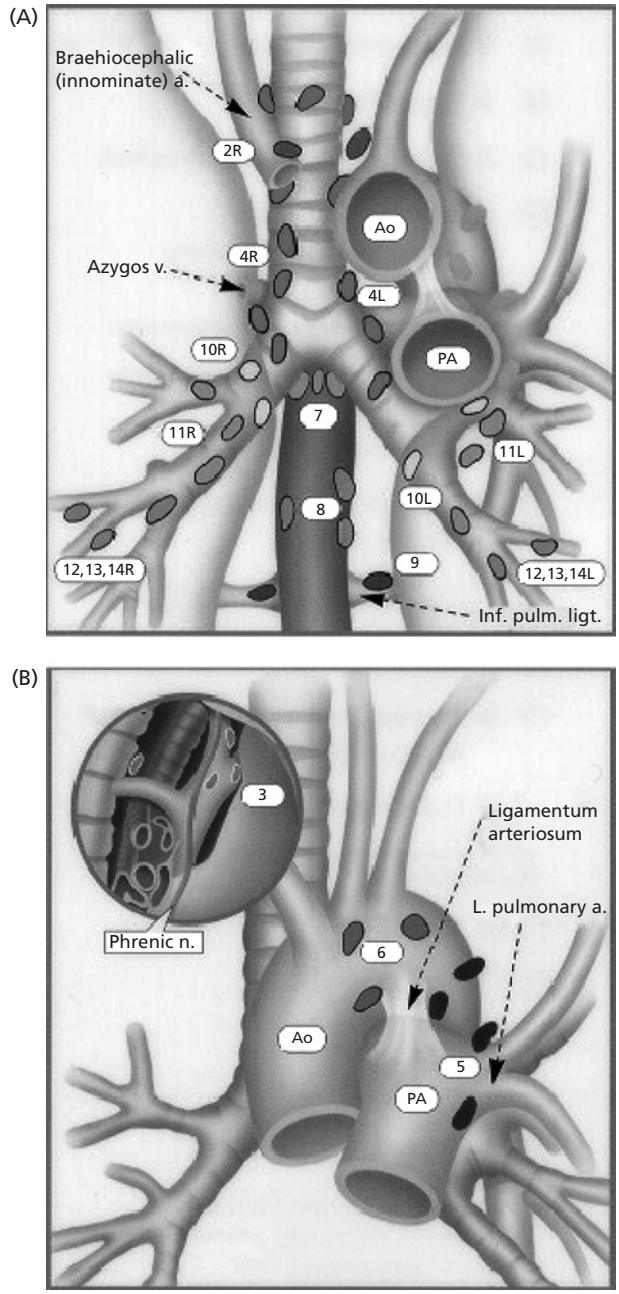

Figure 11.1 The Mountain and Dresler regional lymph node classification.

including 3,829 patients across 20 studies revealed a negative predictive value (NPV) of 82% (18% were found to have advanced disease at surgical staging) [16]. The sensitivity and specificity of CT for mediastinal nodes ranges from 57% to 82% [17].

CT and EUS are complementary approaches. CT is most useful for primary tumor imaging and for a "lay of the land" while EUS provides a focused mediastinal examination and survey of select metastatic sites. Direct comparisons between EUS and CT in detecting mediastinal adenopathy have been performed [18–20] and the sensitivity of EUS for mediastinal lymph node detection was consistently above 90%. Even in patients with an unremarkable chest CT, EUS-FNA detected mediastinal spread and obviated the need for surgical staging in a significant number of individuals [13,21]. In the absence of extrathoracic metastases EUS-FNA is useful regardless of CT findings.

CT with integrated 18F-fluorodeoxyglucose-positron emission tomography (PET-CT) has become the noninvasive gold standard. Despite early enthusiasm that functional imaging would supplant the need for tissue sampling, PET-CT findings are not recognized as definitive proof of N2/N3 disease [22]. PET is widely thought to be more accurate than CT [23], but false positives are common (up to 39%) [24].

While PET-CT alone cannot reliably differentiate left- from right-sided hilar activity, PET-CT remains an excellent and still important part of the metastatic evaluation. A meta-analysis of 18 studies with 1,045 patients reported a pooled sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of PET for staging mediastinal lymph nodes in NSCLC patients of 84%, 89%, 79% and 93%, respectively [24].

EUS-FNA can be used to document suspicious findings on PET-CT with great accuracy (97% accuracy [25], 93% sensitivity and perfect specificity) [12]. In that study EUS confirmed N2/N3 disease in 69% of patients who were PET-avid in the mediastinum. Importantly one third of these lesions were outside the reach of mediastinoscopy. More than a quarter of PET-avid patients were found to have no nodal metastases after EUS-FNA, and 70% of "PET suspicious" patients had no mediastinal spread at surgery. These results underscore the point that functional imaging cannot replace tissue confirmation.

Medical mediastinoscopy

The primary appeal driving the exploding utilization of mediastinal EUS is its safety, efficiency and minimally invasive quality. Combined with endobronchial ultrasound (EBUS) for interrogation of the anterior mediastinum, the concept of complete "medical mediastinoscopy" (a term coined by Dr Mike Wallace) is likely to largely replace surgical staging [26]. Up to 10% of thoracotomies with intent to resect result in "open and close" without resection; an additional 25 to 35% are futile on the basis of postoperative recurrence.

Endobronchial ultrasound

Endobronchial ultrasound (EBUS) is the newest diagnostic tool for mediastinal staging and is being evaluated in large prospective comparisons with EUS and MS. Two prospective studies combined EUS-FNA with endobronchial ultrasound-guided transbronchial needle biopsy (EBUS-TBNA) [27,35]. The difference in sensitivity between the two procedures was not statistically significant, and the combined approach had higher sensitivity and accuracy than either modality alone.

Additional larger trials are necessary to evaluate the utility of a combined approach in unselected populations. We suspect combined EUS-FNA and EBUS-TBNA will be shown to provide total "medical mediastinoscopy" and in all cases obviate the need for surgical exploration.

Addition of EUS to a routine work-up in a small study which included chest CT, TBNA and, in some circumstances, PET, reduced the need for surgical staging by an estimated 78% in patients with enlarged posterior mediastinal nodes [26].

EUS in the patient with early NSCLC

The role of EUS-FNA after a high quality, negative PET-CT remains controversial in the patient with a small peripheral carcinoma. EUS-FNA has been reported to upstage an otherwise resectable patient [24]. Such cases suggest the utility of EUS-FNA even in patients with no significant mediastinal lymph node metastases on PET. However, the yield of EUS-FNA and mediastinoscopy in a negative integrated PET-CT may be low [27]. Considering the high cost and still limited availability of PET ($2,200 Medicare fee), EUS might be applied early in the workup of patients with NSCLC.

Failed bronchoscopy and EUS rescue

Transbronchial needle aspiration (TBNA) is a widely employed blind technique with a poorly defined diagnostic yield [28,29]. It is associated with complications such as bleeding and pneumothorax [39]. EUS-FNA "rescue" can be done immediately after an unrevealing TBNA if on-site cytology demonstrates inadequacy.

EUS and mediastinoscopy

Mediastinoscopy (MS), long considered the gold standard, is the most invasive staging technique. It is relatively costly, requires general anesthesia, and may require hospital admission. While safe, it carries the greatest procedural risk [40,41]. EUS-FNA and MS are both competing and complementary techniques. Two prospective studies directly compared EUS-FNA to MS [17,20]; in one the combination of EUS-FNA and MS increased the sensitivity to 86% compared to EUS-FNA alone (61%) or MS alone (53%) [20].

Compared to MS, EUS-FNA allows wider access to the posterior mediastinum, including the subcarina, the inferior mediastinum and the aorto-pulmonary window (APW).

Getting the examination done

Radial EUS

Experienced and novice endosonographers alike generally adhere to the time-honored "station-based" approach. Of all the EUS

applications, the radial mediastinal examination is the easiest to master due to the straight tubular configuration of the esophagus and the relatively straightforward thoracic vascular anatomy.

Sonographic imaging is maximized when the transducer is coupled closely to the area of interest. This is achieved with constant aspiration of air from the esophageal lumen. We begin the radial examination using the "pull back" technique from the stomach into the distal esophagus. Align the image electronically so that the descending aorta is posterior (the patient's left side) and at the 5 o'clock position. At this level the inferior vena cava (IVC) and liver can be seen immediately to the left of the anechoic aorta. The aorta in this position remains the "home base" of the mediastinal and abdominal examination.

Gently pulling back into the chest will reveal the left atrium and pulmonic vein anteriorly (near the 12 o'clock position); the spine is situated to the left of the monitor at approximately the 7 o'clock position. This orientation is helpful and mimics the configuration on chest CT.

The subcarina (station 7) can be identified approximately 27 to 30 cm from the incisors by pulling up into the chest until observing the bifurcation of the left and right mainstem bronchi. These air-filled structures are impermeable to sound waves and appear as closely parallel echogenic lines. This is a key station in staging NSCLC since metastases denote at least stage III disease.

One can alternatively identify cardiac motion from the left atrium and withdraw until seeing the pulmonary artery. This inter-space is the subcarinal station. Pushing in approximately 1 cm past this region (the carina) is the subcarinal space. At this level, cardiac motion from the left atrium is readily observed and the right pulmonary artery can be seen at approximately 10 o'clock. Here the azygous vein (AZ) is seen just to the left of the descending aorta (DA), and careful inspection can often identify the tiny hypoechoic thoracic duct (TD) situated between the DA and the AZ. The transition to the abdominal examination, to interrogate the celiac axis, left adrenal gland and portions of the liver, can be appreciated endoscopically as the gastric lining and sonographically by the appearance of the IVC, usually directly opposite the DA. The IVC can be seen to drain into the RA upon slow pullback back into the chest. To insure that no adenopathy is missed, it is prudent to repeat this maneuver two to three times until the examiner is satisfied with the quality of the examination.

Linear EUS

We typically begin our linear mediastinal examination at 30 cm from the incisors; at this level one should appreciate the cardiac motion from the left atrium and ventricle. Pulling back slightly will bring into view the subcarinal space where the left atrium is seen to drain into the pulmonary artery. Remember that clockwise rotation of the scope along its axis brings left-sided structures into view. Gentle pullback will then reveal the aortopulmonary window (APW), the space defined by its two named great vessels. The aorta can be seen to round off into its oblong appearing arch by turning clockwise about 90 degrees and pulling back about 2 cm from the APW.

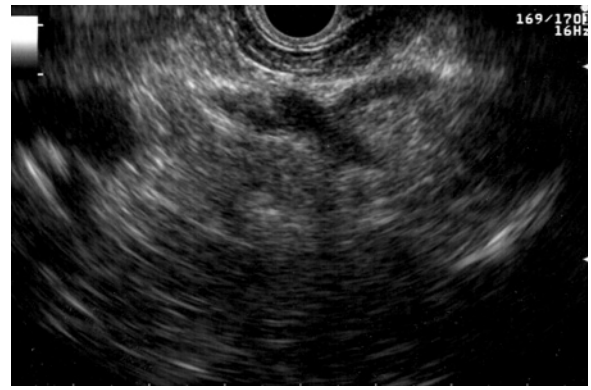

Figure 11.2 Normal appearing "seagull" adrenal gland (curvilinear echoendoscope).

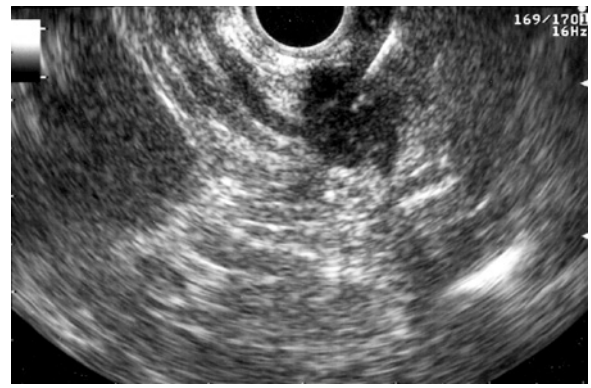

Figure 11.3 Adrenal metastasis. An 11 mm nodule in the left wing of the left adrenal gland. PET scan showed avid uptake (SUV >5). EUS-FNA confirmed malignant involvement.

The descending aorta is identified with the CLA echoendoscope at about 35 cm from the incisor. A continuous and steady push of the CLA endoscope to about 45 cm, while the aorta is maintained in view, leads to identification of the celiac axis bifurcation. A gentle clockwise maneuver will lead to the "seagull" shaped organ (aptly named by Dr Rob Hawes): the adrenal gland. In patients with metastasis to the adrenal, the gland loses its normal shape and takes the form of a mass (Figures 11.2, 11.3). Occasionally one limb of the adrenal is slightly enlarged; commonly this is a benign adenoma.

Which lymph nodes for FNA?

There has been a great deal of interest in identifying nodal characteristics that best predict the likelihood of harboring metastatic disease. In general, suspicious features include sharply demarcated borders, a uniformly hypoechoic appearance, round shape, and a short axis diameter of >1 cm (Figure 11.4). The positive predictive value for lymph nodes that meet all criteria is quite good (80%) but sensitivity is imperfect. Only about 25% of lymph nodes in one study exhibited all of these features [30]. It is important to remember small triangular lymph nodes in

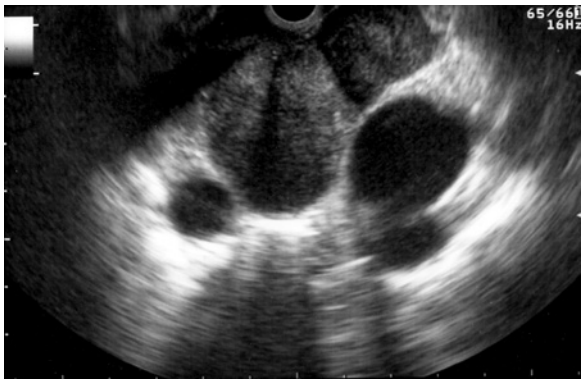

Figure 11.4 Bulky N2 disease. EUS-FNA confirmed N2 disease in a patient with non-small cell lung carcinoma. Surgery was avoided and neoadjuvant therapy was recommended.

the subaortic space (station 5) are relatively common and usually benign, especially in smokers and those with chronic lung disease.

A recent report suggested that those nodes lacking a central Doppler signal (intranodal blood vessel) are much more likely to be malignant [31]. We endeavor to sample all available nodes since features classic for malignancies are not universally reliable. These characteristics can however be used to sample the most suspicious nodes first, and maximize examination efficiency.

FNA: how and how much?

The traditional sonographic criteria for malignant appearing lymph nodes do not reliably distinguish malignant from benign reactive; this is particularly true in the mediastinum. The sensitivity and specificity of EUS without FNA for diagnosing mediastinal lymph node metastases ranges between 54 to 75%, and 71 to 98%, respectively [6,7]. The introduction of FNA for tissue confirmation markedly improved the accuracy to 94 to 95% [8–10]. Typically three or four passes is sufficient for lymph nodes; a primary mass may require additional sampling. We use the smallest gauge needle possible (25 gauge) to minimize hemorrhagic contamination yet still provide sufficient material. Adjunctive use of negative suction through the supplied syringe can increase overall cytological yield but may also draw in more contaminating blood. In cases when EUS-FNA is nondiagnostic, a 19-gauge Trucut biopsy needle designed for use in conjunction with an echoendoscope may be useful to procure larger specimens for histopathological analysis. This approach is particularly useful in evaluating patients with Hodgkin lymphoma.

Special topics

Primary lung lesions

Several reports have described the safety and efficacy of EUS to diagnose centrally located lung lesions (Figure 11.5). Such lesions are inaccessible to trans-bronchial sampling in about one

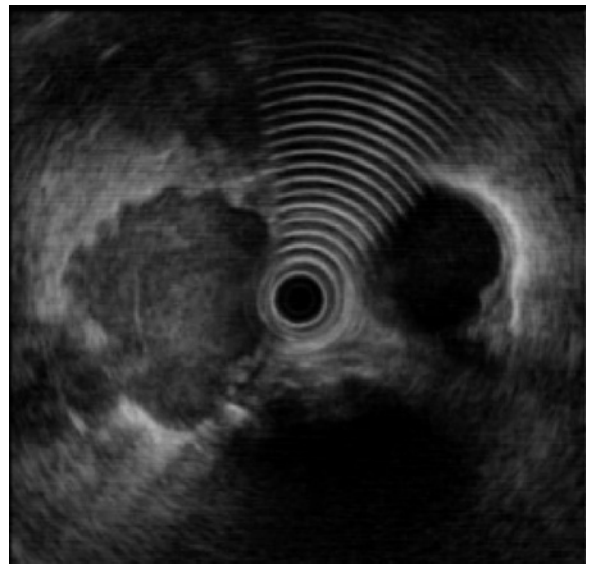

Figure 11.5 Subcarinal mass invading the mediastinum, small-cell lung carcinoma. EUS-FNA confirmed SCLC and surgical staging was avoided.

third of cases and traditionally require a CT-guided or surgical approach. While pneumothorax and bleeding are established complications of transthoracic biopsy, there has been only one case report of pneumothorax after EUS-FNA. For lesions proximal to the esophagus (usually <1 cm), EUS has added value with high resolution imaging defining invasion (T4) and metastases to the liver, celiac axis and left adrenal gland [32].

T4 disease

Studies have also demonstrated both high sensitivity and specificity of EUS-FNA for advanced tumors (T4 by direct invasion of the mediastinum, heart, great vessels, trachea, esophagus, vertebral body, or carina) or malignant pleural effusion retrospectively [25] and prospectively [20]. Surgery is generally contraindicated in T4 disease. The role of EUS in defining T4 disease however remains unclear. One retrospective study [25] assessed the accuracy of EUS in discriminating T4 disease. Among 175 patients, eight were diagnosed at surgery as T4, included two with malignant pleural effusions by EUS-FNA. The sensitivity, specificity, PPV and NPV of EUS for T4 extent was 87.5%, 98%, 70% and 99%, respectively. Three of five patients, thought to have mediastinal invasion at EUS, were surgically staged as T2, highlighting the risk of overstaging. EUS for this purpose should not be routinely applied.

EUS for metastatic disease

A few studies have examined the yield of EUS to detect otherwise occult metastases such as small pockets of pleural effusion or disease below the diaphragm (liver, celiac axis, left adrenal gland). We feel that these indications alone warrant EUS early in the workup, especially in cases where clinical staging suggests advanced disease. These areas are uniquely in the domain of

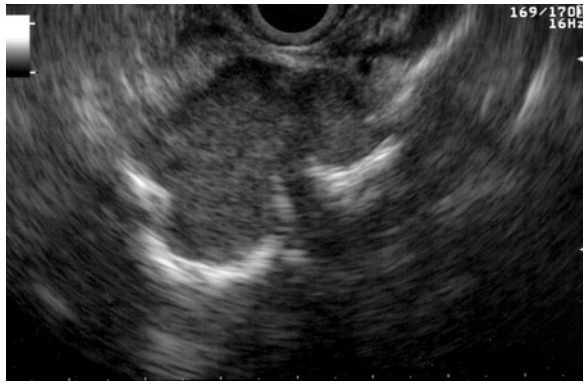

Figure 11.6 Renal cell carcinoma metastasis. EUS-FNA (with immunostains) diagnosed renal cell carcinoma metastatic to the spine. The lesion was identified slightly above the gastroesophageal junction. EUS was the only nonsurgical approach to reach this lesion.

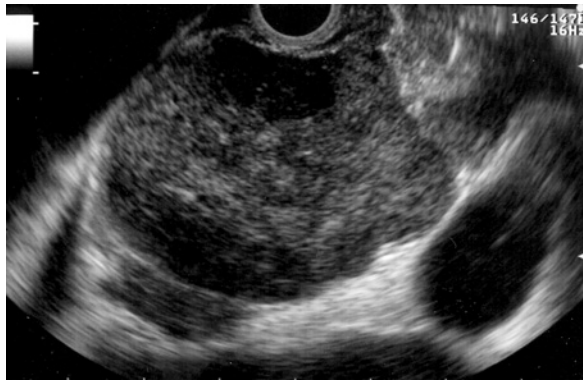

Figure 11.7 Melanoma. EUS-FNA along with immunostains confirmed recurrent metastatic melanoma to the mediastinum.

EUS and have significant impact in the treatment decision and prognosis in patients with NSCLC. Additionally, EUS-FNA can diagnose metastatic disease to the posterior mediastinum from nonpulmonary tumors, such as melanoma, renal cell carcinoma and pancreatic cancer (Figures 11.6, 11.7).

EUS after neoadjuvant therapy

Patients who have completed induction therapy, in anticipation of surgery with intent to cure, present a unique challenge. The problem of "restaging" after therapy relates to scarring and inflammatory change; CT is particularly inaccurate (accuracy 58%). Such scarring limits subsequent surgical staging as mediastinoscopy after induction therapy can suffer from an incompletion rate as high as 40% [33]. A few studies have examined the role of EUS-FNA to evaluate the mediastinal response to neoadjuvant chemotherapy [33,34].

Cost

Cost efficacy has been evaluated prospectively [13] and in decision analysis modeling [28,42]. The studies demonstrated a cost benefit with EUS-FNA compared to mediastinoscopy and concluded EUS-FNA could reduce the cost of staging in the range 16% to 40%. The cost of mediastinoscopy in these studies was however quite conservative, as calculations were based on the assumption that patients would stay in a hospital for a total of 3 days [13].

Training

As EUS continues to establish itself in the community, attention has been given to the training and credentialing of this specialized technique. Performing EUS at a high level requires the completion of a dedicated fourth year fellowship. Among the various indications for EUS, mediastinal examinations are among the most readily learned. In one study the learning curve of EUS-FNA was assessed using two residents [13]. Two residents performed 29 and 25 procedures respectively and, not surprisingly, failed to reach the ability of experienced operators. In practice, among those who perform EUS in the community, the accuracy of EUS-FNA might be lower than reported in this review. The American Society for Gastrointestinal Endoscopy (ASGE) recommends a minimum of 150 cases of supervised EUS, 50 of which should include FNA [29]. Equally controversial is defining who should be performing transesophageal lung cancer staging. Since lung cancer is not in the clinical domain of most gastroenterologists, other specialists are now vying for access to EUS. Short courses in mediastinal EUS are increasingly available to both pulmonologists and thoracic surgeons.

Summary

EUS has revolutionized the way we care for patients with posterior mediastinal masses and especially those with NSCLC. Despite the robust evidence base supporting its utility and efficiency, the integration of routine EUS in patients with NSCLC outside of tertiary care centers has been slow to become standard of care. Continued championing of the virtues of mediastinal EUS is still needed among oncologists, pulmonologists and thoracic surgeons. We hope we have provided that rationale. Together we will continue to provide the best possible care for our patients.

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12 EUS for Esophageal Cancer

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Endoscopic ultrasonography (EUS) has established an important role in the diagnostics and staging of esophageal tumors. For locoregional staging EUS is superior to other imaging modalities such as CT or MRI. Also for diagnosis of different esophageal and periesophageal lesions, EUS combined with FNA has an important impact on the clinical management. For advanced esophageal cancer EUS is an important tool for the decision making of surgery and or neoadjuvant therapy such as chemo- and/or radiotherapy. Early lesions in the esophagus can be evaluated for potentially local endoscopic treatment.

The TNM staging system

Esophageal cancer is usually treated according to tumor stage as defined by the TNM system developed by the American Joint Commission on Cancer [1]. 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). EUS staging, similar to surgical staging, can predict survival in patients with esophageal cancer [2]. Multiple minimally or non-invasive modalities exist to help in the clinical staging of esophageal cancer, including EUS, CT, MRI and PET scanning. EUS has taken a central role in the locoregional staging of esophageal cancer, because of its accuracy of tumor invasion and detection of regional lymph node metastasis. Although EUS is superior to PET and CT for locoregional staging, the latter modalities are better at detecting liver and lung metastasis. Therefore it is logical to perform EUS only when PET and CT have not revealed distant metastasis. This may help to triage the patient to surgery alone, neoadjuvant therapy followed by surgery, chemoradiation therapy or palliative treatment only. A recent study has shown that the combination of CT, PET and EUS reduces the number of unnecessary operations from 44% to 21% [3].

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T stage

The depth of tumor invasion and the involvement of the esophageal wall layers determine T stage. The earliest stage, Tis or carcinoma in situ, is present when the cancer is limited to the epithelium and the lamina propria is intact. This stage usually can only be detected by biopsy and is quite often not visible on EUS, even with high-frequency probes. T1 tumors are defined when cancerous cells invade the lamina propria or submucosa. (Figure 12.1). With the advent of high-frequency catheter probes, T1 tumors have been further classified into T1m (confined to mucosa) or T1sm (tumor invading submucosa). A T1sm lesion has a 20 to 35% rate of lymph node metastasis and is therefore not suitable for local endoscopic therapy [4]. The accuracy of high-frequency probes in distinguishing between mucosal cancer and cancer invading the submucosa has been reported as 81% to 100% [5]. Pathological evaluation of an EMR specimen will eventually lead to the decision whether the local endoscopic therapy is sufficient or whether a patient needs a surgical esophagectomy with a lymph node dissection. When the tumor has invaded the muscularis propria, the tumor is classified as T2. (Figure 12.2). When the tumor further progresses to invade the adventitia, the tumor is classified as T3. Involvement of mediastinal structures, such as the aorta, pleura, azygos vein, or any other adjacent structure, is classified as T4 disease (Figure 12.3). In a recent meta-analysis it was demonstrated that EUS was significantly more accurate than CT in identifying stages T1 through T4 [6]. CT is unable to accurately differentiate between the T stages of the disease, a distinction important when considering the use of neoadjuvant therapy [7].

N stage

Due to rich (peri-)esophageal lymphatics, esophageal cancer has the propensity for early spread to local lymph nodes. It has been clearly shown that patients with N1 disease as classified by EUS have poorer survival than those with N0 disease [8]. Furthermore the number of detected lymph nodes is an important predictor of survival [9]. Lymph node characteristics on EUS can be helpful in classifying benign from malignant lymph nodes. Criteria for malignant lymph nodes include diameter greater than 10 mm,

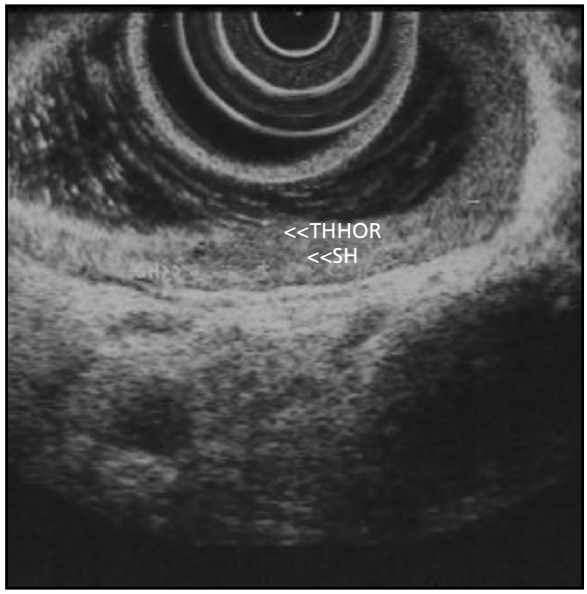

Figure 12.1 EUS stage T1, N0 esophageal cancer in setting of Barrett esophagus. (Courtesy of Thomas Savides, M.D.)

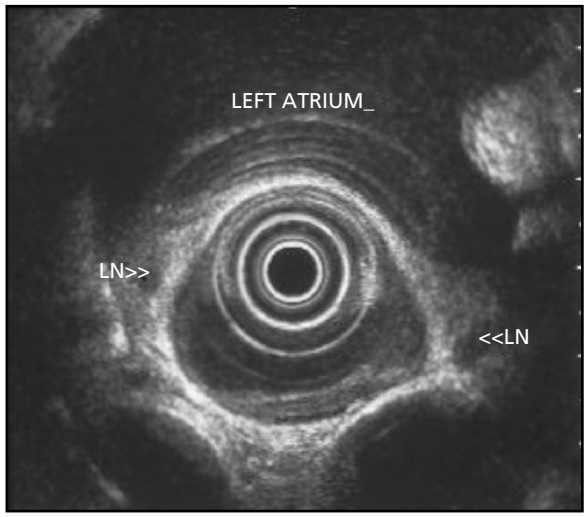

Figure 12.2 EUS stage T2, N0 esophageal cancer. Note that the circumferential mass involves into, but not through, the muscularis propria. (Courtesy of Thomas Savides, M.D.)

uniform hypoechogenicity, a rounded shape, and nodes with a sharp border (Figure 12.3) [10]. Given the subjective nature of these criteria, EUS is generally less accurate in identifying malignant nodes than in evaluating depth of tumor invasion. In a meta-analysis by Kelly et al., the accuracy of conventional EUS for N staging was only 79% [11]. Studies comparing EUS with CT for regional lymph node metastasis have consistently demonstrated that EUS is more accurate for N staging. The use of EUS-guided fine needle aspiration (EUS-FNA) is now becoming more

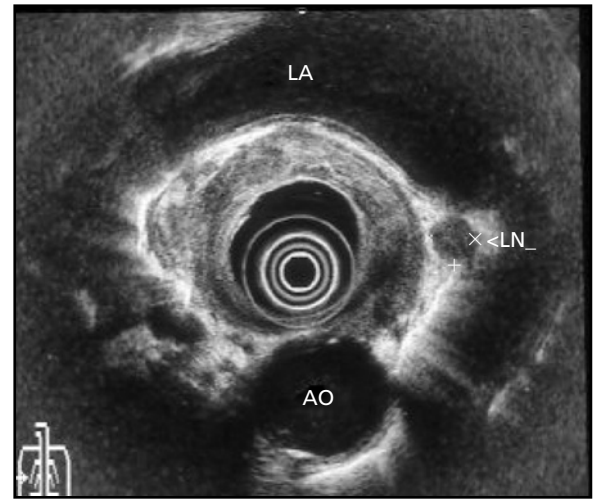

Figure 12.3 EUS stage T4, N1 esophageal cancer. Note that the hypoechoic circumferential mass invades into the wall of the descending thoracic aorta. Also note a round, malignant appearing lymph node in the left anterior peri-esophageal space. (Courtesy of Thomas Savides, M.D.)

widespread, and has shown to improve the accuracy of EUS for N staging by providing cytological involvement of lymph nodes [12]. In this prospective study EUS-FNA for lymph node metastases had a sensitivity and specificity of 98.3% and 100% respectively, which compared favorably with EUS alone. Periesophageal lymph nodes can only be sampled by EUS-FNA when they are not located immediately adjacent to the primary tumor. Puncturing lymph nodes through the tumor will give a high risk of false positivity.

M stage

Involvement of distant organs of the primary tumor via hematogenous seeding or involvement of distant lymph nodes is considered metastatic disease. EUS provides excellent imaging of the medial two-thirds of the liver, but 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. A proximal tumor of the upper esophagus with metastasis to cervical lymph nodes or a distal tumor of the lower esophagus with celiac lymph node metastasis are both considered M1a disease. M1b disease is defined as other distant metastasis. For instance, celiac lymph node metastasis in a patient wit a proximal esophageal tumor is defined as M1b disease. M1b disease is considered not to be curable by surgical resection. There is some controversy about the management of patients with M1a disease [13].

Early cancers

With the advent of endoscopic treatment modalities for early cancers, both in squamous as well in Barrett's epithelium, accurate staging of these early lesions has an important impact.

The depth of tumor invasion correlates with the presence of lymph node metastasis, and therefore it is crucial to determine this prior to EMR. Mucosal lesions can be subdivided in three categories. A T1m1 lesion is confined to the epithelial layer, T1m2 indicates infiltration into the lamina propria and T1m3 indicates infiltration into the muscularis propria. Lymph node metastases in patients with a mucosal lesion are rarely found [14,15]. Tumors invading the submucosa are subdivided into three separate categories, T1sm1 to T1sm3, with T1sm3 disease having a much higher risk of lymph node metastasis in up to 70% of cases [14,15]. Obviously, the assessment of infiltration depth is important to determine the right treatment strategy.

EUS with the regular frequency of 7.5 to 12 MHz can maximally identify seven different layers of the esophageal wall [16]. Still, this appears to be insufficient to reliably distinguish mucosal from submucosal tumors [17]. With newer high-frequency (20 to 30 MHz) miniprobes passed through the accessory channel of the endoscope the muscularis mucosa can readily can be visualized as a additional separate layer [18]. Using these high-frequency probes has resulted in an improved T-staging of early cancers, with a reported accuracy of 85% [19].

Endoscopic vs. EUS staging

While reported accuracy of EUS staging of early lesions is mainly based on early squamous cell carcinoma, these results cannot be extrapolated to early lesions in a Barrett esophagus per se. Barrett's epithelium with its crypts and villi is significantly different from the layered structure of squamous epithelium. In addition the inflammation and the presence of a double muscularis mucosae can make the evaluation of an early lesion very difficult. Expert endoscopists can also make a good judgment on the extent of an early lesion using high-resolution endoscopy. The additional value of EUS for determining infiltration depth of early neoplasia in a Barrett's esophagus can be limited. In a recent study by May et al. the additional value of high-frequency EUS to high-resolution endoscopy was studied in patients with high-grade dysplasia in a Barrett's esophagus [20]. In this study it was shown that careful inspection with a high-resolution endoscope of mucosal and submucosal lesions has a high accuracy, and the additional value of EUS was limited.

Advanced tumors

Resectability

In advanced esophageal cancer the only curative treatment is surgical resection. But even after surgical resection with curative intent, the prognosis is still very poor. In addition, resection is associated with a significant morbidity and even mortality. Therefore it is of great importance to select those patients who will potentially benefit from a surgical procedure. Preoperative staging plays a important role in this selection process. First, distant metastasis should be excluded. For this, CT scanning and external ultrasound of the neck are suitable instruments. When distant metastases are excluded, locoregional staging should be performed. For this EUS has the highest accuracy. In T-staging the delineation between a T3 and T4 tumor is important. When a T4 tumor with ingrowth in the surrounding organs is seen, these patients are poor candidates for surgical resection [21]. Also when M1b lymph node metastases are seen, these patients are generally poor candidates. For the future, neoadjuvant therapies may play a more important role.

Locoregional lymph nodes

The detection of locoregional lymph node metastasis has an important impact on the prognosis of a patient with esophageal cancer. Besides prognosis the detection of locoregional lymph nodes can have a consequence for the surgical treatment. There are two main approaches for surgical esophagectomy in patients with an esophageal carcinoma. The transthoracic approach is more extensive and includes an *en bloc* lymphadenectomy of all lymph nodes in the posterior mediastinum. The transhiatal approach is a less invasive procedure, but the lymph nodes in the proximal mediastinum are left in situ. Therefore a preoperative diagnosis of lymph node metastasis in the mediastinum is useful for deciding the type of surgical treatment [22].

Celiac axis lymph nodes

The detection of celiac axis lymph node (CLN) metastasis has an important implication for patients with esophageal cancer. In patients with distal esophageal cancer, CLN metastases are classified as M1a. In mid- or proximal tumors CLN metastasis are staged as M1b, similar to liver metastases. Patients with esophageal cancer and CLN metastasis have worse survival than those without CLN involvement [23]. In addition it is doubtful whether patients with celiac lymph node metastasis benefit from surgical resection [13]. In patients with esophageal cancer, the identification of CLNs was virtually synonymous with malignant involvement. Regardless of echo features and size, 90% of all detected CLNs were proven to be malignant in one study [24]. Moreover, 100% of lymph nodes greater than 1 cm in size were malignant. The clinical impact that malignant CLNs have on therapy leads to the necessity to perform EUS-FNA, providing proof of malignant involvement prior to neoadjuvant therapy [25]. The detection of metastasis in celiac lymph nodes by EUS-FNA has a reported sensitivity of 98% and specificity of 100% [24].

Liver metastasis

EUS can detect occult liver metastases in patients in whom non-invasive hepatic imaging studies are normal, although the frequency with which such lesions are detected is low [26]. EUS of the liver is best performed with linear instruments and provides excellent imaging of the medial two-thirds of the liver, but cannot exclude metastatic disease to all areas of the liver. Metastases usually appear as discrete, relatively hypoechoic lesions in the liver. Once identified, EUS-FNA can be performed, yielding important diagnostic and prognostic information for management of the patient.

Stenotic tumors

High-grade stenotic tumors often cannot be evaluated by regular echoendoscope. In these patients pre-EUS dilatation may be required in order to pass the echoendoscope. This has been associated with significant complications, such as perforations, in the past [27]. An alternative option is an 8-mm non-optic 7.5 MHz probe, which is advanced through the tumor over a previously placed guide-wire [28]. This option enables adequate staging without dilatation and therefore seems to be preferable. When FNA of lymph nodes is necessary, the new thin-caliber transbronchial linear EUS scopes can obviate the need for dilatation.

Assessment of neoadjuvant treatment

The use of neoadjuvant chemoradiotherapy continues to be an area of active investigation and is becoming more widespread for patients with advanced disease. The ability to assess the response to neoadjuvant therapy is potentially important for further clinical management. Initial studies on preoperative chemoradiotherapy were promising; however these studies were small and the neoadjuvant therapy was ineffective in downstaging the tumor [29]. More effective neoadjuvant modalities have now been developed which are effective in downstaging of the tumor. In this setting EUS has shown considerably less accuracy for restaging of the disease [30,31]. The most frequent error was overstaging, apparently because the fibrosis and inflammation associated with chemoradiotherapy are indistinguishable from residual microscopic foci of cancer within the esophageal wall. Although the tumor stage cannot be reliably established by EUS after neoadjuvant therapy, several studies have shown that reduction in cross-sectional area of the tumor by more than 50% is associated with a response to therapy [32]. But also simply measuring the maximal tumor diameter before and after neoadjuvant therapy can correctly identify the responders and non-responders [33]. Restaging of lymph nodes with EUS-FNA may become more important in the near future.

Technical aspects of EUS in esophageal cancer

Probes

For the highest resolution imaging of the gut wall, high-frequency transducers (12 to 30 MHz) can be used. These are radial transducers incorporated in small catheters and are mechanically rotated. They are advanced through the working channel of an endoscope into the lumen of the gut. High-resolution imaging of the gut wall is an important tool for the evaluation of patients selected for endoscopic mucosal resection of early cancers of the esophagus and stomach [5].

The probes are usually advanced into the lumen of the esophagus through the working channel of a therapeutic gastroscope. It can be difficult to get good acoustic coupling between esophageal wall and the instrument. To assure this acoustic coupling, one of the following three techniques can be used. In the first technique all air is aspirated from the esophagus and some water is sprayed into the lumen of the esophagus through either the instrumentation channel or the spraying channel of the endoscope. Care has to be taken to prevent aspiration in this technique. The second technique uses a soft flexible transparent condom at the endoscope tip. By filling this transparent condom with water, excellent low-pressure coupling is assured. Finally, Olympus manufactures small, single-use balloon sheaths for their miniprobes, which fit through the working channel of a therapeutic gastroscope only.

Echoendoscopes

The technique of all dedicated echoendoscopes is pretty straightforward. For all procedures, the patient goes without food or drink from 4 to 6 hours before the investigation. Conscious sedation is mostly used under careful guidance of an anesthesiologist or nurse. The scope is introduced either under direct vision (forward-viewing echoendoscopes) or under partial view with all the oblique-viewing instruments. It is important to mention that these instruments are not to be used for careful endoscopic inspection of esophageal lesions. Therefore one has to consider always starting with a standard high-resolution gastroscope and performing a quick inspection of the lesion and the rest of the esophagus. Especially in early lesions, a standard gastroscopy seems to be indispensable.

Radial examination

The radial examination starts with the instrument in the stomach and the patient in the left lateral position. After filling the stomach with between 150 and 250 mL of de-aerated water, adequate endoscopic inspection has become impossible and the endoscopist focuses on the ultrasonographic image only. After careful inspection of the left liver lobe and the area around the celiac trunk, the scope is slowly pulled back and the lower margin of the tumor is searched for. During drawback the position of the diaphragmatic crurae is noted. All visualized lymph nodes are carefully described. Once the distal margin of the tumor is visualized, the water-filled balloon can usually be emptied to allow the endoscope to be pulled back smoothly further into the tumor. Here the deepest extension is noted and when suspicion of infiltration into an adjacent organ arises, the movement of the tumor and the adjacent structures during patient breathing is observed. Once the center of the tumor is passed, the balloon usually has to be refilled again to image the esophageal wall and mediastinum. Important parts of the inspection of the mediastinum in the search for metastatic lymph nodes are the areas above the carina. Suspicious lesions in the superior mediastinum will impact the decision of the surgical approach (transthoracic or transhiatal, see above). The endosonographic inspection is extended above the area of the aortic arch and can be stopped once the upper esophagus is reached.

Linear examination

Linear instruments scan along the long axis of the endoscope, which enables real-time visualization of a needle exiting from the

biopsy channel into a target such as a lymph node or organ. In the electronic instruments the image orientation and staging can be assisted by the addition of pulsed, color and power Doppler. Introduction of the echoendoscope can be difficult because of the rather long rigid distal port ion of the endoscope. Most linear EUS in esophageal cancer is done with a specific target already known from CT or radial EUS. It is therefore mandatory to study this information before the start of the procedure. Once the target lesion is visualized, EUS-FNA can be performed in order to confirm the presence of metastasis. Doppler ultrasound can be used to ensure that there are no interposed vessels. The FNA needle system, consisting of a 19, 22 or 25-gauge needle, is inserted through the working channel of the endoscope and advanced through the gut wall into the suspicious lesion under endosonographic guidance. The stylet is removed and suction can be applied with a 10-mL syringe while the needle is manipulated back and forth within the target lesion. The use of suction increases the number of cells in the aspirate at the cost of also collecting more red blood cells. The aspirate is placed on a glass slide and processed with a DiffQuick^{TM} stain. Onsite interpretation of the specimen by a cytologist is preferable to evaluate for adequacy of the specimen and to minimize the number of needle passes. Once the pathologist or cytological technician confirms adequacy of the collected material, the procedure can stop. The pathologist will finally evaluate the presence of malignant cells after fixation and Giemsa or other staining.

Recently Trucut needles have been introduced to obtain histological samples of lymph nodes and lesions of the pancreas [34]. In small series that have been published so far, this technique was shown to be safe without significant complications, but its role and superiority in comparison to FNA remains to be determined. We fear that standard use of these needles will carry the risk of a higher complication rate.

Conclusions

In the evaluation of patients with esophageal cancer, EUS will continue to play an important role. It is currently the only available modality that can image the esophageal wall layers with histological correlates. Additionally, it is the only modality, which enables to obtain tissue for confirmation of locoregional metastatic disease. A surgical esophagectomy is associated with significant mortality and morbidity and therefore a cautious selection of patients who will potentially benefit from the surgical procedure is of utmost importance. The introduction of new effective neoadjuvant modalities has further increased the challenge of staging and further management of patients with esophageal cancer.

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13 EUS of the Stomach and Duodenum

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Background and technique

Endoscopic ultrasound is useful for a variety of benign and malignant lesions of the stomach and duodenum. The usual indications for EUS of this region include evaluation of submucosal masses, abnormal gastric folds or mucosa, staging of gastric cancer, staging and diagnosis of lymphoma, evaluation of nonhealing ulcers, and staging of ampullary carcinoma.

Imaging of the gastric and duodenal lining is most easily accomplished using the radial echoendoscope, which generates a 360-degree cross-sectional image perpendicular to the tip of the instrument. We use the Olympus GF UM-160, which has scanning frequencies of 5 to 20 MHz, and more recently the newer Olympus GF UE-160, which has no rotating parts and provides an electronic image. One of the main advantages of the GF UE-160 is that it has color Doppler capabilities, which were previously only available with linear array echoendoscopes, enabling assessment of whether a structure is vascular without having to change instruments. Another advantage is that because this endoscope has no rotating parts, it is less susceptible to technical malfunction and need for repairs. However, it has a larger diameter of 13 mm compared to 11 mm for the older instruments, which occasionally can be a problem in patients with stenotic lesions. Additionally, this instrument has scanning frequencies only up to 10 MHz. Pentax has 270-degree (EG-3630UR) and 360-degree (EG-3670URK) electronic echoendoscopes with Doppler capability that have an insertion tube diameter of 12.1 mm and scan at 5 to −10 MHz. High-frequency 12 to 20 MHz catheter-based ultrasound probes, which are passed through the working channel of a therapeutic upper endoscope, are also used for imaging superficial lesions of the mucosa and submucosa. One advantage of these probes is that lesions can be assessed during standard upper endoscopy without the need to change to an echoendoscope.

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The major challenge in performing EUS in the stomach and duodenum is obtaining adequate acoustic coupling between the transducer and the gut wall. A water-filled balloon attached to the end of the echoendoscope provides an acoustic interface and is often adequate in the duodenum with its relatively narrow lumen. Removing all the air from the stomach can be challenging, however, resulting in image artifact. If this problem is encountered, pressing the balloon against the gastric mucosa is necessary to visualize the entire gastric wall. Filling the gastric lumen with de-aerated water is also very helpful in reducing air artifact and is also useful when imaging superficial mucosal lesions. We use the Olympus UWS-1 water pump, which is connected by rubber tubing to the Olympus MD-744 valve. This is inserted through the rubber biopsy cap of the echoendoscope, and water can be obtained by pressing the valve simultaneously while depressing the foot pedal of the pump. If the lesion in question is in the antrum, the water may empty rapidly, necessitating repeat filling. Placing the patient into the feet-down (reverse Trendelenberg) position aids in filling the antrum. Water preferentially pools in the fundus of the stomach when the patient is in the left lateral decubitus position, so if a lesion is on the anterior wall or lesser curvature, rotating the patient to the supine or right lateral decubitus position may be necessary to submerge those areas. Care must be taken when placing a sedated patient in the supine position, however, as the risk of aspiration may be significantly higher.

Benign disorders

In addition to submucosal lesions, which will be discussed in Chapter 14, EUS is used to evaluate enlarged gastric folds, which can be caused by a variety of disorders.

Enlarged gastric folds

The stomach wall normally exhibits a five-layer pattern similar to the rest of the gastrointestinal tract, and measures 3 to 4 mm in thickness. The antrum is often thicker and can measure up to 5 mm.

Gastric folds can appear enlarged or thickened on standard upper endoscopy or radiological studies such as CT scan or barium contrast upper gastrointestinal series. Standard endoscopy often cannot determine the cause of enlarged gastric folds, and mucosal biopsies can be negative even in the presence of malignancy. EUS can be used to distinguish between normal anatomy and other causes of enlarged gastric folds, including chronic gastritis, Menetrier disease, gastric varices, Zollinger–Ellison syndrome, lymphoid hyperplasia and infiltrative malignancies (Table 13.1).

The primary objectives when evaluating enlarged gastric folds are to determine if wall thickening is actually present, to identify which layers are involved and to what degree, to assess if any solid tumor is present, and to determine the depth of invasion if tumor is suspected. When performing EUS to evaluate the cause of enlarged gastric folds, filling the stomach with water as previously described is essential to obtain adequate distention to determine the layer or layers that are thickened.

Gastric varices

A primary concern when evaluating thickened gastric folds should be gastric varices, which obviously should not be biopsied. These appear as hypoechoic round or serpiginous structures in the submucosa of the gastric wall, usually in the fundus or cardia area (Figure 13.1). The varices are often numerous and will be Doppler positive. The absence of esophageal varices should not be falsely reassuring, as isolated gastric varices can occur with splenic vein thrombosis, which may be present in patients with pancreatic disorders. If a patient does have isolated gastric varices, it can be helpful to attempt to follow the splenic vein throughout its course to identify a thrombosis, as this may affect future management of gastric varices in the event of variceal hemorrhage. Additionally, careful examination of the pancreas in this situation is necessary to identify chronic pancreatitis or a pancreatic tumor as a cause of splenic vein thrombosis. Patients should also be examined for findings consistent with portal hypertension if gastric varices are found. EUS characteristics of portal hypertension include the presence of esophageal or paraesophageal varices or ascites [1]. Other findings suggestive of portal hypertension include enlargement of the diameter of the azygous vein and thoracic ducts, which are viewed in the mediastinum [2].

Table 13.1 EUS in patients with thickened gastric folds. Reproduced from Ref. 97 with permission

Diagnosis	Layer	EUS findings
Varices	3	Serpiginous hypoechoic structures in body and fundus
Hypertrophic gastropathies	1, 2, ±3	Diffuse thickening of mucosal ± submucosal layers with preserved 5-layer pattern
Infiltrating malignancy	3, 4	Prominently thickened submucosa (3rd) and muscularis propria (4th) layers. Lymphoma may have mucosal thickening with or without deeper involvement

Hypertrophic gastropathies

The hypertrophic gastropathies are a heterogeneous group of disorders that cause giant gastric folds. Etiologies of giant gastric folds include benign conditions such as Menetrier disease, sarcoidosis, amyloidosis, infections (*Helicobacter pylori* gastritis, anisakiasis, cytomegalovirus, herpes simplex, syphilis, tuberculosis, fungal pathogens), Zollinger–Ellison syndrome, and hyperrugosity, which is a normal variant [3–5]. The usual diagnosis which comes to mind when faced with this clinical entity is Menetrier disease, a benign idiopathic disorder, but a study of 52 patients with large gastric folds who underwent excisional snare biopsy revealed that the most common diagnosis was chronic gastritis or lymphoid hyperplasia in 40%, followed by benign tumors in 16%, gastric malignancy in 12%, Zollinger–Ellison syndrome in 10% and Menetrier disease in only 8% [6].

EUS is useful in evaluating patients with enlarged folds by identifying which layers of the stomach wall are thickened (Table 13.1). In the benign conditions, the thickening is usually limited to the mucosal layers (first and second) but may sometimes involve the submucosal (third) layer as well. Although this appearance is not specific for any particular entity and can be seen with malignant tumors, it indicates that large-capacity forceps biopsy will be sufficient to sample the affected tissue, provide a diagnosis and, most importantly, rule out malignancy. Several studies have been performed to evaluate the usefulness of EUS in patients with large gastric folds of uncertain etiology. The most recent attempted to identify EUS features predictive of malignancy in patients with large gastric folds and negative mucosal biopsies [7]. This study of 61 patients found that enlargement of the deeper layers of the gastric wall, the submucosa and the muscularis propria, was the only independently predictive variable for malignancy. The presence of ascites, lymphadenopathy and nondistensibility of the stomach were associated with malignancy only on univariate analysis.

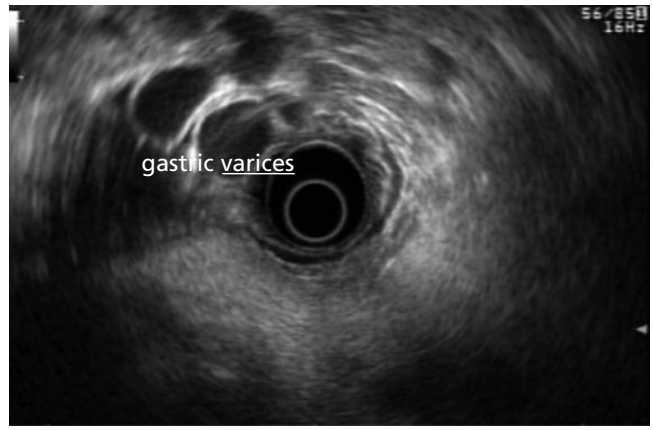

Figure 13.1 Gastric varices. Large cystic-appearing lesions in the submucosa (third layer) of the gastric wall represent varices in a patient with splenic vein thrombosis due to chronic pancreatitis. These were positive on evaluation with Doppler, confirming their vascular nature.

Although the presence of a thickened muscularis propria is a sensitive sign for malignancy, care must be taken when scanning in the regions of the cardia and pylorus. In these areas, the muscularis propria has a thickened or prominent appearance due to normal physiological thickening caused by the gastroesophageal and pyloric sphincters [8]. Artifactual EUS thickening of gastric layers can also mislead the endosonographer if the scanning plane is tangential to the wall, rather than perpendicular to it. This is especially a problem in the cardia and pylorus where the walls normally come together in a sloping fashion, making it difficult to consistently obtain EUS images in a perpendicular plane. Pressing the water-inflated balloon against the wall while imaging can minimize this latter artifact. When there is doubt as to the cause of the thickening, it is prudent to proceed with a surgical full-thickness biopsy to rule out malignancy.

Of the benign conditions, there has been particular interest in EUS imaging of Menetrier disease and *H. pylori* gastritis, because patients with these conditions may have endoscopic findings and clinical presentations that mimic cancer. The etiology of Menetrier disease is incompletely understood. Patients may present with abdominal pain, nausea, vomiting, diarrhea, anemia and weight loss as well as complications of protein-losing enteropathy resulting in profound hypoalbuminemia [9]. In adults, the disease is found primarily in men over age 50. A reversible form of the disease due to cytomegalovirus infection has been reported in children [10]. Menetrier disease is characterized endoscopically by giant folds in the fundus and body, especially along the greater curvature. Histologically, there is elongation and tortuosity of the gastric pits (foveolar hyperplasia) with prominent cystic dilations. The EUS examination in Menetrier disease demonstrates mucosal thickening mainly of the deep mucosa (second layer). EUS does not demonstrate the small cystic spaces that are present in these lesions on histology. When an EUS image consistent with Menetrier disease is seen, large-capacity forceps biopsies are adequate for histological diagnosis, obviating the need for full-thickness surgical biopsy [3,4].

Helicobacter pylori is the most common cause of chronic gastritis, and this infection can cause giant gastric folds. The appearance may raise the question of an infiltrating gastric carcinoma or lymphoma, both of which are associated with *H. pylori* infection [11,12]. When EUS is performed in patients with chronic *H. pylori* infection, the mucosal and submucosal layers of the stomach are thickened. Biopsy reveals a chronic active gastritis with typical curved *H. pylori* bacilli present on the luminal surface of the specimen. Successful eradication of the infection results in regression of the gastric wall thickening and normalization of the EUS appearance [5].

Malignant disorders

Gastric adenocarcinoma

The majority of malignant tumors of the stomach are adenocarcinomas. The incidence of gastric adenocarcinoma in the United States has declined markedly in the last 50 years, with an estimated 12,000 deaths in 2003 [13], although it remains the second leading cause of cancer death worldwide [14]. Primary risk factors include chronic infection with *H. pylori*, chronic atrophic gastritis, hereditary factors (including familial adenomatous polyposis and Lynch syndrome) cigarette smoking, heavy alcohol use, and dietary factors. Patients usually present with abdominal pain, weight loss, nausea and vomiting, early satiety or iron deficiency anemia due to occult blood loss. Because the majority of patients are asymptomatic until they have late stage disease, surveillance programs have become commonplace in Asian countries, where the incidence of gastric cancer is much higher. This has led to an increasing number of patients diagnosed with early gastric cancer in those countries. Most patients in the United States, however, continue to be diagnosed only at the later stages of disease.

Gastric adenocarcinoma occurs in two histological types: intestinal and diffuse (signet ring cell type). The intestinal type is primarily associated with discrete polypoid fungating or ulcerated tumors, and the diffuse type more commonly infiltrates the wall of the stomach, causing the classic leather-bottle morphology of linitis plastica. While the staging system for the two types is the same, their EUS appearances differ.

Intestinal type

Intestinal-type carcinomas are invasive cancers of mucosal origin. The principal objectives when staging these lesions are to determine depth of penetration and assess for local and regional lymph node involvement. In all cases, the TNM staging system should be employed (Table 13.2). The depth of penetration of the tumor into the wall of the stomach determines the tumor stage or T stage. This is best accomplished using the water-fill technique to reduce any artifacts produced by intervening air. The majority of smaller to medium-sized lesions are imaged using high-frequency ultrasound (10 to 20 MHz) to provide high-resolution images. Through-the-scope 12 to 20 MHz miniprobes allow for accurate T-staging without the need for a dedicated echoendoscope, but are limited by shallow imaging depth leading to poor N-stage accuracy [15]. With larger lesions, it may not be possible to image the entire thickness of the tumor at high frequency and the 5 to 7.5 MHz frequency should be used. In very thick tumors it may not be possible to determine the full depth of invasion with EUS.

Gastric carcinomas are generally poorly circumscribed hypoechoic lesions which, at the edges, can be seen to be arising from the mucosal layers. T1 lesions are limited to the mucosa (first and second layers) or may penetrate into the submucosa (third layer). There should be a demonstrable, intact, bright layer of submucosa between the lesion and the dark band of the muscularis propria (fourth layer). T2 lesions extend into but not through the muscularis. Endosonographically, T2 lesions extend through the bright third layer corresponding to where the tumor penetrates through the submucosa into the muscularis. However, the interface at the outer margin of the muscularis where it contacts the

Table 13.2 American Joint Committee on Cancer Staging: TNM classification for gastric cancer

Tumor (T) stage	
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1s	Carcinoma in situ: intra-epithelial tumor without invasion of the lamina propria
T1	Tumor limited to mucosa or submucosa
T2	Tumor invades muscularis propria or subserosa
T2a	Tumor invades muscularis propria
T2b	Tumor invades subserosa
T3	Tumor invades serosa
T4	Tumor invades adjacent structures
Tx	Primary tumor cannot be assessed
Nodal (N) stage	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1–6 regional lymph nodes
N2	Metastasis in 7–15 regional lymph nodes
N3	Metastasis in more than 15 regional lymph nodes
M: distant metastasis	
Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis present (e.g., hepatic metastasis, peritoneal dissemination)
Stage grouping	
Stage 0	Tis N0 M0
Stage IA	T1 N0 M0
Stage IB	T1 N1 M0, T2a/b N0 M0
Stage II	T1 N2 M0, T2 a/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 N2 M0, T4 N1-3 M0, or any T, any N, M1

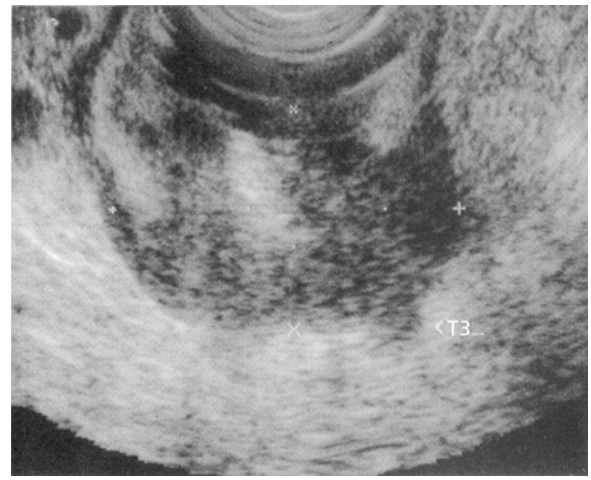

Figure 13.2 T3 gastric cancer. This 2.5 cm (+ marks) by 1.6 cm (x marks) tunor invades all layers of the stomach. A psuedopod of tumor extends through the serosa into the perigastric space (<T3). (7.5 MHz).

serosa (fourth and fifth layers) is smooth and undisturbed by the cancer. In T3 lesions the hypoechoic lesion extends completely through the fourth layer (Figure 13.2) and the serosa (fifth layer), which would otherwise be smooth, is interrupted and clearly invaded. Fingerlike projections of tumor, termed pseudopodia, may be seen extending into the extragastric space. If the lesion extends into a local organ (e.g. liver, pancreas, spleen, diaphragm) or large vessel (e.g. aorta, celiac axis) it is classified as a T4-stage lesion.

The accuracy of EUS T-staging for gastric cancer ranges from 67% to 92% or about 80% overall [16–24]. Sources of error arise from microinfiltration, which may be undetectable by EUS and causes understaging, and peritumoral inflammation, making a tumor appear to be more deeply invasive than it actually is, resulting in overstaging. Inaccuracies in staging T2 versus T3 lesions are a common problem. The TNM system uses serosal invasion as the main criterion to define a T3 lesion. However, the stomach is not uniformly covered by serosa, being absent in areas of the lesser curvature and anterior wall of the antrum. A tumor that on histological examination completely penetrates the muscularis propria without evidence of serosal invasion would be classified as T2, but when seen on EUS would be indistinguishable from a T3 lesion [25]. Nevertheless, despite its limitations, EUS remains the most accurate nonsurgical method for determining depth of invasion and is significantly more accurate than CT, which has a reported accuracy of only 42% [21]. CT scan may improve over time, but is currently not as accurate as EUS and does not allow for lymph node sampling. A study of 48 patients with gastric cancer who had multidetector row CT scan and EUS and subsequently underwent either EMR or surgery found that EUS had an overall accuracy for T stage of 87.5%, with four T1 lesions overstaged, one T2 lesion overstaged and one T3 lesion understaged as T2 [26]. This study found that multidetector row CT had an overall T-stage accuracy of 83.3%, with the main problem area being overstaging.

EUS is also used to assess for local or regional lymph node metastasis in patients with cancer. Complete lymph node assessment requires scanning at 5 to 7.5 MHz. Attention should be paid to the region surrounding the tumor and to the retroperitoneum, celiac axis, aorta, gastrohepatic ligament and splenic hilum. With the stomach water-filled and the balloon distended, the entire perigastric region should be imaged at low magnification from the antrum to the gastroesophageal junction. In areas obscured by air, the air should be suctioned out, more water instilled, or the balloon pressed against the gastric wall to ensure complete visualization of all areas. Malignant lymph nodes are usually imaged by EUS as rounded structures that are well circumscribed and uniformly hypoechoic (dark). The staging system for gastric cancers now classifies nodal stage based on the

number of regional lymph nodes (Table 13.2). It is difficult to assess the exact number of enlarged lymph nodes on EUS, and we continue to stage these tumors based on presence or absence of regional and distant lymph node metastases. The liver should also be examined for hypoechoic nodules that may represent metastases. The presence of ascites is a poor prognostic sign and is discussed later in this chapter. CT is superior to EUS in the detection of distant metastasis and should also be performed as part of a complete preoperative evaluation.

Much has been written about the inaccuracies of EUS for malignant lymphadenopathy, with accuracy rates varying from 50% to 90% in reported series [18–21,23]. This variance is due in part to use of diverse criteria to characterize a malignant node. Most endosonographers regard rounded, well-demarcated and homogeneously dark nodes as being malignant, without regard to size [27], although ex-vivo studies in esophageal and gastric cancer have identified a nodal diameter exceeding 1 cm as the only significant criterion [28]. Inaccuracies in EUS assessment also arise from the inability to detect micrometastases and the fact that benign inflammatory lymph nodes may be enlarged and exhibit "malignant" features. Nevertheless, EUS is the single most accurate modality for N-staging, being significantly more accurate than CT [21], and the absence of identifiably enlarged nodes at EUS is fairly specific (85% or higher) for predicting the absence of nodal metastasis at surgery [23]. The presence of enlarged lymph nodes on EUS, however, is not as helpful in staging these tumors, and histological confirmation (via EUS-guided fine needle aspiration) is essential if the presence of nodal metastases would alter the patient's management [29].

The overall utility of EUS depends on the clinical setting. As previously described, gastric cancer presents at a late stage in Western countries, and gastrectomy is the only option if the tumor is not yet metastatic. In these cases, the primary utility of EUS is in determining resectability and prognosis. For a gastric primary to be resectable, it must not invade surrounding organs (i.e. be T1 to T3). In determining the ability to completely resect a gastric cancer, EUS is at least 85% accurate [22]. EUS T-stage is also predictive for the probability of postoperative recurrence. Among patients undergoing attempted curative resections, recurrence occurred in 15% of those with EUS stage T1 or T2 compared with 77% with T3 or T4 ($P = 0.0002$) [24]. Also, the use of EUS in preoperative evaluation alters clinical treatment plans in as many as 30% of cases [30] and may allow selection of patients for more limited resections [31]. Currently, preoperative neoadjuvant therapy is not routinely used in the United States, although this may change in the future. A trial of 503 patients with adenocarcinoma of the stomach, gastroesophageal junction or lower esophagus randomized patients into surgery alone versus pre- and postoperative chemotherapy and found reduced mortality in the chemotherapy arm (Hazard ratio 0.75, 95% CI 0.6–0.93) [32]. The overall 5-year survival rate for the chemotherapy arm was 36% vs. 23% for surgery alone. In the future, EUS may be a useful tool in selecting patients for preoperative neoadjuvant protocols [33].

EUS imaging may be helpful in the follow-up of patients after surgery for gastric cancer as well. This modality has been used to detect anastomotic recurrence with good sensitivity (95%) and specificity (80%) [34]. When there is anastomotic recurrence, EUS shows nodularity and irregular hypoechoic thickening of the wall in the region of the anastomosis exceeding 7 mm. Thickening to 6 mm with a smooth appearance is normal for an anastomosis. There may be invasion of local organs or the presence of enlarged lymph nodes. Early detection of recurrence may provide prognostic guidance for patient management and improve surgical and oncological outcomes [35].

Early gastric cancer

In terms of natural history, gastric adenocarcinoma can be further divided into early gastric cancer (EGC) and late gastric cancer. EGC comprises the subset of patients with tumors confined to the mucosa or submucosa without invasion of the muscularis propria (T1). Clinically, this is an important lesion carrying a 95% 5-year survival following resection, versus only 15% for gastric cancer overall. The majority of the experience with EGC is from Japan where this presentation comprises over 30% of all patients with gastric cancer [36]. EGC can be further subdivided into two categories: tumors isolated to the mucosa (T1m) which carry a 5% risk for nodal metastasis, and those that invade through the muscularis mucosae into the submucosa (T1sm) which carry a 10% to 20% risk for metastasis [37,38].

Endoscopic resection can be considered for T1m lesions, but for more deeply invasive tumors (T1sm or higher) surgical resection is preferred. EUS using echoendoscopes at standard frequencies may be incapable of differentiating T1m from T1sm lesions with over-and understaging occurring in about 25% [38]. Many endosonographers now feel that catheter-based miniprobes scanning at 20 MHz may be better suited to staging EGC. The 20 MHz frequency resolves the gastric wall into a nine-layer structure, with a fine, hypoechoic line between the conventional second (deep mucosa) and third (submucosa) layers, which is felt to represent the muscularis mucosae [39]. Unfortunately, overstaging of EGC with the 20 MHz probe occurs in 19% to 24% of patients due to peritumoral fibrosis mimicking deeper invasion [40,41]. Accuracy appears to be better for the small elevated type than the depressed type of EGC [41]. In a recent large series of 104 patients, when both the endoscopic appearance and the 20 MHz EUS findings were applied together for tumor classification, a 92% overall accuracy rate was achieved [41]. Thus, when done carefully and consistently, it is possible to use high-frequency EUS to select patients for endoscopic resection of T1m EGC, although long-term outcome studies using strict criterion for the diagnosis of cancer are needed to verify the clinical advantages of this approach.

Diffuse type (linitis plastica)

Linitis plastica carcinomas are poorly differentiated tumors that diffusely infiltrate the stomach wall. Histologically, they consist of single cells or small clusters of cells that contain large mucin vacuoles pushing the nucleus to one side to produce a signet

ring appearance. The result of the diffuse infiltration by the cancer cells is a thickened, rigid stomach that has been likened to a leather bottle. Diffuse type cancers carry a much poorer prognosis than the intestinal type due to their propensity for deep invasion and early metastasis [42].

Similar to patients with the intestinal type of gastric cancer, patients with linitis plastica usually present with symptoms of abdominal pain, weight loss, early satiety and nausea. The tumors differ endoscopically, however; linitis plastica appears as thickened, usually erythematous folds. The stomach is usually difficult to distend and may feel hard to the biopsy forceps. Biopsies obtained with standard forceps may be unable to diagnose cancer in up to 50% of cases [43,44]. More aggressive endoscopic biopsy techniques employing a diathermic snare to obtain a deeper sample carry an increased risk of hemorrhage and perforation [45–47]. As previously noted, there are diverse causes of enlarged gastric folds, including malignancies (adenocarcinoma and lymphoma) as well as a variety of benign conditions. Because it can be difficult to rule out an infiltrating malignancy with standard endoscopy, laparotomy with full-thickness biopsy has been frequently necessary [45].

EUS examination has been found to be exceptionally helpful in evaluating the patient with a suspected infiltrating malignancy. The normal stomach is 3 to 4 mm in thickness. When an infiltrating cancer is present, the stomach is thickened to greater than 4 mm, and one of two EUS patterns may be seen. In the first, there is complete loss of the normal five-layer pattern, with the markedly thickened wall assuming a homogeneously dark appearance. All layers of the stomach are generally involved and these tumors are stage T3. In the second EUS pattern, the thickened stomach maintains its five-layer pattern, but the muscularis propria (fourth layer) is a prominent, thick, dark band beneath a thickened, bright, third layer (submucosa) (Figure 13.3). In this type of pattern, forceps biopsies are often negative due to the fact that most of the tumor cells are in the deeper layers. Deep endoscopic or surgical full-thickness biopsy should be performed when forceps biopsies are negative. When the thickening is limited to the mucosal layers (first and second layers), a benign condition is usually present and large-capacity endoscopic forceps biopsies are sufficient for diagnosis, making surgical biopsy unnecessary [3].

In summary with regard to evaluation of the patient with gastric adenocarcinoma, an abdominal CT scan should be obtained to evaluate for the presence of metastases. If this is negative, EUS is used for locoregional staging, and alters management of the patient in about a third of cases [48]. Liver lesions which appear suspicious on CT scan or EUS examination should be biopsied if the primary tumor is not obviously metastatic. If these are visualized with EUS, sampling via FNA may be feasible.

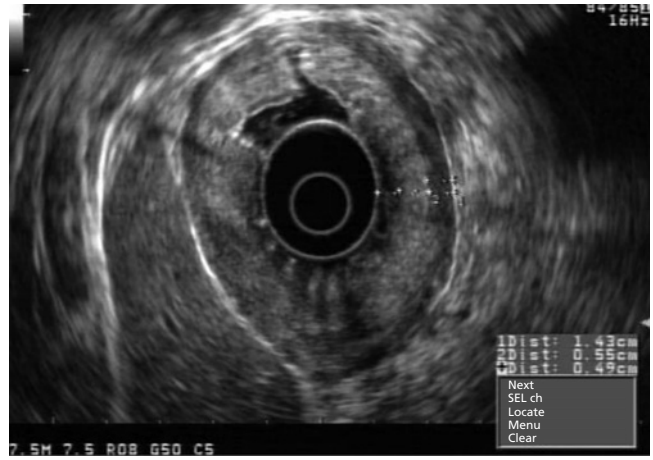

Figure 13.3 Pseudo-linitis plastica. A patient with breast cancer has metastases to the stomach which are infiltrating the wall giving the appearance of linitis plastica. The five-layer wall pattern is preserved, but the wall is markedly thickened to 14.3 mm (normal 4 mm or less) and the muscularis propria is disproportionately thickened to 4.9 mm.

Lymphoma

The stomach is the most common site for primary extranodal lymphoma, comprising one-fourth of all extranodal cases and at least half of all primary gastrointestinal lymphomas. Primary gastric lymphoma (PGL) accounts for 5% of all gastric tumors. These are lymphomas of the non-Hodgkin type and are usually B-cell in origin. They are either high-grade (especially diffuse large cell) or low-grade MALT (mucosa-associated lymphoid tissue) lymphomas. Patients may present with abdominal pain, early satiety, nausea and vomiting, weight loss, or nonspecific dyspeptic symptoms.

Endoscopically, primary gastric lymphomas usually appear as an exophytic mass, although a more diffuse infiltration can occur, causing a linitis plastica appearance. The lymphomas usually occur in patients over the age of 50. The main diagnostic considerations in the differential are gastric adenocarcinoma and the various benign causes of thickened folds previously mentioned.

Gastrointestinal lymphomas are staged differently than carcinomas (Table 13.3). Tumors confined to the gastrointestinal tract are stage IE, and these patients have significantly higher survival rates than those with regional lymph node involvement (stage IIE) [49]. Higher stages are assigned to tumors based on the presence and site of nodal involvement. Patients with stage IE and with low-grade MALT lymphoma have better survival statistics [49,50]. Although the depth of penetration into the wall and lateral extent of the tumor do not alter the stage, these characteristics may have clinical and treatment implications. The use of EUS in the evaluation and treatment of high-grade lymphomas differs from the techniques used for MALT lymphomas and will be considered separately.

Primary gastric lymphoma

When left untreated, high-grade PGL follows a clinical course similar to that seen with gastric adenocarcinoma. Unlike adenocarcinoma, however, high-grade PGL does respond well to treatment

Table 13.3 Ann Arbor staging system for gastrointestinal lymphomas. Adapted from Refs 98, 99, with permission

Stage	Sites of involvement
IE	Tumor confined to GI tract ("E" designates lymphoma outside of lymph nodes)
IIE_1	Tumor with regional nodal involvement
IIE_2	Tumor with extraregional subdiaphragmatic nodal involvement (e.g. para-aortic, iliac, etc.)
IIIE	Tumor with nodal involvement on both sides of the diaphragm
IVE	Tumor with extranodal disseminated involvement (e.g. bone marrow, lungs, liver, etc.)

with radiation and chemotherapy, and these nonsurgical approaches may be used in addition to or instead of surgical resection. Selection of patients for a particular treatment protocol remains difficult. Ideal candidates for primary resection are patients with smaller tumors that can be removed with a subtotal gastrectomy and who do not have nodal involvement. Adjuvant therapy following resection should be given when the tumor invades the muscularis propria or there is nodal involvement. Radiation and chemotherapy remain the primary treatment modalities when there is unresectable disease (stages IIE2, IIIE, IVE). Recent data has shown that for patients with early stage disease (IE and IIE1), chemotherapy is preferable to surgery. In a study published in 2004, 589 patients with primary gastric lymphoma stages IE and IIE1 were randomized to surgery, surgery plus radiation, surgery plus chemotherapy, and chemotherapy alone, with the chemotherapy consisting of CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) at standard doses [51]. Actuarial curves at 10 years showed survival rates of 96% for chemotherapy alone, vs. 54% for surgery alone, 53% for surgery plus radiation, and 91% for surgery plus chemotherapy. As more data is accumulated in this area, surgery may be reserved for those with extensive, high-grade disease, or may become nonstandard therapy. A concern in the past has been the possibility of perforation of transmural disease during chemotherapy and radiation. This concern has not been borne out in clinical trials and does not appear to be a significant risk [52,53].

Similar to the EUS evaluation for gastric adenocarcinoma, the most important considerations when performing an examination for this indication are to determine the local extent of disease, the depth of involvement through the gastric wall, and the longitudinal tumor extent from antrum to fundus. Lymphoma appears as a hypoechoic thickening of the mucosa. As the malignancy extends deeper, there usually appears to be fusion of the wall layers (Figure 13.4).

Older studies have found EUS to be 90% accurate in determining depth of penetration [54–58]. A more recent multicenter study of 70 patients with gastric lymphoma who underwent preoperative EUS evaluation followed by surgery with pathological

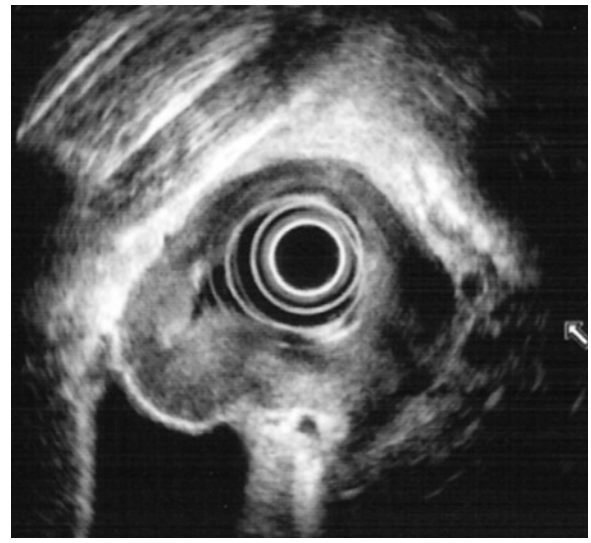

Figure 13.4 Gastric lymphoma. The five-layer wall pattern is obliterated and the gastric wall is markedly thickened.

confirmation of stage showed that EUS correctly determined depth of disease in only 37/70 (53%) of patients [59]. However, this study involved 34 centers, only five of which contributed more than two patients, so conclusions may be difficult to draw as the experience of the endosonographers is not known. Another recent study assessed interobserver agreement on staging of MALT as well as repeat staging following treatment [60]. A total of 54 patients underwent testing prior to treatment and 42 returned for repeat EUS following treatment. Overall agreement for T stage prior to treatment was only fair ($\kappa <= 0.38$) and was similar for restaging after treatment. ($\kappa = 0.37$). Agreement was good for nodal disease before treatment ($\kappa = 0.63$) but fell after treatment ($\kappa = 0.34$). Nonetheless, EUS remains the most accurate diagnostic modality for determining local staging [61]. EUS can also be used to document response to chemotherapy [57].

Another goal of EUS evaluation in gastric lymphoma is to assess for metastatic lymph node involvement. Due to the limited depth of penetration of the high-frequency ultrasound used in EUS, only regional (IIE1 and some IIE2) lymph nodes will be seen. Even with this limitation, EUS has been up to 100% sensitive with an average 80% to 90% accuracy for detecting lymph node disease [54–58]. Accurate detection of metastatic lymph nodes is important because nodal tumor may contraindicate the use of surgery as primary therapy. To increase diagnostic accuracy, EUS-guided FNA with flow cytometry of the aspirated specimen has been used to confirm nodal metastasis [62].

MALT lymphoma

MALT lymphoma, or mucosal-associated lymphoid tissue, is a B-cell lymphoma which accounts for 3 to 5% of all gastrointestinal malignancies. This tumor most commonly occurs in the stomach, and more than 90% of cases are associated with

H. pylori infection. It is now referred to as extranodal marginal zone B-cell lymphoma of MALT type in the World Health Organization classification. It is an indolent malignancy, and most patients have a favorable outcome. Low-grade MALT lymphomas may contain foci of high-grade lymphoma [63], however, and standard endoscopy may not be able to detect persistent submucosal disease. For these reasons, EUS is used as an additional modality to diagnose, stage and monitor the disease.

MALT lymphoma most commonly involves the body of the stomach and can have a variable appearance endoscopically, including a friable, nodular appearance of the mucosa, an ulcerated lesion, infiltrated, thickened mucosa, and occasionally a normal appearance. Lesions can be multifocal. Mucosal biopsies are usually sufficient to make the diagnosis. The sonographic appearance is similar to primary gastric lymphoma, with a hypoechoic infiltrate involving the mucosa and extending deeper into the gastric wall. Staging of MALT is the Ann Arbor staging system used for primary gastric lymphoma (Table 13.3). Some studies in the literature have used the TNM staging system as for gastric cancer, where T1m is disease limited to the mucosa, T1sm involves the submucosa, T2 reaches the muscularis propria, and T3 is through the muscularis propria.

Regression of MALT after treatment of *H. pylori* was first reported over 10 years ago [64]. However, not all patients with MALT will respond to antibiotic therapy. The depth of penetration into the wall may be predictive of which patients will require only antibiotic therapy and which will need more definitive treatment with chemotherapy, radiation, or more rarely surgery. EUS is used to stage these tumors and is therefore a key component of the pretreatment evaluation for this tumor. A study by Sackmann et al. showed that complete regression of MALT with anti-*Helicobacter* treatment occurred in 12 of 14 patients with tumor limited to the mucosa and submucosa on EUS, but none of the 10 patients with either deeper invasion or suspicious lymph nodes present ($P > 0.01$) [65]. Similarly, Nobre-Leitao et al. found a high rate of response to antimicrobial therapy in patients staged E1 by EUS [66]. More recently, a study of 19 patients with MALT who underwent pretreatment EUS staging found that 77.8% of patients with disease limited to the mucosa responded to anti-*Helicobacter* treatment vs. only 12.5% of patients with disease involving the submucosa ($P = 0.007$) [67]. In another recent study, tumors limited to the mucosa were also significantly more likely to respond to antibiotics than more deep-seated tumors, but on multivariate analysis the only predictor of response was absence of nodal involvement [68]. Finally, a study from Italy evaluated 51 patients with MALT who underwent EUS prior to treatment [69]. This study found that 12/16 (75%) of patients with disease limited to the mucosa and 11/19 (58%) of patients with submucosal invasion achieved remission with antibiotics compared to only 4/8 (50%) of those with nodal disease. Taken together, these findings support the ability of EUS to correctly stage and identify those patients with MALT lymphoma most likely to respond to antibiotic therapy.

Detection of ascites

EUS is often performed to evaluate for suspected malignancy or to stage a known malignancy. In patients with cancer, the presence of malignant ascites signifies distant spread and generally predicts a poor prognosis. EUS has been shown to be more sensitive than CT scan for the detection of ascites. In a study by Nguyen et al., CT scan detected ascites in only 14/79 (18%) of patients subsequently found to have ascites by EUS [70].

Ascites appears as a triangle-shaped pocket of anechoic fluid usually in the perihepatic or perigastric area and can often be visualized from both the stomach and the duodenum (Figure 13.5). If ascites is seen in a patient with cancer, consideration should be given to aspiration of the fluid for cytological analysis. If cytology is positive for malignancy, this denotes metastatic disease and may help the patient avoid unnecessary surgery. A recent study of 629 patients who underwent EUS to evaluate known or suspected malignancy found 34 patients with ascites [71]. Aspiration was performed in 33 and surgical confirmation with pathological staging was available for 25 of these patients, 16 of whom (64%) had positive cytology. The sensitivity of EUS-guided paracentesis for diagnosing malignant ascites was 94% in this study, with a positive predictive value of 100% and a negative predictive value of 89%. The complication rate in this study was 4%; one patient developed bacterial infection of the fluid. Another study found ascites in 5.3% of all patients undergoing EUS for any indication [72]. Of these, 46 had EUS-FNA of the fluid, and one third had positive cytology. There were no complications in this series. Underscoring

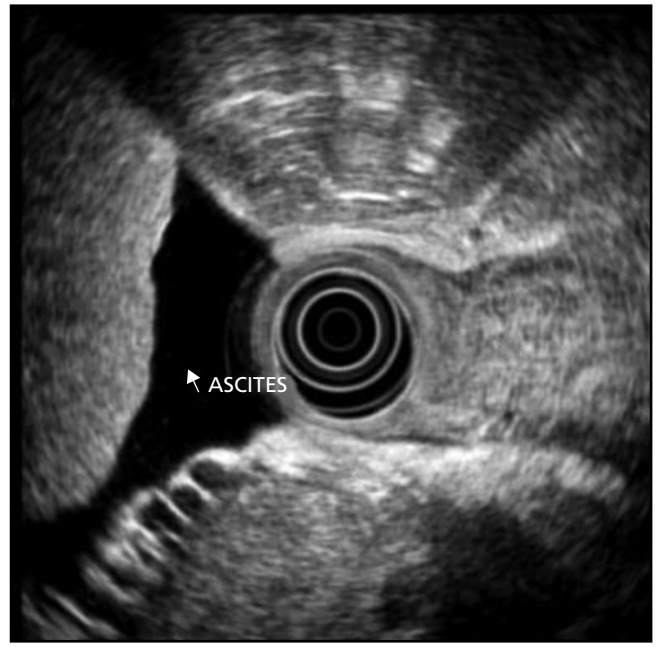

Figure 13.5 Ascites. A large pocket of hypoechoic material is seen next to the liver, located on the left, in a patient with gastric cancer. The ascites was accessed via a 22-gauge needle placed through the duodenum and was positive for malignancy, denoting M1 disease.

the importance of evaluating cancer patients for ascites, a prospective trial of 301 patients with newly diagnosed gastric cancer found 93 patients with ascites, 71 of whom were found to have peritoneal metastases. Findings were confirmed by laparotomy. EUS and CT scan were performed in all patients, and EUS was found to be 87.1% sensitive for the detection of ascites vs. 16.1% for combined ultrasound and CT. On multivariate analysis, detection of ascites by EUS was found to be the only significant predictor for peritoneal metastases, with an OR of 4.7 (95% CI 2–11.2) [73].

Ascites can be aspirated using the linear array echoendoscope and a 22-g needle. The site which reveals the largest volume of fluid should be used. If a tumor or lymph node has previously been sampled during the procedure, a new needle should be used to avoid contamination of the fluid with malignant cells, and also to avoid obtaining a false-positive cytological result on the fluid from malignant cells on the needle. Additionally, care should be taken to avoid passing the needle through tumor to access the ascites, for similar reasons. Although data to support prophylactic antibiotics in EUS-guided paracentesis is lacking, usual practice is to administer a dose of intravenous antibiotics, usually a fluoroquinolone, during the procedure followed by a 7 to 10 day course of oral antibiotics.

Refractory gastric ulcer

The patient with a nonhealing gastric ulcer presents a difficult clinical problem. Aggressive biopsy protocols will detect the majority of, although not all, gastric malignancies. EUS may be employed to search for and stage an underlying tumor. EUS may detect an obvious tumor mass or evidence for an infiltrating malignant process in the surrounding stomach. The water-fill techniques should be used to image the ulcerated area as well as the surrounding uninvolved stomach for evidence of a tumor or wall thickening and infiltration. The 5 to 7.5 MHz frequency should be used to examine contiguous organs to rule out extrinsic invasion of the stomach by a nongastric tumor. The presence of enlarged, hypoechoic, round lymph nodes is worrisome for malignancy particularly if found in the region of the celiac axis or gastrohepatic ligament. However, it is not possible to make a definitive diagnosis of gastric cancer or exclude the diagnosis using EUS alone. The inflammatory process associated with the ulcer may extend into the fourth layer, causing changes on EUS that are indistinguishable from malignancy [74], and enlarged lymph nodes may be benign due to inflammation. Therefore, while EUS may provide a more accurate preoperative diagnosis, in the absence of a clearly unresectable tumor, it does not make surgical exploration unnecessary.

Benign lesions of the duodenum, ampullary adenomas and ampullary carcinoma

Evaluation of submucosal and mucosal lesions of the duodenum are another common indication for evaluation by endoscopic ultrasound. These are often discovered incidentally at the time of upper endoscopy performed for various indications, although periampullary tumors are often symptomatic and discovered during endoscopic evaluation.

Submucosal lesions in the duodenum have a variety of etiologies, including carcinoid tumors, lipomas, granular cell tumors, gastrointestinal stromal tumors, leiomyomas, hemangiomas and Brunner's gland hyperplasia, among others. EUS can be used to evaluate the layer these lesions arise from, and if they are limited to the mucosa or submucosa, endoscopic submucosal resection can often be used to remove them for definitive diagnosis and therapy.

Duodenal adenomas

Adenomatous polyps of the duodenum can be found incidentally or during surveillance upper endoscopy in patients with familial adenomatous polyposis (FAP). These usually have a tubulovillous or villous histology due to the villous nature of the small bowel mucosa. Duodenal adenomas have a distinct adenoma-to-carcinoma sequence similar to adenomatous polyps in the colon and therefore are treated when detected, either by excision or by ablation therapy. The precise role of EUS in examining adenomas of the duodenum (excluding periampullary tumors) is unclear. It may be helpful to exclude deeper invasion if there is some question about whether the lesion is actually malignant prior to attempted endoscopic treatment, especially in larger polyps. Endoscopic features suggestive of malignancy (presence of ulceration, friability and bleeding, firmness, and non-lift on injection of saline into the submucosa) may not be present in some cases. EUS can also identify whether the polyp is involving the ampulla if this is unclear endoscopically, as the technique for resection of lesions in this area differs from the technique for the rest of the duodenum.

If EUS is used to evaluate duodenal adenomas, the through-the-scope radial miniprobe is a good option for imaging, as the lesion can then be treated with the therapeutic upper endoscope without having to change instruments. The duodenum can be filled with water as previously described, and the probe positioned over the lesion to determine if layers deeper than the mucosa are involved. Adenomas appear as a polypoid growth projecting into the lumen, involving the mucosa only, and they are usually of the same echogenicity as the mucosa. If there is invasion of the lesion into deeper layers, suggesting malignancy, or if the polyp is very large, surgery may be necessary for removal. One study examined the safety and feasibility of removing large duodenal and ampullary adenomas endoscopically. This retrospective single-center series examined 29 cases of attempted endoscopic removal of duodenal and ampullary adenomas greater than 3 cm in size and compared them to 22 cases of polyps less than 3 cm in size [75]. They found a 92.2% overall success rate, with no differences between the groups in mean number of treatments necessary. There is no consensus on what diameter of lesion is too large for endoscopic removal, although if a lesion involves more than one-third of the circumference of the lumen, surgical resection should be considered [76].

Endoscopic treatment of duodenal adenomas consists of snare excision, often with saline-lift assistance. Ablation therapy with argon plasma coagulation is also used for large flat areas of adenomatous tissue and to cauterize residual tissue following snare excision. A study of 21 patients with nonampullary duodenal adenomas treated with endoscopic therapy found that the success rate for removal was 55% when these were visualized at 3 months after initial treatment [77]. Local recurrence was seen in 25% of patients after a mean follow-up of 71 months, demonstrating the need for consideration of endoscopic surveillance. The most recent guidelines from the American Society of Gastroenterology did not make specific recommendations for surveillance interval for duodenal adenomas occurring sporadically due to limited available data [76].

Ampullary adenomas and ampullary adenocarcinoma

Similar to adenomas of the duodenum, adenomas involving the major duodenal papilla can occur sporadically and in association with FAP, and they have the ability to undergo malignant transformation into adenocarcinoma. Ampullary lesions are most commonly adenomas, although other neoplasms such as gangliocytic paragangliomas and carcinoid tumors can occasionally involve the ampulla. Malignant lesions of the ampulla (periampullary tumors) can arise from or near the major duodenal papilla and can originate from the ampulla itself, the pancreas, the distal common bile duct and the duodenum. Primary ampullary cancers are rare, accounting for about 0.2% of all gastrointestinal malignancies and only 6% of periampullary tumors [78,79].

The usual age at diagnosis of primary ampullary carcinoma occurring outside of a genetic syndrome is 60 to 70 years old, and the most common presenting symptoms include painless jaundice, nonspecific abdominal pain or back pain and weight loss [80]. Less commonly, cholangitis and pancreatitis can occur. Patients may also be asymptomatic and have these lesions discovered during endoscopy performed for other reasons.

Endoscopically, ampullary tumors appear as a friable mass of the papilla, although with smaller adenomatous polyps and adenomatous changes, the papilla may appear normal. With larger tumors, the ampullary orifice may no longer be visible. In tumors with ulceration or those which are very large, malignancy should be strongly suspected, even with negative biopsy results. It is can be difficult to differentiate endoscopically between cancers which originated in the ampulla and periampullary cancers, especially those of the pancreas which are invading through the wall of the duodenum. Even after biopsies and histological evaluation, the origin of the tumor may still be unclear, and only become apparent after surgical resection with evaluation of the entire specimen.

Because there are different options for treatment of benign ampullary adenomas, one of the primary objectives in evaluating these lesions is to assess whether malignancy is present, which can be difficult as foci of adenocarcinoma can be present within benign appearing lesions. The traditional treatment for benign adenomas has been pancreaticoduodenectomy (Whipple procedure). Transduodenal surgical ampullectomy is an alternative with less morbidity, although residual tissue can be left behind, requiring surveillance [81]. Endoscopic ampullectomy, performed at the time of ERCP, has emerged as a less invasive, viable treatment option for benign ampullary adenomas. In a multicenter retrospective study of 103 patients who underwent endoscopic ampullectomy for ampullary adenomas, endoscopic treatment was successful long-term in 80% and failed in 20% (recurrent tumor or failed initial treatment) [82]. For ampullary lesions which are known to be malignant, surgical resection via Whipple procedure is the procedure of choice, although local surgical resection of early tumors is reported. Endoscopic ampullectomy is not recommended for ampullary cancer, although case reports exist [83,84]. When a focus of adenocarcinoma is found after endoscopic resection, patients should be considered for surgery to ensure complete resection. Palliative options for malignant tumors in patients who are unable or unwilling to undergo surgery include endoscopic stenting for relief of jaundice and ablation of tumor with photodynamic therapy or laser ablation with argon or Nd-YAG.

Evaluation of ampullary lesions

EUS is useful in the evaluation of ampullary adenomas to exclude deeper invasion prior to attempted endoscopic resection and for the staging of ampullary cancers. It can assess for deeper invasion, indicating a malignancy, and also determine the degree to which the lesion extends into the ducts. In the past, the initial procedure of choice has been an ERCP. Biopsies of the ampulla are necessary to ascertain whether malignancy is present, and these can be done at the time of EUS using side-viewing endoscopes. Prior to attempted endoscopic resection, cholangiograms and pancreatograms should be obtained as these can identify whether the tumor extends proximally into the ducts. Biopsies may be negative in up to 50% of malignant tumors [85], and if malignancy is strongly suspected, based on the endoscopic or EUS appearance, surgical evaluation is recommended rather than attempted endoscopic resection. Endoscopic sphincterotomy followed by deeper biopsies may improve sensitivity. A study of 26 patients with ampullary tumors who underwent surgical resection (20 malignant, 6 benign) evaluated the accuracy of biopsy before and after endoscopic sphincterotomy in assessing for malignancy [86]. Biopsies were accurate in only 69% of patients, improving to 77% after sphincterotomy. Additionally, ERCP cannot assess local extent of the tumor into surrounding tissues or assess for lymph node involvement.

Technique

The major duodenal papilla can be imaged sonographically after endoscopic visualization followed by placement of the balloon directly on the lesion. Alternatively, it can be seen during pullback of the echoendoscope after deeper intubation of the duodenum. Through-the-scope probes can also be used to image the papilla, but due to their higher scanning frequencies and decreased depth of penetration, they are not recommended for

staging of suspected ampullary cancer. The ampulla appears as a hypoechoic structure arising from the duodenal wall and usually measures 8 to 12 mm in cross-section. On continued withdrawal of the echoendoscope, the origin of the pancreatic and common bile ducts will be seen emerging from within the papilla. The pancreatic duct orifice usually appears first during pull-back, followed by the bile duct, which is located more proximally.

Ampullary adenomas may appear as an enlargement of the papilla, with the same hypoechoic echotexture as seen in the normal ampulla. Careful attention should be given to ascertaining whether the lesion invades deeper structures such as the ducts or the pancreatic head (Figures 13.6, 13.7). Additionally, loss of interface between the duodenal wall and the ampulla suggests malignancy. Invasion of the bile duct appears as a hypoechoic mass within the lumen of the duct, usually accompanied by some degree of duct dilation. A search should be undertaken for peritumoral enlarged lymph nodes, similar to the staging of other tumors of the upper gastrointestinal tract.

In lesions which are felt to be benign, EUS can demonstrate whether the lesion extends proximally into the bile duct or pancreatic duct. In general, evidence of adenomatous tissue extending into the distal bile duct is a contraindication to attempted endoscopic resection, although some endoscopists feel that a small degree of ductal involvement (<1 cm) is acceptable. A study of 106 patients who underwent endoscopic ampullectomy for ampullary tumors found that follow-up surgery was required for 37% of patients with intraductal growth for incomplete removal or recurrence compared to 12% of those without ($P < 0.01$) [87]. At a mean follow-up of 43 months, endoscopic resection was curative in just under half of those patients with intraductal growth. These results support the use of surgery in patients with intraductal growth rather than endoscopic resection. For patients unwilling or unable to undergo surgery, endoscopic removal is a viable option but patients need close surveillance to assess for recurrence.

Staging of ampullary adenocarcinoma

The prognosis of ampullary cancer is directly related to the stage. The TNM classification system is used, where T1 lesions are limited to the ampulla itself, with preservation of the duodenal wall layers, T2 lesions invade the duodenal wall, T3 lesions invade less than 2 cm into the pancreas, and T4 lesions invade >2 cm into the pancreas or invade surrounding organs or vessels (Table 13.4). The prognosis for completely resected cancers of ampullary origin is significantly better than for tumors of pancreatic origin, with 5-year survival rates of 30 to 50% even with positive lymph nodes, compared to less than 10% for node-positive pancreatic cancer [80,88]. In ampullary cancers which do not involve the sphincter of Oddi, the 5-year survival rate approaches 100% [89].

EUS is superior to CT scan and transabdominal ultrasound in local staging (T stage and N stage) of ampullary cancers, while CT scan is superior for detection of metastases. EUS has been shown to be 70 to 90% accurate for T-staging [90,91]. Accuracy may be adversely affected by the presence of a biliary stent. A recent study compared EUS to standard CT and ERCP in detection

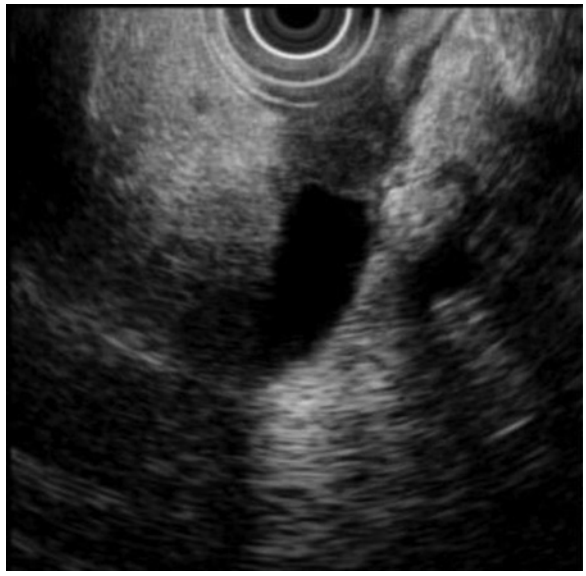

Figure 13.6 Ampullary carcinoma. The ampulla is hypoechoic and enlarged to 1.8 cm. It obstructs the pancreatic duct but does not invade it. The lesion was staged as T3 due to invasion of the pancreas <2 cm. Biopsies at the time of ERCP were negative for malignancy but EUS-guided FNA was positive for adenocarcinoma.

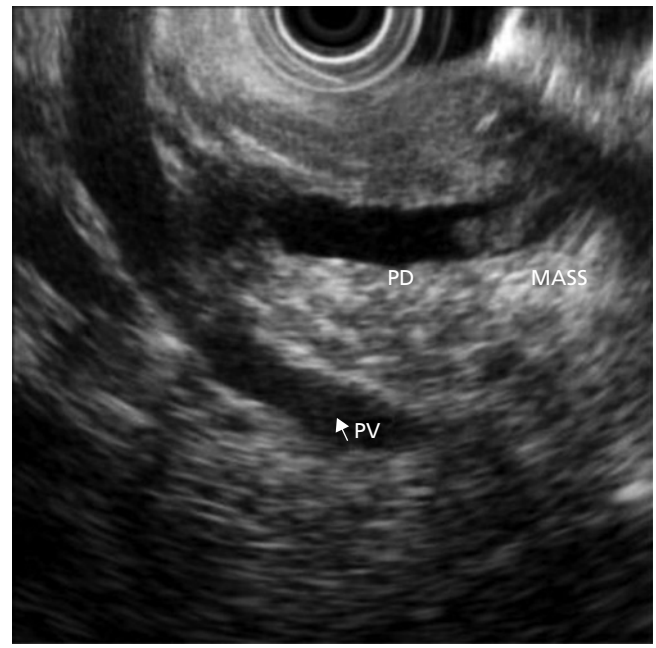

Figure 13.7 Ampullary carcinoma. The pancreatic duct (PD) is dilated. At its distal end is a hypoechoic mass which is an ampullary cancer, obstructing the duct. Hypoechoic material is seen within the duct, which represents tumor growing proximally from the ampulla. PV, portal vein.

Table 13.4 Staging of ampullary cancer. Reproduced from Ref. 97 with permission

Tumor (T) stage	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor limited to ampulla or sphincter of Oddi
T2	Tumor invades the duodenal wall
T3	Tumor invades the pancreas < 2 cm
T4	Tumor invades the pancreas > 2 cm or other adjacent organs
Nodal (N) stage	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph nodes
N1	Regional lymph node metastasis
Distant metastasis (M) stage	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
Stage grouping	
Stage 0	Tis N0 M0
Stage IA	T1 N0 M0
Stage IB	T2 N0 M0
Stage IIA	T3 N0 M0
Stage IIB	T1-3 N1 M0
Stage III	T4 any N M0
Stage IV	Any T, any N, M1

and staging of periampullary cancers and found that EUS was superior to CT in sensitivity for detection of tumors, with a sensitivity of 97% for EUS versus 39% for CT ($P < 0.001$) [91]. In this study, the accuracy of EUS for T-staging was 81% and for N-staging was 80%. The accuracy of T-staging was adversely affected by the presence of a biliary stent although the difference was not statistically significant. Another study comparing EUS to CT and MRI found that EUS had a T-stage accuracy of 78%, vs. 24% for CT and 46% for MRI [90]. When a biliary stent was present, EUS had an accuracy of 72%. The presence of a stent tended to result in understaging, most commonly in T3 lesions staged as T2. The three modalities had similar N-stage accuracies (EUS 68%, CT 59%, MRI 77%).

Intraductal ultrasound has been explored as a staging tool for periampullary cancers. In this technique, a 20 to 30 MHz ultrasound probe with a diameter of 1.1 to 2 mm is passed into the bile duct at the time of ERCP. If a wire-guided probe is used, sphincterotomy is generally not necessary. If a non-wire-guided probe is used, sphincterotomy is required in many cases to achieve cannulation [93]. The normal bile duct has a two to three layer appearance and is 1.8 to 2 mm in thickness [94]. After cannulation of the common bile duct, the probe is passed proximally. Scanning is performed during withdrawal of the probe to assess for thickening of the bile duct signifying proximal invasion. At the level of the ampulla, the tumor is assessed for extension beyond the ampulla, involvement of the sphincter of Oddi, invasion into periampullary tissues, and peritumoral lymph nodes.

A prospective, randomized trial comparing intraductal ultrasound (IDUS) to conventional EUS and CT evaluated 27 patients with benign ampullary adenomas ($n = 12$) and ampullary carcinomas ($n = 13$) [95]. All patients had the three imaging modalities and all underwent surgical resection, with pathological stage serving as the gold standard. IDUS was found to be superior to both conventional EUS and CT scan for overall accuracy at detection of the presence of tumor (benign or malignant). IDUS identified 100% of tumors, EUS 59.3%, and CT 40.7% ($P < 0.05$ for all comparisons). For T-staging, IDUS was 86.7% accurate vs. 53.3% for EUS. Another study of 32 patients found IDUS to have an overall accuracy of 87.5%, with an N-stage accuracy of 66.7% when compared with pathological specimens [92]. However, IDUS is not widely available, and with larger tumors of the papilla, cannulation of the bile duct may not be possible, which may limit the applicability of this method. Additionally, the catheter probes are prone to damage from the elevator on the side-viewing endoscope, which may necessitate frequent replacement at significant cost.

Other applications

There have also been case reports of EUS being used to access an obstructed common bile duct when ERCP results in failed cannulation, as can be the case in ampullary tumors. A case series of six patients, two of whom had a deformed papilla due to malignancy, underwent transduodenal puncture of the common bile duct or main pancreatic duct, and a wire was subsequently passed antegrade through the papilla [96]. The wire can subsequently be cannulated via standard ERCP, allowing biliary access.

Summary

EUS is used to evaluate a variety of benign and malignant conditions of the stomach and duodenum. Optimal imaging requires the use of the water-fill technique and scanning at 10 to 20 MHz for small intramural lesions and 5 to 7.5 MHz to assess larger masses and surrounding organs and lymphadenopathy. In the evaluation of thickened gastric folds, EUS can rule out the presence of varices and identify which layers of the stomach are involved. Thickened mucosal layers are seen in benign conditions and indicate that endoscopic large-capacity forceps biopsies will be sufficient to provide a tissue diagnosis and exclude malignancy. The presence of prominently thickened submucosa and muscularis propria layers should raise the question of an infiltrating malignancy (adenocarcinoma or lymphoma) and may require deep or full-thickness biopsy.

In patients with gastric cancer, EUS provides an accurate assessment of depth of invasion and nodal metastasis, predicting resectability and the likelihood of postoperative recurrence. Following resection, EUS may detect anastomotic recurrence at an earlier stage, which may allow for better patient outcome. EUS using higher-frequency ultrasound, perhaps with 20-MHz miniprobes, may allow selection of patients with early gastric cancer for minimally invasive endoscopic resection, although this therapy is not yet commonly used in the United States. In patients with gastric lymphoma, EUS determination of depth, longitudinal spread and lymph node involvement allows for rational planning among the three treatment modalities: surgery, radiation and chemotherapy. For low-grade MALT lymphomas, EUS predicts which patients are likely to respond to anti-*Helicobacter* therapy, and is useful in identifying residual and recurrent disease following treatment.

EUS is also helpful in evaluating adenomas of the duodenum and periampullary region to exclude deeper invasion prior to attempted endoscopic resection, and to stage ampullary cancers for resectability and prognostic purposes.

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14 Gastrointestinal Subepithelial Masses

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The term "subepithelial mass" describes any gastrointestinal tract mass with normal overlying mucosa. These are sometimes also called "submucosal lesions," although this is a misnomer as some lesions could be within the mucosal layer, or from a deeper layer than the submucosal layer. Usually these lesions are detected incidentally as smooth masses on endoscopy or barium studies. Because these lesions are located below the mucosal layer, endoscopic biopsies usually reveal only normal mucosa.

Before the development of endoscopic ultrasound, these lesions were generally assumed to be benign, and often were thought to be either lipomas or leiomyomas. Endoscopic ultrasound (EUS) now allows the gastroenterologist to identify the actual wall layer from which these lesions originate. Subepithelial masses can be located in the histological submucosa, muscularis propria, or as extrinsic compression by a structure adjacent to the gastrointestinal tract (Table 14.1). EUS allows a much more accurate diagnosis of these subepithelial lesions, and helps determine which lesions require additional tissue sampling, endoscopic follow-up or surgical resection [1–3].

Table 14.1 Differential diagnosis of subepithelial masses based on site of origin

Site	Differential diagnosis
Mucosal	Polyp (hyperplastic, fundic gland, adenoma) Duplication cyst Gastrointestinal stromal tumor or leiomyoma (arising from the muscularis mucosa)
Submucosal	Lipoma Carcinoid Pancreatic rest Varices Duplication cyst Granular cell tumor Gangliocytic paraganglioma Adenomyoma Gastrointestinal stromal tumor or leiomyoma (arising from the muscularis mucosa or muscularis propria)
Muscularis propria	Gastrointestinal stromal tumor or leiomyoma (arising from the muscularis propria)
Extrinsic compression	Adjacent normal organs (i.e. liver or spleen) Lymph nodes Malignancy Pseudocyst

Endoscopic findings

Standard videoendoscopy is sometimes performed prior to EUS visualization of subepithelial masses because direct visual imaging and mucosal biopsy is often superior with dedicated video endoscopes than with oblique-viewing echoendoscopes. Forward-viewing echoendoscopes are now becoming available, which are sufficient to use as both a forward-viewing endoscope (with biopsies) and as an EUS scope.

The video endoscopy appearance is important in terms of identifying the actual location of the mass in relation to other structures (i.e. the gastroesophageal junction or the ampulla), noting overlying mucosal ulceration and identifying other lesions. Subepithelial masses in the second part of the duodenum should be examined with a side-viewing duodenoscope to accurately characterize the lesion and the relationship to the ampulla.

Careful endoscopic evaluation of subepithelial masses may help suggest the etiology of the mass, although superficial biopsies of these masses usually only reveal normal mucosa. The characteristic endoscopic findings of lipomas include the "cushion sign," in which the biopforceps indent the lesion as if it were a pillow, and the ability to separate or "tent" the normal overlying mucosa easily from the underlying lipoma with a biopsy forceps. Stromal cell tumors may appear as bilobar or "dumbbell-shaped" masses. Pancreatic rests often have a central dimple, orifice or diverticulum. Varices appear tubular and blue. Some subepithelial masses disappear with insufflation, such as varices, cysts and thick folds.

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EUS imaging techniques

Endoscopic ultrasound is very useful in identifying the exact histological layer from which subepithelial masses arise. Imaging can be performed with dedicated echoendoscopes (radial scanning or linear array) and with catheter-based ultrasound probes.

Subepithelial masses are best imaged with the lesion submerged in water and by using little water in the balloon around the transducer. The water bath provides the acoustical imaging medium to allow the transducer to be placed 1 to 2 cm away from the lesion, which is the focal length of most transducers. This results in the most accurate ultrasound images of the normal five-layer wall pattern, and also prevents physical distortion of the lesion by the probe. In order to prevent air bubbles which can produce ultrasound artifact, simethicone is often added to the water which is slowly infused into the intestinal lumen [4].

Great care must always be taken when infusing large amounts of water into the upper gastrointestinal tract in order to avoid regurgitation and aspiration. When using the water-filled stomach technique, the head of the patient's bed should be elevated at least 45 degrees, the least amount of water possible should be instilled, all air should be removed with suction, and the nurse should watch for signs of regurgitation. At the end of the relevant imaging period, all water should be removed from the stomach using echoendoscope suction.

The larger the subepithelial mass, the easier it is to image with a dedicated echoendoscope. Large masses require an ultrasound which can penetrate several centimeters of thickness. Very small lesions, such as less than 1 cm in diameter, can be sometimes be difficult to image with echoendoscopes, and occasionally are better seen using catheter-based ultrasound probes passed through a standard endoscope under direct visualization.

Esophagus

Imaging in the esophagus can be challenging because of the inability to create a pool of water in the esophagus. It is generally not practical to infuse much water into the esophagus, because either the water may flow proximally and place the patient at risk for aspiration, or the water will rapidly flow into the stomach. Often these esophageal lesions are small, and the ultrasound transducer should be placed against the lesion under direct visualization, if possible. All air should be removed with suction. Very little balloon inflation is needed, and may be detrimental if it distorts or compresses the lesion. Small lesions in the esophagus are occasionally better imaged with a catheter probe.

Stomach

Imaging in these areas should be done with the lesion submerged under water. As much as 500 mL of water may be needed to obtain an adequate water bath. The head of the patient should be elevated in order to minimize the risk of aspirating the water. Lesions along the greater curve of the stomach can be imaged with the patient in the standard left lateral decubitus position. Lesions along the lesser curve, antrum and pylorus are more difficult to image when the patient is in the left lateral decubitus position because the water pools in the dependent portion of the fundus. Sometimes these lesions can be imaged by a combination of a large amount of water in the stomach, removing all air from the stomach, and using the water-filled balloon. The patient can also be positioned onto the back stomach, or right side to get the lesion under water, again using great care to avoid gastroesophageal reflux of fluid and subsequent aspiration.

Duodenum

Using a duodenoscope to image duodenal subepithelial lesions will often result in a better view of the lesion than with a standard endoscope, and will also allow for visualization in relationship to the ampulla. Usually a large amount of water can be instilled into the duodenum to help create an acoustic window. Duodenal motility can cause difficulty with imaging, and administration of intravenous glucagon (0.5 mg to 1.0 mg) may help relax the duodenum. Ultrasound imaging using a standard radial echoendoscope can often be difficult, especially with small lesions or lesions located on an angulated portion or just inside the pyloric channel. These lesions may be better imaged using a catheter probe passed through a standard endoscope or a duodenoscope, or possibly with a linear array scope. EUS should evaluate not only the subepithelial lesion, but also examine the ampulla, common bile duct and pancreatic head for involvement.

Rectum and colon

Before imaging rectal lesions, the bowel should be prepared with either oral purge or enemas. Flexible sigmoidoscopy should first be performed to identify the lesion, characterize the overlying mucosa, and to remove any remaining fecal material. Water should be instilled into the rectum and the patient positioned such that the lesion is covered with water. Patients with anterior lesions may need to lie on their stomachs, those with posterior lesions lie on their backs, those with left-sided lesions lie on their left sides, and with right-sided lesions lie on their right sides. Rectal EUS examinations are usually performed without intravenous sedation or glucagon.

Rectal ultrasonography is performed after filling the rectum with water and aspirating out any residual air. A small amount of water in the balloon may be needed. Ultrasound imaging should document not only the location of the lesion, but also the relationship to the adjacent organs such as the prostate, seminal vesicles, bladder and uterus.

Colonic subepithelial lesions located proximal to the sigmoid colon usually require a catheter probe ultrasound or dedicated colonic echoendoscope in order to reach the lesion of interest. Occasionally, sigmoid lesions may be within reach of a standard upper echoendoscope. In general EUS of the colon proximal to the rectum is not performed as there are technical difficulties and probably slightly increased risk for perforation due to the oblique viewing nature of most echoendoscopes.

Lesions located in the mucosal layer

Mucosal polyps

These will generally be superficial polyps such as hyperplastic, fundic gland or adenomatous polyps. Routine mucosal biopsies should provide a diagnosis, although sometimes large lesions suggest deeper involvement, and therefore EUS is warranted to confirm just a superficial lesion.

Mucosal cysts

These are small cysts located within the mucosal layer. These are discussed further below.

Gastrointestinal stromal tumors or leiomyomas

These are discussed further below, but occasionally can develop from the muscularis mucosa rather than the muscularis propria.

Lesions located in the submucosa

Lipoma

Lipomas are benign growths of mature lipocytes which are usually found in the submucosal layer [5]. They can involve any part of the intestinal tract, and are usually asymptomatic. Gastric lipomas account for about 5% of all gastrointestinal lipomas, and 75% are located in the antrum [6]. Usually they are discovered incidentally during endoscopy, but occasionally they cause symptoms such as pain, bleeding or obstruction.

Characteristic endoscopic findings include a yellow color. Pressing against the surface of a submucosal lipoma with a closed biopsy forceps leaves an indentation, as if it were a pillow ("cushion sign"). Grasping the normal overlying mucosa with biopsy forceps can easily pull the mucosa away from the underlying mass ("tent sign"). Routine biopsies yield normal mucosa, as the lesion is in the submucosa. Deep well biopsy or fine needle aspiration (FNA) may reveal lipocytes.

Endoscopic ultrasound shows a characteristic hyperechoic mass located in the submucosa (Figure 14.1). This finding is virtually diagnostic of a lipoma. Because of the high accuracy of EUS in diagnosing lipomas, biopsies or FNA are generally not needed.

The malignant potential of these lesions is extremely low or nonexistent, and malignant liposarcomas are very rare. Surgical removal of these lesions should be performed for symptomatic or enlarging lesions. Additionally, lesions which seem to be infiltrating multiple wall layers or do not have an echopattern entirely consistent with a lipoma should be considered for FNA biopsy or resection. Small, asymptomatic lesions which appear to be lipomas on EUS may not need any further follow-up, or at most perhaps periodic re-evaluation to confirm no increase in size.

There have been reports of snare resection of gastrointestinal lipomas [7]. However the risk of perforation seems to greatly increase if the lipoma is greater than 2 cm in diameter [8].

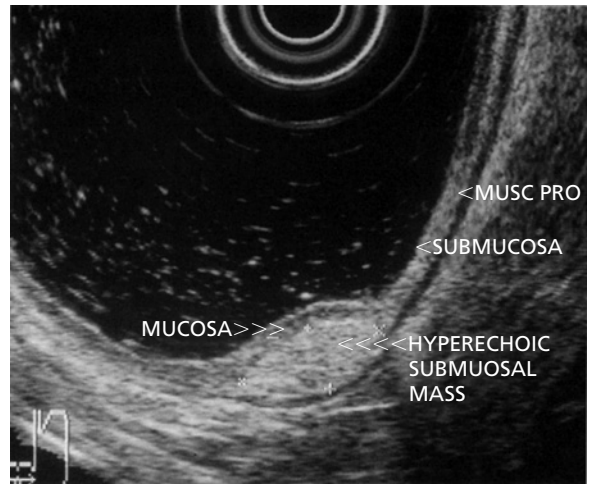

Figure 14.1 Gastric lipoma. Note the characteristic hyperechoic mass in the submucosal layer. Musc prop, muscularis propria.

Despite this risk, a recent case series of 15 patients in China reported the successful snare resection of large lipomas (≥ 2 cm) without perforation or bleeding with at least one year of follow-up [9]. However, given that lipomas are almost universally benign, it does not seem that routine removal of lipomas is worth the potential risk of perforation in asymptomatic patients [10].

Carcinoid tumors

Carcinoid tumors are a type of neuroendocrine tumor, also known as amine precursor uptake and decarboxylation (APUD) tumors. The term "carcinoid" was originally used to describe tumors of a characteristic pathological appearance arising in the epithelial layer but with a less aggressive clinical course than that of typical adenocarcinoma. They are thought to originate in the mucosa, from the peripheral neuroendocrine system, and then penetrate the muscularis mucosa to form a submucosal lesion [11,12]. Histologically they appear as small, round or polygonal, uniform cells arranged in nests and often stain argentaffin positive.

Carcinoid tumors can produce a variety of functionally active substances, including serotonin, histamine, gastrin, somatostatin, pituitary hormones, catecholamines, kinins and prostaglandins. Most of these tumors produce very small amounts of these substances, and therefore are clinically silent.

Carcinoid tumors are divided into foregut, midgut and hindgut neoplasms based on their anatomic location and functional characteristics. Foregut carcinoids include the bronchi, stomach, duodenum and pancreas. Foregut carcinoids may cause flushing. Patients with pernicious anemia are at increased risk of gastric carcinoid tumors because the enterochromaffin-like cells (ECL) are stimulated by the elevated levels of gastrin, resulting in hyperplasia and eventually carcinoid tumors. Midgut carcinoids involve the small bowel, appendix and right colon. Midgut carcinoids are associated with the carcinoid syndrome (flushing, diarrhea and asthma) once they have metastasized to the liver. One-third of all carcinoid tumors in the United States are

appendiceal. Hindgut carcinoids involve the transverse colon, sigmoid colon and rectum. These patients rarely present with systemic symptoms, but rather with local complications. In the United States, most cases are located in the appendix, rectum and ileum, while in Japan they are located in the stomach, rectum and duodenum [12,13].

Features associated with increased metastatic risk of duodenal or rectal carcinoid tumors include size greater than 2 cm and involvement into the muscularis propria [13–15].

Endoscopically, carcinoids usually appear as smooth, round, yellowish masses which can have a central erythematous depression or ulceration [16]. Unlike other submucosal tumors, the diagnosis of carcinoids can often be made with standard biopsy forceps [16,17].

The EUS appearance of carcinoid tumors is a hypoechoic, homogenous lesion with distinct smooth margins, located in the submucosal layer (Figure 14.2) [17]. The lesions are less hypoechoic than the second or fourth layers. EUS has an accuracy rate of 90% for diagnosing the exact wall layer involved [17]. Lymph node metastases tend to occur in lesions greater than 15 mm in diameter by EUS, and there can be malignant lymph node invasion in tumors limited to the submucosa [17].

Treatment of carcinoids may depend on site. Gastric carcinoids may be multicentric and, at least in Japan, have a high risk of metastases [17]. Small lesions (< 1 cm) located in the mucosa can be endoscopically resected, but larger lesions (> 2 cm) located in the submucosa or muscularis propria should be considered for surgical resection. Duodenal carcinoids do not seem to metastasize until they have penetrated the muscularis propria, which allows for small lesions in the mucosa/submucosa to be considered for endoscopic resection. Rectal carcinoid tumors should be surgically resected if the diameter is greater than 15 mm. Small rectal carcinoids, less than 10 mm, limited to the mucosa/submucosa, and without adjacent lymphadenopathy can be considered for endoscopic resection [17]. A recent pilot study in Japan compared conventional endoscopic resection with snare cautery to endoscopic mucosal resection (EMR) of rectal carcinoid tumors [18]. EMR was associated with higher initial rate of complete resection, although 3-year survival and recurrence rates were similar.

Any carcinoid tumor which is resected endoscopically should have follow-up endoscopy with biopsies and EUS to ensure there is no recurrence over time. Now that EUS can identify and accurately stage carcinoid tumors, long-term data after endoscopic resection of carcinoids is needed to help determine the efficacy of this procedure in preventing metastatic disease.

Granular cell tumor

Granular cell tumors originate from either Schwann cells or smooth muscle [5]. They are usually found in the tongue, oropharynx, skin, subcutaneous tissue and breast, but can be found anywhere in the body [19]. In the gastrointestinal tract, the most common site is the tongue, followed by the esophagus, stomach and colon. They are usually found in the mucosa or submucosal layers [20]. They consist mainly of large polygonal cells containing numerous eosinophilic granules. Up to 15% of patients with granular cell tumors will have multiple tumors.

Granular cell tumors are detected incidentally during endoscopy. Endoscopically, these appear as polypoid masses which may have a yellowish color. Esophageal granular cell tumors are usually found in the distal esophagus. Deep mucosal biopsies will often yield the diagnosis.

A recent EUS study found that among 21 granular cell tumors, 95% were less than 2 cm in diameter, 95% were located in the mid or distal esophagus, 100% had a hypoechoic appearance, 95% had smooth margins and 71% seemed to originate from the second hypoechoic layer and 24% from the third hyperechoic layer (Figure 14.3) [21].

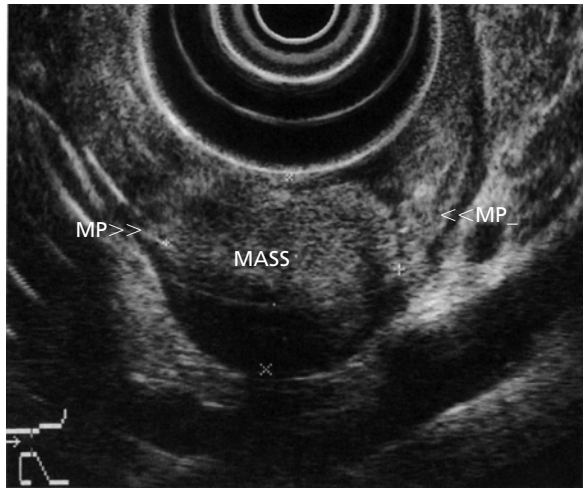

Figure 14.2 Duodenal carcinoid tumor. The subepithelial mass has mixed hypo- and hyperechoic areas and is clearly different from the typical hyperechoic lipoma or hypoechoic stromal tumor.

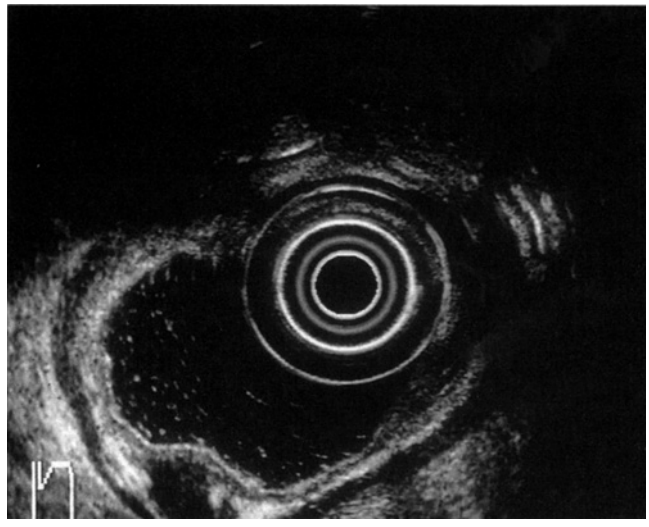

Figure 14.3 Granular cell tumor of the stomach. Note the slightly irregular hypoechoic mass in the submucosa with internal echoes. This is different from a typical lipoma or stromal cell tumor.

The natural history of these lesions seems to be a benign course, based on long-term follow-up of lesions diagnosed by biopsy and not removed, as well as by lesions which were removed endoscopically [22]. The rare reported malignant granular cell tumors of the esophagus have ranged in size from 4 to 10 cm in diameter [22]. This suggests that, although historically these have been managed surgically, perhaps surgical resection could be reserved for lesions causing symptoms, measuring greater than 2 cm diameter, with EUS findings suggesting infiltration through the intestinal wall, or which increase in size on serial endoscopy or EUS. Tumors which are not removed should be followed with EUS every 1 to 2 years to observe for growth.

Previously, endoscopic removal of small granular cell tumors involved multiple biopsies with pinch forceps or snare polypectomy [23–25]. There have also been case reports of tumor ablation using alcohol, polidocanol and laser [26–28]. Recently EMR has been evaluated in the diagnosis and treatment of granular cell tumor following endoscopic ultrasound evaluation [29,30]. EMR is a curative procedure that is successful in removing granular cell tumors generally less than 2 cm. In addition EMR provides near complete histology for further characterization of granular cell tumor. EMR, as a curative procedure, obviates the need for further surveillance of granular cell tumors [28]. Longer-term follow-up to determine the natural history of these lesions, based on their EUS characteristics, will help decide optimal patient management.

Duplication cyst

Duplication cysts arise during embryonic development, and can be located anywhere within or adjacent to the luminal gastrointestinal tract [31]. They are spherical or tubular, contain mucin, possess a smooth muscle layer, and are lined by the same mucosa as the adjacent bowel. They occasionally communicate with the adjacent intestinal lumen. Approximately 50% of duplication cysts are found in the small intestine, with the remainder in the esophagus, stomach and colon.

Duplication cysts are usually asymptomatic, but can result in symptoms due to a mass effect, bleeding, or perforation [32]. Cysts located near the ampulla of Vater may cause pancreatitis [33]. Most cysts are diagnosed in infants or children, and there is a female preponderance. These cysts, when located in the mediastinum, can be confused with bronchogenic cysts and therefore may also be referred to as foregut cysts. Duplication cysts rarely have been reported to have malignant transformation.

EUS of duplication cysts usually reveals a round, anechoic lesion in the third hypoechoic layer (Figure 14.4) [34,35]. They may have endosonographic findings of distinct wall layers. EUS may also show the cysts to be located adjacent to the tubular gastrointestinal tract [36]. They have been reported to have echogenic material due to thick mucinous material or debris [37]. There can be a fluid interface seen between the debris in the cyst and the rest of the fluid [38]. The diagnosis can be confirmed with FNA of the fluid, although this is not generally necessary [35,39].

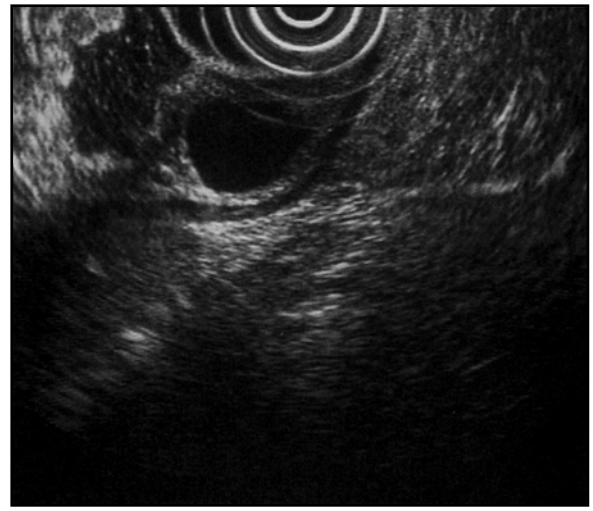

Figure 14.4 Duplication cyst in the gastric antrum. Note the round, anechoic structure in the third (submucosal) layer.

Treatment of symptomatic or enlarging lesions has traditionally been surgical resection or marsupialization. Endoscopic treatment has been successfully achieved by needle aspiration, needle knife cystostomy and snare cautery [33,36,40–42]. The optimal management of asymptomatic cysts is unknown, and could consist of surgical resection, endoscopic treatment, or only periodic EUS surveillance to observe for enlargement.

Heterotopic pancreas (pancreatic rest)

Heterotopic pancreas, also known as pancreatic rest or ectopic pancreas, is usually found within a few centimeters of the gastroduodenal junction; 75% are found in the stomach, duodenum or jejunum. They are found in 0.55% to 13.7% of autopsies [43]. They are thought to form during rotation of the foregut when portions of the pancreas become separated. Histologically, they contain a mixture of pancreatic tissue, including ducts and parenchyma.

Endoscopically, they appear as submucosal masses, which may have a central umbilication through which secretions drain. With EUS these appear as hypoechoic or intermediate echogenicity in any layer of the intestinal wall. Usually diagnosis can be made with deep mucosal biopsies.

Heterotopic pancreas is usually asymptomatic and found incidentally during endoscopy. Any pathology which can affect the pancreas can also occur in the pancreatic rest, such as malignancy, cysts and islet cell tumors. Incidentally found asymptomatic pancreatic rests require no further evaluation or treatment [43].

Varices

Endoscopic ultrasound can visualize many aspects of the normal portal venous system, such as the portal vein, splenic vein, superior mesenteric vein and azygous vein. In the setting of portal hypertension, esophageal and gastric submucosal veins (endoscopic varices), periesophageal and perigastric collateral veins,

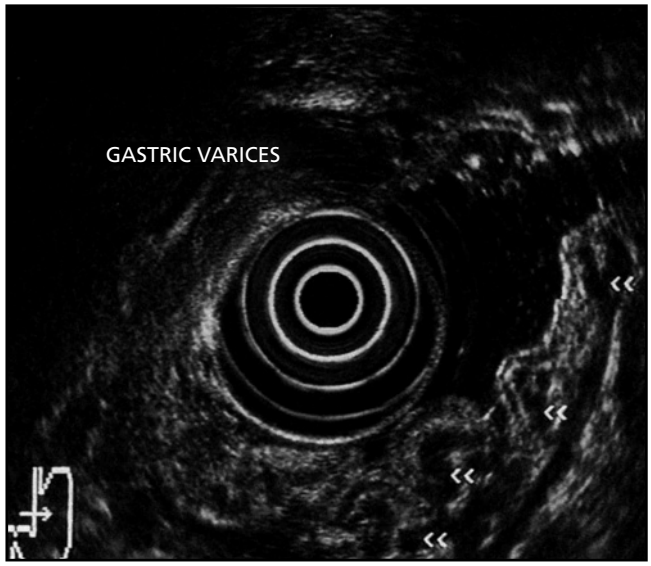

Figure 14.5 Gastric varices. The arrows point to hypoechoic, tubular structures in the submucosal layer which correspond to intramural varices.

and perforating veins connecting the adventitial and submucosal veins can be easily seen (Figure 14.5) [44]. Compared to standard video endoscopy, EUS using a dedicated echoendoscope does not improve diagnosis of esophageal varices but does improve diagnosis of gastric varices [44–46]. EUS appears accurate for diagnosing moderate or large esophageal varices, but not small esophageal varices [46]. The use of miniature Doppler ultrasound probes may be a more accurate and accessible modality for diagnosing gastric varices [47].

Lesions located in the muscularis propria

Gastrointestinal stromal cell tumors

These lesions or GISTs, formerly known as "leiomyomas" and "leiomyosarcomas," are mesenchymal tumors which are usually composed of spindle cells, and were originally considered to be of smooth muscle origin; further investigation found that many had little evidence of smooth muscle or neural differentiation [5]. Some evidence suggests that some stromal cell tumors may originate from the interstitial cells of Cajal (ICC), which are the pacemaker cells for the gut.

A seminal change in our understanding of GIST's occurred in 1998, when Hirota reported a gain of function mutation in KIT proto-oncogene (c-kit) that was present in approximately 90% of all GISTs [48]. The KIT proto-oncogene encodes for a transmembrane receptor for stem cell factor (also known as KIT ligand, steel factor and mast cell growth factor). The KIT protein is expressed on ICC as well as hematopoietic, mast and germ cells [49]. Activation of the KIT promotes cell proliferation and survival. In GISTs the gain of function mutation in KIT results in ligand-independent activation of the receptor and tumorigenesis [50]. Of the 10% of GISTs without a KIT mutation, 3 to 5% have a mutation resulting in a similar gain of function in the related receptor platelet-derived growth factor-α (PDGFA) [51].

Much of the intense interest in GISTs stems from the introduction of imatinib mesylate (Gleevec®) a selective inhibitor of certain tyrosine kinases including KIT, ABL, BCR-ABL, ARG and c-FMS. Imatinib was first used successfully in the treatment of chronic myeloid leukemia with the Philadelphia chromosome that results in uncontrolled activation of receptor BCR-ABL [52].

Histologically, stromal tumors can appear as spindle cell tumors or epithelioid tumors [5]. Some pathologists divide GISTs into four major categories, based on their phenotypic features: (1) tumors showing differentiation towards smooth muscle cells; (2) tumors showing differentiation toward neural elements; (3) tumors showing dual differentiation between smooth muscle and neural elements; (4) tumors lacking differentiation towards either smooth muscle or neural cells [53]. None of the phenotypic features or immune markers seem to have any certain prognostic significance for stromal tumors, and generally are not clinically useful.

Approximately two-thirds of all gastrointestinal stromal tumors occur in the stomach. The reported incidence of gastric stromal tumors is quite variable, ranging from 0.18% to 46% based on autopsy or surgical resection specimens [53]. Using a whole organ stepwise cutting method, Yamada showed that in 286 resected stomachs the rate of leiomyomas was 16%, with most being less than 5 mm in diameter and located in the upper half of the stomach [53]. They are often detected as incidental findings during other imaging studies, but may present with bleeding, pain, or obstructive symptoms.

Malignant stromal tumors can metastasize to the liver, peritoneum and lungs [54]. The malignant potential of these tumors is classified into three categories: no malignant potential, low (or uncertain) malignant potential, or high malignant potential [5]. One pathological grading system suggests that unequivocal risk factors for metastatic disease include histologically confirmed metastatic disease and invasion into adjacent organs. High risk factors for malignancy include size greater than 5 cm, greater than five mitoses per 50 high power fields, tumor necrosis, nuclear pleomorphism, dense cellularity, microscopic invasion of the lamina propria or blood vessels, and an alveolar pattern in the epithelioid variant [5]. Malignant stromal tumors have one unequivocal or two high-risk factors. Stromal tumors of uncertain malignant potential have only one high-risk factor. Benign stromal tumors have no high-risk factors. Caution must be given to any prognostic pathological criteria for GISTs, because there are reports of metastatic disease occurring years after removal of small, benign-appearing stromal cell tumors [55]. Generally true GISTs (c-Kit positive) are considered to have some malignant potential, while true leiomyomas (c-Kit negative) are felt to have little or no malignant potential.

Carney's triad is the rare association of gastric leiomyosarcomas with pulmonary chondroma and functioning extra-adrenal

paragangliomas [56,57]. Carney's triad usually involves women less than 40 years of age, and is diagnosed in patients with two triad components. In young or middle-aged women with stromal cell tumors of indeterminate or high malignant potential, consideration should be give to obtaining a chest radiograph and possibly urine catecholamines [57]. GISTs have also been associated with von Recklinghausen's disease [58,59].

Endoscopy of stromal tumors reveals a submucosal mass which is often dumbbell-shaped and may have a central umbilication or ulceration. Endoscopic biopsies usually only reveal normal overlying mucosa.

The EUS appearance of stromal cell tumors is usually a hypoechoic mass originating from the muscularis propria (fourth hypoechoic layer) (Figure 14.6) [60]. Occasionally, the hypoechoic lesion may be seen in the submucosa (third hyperechoic layer), and have a suggestion of origination from either the muscularis mucosa or muscularis propria (Figure 14.7).

The EUS features associated with malignant stromal tumors include tumor size greater than 4 cm, irregular extraluminal border, echogenic foci (greater than 3 mm) and cystic spaces (greater than 4 mm) [61]. The cystic spaces seen in stromal cell tumors of high malignant potential may correspond to cystic degeneration and liquefaction necrosis [62,63]. If two or more of these criteria are present, the lesion is likely of high malignant potential, and if none of the criteria are present, then it is of low malignant potential [61]. Expert endosonographers, using the above criteria, only had fair agreement using kappa statistics [61]. EUS cannot accurately predict malignant versus benign with certainty, and should not be depended on to definitely make this distinction.

Deep mucosal biopsies and FNA do not yield enough tissue for accurate pathological assessment of the malignant potential of these lesions in terms of number of mitotic fields. Biopsy and FNA of suspected stromal tumors should only be performed if there is doubt regarding the diagnosis of the submucosal mass, and if the tissue diagnosis will change clinical management. If FNA or biopsy is performed, then material should be sent for c-Kit analysis, as if positive then this means a true GIST with some malignant potential while if c-Kit negative then a leiomyoma with little or no malignant potential.

The optimal management of submucosal masses which are suspected to be stromal cell tumors by EUS is unknown. Surgical resection should be performed for all lesions which are causing symptoms (i.e. bleeding, obstruction, pain), lesions greater than 3 cm diameter, lesions with suspicious EUS findings as above, and lesions which increase in size on serial EUS examination. Small, less than 3 cm diameter, asymptomatic, incidentally discovered lesions which are suspected to be benign stromal cell tumors may be observed with repeat EUS every 6 to 12 months. These small lesions might never become clinically significant, especially given their high incidence in resection studies, and therefore serial EUS might be a reasonable alternative to surgery. If the lesions increase in size, develop suspicious appearing EUS features, or become symptomatic, they should be resected.

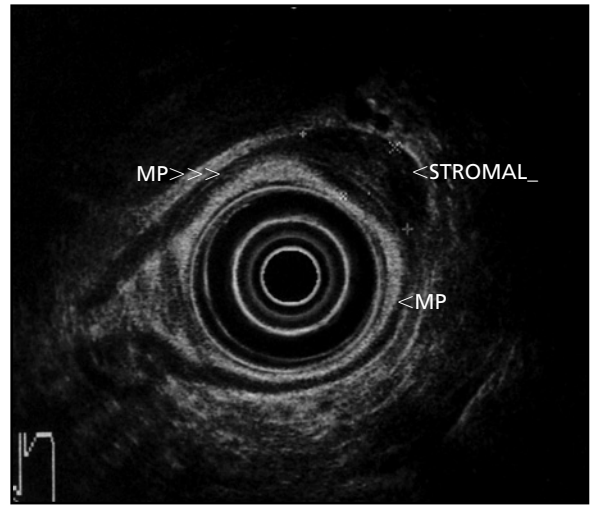

Figure 14.6 Stromal cell tumor of stomach. Note that this lesion is located within the muscularis propria (MP), which is typical for stromal cell tumors.

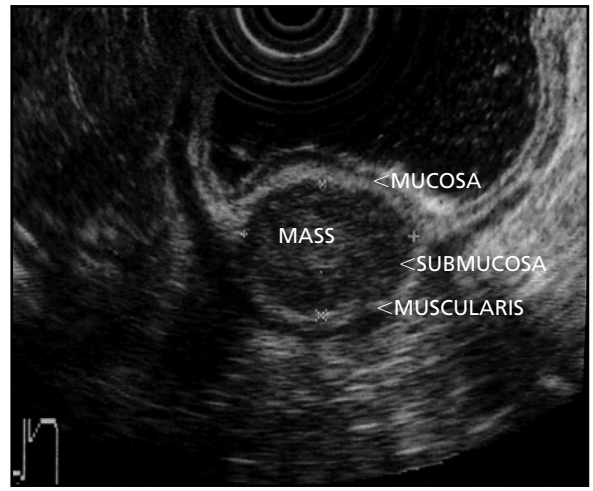

Figure 14.7 Stromal cell tumor of the stomach. Note that this lesion is diffusely hypoechoic and located in the submucosa. This tumor probably developed as a bud from either the muscularis propria or muscularis mucosa, and grew within the submucosa.

Additionally, EUS-FNA can be performed into these lesions with material sent for c-Kit staining, although it is unknown whether small c-Kit positive GISTs need surgical resection or can be observed for change over time.

Whereas surgical resection is considered standard of care for primary disease, metastatic disease is treated with imatinib. Up to 65 to 70% of patients treated with imatinib will achieve a partial response and an additional 15 to 20% will have stable disease [64]. Response to imatinib varies with the longest response now approaching 5 years [65]. The 2-year survival is approximately 70% and the median survival has been reported as 4.8 years [65]. Adjuvant or neoadjuvant imatinib is currently being investigated in several phase II trials. Data from these trials will be

forthcoming with new recommendations for the use of imatinib in relation to surgery, especially in those cases where the tumor is large, partially unresectable, and a larger surgery can be converted into a less involved procedure [49]. Interestingly, even those tumors that are not KIT or PDGFRA positive respond to imatinib approximately 39% of the time [66]. Therefore imatinib should be considered in the treatment of all metastatic GISTs.

Endoscopic resection of stromal tumors has been reported [67–71]. This should only be considered in cases where the lesion is less than 2 cm and seems to originate from the muscularis mucosa and not the muscularis propria. Follow-up endoscopy with endoscopic ultrasound should possibly be done one year later to make sure there is no residual stromal tumor.

Duodenal gangliocytic paraganglioma

Gangliocytic paragangliomas (GPs) are an extraordinarily rare tumor occurring most frequently in the second portion of the duodenum. Approximately 130 cases have been reported since this tumor was recognized by Dahl in 1957 [72]. Patients are often asymptomatic, but when symptomatic they present with gastrointestinal hemorrhage, abdominal pain and rarely obstruction [73]. On endoscopy gangliocytic paragangliomas appear submucosal, but can seem pedunculated or sessile. Gangliocytic paragangliomas often have overlying erosions and ulcers that result in gastrointestinal bleeding [72]. EUS findings have been varied and not well described in the literature, but do confirm the submucosal location [74]. Histologically gangliocytic paragangliomas consist of varying ratio of three types of cells: spindle-shaped Schwann cells, ganglion cells and epithelioid cells arranged in an endocrine pattern suggesting either carcinoid or paraganglioma-like appearance [75]. Gangliocytic paragangliomas are generally benign, however rare lymph node metastases have been reported [76]. Gangliocytic paragangliomas are traditionally removed surgically, but case reports have suggested that endoscopic resection is a reasonable alternative for nonmetastatic gangliocytic paragangliomas [74].

Duodenal adenomyomatosis

Adenomyosis usually occurs in the gallbladder, but can rarely appear elsewhere throughout the luminal gastrointestinal tract. Within the gastrointestinal tract they are usually in the submucosal layer. In one series of ERCPs, adenomyomas of the duodenum, specifically occurring at the ampulla of Vater, occurred with a frequency of 0.13% [77]. Patients with adenomyomas of the ampulla usually present with obstructive jaundice although this lesion is most often asymptomatic [78]. Ampullary adenomyomas are diagnosed by histology because imaging, laboratory tests and endoscopy cannot reliably differentiate these lesions from adenomas and carcinomas. Adenomyomas are considered non-neoplastic lesions that are treated with endoscopic resection or localized surgical resection if the patient is symptomatic. Unfortunately adenomyomas are difficult to diagnose on routine endoscopic biopsies thereby often necessitating pancreaticoduodenectomy to rule out malignancy [79].

Extrinsic compression lesions

Normal abdominal organs can cause indentations in the gastrointestinal tract which may mimic a submucosal tumor. In the esophagus, compressions can be seen by the aortic arch and left atrium. Pathological compression in the esophagus may occur from malignant lymph nodes or masses, especially from lung cancer. Benign lymph nodes, such as due to histoplasmosis, can sometimes present as a submucosal esophageal mass (Figure 14.8) [80]. In the stomach, the left lobe of the liver and the spleen can cause compression. Pancreatic pseudocysts or extrinsic tumors can cause extrinsic compression (Figure 14.9). In the rectum, the

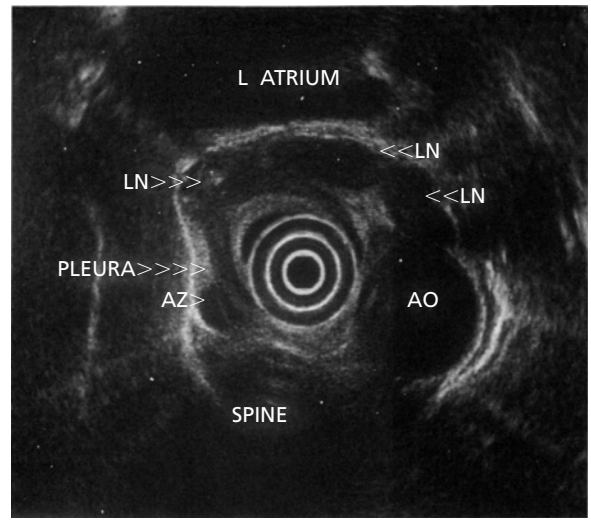

Figure 14.8 Posterior mediastinal lymph nodes (LN). These are suspected to be due to histoplasmosis infection. AO, aorta; AZ, azygous vein; L, left.

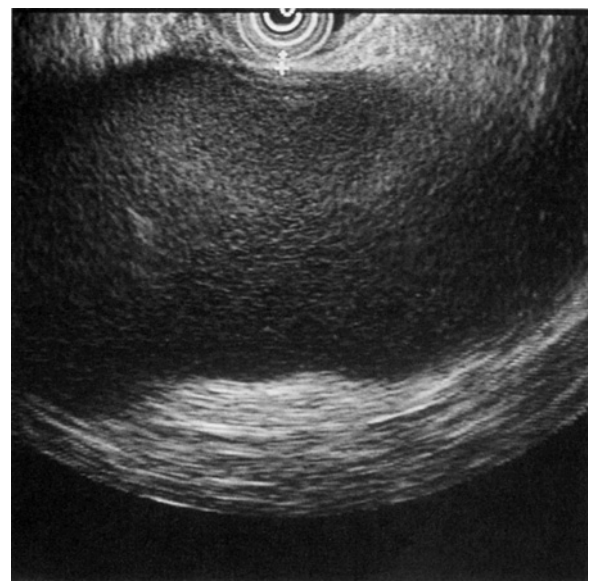

Figure 14.9 Pancreatic pseudocyst pressing against the stomach.

prostate or cervix can cause an extrinsic compression which may mimic a submucosal mass. Accurate diagnosis of these extrinsic compressions can preclude further expensive testing.

Comparison of imaging studies for submucosal masses

Rosch compared EUS versus barium upper gastrointestinal series versus CT scan and found that EUS detected 37 of 37 lesions, barium study detected 11 of 13 lesions, and CT detected 16 of 24 lesions [81]. These tumors ranged in size from 0.5 cm to 10 cm, with a mean of 2.8 cm.

Endoscopic tissue sampling

Which lesions need sampling

EUS results can help determine when it is safe and useful to obtain tissue sampling by FNA or large particle biopsy. While the various techniques can obtain tissue for cytological or histopathological diagnosis, they should be used selectively in only those cases in which the information will change management. For example, a hyperechoic structure in the submucosa is almost certainly a lipoma, and needs no confirmation with FNA. A hypoechoic lesion in the muscularis propria is almost certainly a stromal cell tumor, and FNA cytology or even large-particle biopsies will not yield enough tissue for the pathologist to determine the malignant potential of the lesion. FNA and snare resection are potentially very useful when the diagnosis is in doubt, such as a heterogeneous lesion in the submucosal layer, which could be a carcinoid, granular cell tumor, pancreatic rest, or other lesion. Contraindications to FNA or snare resection are EUS findings of a vascular lesion, such as varices, or an extrinsic mass, such as the liver or spleen.

Tissue sampling should be attempted on submucosal masses which are not typical lipomas or stromal cell tumors. This is especially important as sometimes lesions with malignant potential, such as carcinoid tumors, may be diagnosed. Extrinsic masses which are suspicious for malignancy should be considered for transintestinal FNA.

Biopsy forceps

If standard forceps biopsies are performed, jumbo biopsy forceps (3.2 mm diameter) should be used to maximize the chances of obtaining deep tissue. Biopsies should be obtained from any areas of mucosal ulceration. The "deep-well" or "tunneling" biopsy technique can also be tried, in which successive biopsies are taken from the same spot, with the idea of removing the mucosa with the first biopsy and then obtaining deeper tissue from the underlying lesion with the next biopsy.

Fine needle aspiration

FNA can be performed either through a standard endoscope or through a dedicated FNA echoendoscope [82]. Various FNA needles exist, ranging from sclerotherapy-type needles which are 15 mm long and 23 Fr, to dedicated EUS FNA needles which can be 22 Fr and up to 8 cm long. Generally, the needle is pierced into the lesion, the stylet is removed, a 10 mL syringe is placed on the end of the catheter and withdrawn, and the needle is moved in and out of the lesion for several passes of the needle. Suction on the syringe is then released, the needle is retracted, the catheter is removed, and the contents are then flushed onto a glass slide by air through the syringe. Often several passes are repeated. Caletti has devised a needle for sampling submucosal lesions in which there is a guillotine device which obtains samples 8 mm in length and 1 to 2 mm in diameter [83].

EUS-guided Trucut biopsy

The difficulties associated with FNA include the need for concurrent pathological interpretation to reduce the number of aspirations, impaired cytological reading secondary to blood and epithelial cells, as well as the difficulty diagnosing well-differentiated tumors on cytological examination alone [84,85]. These obstacles led to the development of a Trucut biopsy needle for use with echoendoscopes (EUS-TCB). EUS-TCB results in larger specimens suitable for histology as well as obviates the need for on-site pathological interpretation. The EUS-TCB technique has been particularly useful in the diagnosis of stromal tumors, lymphomas and well-differentiated pancreatic cancer. Although studies to date include only small numbers of submucosal masses the overall accuracy of Trucut biopsy is reported as approximately 80% for submucosal lesions as compared to 20% for FNA [86]. A recent technical review in *Gastrointestinal Endoscopy* assigned submucosal tumors a class IIa indication for EUS-TCB, indicating that the existing evidence favors the efficacy and diagnostic accuracy of EUS-TCB over EUS-FNA [84].

Mucosectomy followed by deep biopsy

Another means of obtaining tissue from beneath the mucosal layer is by first removing the overlying mucosa and then biopsying the underlying lesion. The process of endoscopic mucosectomy is performed with snare resection of a portion of the overlying mucosa. This may be preceded by either submucosal saline or epinephrine injection to raise the mucosa off the underlying mass, or by rubber band ligation of mucosa overlying the lesion. Snare resection then follows. This will generally result in access to the underlying lesion, which can be biopsied. Occasionally the entire lesion may actually extrude through the unroofed mucosa.

Endoscopic and larascopic resection of submucosal masses

If EUS shows the mass to be located in the submucosal layer and less than 2 cm in diameter, then consideration can be given for endoscopic removal if this would help in diagnosis [24,71]. In general, submucosal lesions suspicious for lipomas do not need resection as they are benign, and stromal cell tumors should not be removed if they communicate with the muscularis propria.

Endoscopic mucosal resection of submucosal lesions less than 2 cm in diameter has become the procedure of choice as it is curative and provides large samples of tissue for histology. Pre-injection with saline or epinephrine beneath the lesion may potentially decrease the risk of perforation or bleeding. Very small lesions can also undergo rubber band ligation, as is done with varices, to form a more polypoid lesion which can then be removed with snare cautery [70].

Gastric submucosal masses which require surgical removal can sometimes be resected using a laparoscopic approach. This can be tremendously aided by the use of intraoperative endoscopy to identify the lesion and push it into a favorable position for laparoscopic transection with a stapling device. There has also been a case reported of performing endoscopic resection of a 2 cm stromal cell tumor during simultaneous laparoscopy to confirm lack of perforation at the time of resection [69].

Regardless of the technique used to remove a submucosal tumor, attention should be given to complete removal of the tissue. If there may be residual tissue, then periodic endoscopic ultrasound surveillance should be performed.

Utility of EUS for management of submucosal masses

Interobserver agreement of EUS for evaluating submucosal masses

EUS agreement is generally good for submucosal masses. One study in which ten experienced endosonographers reviewed videotapes of EUS examinations found that there was excellent agreement for cystic lesions and extrinsic compression, good agreement for lipomas, and fair agreement for stromal tumors and vascular lesions [87]. Other submucosal lesions had poor agreement.

Outcome studies

There are increasing numbers of outcome studies which suggest that EUS is useful for evaluating and managing submucosal masses. One large multicenter study asked endosonographers to assess whether the EUS changed management plans. They reported that EUS resulted in a major management change in 67% of patients with submucosal tumors [88].

Conclusion

EUS is the most accurate imaging modality for lesions located within, or compressing, the gastrointestinal wall. EUS findings can be diagnostic based on ultrasound characteristics alone, or can select lesions which require tissue sampling. Now that subepithelial lesions can be diagnosed with a high degree of accuracy in vivo, the natural history of these lesions will need to be studied to determine when these lesions can be observed, and when removal is required.

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15 Diagnosis and Staging of Solid Pancreatic Neoplasms

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Introduction

The evaluation of patients with confirmed or suspected pancreatic neoplasia is one of the most common indications for EUS referral. Patients with pancreatic neoplasia may come to clinical attention for a variety of reasons. In our practice, the most common indications are the presence of unexplained jaundice and the finding of an abnormality on another imaging test such as CT, ultrasound or MRI (typically obtained during the evaluation for unexplained abdominal pain, weight loss or jaundice). Often patients have already had numerous prior imaging studies which have been either negative or nonspecific. Depending upon regional referral practices, patients may also be referred for the further evaluation of biliary or pancreatic duct strictures seen at ERCP. Less common indications for referral include the need for localization of a confirmed or suspected hormonally active pancreatic endocrine neoplasm, the evaluation of unexplained acute pancreatitis, or the assessment of unexplained cystic lesions of the pancreas.

In 2006, an estimated 33,730 patients were diagnosed with pancreatic carcinoma in the United States [1]. A disturbingly similar number, 32,300, died of the disease. Based on current rates, 1.27% of children born today will be diagnosed with pancreas cancer. Although these statistics make pancreatic cancer only the tenth most common primary site of cancer diagnosis in the US, the typically advanced stage at time of diagnosis and poor response to therapy results in pancreatic cancer being the fourth most common cause of cancer deaths among both men and women [1,2].

The majority of pancreatic tissue is comprised of exocrine tissue (the acini) and endocrine tissue (the islets of Langerhans). These tissues are, however, disproportionately rare sites of tumorogenesis. Most (85 to 90%) solid tumors of the pancreas originate from pancreatic ductal epithelium (leading to primary pancreatic ductal adenocarcinoma). A variety of other benign and malignant conditions may result in focal mass lesions, however, and it is important to keep in mind that there is a differential diagnosis for primary pancreatic masses (Tables 15.1, 15.2) [3,4]. Tissue types other than ductal adenocarcinoma may have markedly different prognoses which may influence patient and physician decisions regarding possible intervention.

This chapter will highlight the techniques involved in the detection, cytological diagnosis and staging of pancreatic solid

Table 15.1 WHO histological classification of tumors of exocrine and endocrine pancreas. Modified from Ref. 3 with permission

Tumors of the exocrine pancreas
Epithelial tumors
Benign
Serous cystadenoma
Mucinous cystadenoma
Intraductal papillary-mucinous adenoma
Mature cystic teratoma
Borderline
Mucinous cystic neoplasm with moderate dysplasia
Intraductal papillary-mucinous neoplasm with moderate dysplasia
Solid-pseudopapillary neoplasm
Malignant
Ductal adenocarcinoma
Mucinous noncystic carcinoma
Signet ring cell carcinoma
Adenosquamous carcinoma
Undifferentiated (anaplastic) adenocarcinoma
Undifferentiated carcinoma with osteoclast-like giant cells
Mixed ductal-endocrine carcinoma
Serous cystadenocarcinoma
Mucinous cystadenocarcinoma
noninvasive
invasive
Intraductal papillary-mucinous carcinoma
noninvasive
invasive

(Continued)

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Table 15.1 (Continued)

Tumors of the exocrine pancreas
Acinar cell carcinoma
Acinar cell cystadenocarcinoma
Mixed acinar-endocrine carcinoma
Pancreatoblastoma
Solid-pseudopapillary carcinoma
Others
Nonepithelial tumors
Secondary tumors
Tumors of the endocrine pancreas
Well-differentiated endocrine tumor
Functioning
Insulin-producing (insulinoma)
Glucagon-producing (glucagonoma)
Somatostatin-producing (somatostatinoma)
Gastrin-producing (gastrinoma)
VIP-producing (VIPoma)
Others
Nonfunctioning
Microadenoma
Others
Well-differentiated endocrine cancer
Functioning
Insulin-producing (insulinoma)
Glucagon-producing (glucagonoma)
Somatostatin-producing (somatostatinoma)
Gastrin-producing (gastrinoma)
VIP-producing (VIPoma)
Serotonin-producing with carcinoid syndrome
ACTH producing with Cushing syndrome
Nonfunctioning
Poorly differentiated endocrine carcinoma-small cell carcinoma
Mixed exocrine-endocrine carcinoma

Table 15.2 Incidence of primary pancreatic tumors. Modified from Ref. 4 with permission

Origin	Tumor	Incidence (%)
Ductal origin		90
	Adenocarcinoma	80
	Mucinous noncystic carcinoma	1–3
	Adenosquamous carcinoma	3–4
	Undifferentiated(anaplastic) carcinoma	2–7
Others		8–10
	Serous cystadenoma	1
	Mucinous cystic tumor	2
	Intraductal papillary-mucinous tumor	1
	Acinar cell carcinoma	1
	Pancreatoblastoma	<0.5
	Solid pseudopapillary tumor	1
	Endocrine tumor	2
Variety of very rare other types (see Table 15.1)		

mass lesions via EUS. A detailed discussion of cystic lesions of the pancreas will be discussed separately in Chapter 16. Other relevant issues, such as the palliation of cancer pain via EUS-guided celiac plexus neurolysis, the evaluation of suspected nodal metastases and detection of hepatic metastatic disease are discussed elsewhere.

Pancreatic and peripancreatic anatomy

Accurate and clinically useful EUS examination mandates thorough knowledge of pancreatic and peripancreatic anatomy. The choice of surgical procedure is dependent upon the location of the mass within the pancreas. It is therefore incumbent upon the endosonographer to be familiar with surgical options for pancreatic resection, including standard and pylorus-sparing pancreaticoduodenectomy (Whipple procedure), distal pancreatectomy (with and without splenectomy), total pancreatectomy and mid-segment/central pancreatectomy [5]. The feasibility of resection is critically dependent upon the relationship between the mass and the adjacent major vascular structures. An endosonographer must therefore be intimately aware of this vascular anatomy as well as relevant common congenital anomalies – issues which are generally not emphasized during standard gastroenterology fellowships.

Pancreatic anatomy

The pancreatic head is defined as the portion of pancreas to the right side of the mesenteric-portal vein confluence. The neck region is that portion directly anterior to the portal vein. That portion of the pancreatic head which protrudes posteriorly behind the superior mesenteric vein is referred to as the uncinate process. The body of the pancreas extends from the mesenteric-portal vein confluence to the left border of the abdominal aorta. The pancreatic tail then extends leftward from this region laterally and superiorly into the splenic hilum. The pancreas is formed embryologically by the fusion of the ventral and dorsal pancreatic buds. The portion of pancreas which originated in the ventral bud (termed the ventral anlage) is often hypoechoic relative to the remaining pancreas and thus seen as a distinct structure (Figure 15.1). This difference in echogenicity likely reflects variable fat distribution between the ventral and dorsal pancreatic anlagen. Care must be taken to avoid confusing a normal ventral pancreas for a pancreatic mass. Clues to help differentiate between a normal ventral pancreas and a neoplasm include the presence of an irregular or rounded border with the dorsal pancreas, displacement of adjacent vessels or a change in pancreatic or bile duct caliber in the region of echogenicity change.

Venous anatomy

Several important venous structures pass adjacent to the pancreas and may be invaded by pancreatic neoplasms. The splenic vein passes along the posterior aspect of the pancreatic body and

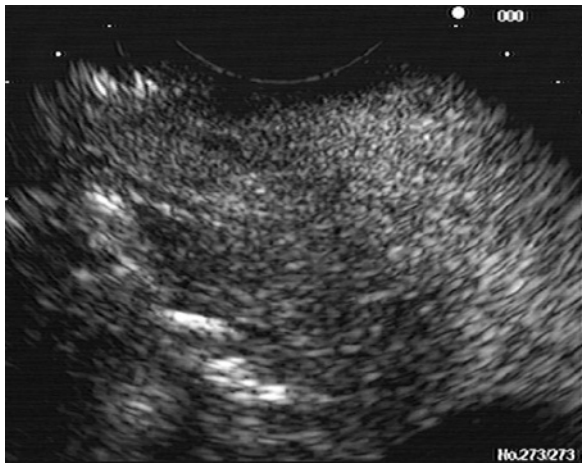

Figure 15.1 Normal ventral pancreas as imaged from the region of the major papilla using a linear array echoendoscope. A distinct border is seen between the hypoechoic ventral portion of the pancreas and the superior pancreatic head.

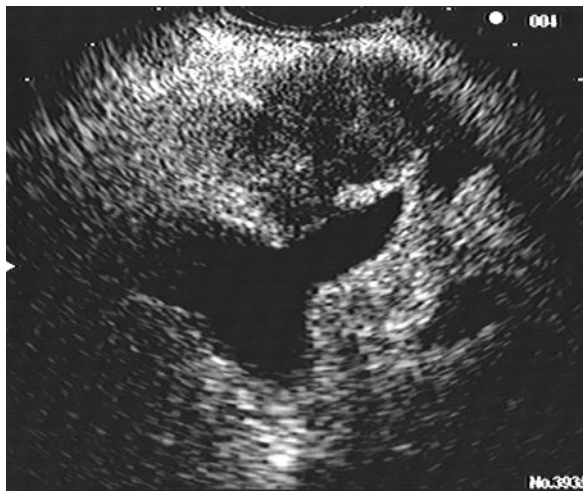

Figure 15.2 Normal confluence of splenic vein with superior vein to form portal vein as imaged from the gastric antrum or duodenal bulb with a linear instrument.

tail. This vessel may be either adjacent to or within the pancreatic parenchyma. The superior mesenteric vein (SMV) approaches the pancreas inferiorly roughly perpendicular to the splenic vein. The SMV passes through a groove in the pancreatic head, anterior to the uncinate process and then posterior to the pancreatic neck. Here it joins with the splenic vein to form the portal vein (at a location termed the portal confluence or splenoportal confluence) (Figure 15.2). The portal vein then passes superiorly behind the duodenal bulb and enters the liver at the hepatic hilum (along with the common bile duct and common hepatic artery). The inferior mesenteric vein (IMV) generally joins with the splenic vein, although this occurs at a wide variety of locations between the portal confluence and the spleen. The inferior vena cava (IVC) passes posterior to the right margin of the pancreatic head and second portion of the duodenum to enter the posteroinferior surface of the liver.

Arterial anatomy

Arterial structures of relevance with regard to pancreatic disease include the proximal abdominal aorta and its major branches. The celiac artery extends anteriorly for a variable length from the aorta before dividing to typically form the splenic, left gastric and common hepatic arteries. The common hepatic artery passes to the right near the superior pancreatic border towards the portal vein, where it gives rise to the gastroduodenal artery and becomes the proper hepatic artery. The proper hepatic artery then passes superiorly and divides into the right and left hepatic arteries in the region of the hepatic hilum. The superior mesenteric artery (SMA) arises from the anterior surface of the aorta immediately inferior to the celiac trunk and then passes inferiorly along the left posterolateral edge of the SMV. The SMA is typically surrounded by a well-defined hyperechoic fat plane. Pancreatic blood supply generally is derived from small-caliber vessels which are not readily identified via EUS, including the superior pancreaticoduodenal artery (which arises from the gastroduodenal artery), the inferior pancreaticoduodenal artery (which arises from the SMA) and small unnamed arteries which arise from the splenic artery and feed the body and tail. There is considerable anatomic variation in the vascular branches of the celiac artery and SMA. One of the most important, which occurs in roughly 11% of individuals, is the presence of an aberrant ("replaced") right hepatic artery [6]. This aberrant artery arises directly from the superior mesenteric artery, rather than the celiac trunk, and passes posterior to or through the pancreatic head to enter the liver separately from the left hepatic artery (Figure 15.3).

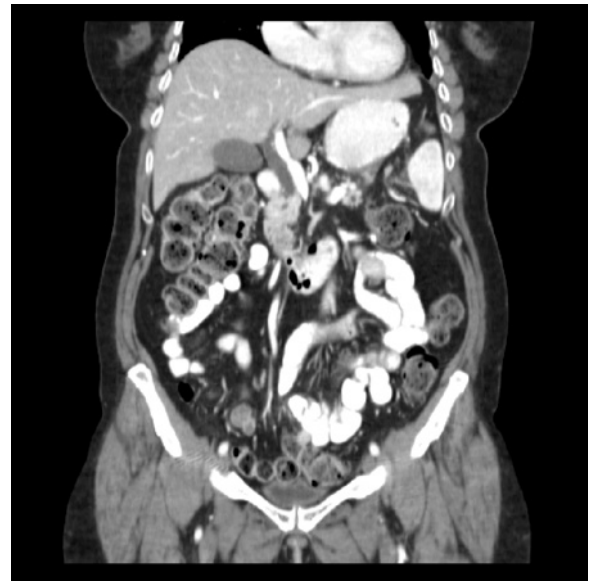

Figure 15.3 Aberrant right hepatic artery. A small-caliber vessel is seen arising from superior mesenteric artery and heading superiorly towards the liver and portal vein.

Lymphatic drainage of the pancreas

The lymphatic drainage of the pancreas originates in small perilobular capillaries. These small lymphatics then pass through the interlobular spaces and combine to form larger lymphatic structures which follow the venous and arterial structures to the surface of the gland. Lymphatic drainage from the anterior pancreatic body and tail then generally flows superiorly to enter lymph nodes located along the splenic artery and vein. These nodes then drain into the celiac nodes, which are in direct connection to nodes along the left gastric and hepatic arteries. Connections also exist with lymph nodes in the splenic hilum. The anterior and superior portions of the pancreatic head drain via pyloric nodes located along the superior pancreaticoduodenal vessels. These pyloric nodes are also connected with celiac, hepatic and right gastric nodes. The more inferior and posterior portions of the head and uncinate process follow either the posterior superior pancreaticoduodenal vessels to the hepatic and celiac nodes or the posterior inferior pancreaticoduodenal vessels to mesenteric nodes which are located in the root of the transverse mesocolon (where the SMA and SMV pass anterior to the distal third portion of duodenum). The posterior surface is also in direct contact with the retroperitoneal fat (without an intervening layer of peritoneum), and there are rich lymphatic connections with the adjacent retroperitoneal structures. Drainage from the celiac region then passes through the mediastinum, with connections to cervical nodes which may lead to distant nodal spread. The lymphatic drainage of the pancreas is characterized by rich connections to lymphatics from adjacent organs. Although retrograde flow of lymph is theoretically inhibited by the presence of valvular structures, clearly these valves are insufficient and extensive diffuse lymphatic spread occurs early in the course of disease. This is one of the many reasons why attempted curative resection of pancreatic cancer is so often unsuccessful.

EUS imaging and diagnosis of solid pancreatic lesions

Detection

Most solid pancreatic neoplasms are seen sonographically as focal, hypoechoic masses (Figure 15.4). The overall sensitivity of EUS for pancreatic tumors is extremely high (see Table 15.3 [7–30]) and does not appear to decline significantly for small lesions (as opposed to other modalities such as CT or MRI) (see Table 15.4 [11,15,20–23,26,29,31]). Lesions as small as 3 to 4 mm may be detected by EUS and the tissue diagnosis confirmed via needle aspiration (Figure 15.5); however, such lesions are rarely encountered. While many endosonographers are most concerned regarding the potential to miss small lesions, it is important to recognize the potential to miss large, diffusely infiltrative lesions which may be misinterpreted as chronic pancreatitis. This issue should be kept in mind when encountering diffuse areas of abnormality, particularly in a clinical setting in which chronic pancreatitis would not be expected.

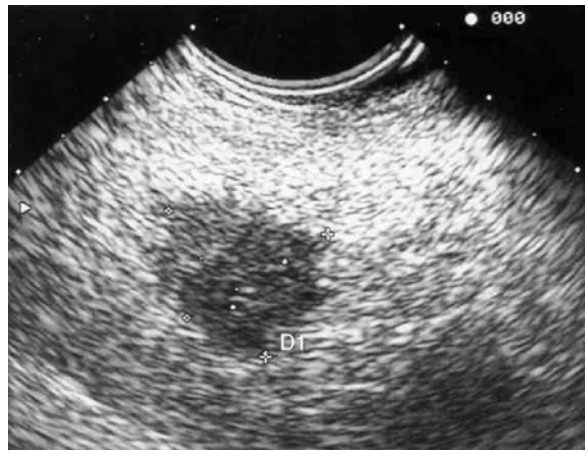

Figure 15.4 Hypoechoic mass in pancreas. The mass is approximately 1 cm in diameter.

Table 15.3 Sensitivity of EUS for imaging of pancreatic masses. Source: Refs 7–30

Reference	Year	n	Sensitivity (%)
Yasuda [29]	1988	50	100
Lin [16]	1989	33	94
Rosch [26]	1991	102	99
Rosch [25]	1992	60	85
Snady [27]	1992	60	85
Palazzo [23]	1993	49	91
Muller [21]	1994	33	94
Marty [17]	1995	37	92
Nakaizumi [22]	1995	232	94
Melzer [18]	1996	12	100
Dufour [12]	1997	24	92
Howard [30]	1997	21	100
Sugiyama [28]	1997	73	96
Legmann [15]	1998	30	100
Akahoshi [10]	1998	37	89
Harrison [14]	1999	19	89
Gress [13]	1999	81	100
Midwinter [20]	1999	34	97
Mertz [19]	2000	31	93
Rivadeneira [24]	2003	44	100
Ainsworth [9]	2003	22	87
Agarwal [8]	2004	71	100
Dewitt [11]	2004	80	98
Borbath [7]	2005	48	98
Total		1283	94.7

Although the endosonographic and/or endoscopic appearance may provide clues, it may be impossible at times to determine whether a mass lesion in the pancreatic head is in fact a primary pancreatic cancer, ampullary carcinoma or intrapancreatic cholangiocarcinoma. Although this differentiation may influence staging criteria, surgical management is generally the same

Table 15.4 Sensitivity of EUS compared with CT for detection of small pancreatic masses. Source: Refs 11,15,20–23,26,29,31

Reference	Sensitivity (%) EUS	Sensitivity (%) CT
Yasuda 1988 [29] ($n = 7$, <2 cm)	100	29
Rosch 1991 [26] ($n = 27$, <3 cm)	100	55
Palazzo 1993 [23] ($n = 7$, <2.5 cm)	100	14
Muller 1994 [21] ($n = 15$, <3 cm)	93	53
Nakaizumi 1995 [22] ($n = 8$, <2 cm)	88	38
Legmann 1998 [15] ($n = 6$, <1.5 cm)	100	67
Midwinter 1999 [20] ($n = 17$, resectable)	94	65
Ardengh 2000 [31] ($n = 12$, mean size <1.48 cm)	83.3	16.7
Dewitt 2004 [11] ($n = 19$, <2.5 cm)	89	53

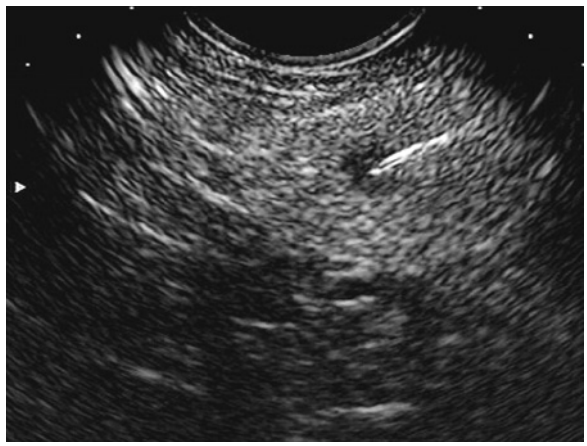

Figure 15.5 Fine needle aspiration of a small pancreatic mass lesion. The lesion measures 4 × 5 mm in diameter. Cytology confirmed the presence of a pancreatic endocrine neoplasm.

and this differentiation does not influence immediate treatment recommendations. Smaller ampullary lesions can typically be identified based upon the endoscopic appearance. Small cholangiocarcinomas are suggested by a rounded, well-circumscribed nodule centered on the long axis of the bile duct (Figure 15.6).

Factors contributing to missed tumors

Factors which may contribute to failure to identify a pancreatic mass at EUS were recently assessed in a multicenter study (the NEST study) [32]. Of the 20 missed cases of pancreatic cancer in this study, 12 occurred in the setting of EUS features of chronic pancreatitis. Other factors reported to increase the likelihood of false-negative examination were the presence of a diffusely infiltrating carcinoma, a prominent dorsal/ventral split and performance of the examination in the setting of recent (within 4 weeks) acute pancreatitis. Foremost among the factors which may decrease the sensitivity of EUS is the presence of underlying pancreatitis. The presence of acute or chronic pancreatitis results in a change in the echogenicity of benign parenchyma. The benign parenchyma becomes abnormally hypoechoic and lobular – similar to that of most mass lesions. When this occurs, the borders

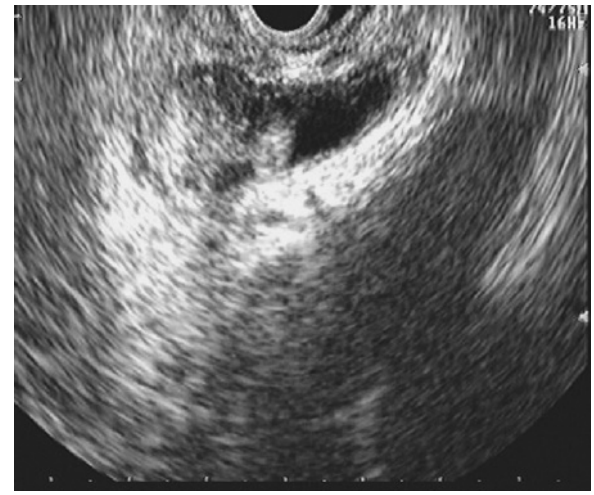

Figure 15.6 Cholangiocarcinoma. A nonshadowing, hypoechoic polypoid filling defect is seen within the lumen of the common bile duct.

of the mass become sonographically indistinct (or absent). This same effect may occur in the normal ventral pancreas (which often is relatively hypoechoic). Compounding this issue is the fact that chronic ductal obstruction may lead to the development of sonographic features of chronic pancreatitis in the portion of benign pancreas upstream from the obstruction. Because of these issues, an underlying pancreatic neoplasm should always be considered when encountering pancreas with unexpected features of chronic pancreatitis. When searching for a neoplasm in the setting of background chronic pancreatitis, the location of pancreatic and/or bile duct narrowing is a critical clue to the margins of the mass (although this may significantly underestimate the margins and obviously ductal narrowing may occur due to benign fibrotic stricturing). The presence of biliary or pancreatic stents eliminates this clue and is one of many reasons why we strongly prefer performing EUS prior to ERCP. When the margins of a mass are indistinct, searching for evidence of obvious extension beyond the expected border of the pancreas (such as adjacent to the celiac or mesenteric vessels or adjacent to the gastric or duodenal wall) may provide a more fruitful location for diagnostic needle aspiration. In severe calcific pancreatitis, a region devoid of calcification and ductal structures is also suspicious. In addition to reducing the sensitivity for detection of a mass, the presence of chronic pancreatitis has also been shown to reduce the sensitivity of EUS-guided needle aspiration [33,34].

The location of a mass may also influence the ability to detect via EUS. As mentioned previously, a small lesion may be missed in the ventral anlage due to the normally hypoechoic nature of the surrounding tissue [32]. Other areas which can be overlooked (based upon literature regarding localization of small neuroendocrine tumors [25] as well as personal experience) include the uncinate process and lateral tip of the tail. Missing lesions in these locations is more likely related to incomplete pancreatic imaging than any tissue-specific issues. Complete assessment of the uncinate process requires imaging from the distal third/

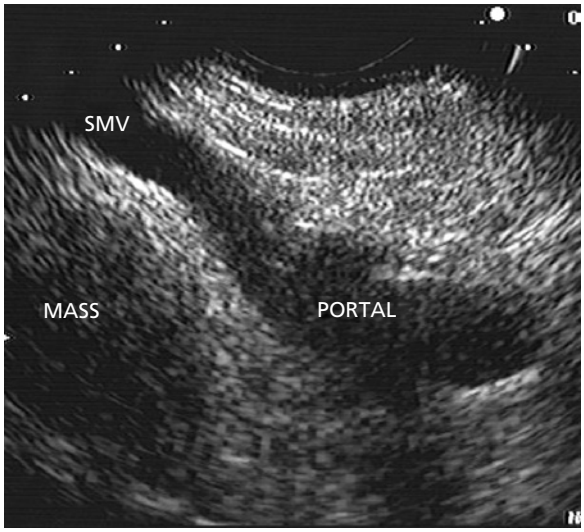

Figure 15.7 Mass in the uncinate process. In this case, a mass is seen in the uncinate process on the opposite side of the superior mesenteric vein as viewed from the gastric antrum.

fourth portion of the duodenum and/or the gastric antrum. In the latter case, the uncinate process may be seen (with a linear device) with the scope positioned such that the SMV is seen in longitudinal section (Figure 15.7). We have encountered several humbling instances in which small lesions were seen on CT in this region and were initially missed during our EUS examination. Complete imaging of the tail requires carefully following the pancreas into the splenic hilum, as well as confirmation that the tail is not bifid or in an atypical location (such as more inferior across the anterior surface of the left kidney).

EUS-guided tissue sampling

With rare exception (such as some pancreatic endocrine tumors or serous cystadenomas), the sonographic appearance alone cannot provide significant clues to the underlying histopathological type. Statistically, roughly 85 to 90% of pancreatic tumors are exocrine carcinomas (see Table 15.2), however other tissue types may occur and specific diagnosis requires either diagnostic needle aspiration/biopsy or surgical resection. The technical aspects of EUS-guided biopsy are discussed elsewhere (see Chapter 8). A few specific issues related to the pancreas bear discussion here, however.

There is considerable controversy regarding whether pancreatic tissue sampling should be pursued in the setting of a focal, apparently resectable mass. Clearly tissue sampling of an unresectable lesion is beneficial. The tissue diagnosis allows initiation of chemotherapy and/or radiation therapy, is mandatory for enrollment in clinical trials, and clarifies the appropriateness of permanent biliary stent placement. In the 5 to 25% of cases in which the mass lesion is resectable, however, some institutions have argued that tissue sampling is unnecessary. The arguments against tissue sampling are generally centered on the low negative predictive value of EUS or percutaneous biopsy (generally in the 25% range) and the potential for needle tract seeding with tumor cells. It is clear that a negative biopsy cannot exclude the presence of malignancy and clinicians must avoid being falsely reassured. The risk of spreading tumor via biopsy is difficult to assess and estimated rates vary widely. Clearly there are scattered, irrefutable reports of documented tumor recurrence in previous biopsy tracts, including the gastric wall or abdominal wall [39]. These reports are rare, however, and the overall risk is probably quite low. Although one retrospective study suggested a higher rate of positive cytology in peritoneal washings among patients with previous biopsy, this was in an uncontrolled setting with numerous confounding variables [41]. Micames et al. showed a lower rate of peritoneal carcinomatosis among patients with prior EUS-FNA compared to percutaneous FNA (2.2% vs. 16.3%; $P < 0.025$), although this study has similar limitations [42]. These issues become irrelevant in the setting of pancreatic head masses when EUS-FNA is performed through the retroperitoneal duodenal wall. In these cases, the needle does not traverse the peritoneal cavity and the entire needle tract is resected with the surgical specimen.

We believe that there are several advantages to preoperative biopsy. Biopsy is useful in identifying the roughly 10% to 15% of patients with tumors which are not adenocarcinoma [4]. Many of these tumors (such as neuroendocrine tumors) have more favorable prognoses for cure compared to the dismal results with adenocarcinoma and we find this information valuable in counseling our patients [44,45]. We also believe that it is beneficial for patients to be aware of their diagnosis prior to deciding whether or not to proceed with resection.

EUS-guided fine needle aspiration of pancreatic mass lesions is highly accurate (see Table 15.5) [40,46–67]. It is our opinion that smaller-caliber, 25-gauge needles are preferable as they produce less bloody specimens which are easier to interpret at the bedside. In addition, larger-caliber 19-gauge needles are difficult (but not impossible) to use in the duodenum. These larger needles are difficult to advance when bent and may become permanently deformed by passing through a tortuous echoendoscope and subsequently bend out of the plane of the ultrasound beam. The newer core biopsy needles are rarely needed for pancreatic biopsy and cannot be used via the duodenum as the bent orientation prevents adequate movement of the outer biopsy sheath during firing.

Pancreatic endocrine neoplasm

Pancreatic endocrine neoplasms (also known as PEN, islet cell tumors or neuroendocrine tumors) represent a unique subset of solid pancreatic neoplasms which arise from the endocrine, rather than exocrine or ductal, structures within the pancreas. Sometimes these lesions are suspected due to the unique clinical syndromes which arise due to the secretion of a variety of hormones – insulin (hypoglycemia), gastrin (refractory ulcer disease, diarrhea and thickened gastric folds), glucagon (migratory necrolytic erythema) or VIP (watery diarrhea). These

Table 15.5 EUS-FNA for pancreatic masses: sensitivity, specificity and accuracy. Source: Refs 8,40,46–67

Reference	Year	*n*	Sensitivity (%)	Specificity (%)	Accuracy (%)
Giovannini [54]	1995	43	91	100	79
Wegener [63]	1995	11	44	100	55
Cahn [49]	1996	50	88	100	87
Bhutani [47]	1997	47	64	100	72
Chang [50]	1997	44	92	100	95
Erickson [52]	1997	28	—	—	96
Faigel [53]	1997	45	72	100	75
Gress [56]	1997	95	—	—	86
Wiersema [64]	1997	124	87	100	88
Binmoeller [48]	1998	58	76	100	92
Hunerbein [58]	1998	26	88	100	—
Williams [65]	1999	144	82	100	85
Suits [61]	1999	96	96	100	96
Voss [62]	2000	90	75	88	—
Gress [55]	2001	102	93	100	96
Harewood [57]	2002	185	94	—	92
Mallery [40]	2002	68	74	100	76
Ylagan [67]	2002	80	78	100	—
Afify [46]	2003	69	80	82	—
Raut [59]	2003	233	91	100	92
Eloubedi [51]	2003	158	84	97	84
Agarwal [8]	2004	81	89	100	90
Ryozawa [60]	2005	50	82	100	89
Wittmann [66]	2006	83	60	100	77
Overall		2010	81	98	85

hormonally related symptoms may lead to a clinical presentation at a point at which the neoplasm is quite small, as opposed to typical ductal adenocarcinoma. Because of this smaller size, standard imaging tests are frequently unable to locate PENs [31,68–70]. Radiolabelled octreotide scanning (somatostatin scintigraphy, Octreoscan) and EUS are the main tests for localization. Overall, both tests have similar sensitivity for the localization of PENs [68–70]. Somatostatin scintigraphy has the advantage of allowing imaging of the entire body, including lungs and bone. It is our opinion that EUS allows more precise localization (e.g. pinpointing a lesion in the right upper quadrant as being located within the pancreas, the duodenal wall, the liver or a lymph node). In addition, EUS allows simultaneous tissue sampling. Of note, a large percentage (approximately 60%) of insulinomas lack the specific somatostatin receptor necessary for uptake on scintigraphy, thereby favoring EUS for localization of insulinoma [31,70,71].

The endosonographic appearance of endocrine neoplasms is typically different than ductal adenocarcinomas. Endocrine tumors tend to be relatively brighter than adenocarcinoma, and may be nearly isoechoic to the surrounding pancreas (Figure 15.8 and Plates 15.1A&B). They are typically well-circumscribed and may appear encapsulated. They typically displace and indent into adjacent structures rather than directly invading (although invasion is still possible). Some endocrine tumors contain cystic components. In our experience, these cystic endocrine tumors typically appear different from other cystic neoplasms, with the cystic component tending to be irregularly shaped, centrally located and with an irregular, thick solid wall (Figure 15.9A). This appearance is reminiscent of what one might expect if a volume of fluid was injected into the center of a solid tumor. Fluid aspiration often results in a residual, round, well-circumscribed mass (Figure 9B).

Several other unique issues exist in the evaluation of endocrine tumors. In particular, these lesions may occur in the setting of other systemic syndromes (e.g. MEN-1, von Hippel–Lindau disease, von Recklinghausen disease and tuberous sclerosis). Whether these masses are sporadic or associated with other syndromes influences the likelihood of multifocality, the likely location and the possibility of mass lesions in other organs which could also be detected via EUS. Sporadic gastrinomas are generally solitary; however, in the setting of MEN-1 they are commonly multifocal. Insulinomas are also occasionally multifocal in the setting of MEN-1. As such, the finding of a single lesion early in the course of an EUS examination does not obviate the need for a careful search of other regions. In addition, gastrinomas frequently arise from within the duodenal wall (particularly in MEN-1). Because of this, and the propensity for multifocal disease, EUS examination of gastrinoma patients should include careful endoscopic and duodenoscopic examination of the

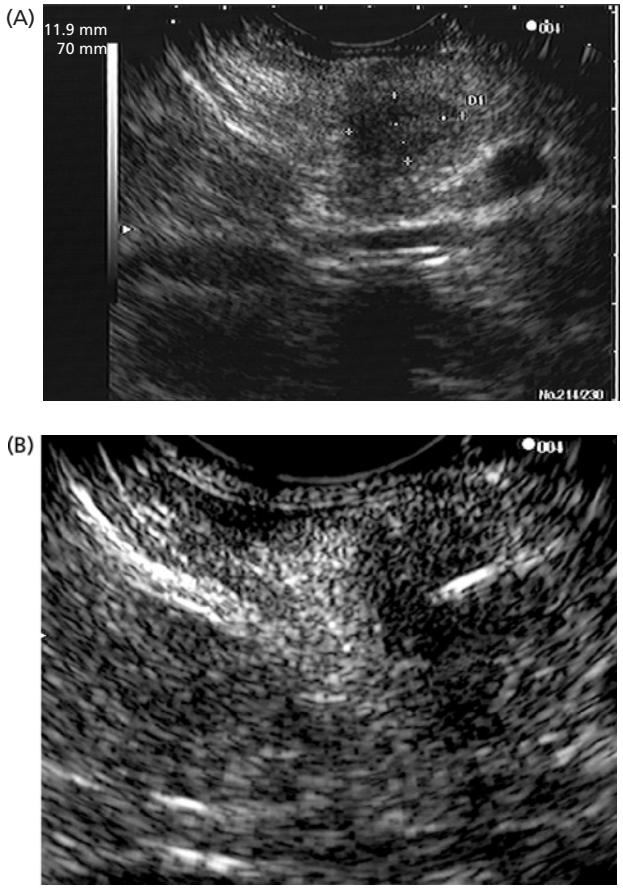

Figure 15.8 Pancreatic endocrine neoplasm. (A) A well-circumscribed, 12 × 7 mm mass is seen within the pancreatic body between the calipers. The mass is nearly identical in echogenicity to the surrounding pancreas. (B) Needle aspiration is performed using a 25-gauge needle. Cytology returns relatively bland, uniform cells (see Plate 15.1A, DiffQuik stain) which show characteristic positive staining for chromogranin (see Plate 15.1B). All cytology images 400 × magnification.

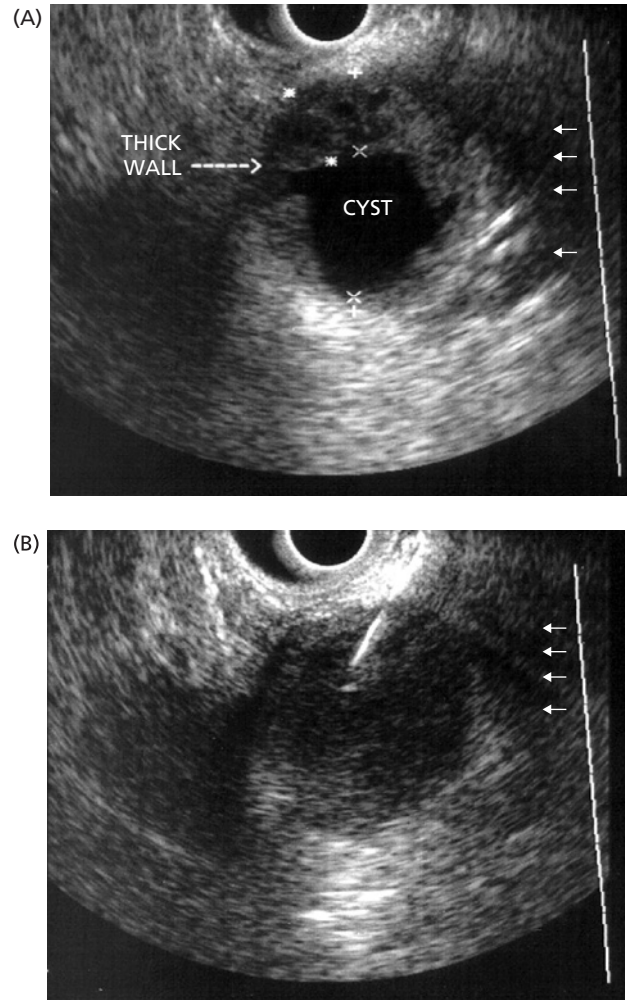

Figure 15.9 Cystic pancreatic endocrine neoplasm. (A) A thick-walled, well-circumscribed isoechoic mass is seen with an eccentric, irregularly shaped central cyst. (B) After needle aspiration of the fluid contents, the lesion appears to be a spherical, well-circumscribed solid lesion similar to standard endocrine neoplasms.

duodenal wall for nodules. The use of high-frequency miniprobe examination of the duodenal wall has also been proposed to improve yield. Von Hipple–Lindau disease is associated with the development of pancreatic serous cystadenomas, pheochromocytomas and renal cell carcinoma – all of which are theoretically detectible by EUS.

Solid pseudopapillary tumor

Another solid pancreatic neoplasm which may have a characteristic sonographic appearance is the solid pseudopapillary tumor (also known as a solid and cystic neoplasm; Plate 15.2). These lesions tend to be relatively large at the time of diagnosis and are more commonly seen in the pancreatic tail of young women [72,73]. There is typically a distinct outer rim which often contains irregular areas of calcification. The central region is filled with neoplastic tissue characterized by numerous papillary fronds. The resulting sonographic appearance demonstrates solid-appearing, heterogenous tissue with small anechoic, irregularly shaped lakes of fluid (Figure 15.10A). The overall echogenicity is brighter than that of adenocarcinoma, with a glistening/refractile appearance that is similar to that of large adenomatous polyps (as can be seen with large ampullary adenomas) (Figure 15.10B). Needle aspiration with immunohistochemistry is diagnostic, showing a characteristic staining pattern with positivity for vimentin and focal weak keratin reactivity. The characteristic branching papillae with myxoid stroma are best seen in cell block [74]. Surgical resection is generally recommended, although the natural history of the lesion is somewhat uncertain given its rarity (Plate 15.2) [75].

Pancreatic metastases

Although the majority of pancreatic neoplasms arise primarily in the pancreas, occasionally the pancreas may become of site of

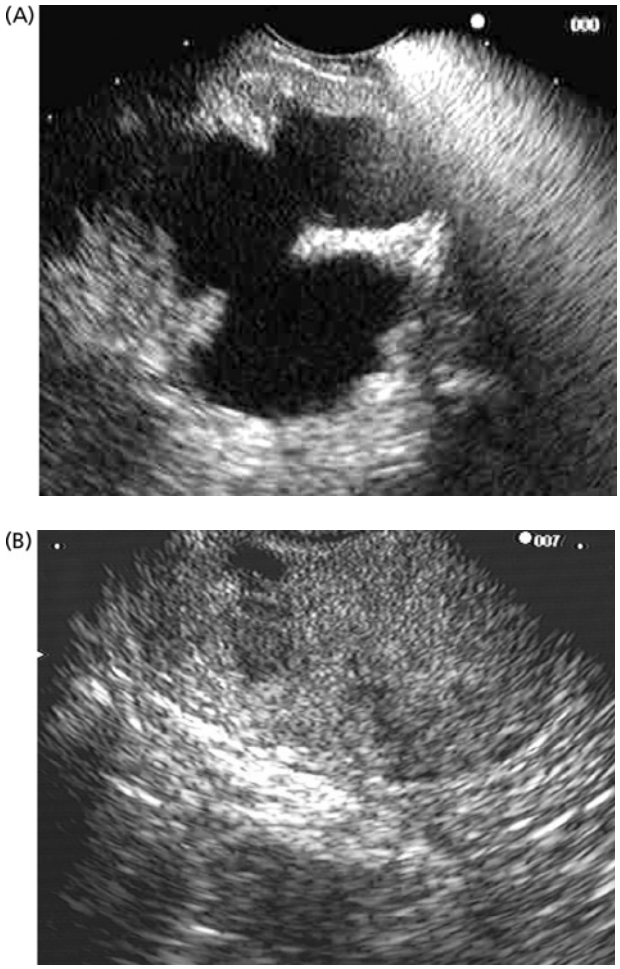

Figure 15.10 Solid pseudopapillary tumor of the pancreas. The lesion is a complex collection of irregularly shaped cystic components of variable size (A) and isoechoic/hypoechoic solid portions (B). The lesion is encapsulated. Surgical pathology demonstrates an encapsulated lesion filled with papillary excrescences (see Plate 15.2).

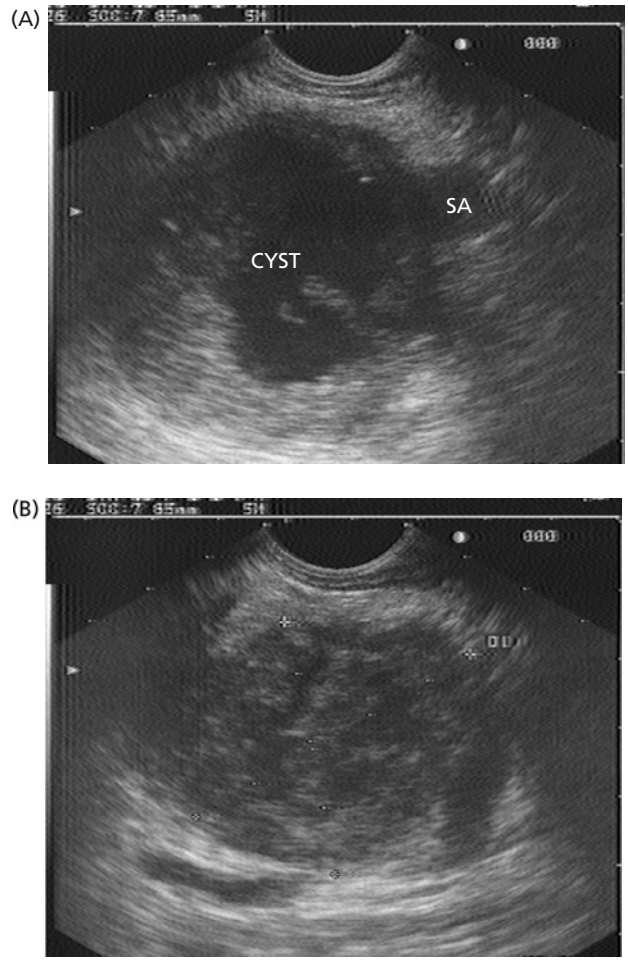

Figure 15.11 Metastatic squamous cell (lung primary) to the pancreas. A complex mass is seen in the pancreatic tail with cystic (A) and solid (B) components in a patient undergoing treatment for primary squamous cell carcinoma of the lung. Needle aspiration shows evidence of squamous cell carcinoma (see Plate 15.3, 400 × magnification).

metastatic disease [76–78]. To our knowledge, there are no specific sonographic criteria that can differentiate a primary from a metastatic mass lesion. Metastases may occur in a variety of settings. In our experience, the most common tumors of origin are ductal breast cancer, renal cell carcinoma and melanoma although other sites are possible (Figure 15.11, Plate 15.3). Accurate diagnosis requires tissue sampling (either fine needle aspiration with cell block or core biopsy) and subsequent immunohistochemistry analysis. More importantly, diagnosis requires an understanding of the patient's past medical history, acknowledgement of the possibility of metastatic disease (even many years following previously presumed curative therapy) and discussion of the situation with one's cytopathology colleagues. Comparison of the staining pattern of the pancreatic mass with the original primary should allow clarification of origin and, in the case of breast cancer, assess the potential responsiveness to hormonal therapy. In some selected cases, such as renal cell carcinoma, solitary metastases may be considered for resection. In this situation, it is important to realize that multiple pancreatic lesions may be present (Figure 15.12) and careful examination of the remainder of the pancreas and other potential metastatic sites should be performed during EUS.

Benign mass lesions

Focal benign masses may occur in a variety of settings. Most commonly this will occur due to focal chronic pancreatitis. The sonographic appearance of chronic pancreatitis is quite variable. The presence of diffusely shadowing calcifications in highly suggestive of chronic pancreatitis but, as noted previously, cannot entirely exclude a concomitant underlying malignancy because chronic pancreatitis is a risk factor for malignancy. Chronic pancreatitis may produce biliary strictures which are concerning for malignancy, although the cholangiographic appearance is typically that of a more smoothly tapered stricture than malignancy

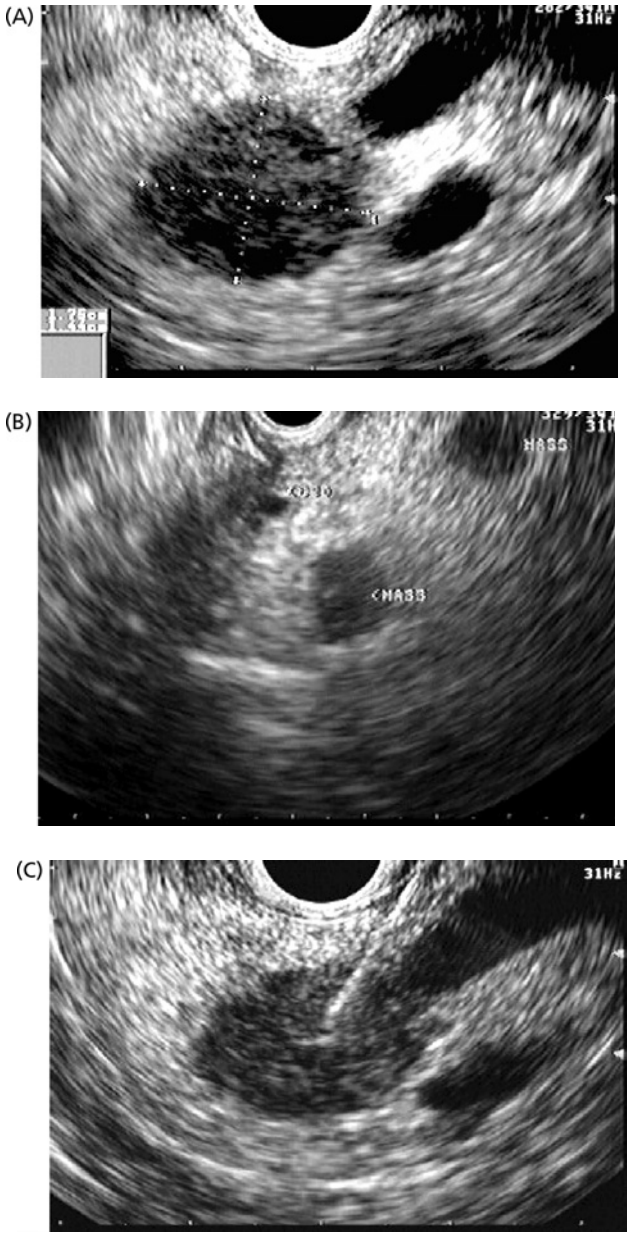

Figure 15.12 Metastatic renal cell carcinoma to the pancreas. (A) A large mass was identified in the pancreatic body on CT in this patient with abdominal pain. There was a remote history of renal cell carcinoma approximately 7 years earlier. EUS biopsy was requested to determine whether this was of primary pancreatic origin. (B) EUS demonstrated two additional focal masses in the pancreatic head which were not seen on CT. (C) Needle aspiration was performed and documented metastatic renal cell carcinoma.

[79,80]. There are certainly also cytological features consistent with chronic pancreatitis as well [81].

A specific scenario exists which is highly suggestive of benign disease. In patients with previous peripancreatic fat necrosis due to acute pancreatitis, CT imaging may suggest a well-circumscribed hypodense mass [32]. The density may be indeterminate

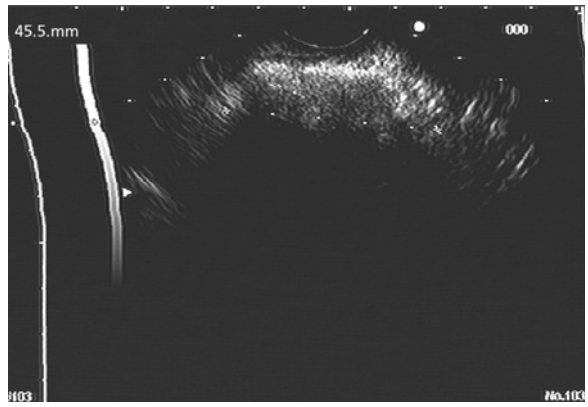

Figure 15.13 Calcific debris following acute pancreatitis. The patient had a well-circumscribed, hypodense pancreatic mass seen on CT interpreted as concerning for malignancy. There was a very remote history of acute pancreatitis managed at another institution. EUS demonstrated a 4.5 cm hypoechoic region which produced acoustic shadowing. Diagnostic needle aspiration returned pasty material with cytology showing necrotic, acellular debris with crystalline structures (see Plate 15.4). DiffQuik stain at 200 × magnification.

for solid vs. fluid contents. When this is in fact due to fat necrosis, the EUS will demonstrate a solid-appearing structure which produces diffuse, incomplete acoustic shadowing due to the presence of calcific debris (Figure 15.13). Although frequently not clinically necessary, needle aspiration will return a characteristic white, toothpaste-like material and cytology will show acellular necrotic debris with crystalline material (Plate 15.4). If we encounter this scenario we will generally avoid needle aspiration. If needle aspiration is performed we administer prophylactic antibiotic as is recommended for cystic neoplasm aspiration. This material is not amenable to endoscopic drainage and rarely requires intervention.

The increased utilization of CT imaging has also led to the detection of pancreatic pseudotumors due to focal fatty infiltration [82]. In this case, the pancreas will appear hypodense on CT. Often this is confined to the head or uncinate process, raising concern regarding a possible occult neoplasm. This fatty infiltration should not result in biliary or pancreatic ductal obstruction. EUS in this setting will demonstrate a markedly hyperechoic region of pancreas which produces diffuse shadowing reminiscent of looking though fog. This shadowing "fog" makes it impossible to visualize the mesenteric vessels when imaging through the pancreatic head from the descending duodenum (Figure 15.14). Because of this shadowing it can be difficult to convince oneself that the entire pancreas has been adequately visualized to reliably exclude an underlying mass. In this case, MRI can be useful for confirmation of the presence of fat density in the region of CT abnormality [82].

Autoimmune pancreatitis (lymphoplasmacytic pancreatitis, sclerosing pancreatitis) is a recently described inflammatory disease which may be either a diffuse process or result in focal mass lesions which are sonographically indistinguishable from

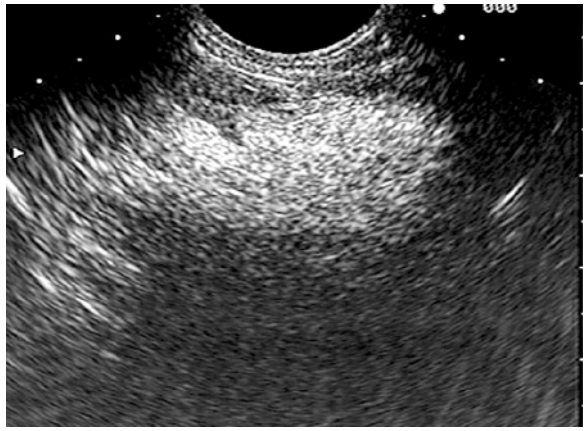

Figure 15.14 Fatty infiltration of the pancreas. The patient underwent CT scanning of the abdomen for unrelated issues, with an incidental note of a focal hypodense mass in the pancreatic head. EUS demonstrates abnormally hyperechoic tissue in the expected region of the pancreatic head which shadows and precludes visualization of deeper structures. Subsequent MRI confirmed increased fat density and the absence of a mass to correspond to the region of concern on CT.

adenocarcinoma (Figure 15.15) [83,84]. In this situation, a high degree of clinical suspicion is necessary to establish the diagnosis. Diagnosis should be suspected in relatively young patient, particularly if the lesion is identified during the evaluation of unexplained acute pancreatitis or as an incidental imaging finding. This disorder may be associated with new-onset diabetes which, paradoxically, improves with corticosteroid therapy. The diagnosis may be suggested by the finding of elevated IgG subclass-4 levels or forceps biopsy of the major papilla with positive immunohistochemistry staining for IgG-4. The diagnosis is rarely established by fine needle cytology. This is one instance in which core biopsy of the pancreas may be necessary and diagnostic, as described by Levy et al. [85]. A therapeutic trial of steroid therapy may establish the diagnosis by resulting in resolution of the mass lesion and, if present, also resolution of the associated ductal strictures [86]. In young patients, a therapeutic trial of steroids may be warranted in the setting of an undiagnosed mass lesion or stricture, especially in light of the lower clinical likelihood of carcinoma in young age, the low likelihood of cure with resection if malignancy is in fact present, and the potential morbidity of surgical resection.

Overview of pancreatic cancer staging and surgical context

As with other cancers, pancreatic adenocarcinoma is staged using a TNM classification system established by the American Joint Committee on Cancer (AJCC) [87]. T-classification is determined by the tumor size and degree of local extension. Tumors limited to the pancreas are classified T1 if 2 cm or less in greatest dimension and T2 if greater than 2 cm (see Table 15.6) [87].

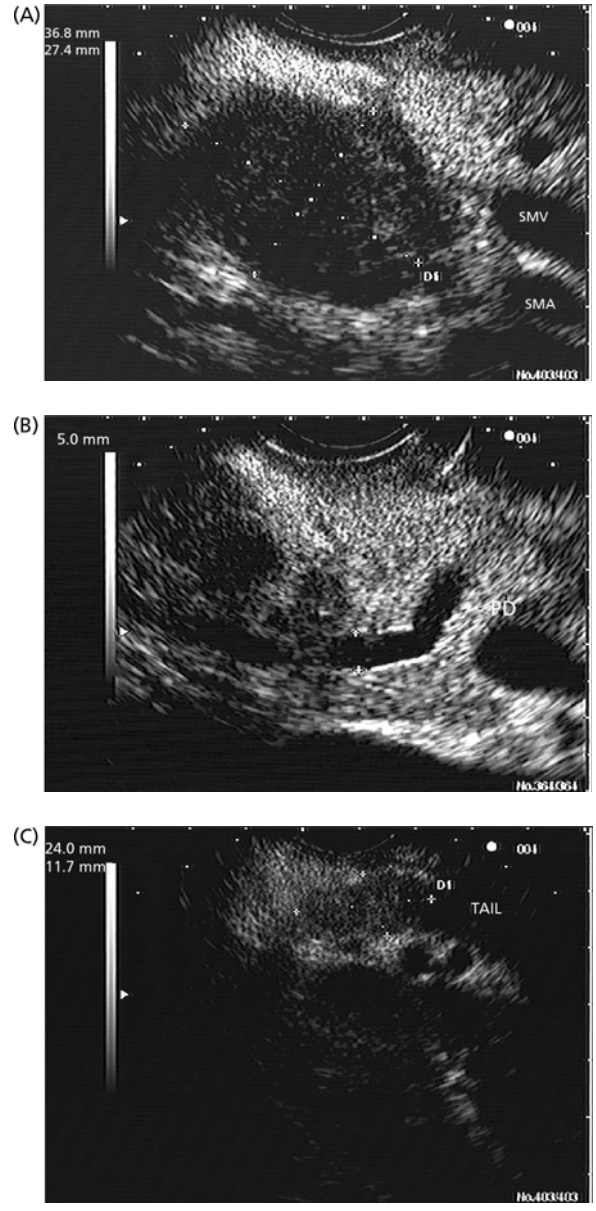

Figure 15.15 Autoimmune pancreatitis. A focal, well-circumscribed mass was seen in the pancreatic head on CT imaging of a young woman with abdominal pain and elevated lipase. EUS demonstrated a 37 × 27 mm hypoechoic mass in the pancreatic head (A) resulting in upstream pancreatic duct dilation (B). The pancreatic body was relatively normal. A second hypoechoic lesion was seen in the pancreatic tail (C). Needle aspiration of the pancreatic head was performed and interpreted by cytopathology as showing adenocarcinoma. Outside cytology review confirmed the diagnosis, however surgical resection revealed autoimmune pancreatitis without malignancy. This is the only instance of false positive cytology in our experience.

Tumors which extend beyond the limits of the pancreas are classified either T3 or T4. T3 lesions extend beyond the pancreas, possibly to include adjacent venous structures without involvement of major arteries. Involvement of adjacent major arterial structures is classified as T4. Invasion of some adjacent solid

Table 15.6 AJCC TNM classification of pancreatic tumors. Modified from Ref. 87 with permission

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

organs is also considered T4, although this is extremely rare. The precise definition of which structures constitute T3 vs. T4 disease is summarized in Table 15.7 [88]. It is extremely unusual to encounter tumors with solid organ invasion without associated arterial invasion. The intent of these criteria is that lesions up to class T3 are potentially surgically resectable, whereas T4 lesions are universally considered unresectable. In previous versions, involvement of the portal vein or SMV was considered T4; however the criteria were changed to reflect the fact that some centers will offer surgical resection with venous grafting in the setting of venous invasion. Whether patients benefit from venous resection is, however, a point of contention. Carcinoma in situ (typically seen in the setting of intraductal papillary mucinous neoplasm or PanIN III) is classified Tis.

Regional lymph nodes in pancreatic cancer include celiac lymph nodes, hepatic artery nodes, pyloric nodes and splenic nodes. Metastatic nodes which are peripancreatic but distant from the primary tumor, such as splenic nodes in the setting of a pancreatic head mass, are uncommon but would still be considered regional as they would be resected with total pancreatectomy. The presence of any regional nodal metastasis is classified N1, regardless of the number of nodes present (in contrast to gastric cancer) (see Table 15.7). Issues related to sonographic criteria predictive of nodal metastases and EUS-guided FNA of lymph nodes are discussed elsewhere. It is our opinion that the EUS report should specifically clarify whether classification as N1 is being determined solely by sonographic criteria or has been confirmed by FNA as this influences the sensitivity and accuracy of the determination.

The presence of distant metastatic disease is classified M1. Distant spread most commonly occurs in the liver, lungs or peritoneal cavity. Hess et al. reviewed 270 patients with pancreatic tumors and found that the liver was the most common site of metastases, with other common sites including the abdominal cavity, lungs and bone [89]. Positive cytology on fluid obtained from peritoneal washings in the absence of ascites or macroscopically identified peritoneal implants is also considered M1 and such patients usually have a poor outcome [41].

The T, N and M classes are combined to determine an overall stage as defined in Table 15.8 [87]. Stages I and II are considered localized and potentially resectable (keeping in mind that this includes a subset of patients with portal or mesenteric venous invasion). Stage III is locally advanced and unresectable. Stage IV is associated with distant metastasis. According to SEER data, between 1996 and 2002 roughly 7% of all cases presented at a localized stage, 26% were regional and 52% had distant metastatic disease (15% were unstaged). Localized disease was associated with a 5-year adjusted survival of 19.6%, compared to 8.2% for regional disease and 1.9% for metastatic disease (see Figure 15.16) [90].

The extent to which TNM classification determines clinical management varies widely from institution to institution and needs to be carefully discussed with the referring physician and one's surgical and oncology colleagues. It is our practice to not recommend vascular resection (outside clinical trials following neoadjuvant chemoradiotherapy). In this scenario, patients with extension beyond the pancreas (and thus T3 disease) but without venous or arterial invasion will be surgically explored. This issue is relevant when interpreting literature addressing the staging accuracy of various imaging tests. In our practice, and many others, the accuracy of T-classification per se is less important than the accuracy of detection of vascular invasion. EUS has been found to be highly sensitive, specific and accurate for the determination of resectability and is at least comparable to, if not superior to, high-quality thin-cut spiral CT scan (Table 15.9) [11,13,15,19,20,91–94,99].

EUS staging

Venous invasion

Each of the relevant venous structures which may be affected by pancreatic cancer may be readily assessed by EUS. The most common location of concern is the right lateral surface of the portal vein and proximal SMV in the setting of a pancreatic head mass. There are a variety of potential sonographic findings with regard to the relationship between a mass and adjacent vascular structures (ranging from vascular contact to vascular obliteration or intraluminal growth). Each of these is associated with variable degrees of certainty regarding resectability (Table 15.10) [95–97]. The subtle variations in vascular findings cannot be adequately communicated in a procedure report by a simple statement of T-classification and should be carefully described in the report and in discussions with one's oncology and surgery colleagues.

In the absence of invasion, there should be an intact hyperechoic tissue plane separating the mass and vein in all views. A loss of this interface is suggestive of invasion (Figure 15.17).

	Pancreas head	Pancreas body and tail
T3	Extension to peripancreatic tissue	Extension to peripancreatic tissue, NOS
	Fixation to adjacent structures	Fixation to adjacent structures, NOS
	Ampulla of Vater	Ampulla of Vater
	Duodenum	Duodenum
	Extrahepatic bile ducts	Extrahepatic bile duct(s)
		Spleen
	Adjacent stomach	
	Stomach NOS	
		Hepatic artery
		Portal vein
	Gastroduodenal artery	Spelnic artery/vein
	Hepatic artery	Superior mesenteric vein
	Pancreaticoduodenal artery	Splenic flexure of colon
	Portal vein	Kidney, NOS
	Superior mesenteric vein	Left adrenal (suprarenal) gland
		Left kidney
	Transverse colon	Left ureter
	Mesenteric fat	Mesenteric fat
	Mesentery	Mesentery
	Mesocolon	Mesocolon
	Peritoneum	Peritoneum
	Gall bladder	Retroperitoneal soft tissue (retroperitoneal space)
T4	Superior mesenteric artery	Superior mesenteric artery
	Omentum	Aorta
	Liver (including porta hepatis)	Celiac artery
	Aorta	Stomach
	Celiac artery	Ileum
	Adrenal	Jejunum
	Ileum	Gallbladder
	Jejunum	Liver (including porta hepatis)
	Kidney	Colon (other than splenic flexure)
	Retroperitoneum	Diaphragm
	Ureter	Right adrenal (suprarenal) gland
	Further continuous extension	Right kidney
		Right ureter
		Further contiguous extension
N1	Celiac	Regional lymph node(s)
	Gastroepiploic (gastro-omental), left	Hepatic
	Infrapyloric (subpyloric)	Lateral aortic (lumbar)
	Lateral aortic (lumbar)	Pancreaticosplenic (pancreaticolienal)
	Peripancreatic, NOS	Peripancreatic, NOS
	Anterior, NOS	Anterior, NOS
	Anterior pancreaticoduodenal	Anterior pancreaticoduodenal
	Anterior proximal mesenteric	Anterior proximal mesenteric
	Pyloric	Pyloric
	Inferior to the head and body of pancreas	Inferior to the head and body of pancreas
	Pericholedochal (common bile duct)	Pericholedochal (common bile duct)
	Posterior pancreaticoduodenal	Posterior pancreaticoduodenal
	Posterior proximal mesentery	Posterior proximal mesentery
	Superior to the head and body of pancreas	Superior to the head and body of pancreas
	Retroperitoneal	Retroperitoneal
	Superior mesenteric	Splenic (lienal)
	Pancreaticosplenic (pancreaticolienal)	Gastroepiploic
	Splenic (lienal), NOS	Splenic hilum
	Superior hilum	Suprapancreatic
	Suprapancreatic	Superior mesenteric
		Celiac
		Infrapyloric (subpyloric)
M1	Distant lymph node(s)	Same structures
	Distant solid organ metastases (includes peritoneal spread even if limited to the lesser sac region or positive peritoneal cytology)	
	Carcinomatosis	

Table 15.7 AJCC details of T3 and T4 of TNM classification for pancreatic tumors. Modified from Ref. 88 with permission

Table 15.8 AJCC stage groupings for pancreatic cancer. Modified from Ref. 87 with permission

Stage 0	Tis, N0, M0
Stage IA	T1, N0, M0
Stage IB	T2, N0, M0
Stage IIA	T3, N0, M0
Stage IIB	T1, N1, M0
	T2, N1, M0
	T3, N1, M0
Stage III	T4, any N, M0
Stage IV	Any T, any N, M1

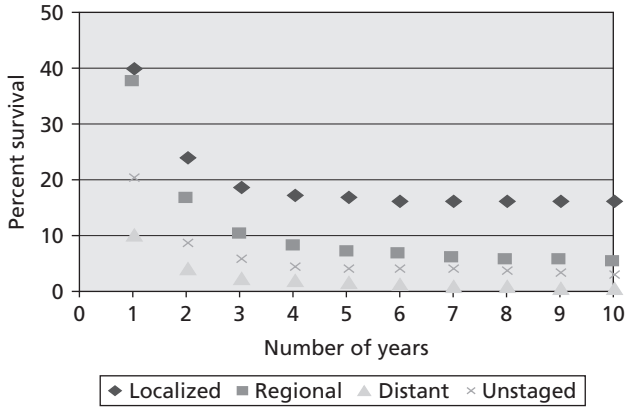

Figure 15.16 Disease-specific 5-year survival as per AJCC stage for pancreatic adenocarcinoma. Localized: stage I; regional: stage II and III; distant: stage IV. (Reproduced from Ref. 90 with permission.)

The degree of certainty regarding invasion increases with the length of interface loss and the percent of cross-sectional vascular encasement (Figure 15.18). Careful examination should be made of the venous wall in the region of contact with a mass. Irregularity of the inner vascular lumen is a more specific feature of invasion. Luminal narrowing is also predictive of invasion. Venous compression with luminal narrowing may occur, however, without contact with the venous wall and is suggested by the presence of an intact hyperechoic tissue plane (Figure 15.19).

The most specific features of venous invasion are the presence of intravascular filling defects and venous occlusion. Small, subtle intravascular filling defects may be missed by CT (Figure 15.20A) whereas others are more obvious (Figures 15.20B). In either case, the presence of intravascular material is unequivocal evidence of vascular involvement and provides definitive staging. The presence of venous occlusion is typically associated with significant collateral formation which may at times be misinterpreted as a "vascular tumor" by CT. Occlusion of the portal vein or SMV will lead to an appearance of "cavernous transformation of the portal vein" (Figure 15.21), with numerous venous collaterals coursing though the pancreatic head and porta hepatis. Occlusion of the splenic vein with a patent portal vein will lead to isolated gastric varices ("left-sided" portal hypertension). Invasion/occlusion of the splenic vein does not preclude surgical resection, but mandates the performance of simultaneous splenectomy. Splenectomy will eliminate the source of blood flow into the varices (the splenic artery) and thus lead to variceal resolution. Invasion of the portal vein/SMV requires venous resection and grafting (if offered) [98].

Arterial invasion

Each of the relevant arterial structures is readily assessed via EUS. The SMA may be visualized from the stomach, descending duodenum or transverse duodenum (where it crosses directly anterior to the duodenal wall). The celiac trunk and its branches are best viewed from the proximal stomach. Additional portions of the hepatic artery are also seen from the duodenal bulb. Some studies suggest that EUS may have limitations with regard to assessment of SMA involvement. We suspect that this may be in part related to the widespread use of radial instruments and a failure to completely image the vessel from the distal duodenum.

Table 15.9 Resectability and vascular invasion (EUS vs. CT scan). Source: Refs 11,13,15,19,20,91–94,99

Reference	Resectability						Vascular invasion	
	Sensitivity (%)		Specificity (%)		Accuracy (%)		Sensitivity (%)	
	EUS	CT	EUS	CT	EUS	CT	EUS	CT
Legmann 1998 [15]					90	90		
Midwinter 1999 [20]					83	76	81	56
Gress 1999 [13]	95	97	92	19	93	60	91	15
Mertz 2000 [19]					100	81	100	50
Ahmad 2000 [91]	61	73(MRI)	63	72(MRI)	69	77(MRI)		
Tierney 2001 [94]			93	100	96	80	89	43
Yousaf 2003 [99]	61		65				69	
Ramsay 2004 [92]	56	79	83	67	63	76	56	80
Soriano 2004 [93]	23	67	100	97	67	83	42	67
Dewitt 2004 [11]	88	92	68	64	77	77		

Table 15.10 Sensitivity and specificity of EUS criteria for vascular involvement by pancreatic carcinoma

	Venous collaterals		Tumor in lumen		Irregular vein wall		Loss of interface		Proximity of mass	
	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
Snady 1994 [97]	19	100	38	100			33	100		
Brugge 1995 [95]					40	100	50	85	87	55
Rosch 2000 [96]	36	94	10	79	Sensitivity 12	Specificity 79				

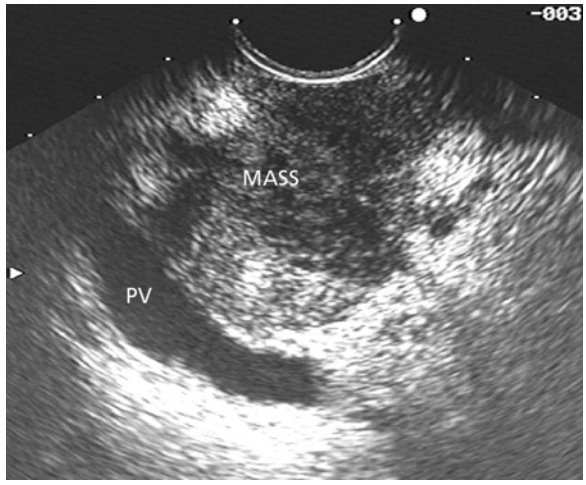

Figure 15.17 Venous interface loss. A hyperechoic tissue plane is seen separating the mass and portal vein below the mass in this picture. This interface is loss, however, in the region labeled "PV."

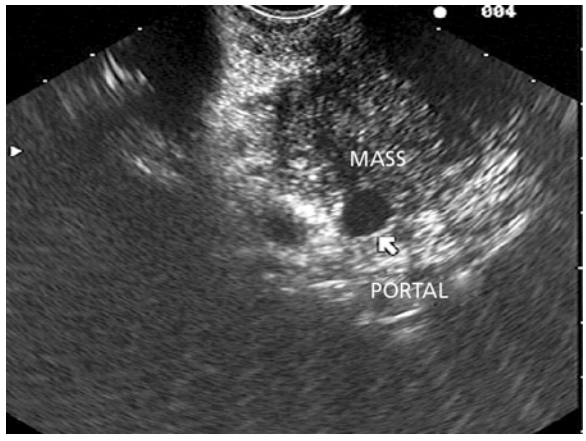

Figure 15.18 Partial venous encasement. This mass encircles approximately 50% of the circumference of the portal vein.

A linear array instrument allows imaging caudally along the long axis of the SMA from the stomach for a greater length than a radial instrument. In any event, one must realize that evaluation of the SMA has been an area of relative weakness for EUS and we recommend taking extra time assessing this vessel from multiple different angles in the duodenum and stomach.

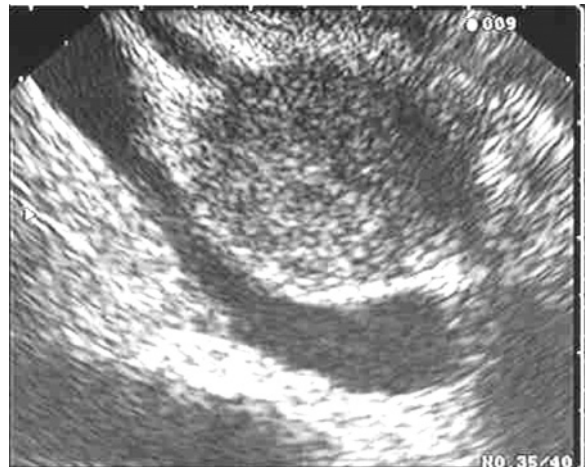

Figure 15.19 Venous compression. In this case, a large mass was seen on CT and MRI, both of which demonstrated portal vein narrowing and suggested unresectability (without venous reconstruction). Although EUS confirmed a large mass, there was an intact hyperechoic tissue plane between the mass and portal vein in all views, suggesting a lack of venous adherence. The lesion was successfully resected without venous reconstruction.

As is the case with venous staging, there are varying degrees of certainty with regard to arterial invasion. Vascular compression and occlusion are much less common with arterial structures (probably due to the thicker, muscular wall and higher flow). Invasion is suggested by a loss of vascular interface; however, vascular encasement is highly specific. Again, the level of certainty regarding these findings should be discussed in the procedure report.

Encasement of the splenic artery does not preclude surgical resection, as the spleen can be resected with the specimen. Invasion of the hepatic artery or celiac trunk however does preclude resection as this would compromise hepatic blood flow. Attempts at arterial resection and grafting have not been encouraging and are generally no longer pursued. This highlights the importance of assessing for an aberrant right hepatic artery arising from the SMA (described previously, and occurring in 10% of the population). The aberrant right hepatic artery will pass adjacent to the posterior margin of the pancreatic head and may be invaded even in the absence of celiac or left hepatic artery (seen as a major branch of the celiac in place of the typical common hepatic artery). This situation typically cannot be detected surgically until late in the sequence of resection (after mobilization of

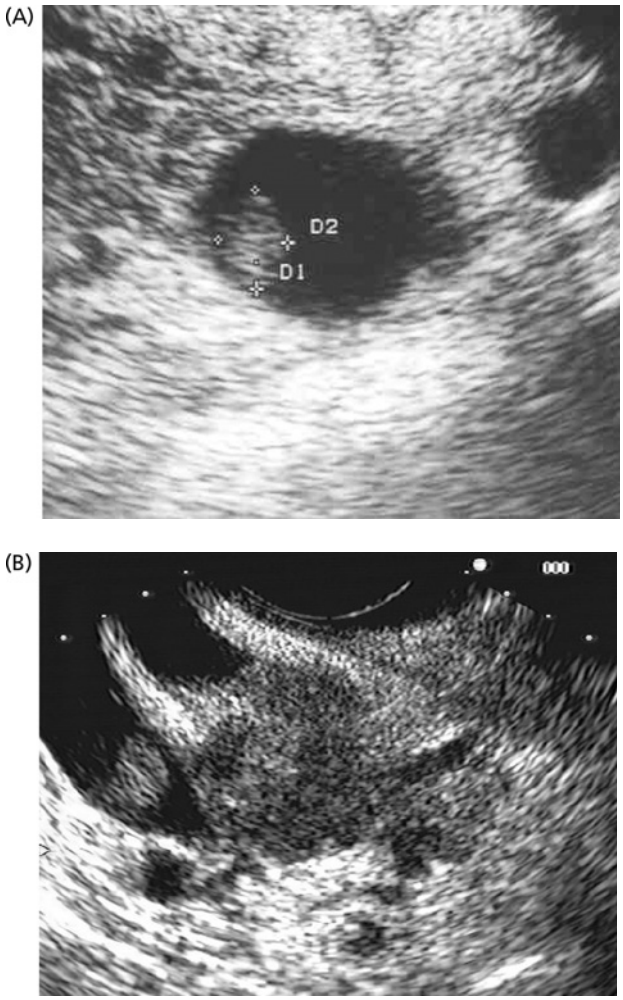

Figure 15.20 Intravenous filling defects associated with tumor invasion. A small defect is seen in (A) which was not evident on CT. (B) shows a more obvious region of tumor ingrowth directly extending from a large mass which is compressing the portal vein.

the pancreatic head and often after transection of the pancreas) due to the retropancreatic location of the aberrant vessel. In this setting, attempting resection without knowledge of the anomaly will jeopardize blood supply to the right hepatic lobe.

Nodal and distant metastases

The endosonographic approach to nodal classification has been discussed elsewhere in detail. It should be mentioned, however, that the sonographic criteria for nodal malignancy were developed primarily in the setting of esophageal cancer staging. It is our anecdotal opinion that these criteria underestimate the risk of malignancy in lymph nodes in pancreatic cancer. In our practice, if a node is seen sonographically which would alter management we favor pursuing needle aspiration regardless of size or echogenicity. Exceptions to this general rule include the presence of isoechoic nodes in the porta hepatis in the setting of biliary obstruction or stenting (which are commonly seen as a reactive

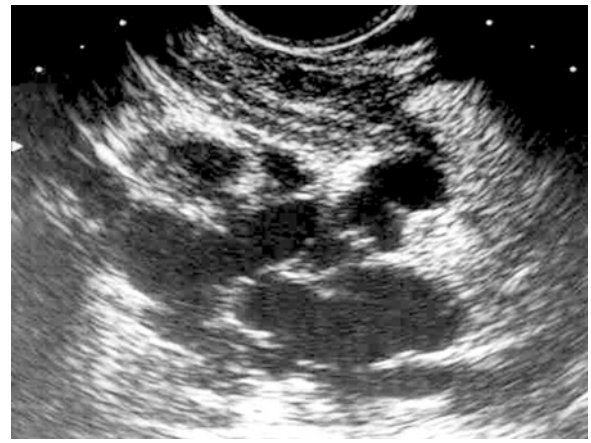

Figure 15.21 Cavernous transformation of the portal vein. Numerous anechoic structures are seen in the region of the porta hepatica. The bile duct passed through the region. Doppler examination showed flow with a venous waveform. The portal vein could not be identified in the region of a large mass.

phenomenon) and nodes in the subcarinal space (unless highly suspicious by sonographic criteria) which are almost universally seen in normal examinations.

As with the performance of EUS-FNA of apparently resectable pancreatic masses, the decision regarding whether to pursue diagnostic needle aspiration of regional lymph nodes is also controversial. Regional nodal metastases do not technically make a lesion unresectable but they do influence prognosis and may affect decisions regarding whether to pursue resection or consider alternative treatments under protocol. If nodal metastases are suspected, we will preferentially favor needle aspiration of this site over the primary mass as positive cytology will provide more definitive staging information and reduces any potential clinical concerns regarding needle tract seeding (as the disease has already spread beyond the pancreas). Additionally, cytological interpretation of a well-differentiated neoplasm is easier when differentiating from an expected background of lymphocytes as opposed to benign pancreatic parenchymal tissue which may closely resemble the carcinoma (Figure 15.22).

Careful assessment of the liver is critically important. Identification and confirmation of a focal hepatic metastasis can save considerable time haggling over the presence or absence of subtle vascular invasion (which is moot in the presence of M1 disease).

Summary

Endoscopic ultrasound is an extremely useful test in the evaluation of patients with suspected or confirmed pancreatic neoplasia. The current literature would suggest that EUS is the most sensitive test for the detection of pancreatic malignancy and is reasonably accurate for the detection of vascular invasion. EUS-guided needle aspiration (or core biopsy) is an accurate method of obtaining a cytological diagnosis prior to treatment and may

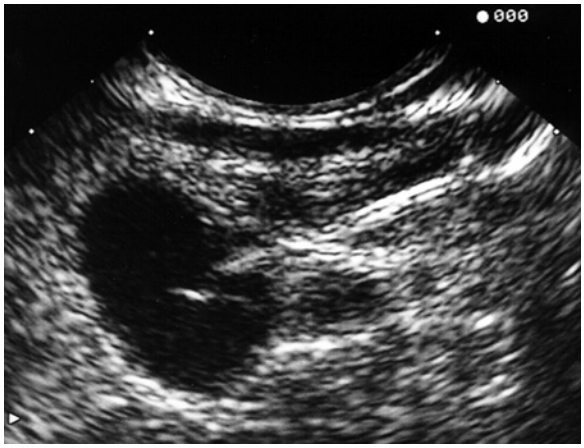

Figure 15.22 EUS-guided needle aspiration of a lymph node metastasis.

identify unsuspected tissue diagnoses. Accurate assessment requires a thorough knowledge of pancreatic and peripancreatic anatomy. EUS only provides useful information when this information is accurately interpreted by a skilled endosonographer and carefully conveyed to one's surgical and oncology colleagues.

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16 EUS for Pancreatic Cysts

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Pancreatic cystic lesions are being detected ever more frequently due to increased use of abdominal imaging studies. It is estimated that approximately 1% of the population may harbor a pancreatic cyst [1]. With many of these being incidental findings, assessment and classification are required for appropriate management, be it surgical resection or conservative follow-up. As such, given proximity coupled with high frequency imaging, endoscopic ultrasound (EUS) has emerged as the best modality to further evaluate pancreatic cysts. This is of significant clinical importance, as neoplastic mucinous lesions are now the most frequently encountered pancreatic cyst [2]. This chapter will discuss the role of EUS and the added benefit of fine needle aspiration (FNA) in evaluating the major types of cystic pancreatic lesions.

EUS morphology

The pancreas can be imaged in great detail with both radial and curvilinear echoendoscopes, where a cyst typically appears as an anechoic structure with posterior enhancement. The purpose of pursuing EUS in evaluating a pancreatic cyst is to differentiate between a neoplastic and non-neoplastic cyst (Table 16.1), as neoplastic cysts may require surgical resection in the appropriate candidate. Symptomatic cysts, regardless of type, generally require resection and thus do not necessarily need EUS evaluation as it may not affect ultimate management. Mucinous cysts are not only the most common neoplastic cysts, but also appear to be the most frequently encountered cysts in practice, many of which are incidental [2]. They are considered premalignant, however their natural history is poorly understood. In a large surgical series, 37% of cystic lesions were discovered incidentally. Compared to symptomatic cysts, the incidental cysts were smaller, occurred in older patients, and were far less likely to be pseudocysts. Indeed, of these, 42% were premalignant and 17% harbored in situ or invasive cancer [2]. Thus, pancreatic cysts require further evaluation.

Table 16.1 Pancreatic cystic lesions

Non-neoplastic cysts
Congenital true cysts
Cystic fibrosis
Autosomal dominant polycystic disease
Von Hippel-Lindau disease
Dermoid cysts
Acquired cysts
Pseudocyst
Retention cyst
Other
Lymphoepithelial cyst
Neoplastic cysts
Mucinous cystic neoplasms
Mucinous cystadenoma
Mucinous cystadenocarcinoma
IPMN
Main duct
Branch duct
Nonmucinous cystic neoplasms
Serous cystadenoma
Other
Cystic degeneration of pancreatic adenocarcinoma
Cystic islet cell tumor
Solid pseudopapillary tumor

Unfortunately, it has proven difficult to classify cystic lesions based on EUS morphology alone. Given morbidity associated with pancreatic surgery, endosonographers need to be confident in their diagnosis prior to surgical referral. The first EUS study of pancreatic cysts classified lesions into six types based on morphology (Figure 16.1) [3]. Neoplastic cysts demonstrated thick walls, protruding tumors, thick septations and microcystic morphology; non-neoplastic cysts had thin septations or were unilocular. In this study, correlated with surgical pathology, radial EUS morphology could accurately differentiate between benign and malignant tumors based on interpretation by two reviewers [3].

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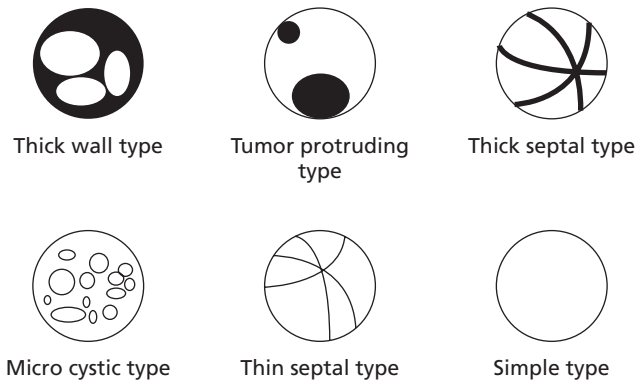

Figure 16.1 EUS classification of pancreatic cystic lesions (Reprinted from Ref. 3 with permission from the American Society for Gastrointestinal Endoscopy.)

Unfortunately, in more recent studies, the accurate differentiation of cystic lesions by EUS morphology alone has been questioned. A similar study concluded that EUS features could not reliably differentiate benign from malignant pancreatic cysts, based on blinded interpretation [4]. The limiting factor appears to be the extent to which expert endosonographers can agree on morphologic features. This was further portrayed in the study by Ahmad et al. [5] which formally evaluated interobserver agreement among endosonographers for the diagnosis of neoplastic versus non-neoplastic pancreatic cystic lesions. Eight blinded experienced endosonographers reviewed EUS videotapes to identify cyst morphologic features and give a specific diagnosis. Kappa scores were disappointing, leading the authors to conclude that there was little more than chance interobserver agreement among endosonographers to diagnose cysts based on morphology alone [5].

EUS-guided fine needle aspiration

Given the limitations of morphologic classification, EUS-guided fine needle aspiration (EUS-FNA) has become an important tool to increase diagnostic accuracy for pancreatic cystic lesions. However, cyst aspirate cytology suffers from poor sensitivity due to the general paucicellular nature of the sample [6,7]. The epithelial component that defines the cyst type lines the cyst cavity; unfortunately, it is difficult to obtain a true representative cellular sample with a fine needle aspirate. As a result, tumor marker levels in the cyst fluid have been studied in the attempt to more accurately differentiate cystic lesions. A variety of glycoproteins present in mucinous epithelium are secreted into the cyst fluid in measurable quantity. Carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) 72-4 have been shown to be useful in identifying mucinous lesions [6,8–10]; conversely, cyst fluid concentration of these tumor markers are very low in serous cystadenomas [9,10]. The most comprehensive study to date evaluating EUS-FNA for diagnosing pancreatic cysts is the Cooperative Pancreatic Cyst study [6]. This multicenter study enrolled 341 patients, all of whom underwent EUS-FNA for cytology and cyst fluid tumor marker (CEA, CA 72-4, CA 125, CA 19-9, and CA 15-3) analysis. A total of 112 patients (33%) ultimately underwent surgical resection with pathologic correlation. Cyst fluid CEA measurement proved to be the best test for diagnosis of a mucinous cystic lesion, with a cut-off value of 192 ng/mL providing a diagnostic accuracy of 79%. The overall accuracy of CEA was significantly greater than the accuracy of cytology (59%) or morphology (51%; $P < 0.05$) [6]. Additionally, there was no combination of tests that provided greater accuracy than CEA alone. Thus, this study provided further evidence that diagnosis based on morphologic assessment alone was no better than a coin toss, and portrays the significant added benefit of FNA for cyst diagnosis.

Given wide overlap of CEA values among pancreatic cystic lesions, other studies have suggested higher cut-off values for CEA to diagnose mucinous cysts. Frossard et al., in a study also revealing the poor performance of EUS morphology alone to predict a mucinous cystic neoplasm (MCN), suggested a CEA value >400 ng/mL [8]; Linder et al. suggested a level >480 ng/mL [11]. A meta-analysis of 12 studies found a diagnostic accuracy of 79% for a CEA value >800 ng/mL [10]. Thus, controversy regarding optimal CEA values exists, likely reflected in individual laboratory variation due to the assay and equipment used, in addition to whether the sample was measured before or after centrifugation for cytology. Future studies should address a standardized protocol for measurement of cyst fluid CEA levels.

Characteristics of major pancreatic cysts

Despite the inaccuracy of cyst morphology for diagnosis, certain pancreatic cystic lesions have some characteristic features (Table 16.2), where their recognition may aid in diagnosis and help direct FNA. Neoplastic mucin-producing cystic tumors are most important, given their malignant potential and increasing recognition [2]. Included within this category are mucinous cystic neoplasms (MCNs) and intraductal papillary mucinous neoplasia (IPMN).

MCNs are classified as mucinous cystadenomas or mucinous cystadenocarcinomas (if they undergo malignant transformation). These tumors are diagnosed almost exclusively in women, with a peak incidence in the fifth to sixth decade [12–17]. The vast majority (~75%) are located in the pancreatic body and tail [12,13,15,18]. MCN appear as thinly septated cystic lesions comprised of several fluid-filled compartments (Figure 16.2), or as unilocular cysts. The wall is typically thin; "egg-shell" or eccentric calcifications can occur (~15%) and are considered pathognomonic [14,19–21]. The presence of an associated mass or mural nodule is a harbinger for malignant transformation. The cyst aspirate is generally slightly viscous to thick and mucoid [17], however a thin watery aspirate does not exclude MCN. CEA is generally elevated, with marked elevation more frequently seen in malignant lesions [6,7,22]. The cyst cavity is lined by tall columnar mucin-producing cells; agitating the cyst wall or septa

Table 16.2 Characteristics of pancreatic cystic lesions. Adapted from Ref. 52 with permission from the American Society for Gastrointestinal Endoscopy

Lesion	Clinical features	Morphology/EUS findings	Fluid characteristics	Cytology	Malignant potential
Mucinous cystic neoplasm	Usually found incidentally but can cause abdominal pain and a palpable mass	Macrocystic, occasionally septated; peripheral calcifications, solid components and regional adenopathy when malignant	Viscous or stringy, clear; CEA level increased	Mucinous columnar cells with variable atypia, fluid stains positive for mucin	Yes
Intraductal papillary mucinous neoplasm (IPMN)	History of pancreatitis, abdominal pain, or found incidentally	Dilated main pancreatic duct or side branches; may appear as a septated cyst; may have a solid component	Viscous or stringy, clear; CEA level increased	Mucinous columnar cells with variable atypia, fluid stains positive for mucin	Yes
Serous cyst adenoma	Usually found incidentally but can cause abdominal pain and a palpable mass if large	Microcystic with a "honeycomb" appearance; rarely has a macrocystic component; central calcification	Thin, clear to sero-sanguinous; CEA level low or absent	Cuboidal epithelium that stains positive for glycogen	Almost none, rare reports
Solid pseudopapillary tumor	Usually found incidentally; rarely causes abdominal discomfort	Solid and cystic components	Bloody + necrotic debris	Monomorphic cells with round nuclei and eosinophilic or foamy cytoplasm; stains positive for vimentin, α-1-antitrypsin, CD10, CD56 and beta-catenin	Yes
Cystic islet cell tumor	May have clinical features of solid pancreatic endocrine neoplasm	Unilocular cyst occupies most of neoplasm	Thin, clear	Monomorphic endocrine tumor cells; stains positive for chromogranin and synaptophysin	Yes
Adenocarcinoma with cystic degeneration	Presents with painless jaundice, abdominal/back pain or rarely pancreatitis	Primarily solid mass with cystic spaces	Bloody $\pm$ debris; CEA level markedly increased	Malignant adenocarcinoma may be seen, but varying degrees of atypia may be present in the specimen	Already present
Pseudocyst	History of moderate to severe pancreatitis	Anechoic, thick-walled, rare septations, regional inflammatory nodes may be seen	Thin, muddy-brown; CEA level low; amylase increased (>5000)	Neutrophils, macrophages histiocytes; negative staining for mucin	None

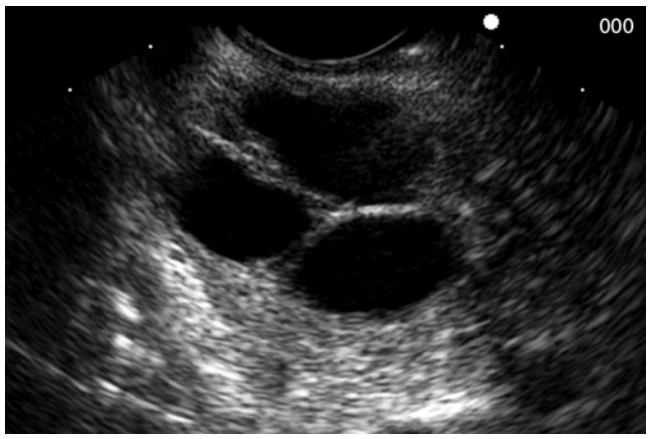

Figure 16.2 A 3 cm septated mucinous cystadenoma in the body of the pancreas.

with the FNA needle may increase the cytology yield. From a histologic perspective, the presence of ovarian-type stroma is required to render a diagnosis of MCN [23,24].

Although premalignant, the natural history of MCN is largely unknown. In a recent large surgical series, 17% of resected MCN were malignant, 12% of which were invasive [25]. All malignant MCN were either $\geq$4 cm or harbored mural nodules. Five year disease specific survival was 100% for non-invasive MCN and 57% for those with invasive cancer. Therefore, consensus guidelines recommend that MCN be resected in acceptable surgical candidates [24].

IPMN is a neoplastic disorder of varying degree and extent that affects the pancreatic ductal epithelium. It is defined as an "intraductal mucin-producing neoplasm with tall columnar mucin containing epithelium with or without papillary projections, involving the main pancreatic duct and/or major side

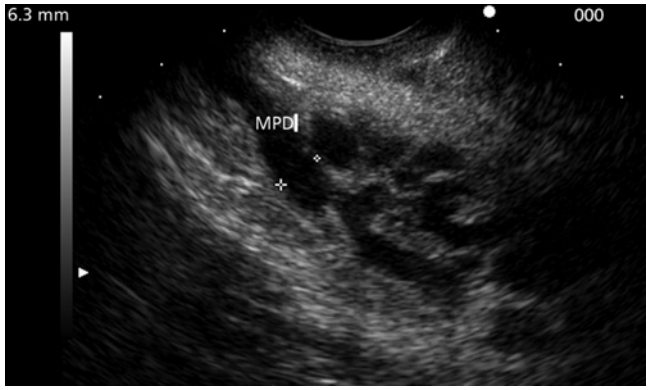

Figure 16.3 Mixed-type intraductal papillary mucinous neoplasia. The main pancreatic duct (MPD) is dilated (6.3 mm), and tubular anechoic branch ducts are seen arising from the MPD.

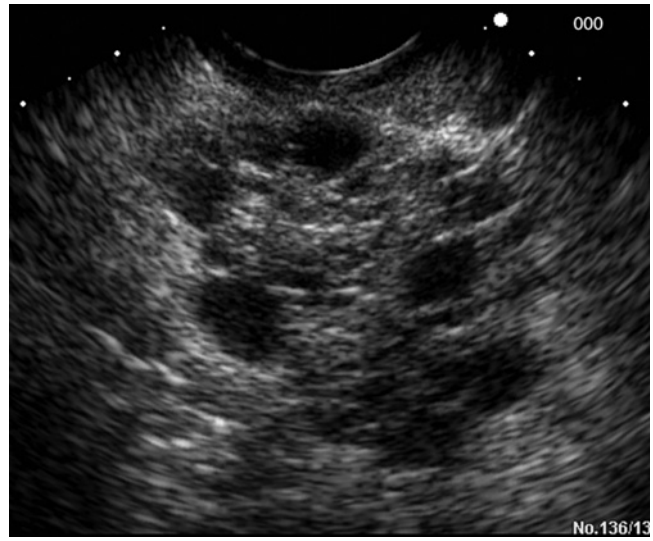

Figure 16.4 A 3 cm serous cystadenoma in the body of the pancreas portraying the typical honeycomb appearance.

branches, and lacking ovarian stroma characteristic of mucinous cystic neoplasms" [26]. IPMNs are characterized by cystic dilatation of the main pancreatic duct or its branches due to intraductal proliferation of the neoplastic mucin-producing epithelium, thus disease types include main duct, branch duct and mixed types (Figure 16.3). The cystic dilatations of branch ducts mimic true pancreatic cysts, however communication of the cyst with the pancreatic ductal system helps to distinguish IPMNs from mucinous cystic neoplasms (MCNs), which do not typically communicate with the ductal system.

IPMN has an equal sex distribution with a peak incidence in the sixth to seventh decade of life [27–29]. While most IPMNs arise within the head of the gland, they can be seen in any location and can occasionally involve the entire ductal system [30]. When evaluating cystic pancreatic lesions or duct dilation with EUS, IPMN should be considered in the absence of parenchymal changes typical of chronic pancreatitis [31]. The finding of multiple pancreatic cysts, representing multifocal branch duct disease, supports the diagnosis of IPMN. EUS-guided aspirates can be obtained from cystic branch ducts or the main duct itself, where a mucoid aspirate is essentially diagnostic. Cytologic analysis of pancreatic juice and mucin can reveal neoplastic epithelium, but in our experience, suffers from poor sensitivity. Regardless, main or branch duct aspirates should be sent for cytology, CEA level and amylase content. Harbingers of malignancy include a main duct diameter ≥10 mm, branch duct ≥30 mm in size or the presence of mural nodules; appropriate candidates with these findings should be referred for surgical resection [24,32]. Analysis of pooled data has revealed malignancy (invasive or carcinoma in situ) in ~ 70% of resected main-duct IPMN [24]. Therefore, in patients with good life expectancy, main duct and mixed-type IPMN should be resected. On the other hand, small incidental branch duct lesions appear indolent with a low risk of malignant progression in the short term. As the natural history of branch duct IPMN is unknown, in those without consensus-guideline indications for resection (CIR – symptoms, size ≥3cm, mural nodules, or cytology suspicious for malignancy), conservative monitoring is an acceptable option [24,33]. Subsequent development of CIR or increase in cyst size ≥ 5 mm should prompt surgical consultation in appropriate candidates [24,34]

Serous cystadenomas (SCAs), on the other hand, are cystic neoplasms without significant malignant potential. These cystic tumors are most commonly seen in women (65–80%). The peak incidence is reported to be the seventh decade, however these are being increasingly discovered as incidental lesions in younger patients [35–37]. SCAs generally contain multiple small cystic spaces with fibrous septations, creating a honeycomb or sponge-like appearance (Figure 16.4)[38]. A central scar or calcification, more common in large lesions, is seen in ~ 10% of patients and is considered pathognomonic [17,39]. Macrocystic or oligocystic variants exist, comprised of larger (> 2 cm) cystic spaces [40,41]. Additionally, a microcystic variant can be seen, which frequently mimics a solid mass on cross-sectional imaging. Cystic qualities, such as posterior enhancement, are clues at EUS examination.

Cytologic diagnosis by EUS-FNA is challenging in these lesions. Unless a larger (≥ 1 cm) cyst component can be targeted, it is rare to obtain enough fluid for appropriate tumor marker analysis. The aspirate is clear and thin, with a low CEA level (< 5 ng/mL) [6,22]. Cytologic analysis, in our experience, is rarely helpful given scant cellularity; however, the presence of cuboidal glycogen-staining epithelial cells can establish the diagnosis [42,43]. In the absence of a macrocystic variant, EUS-FNA generally yields a serosanguinous aspirate given the vascularity of SCAs. In asymptomatic lesions with a classic honeycomb or sponge-like appearance, we now refrain from FNA given the low yield. We perform FNA in macrocystic variants to exclude an MCN, and in mass-like microcystic variants to exclude other neoplastic tumors. SCAs do not require surgical resection unless symptomatic.

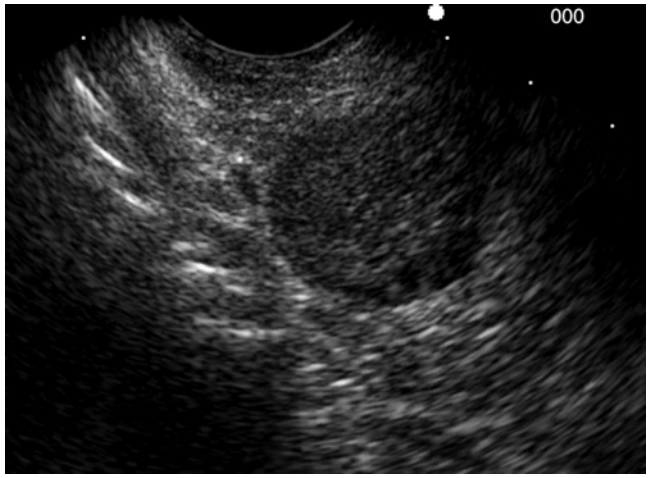

Figure 16.5 A 2 cm solid pseudopapillary tumor in the pancreatic head. It is a well-demarcated mass with microcystic spaces.

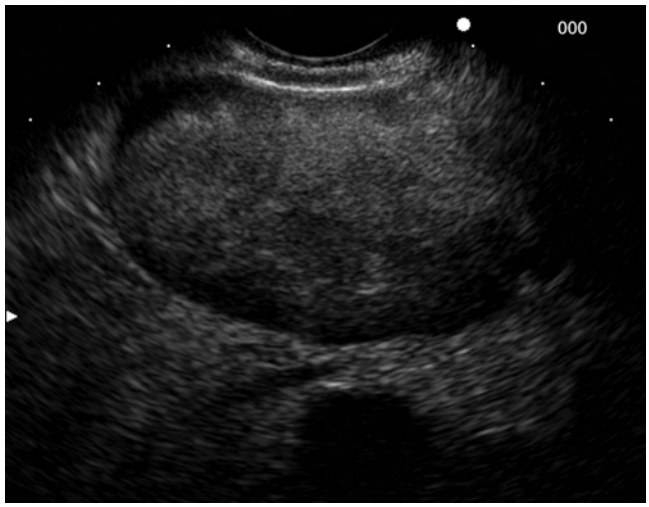

Figure 16.6 A 6 cm heterogeneous but well-demarcated lymphoepithelial cyst arising from the pancreatic neck. The pancreatic duct can be seen below the lesion.

Other cystic lesions that can mimic a solid tumor include solid pseudopapillary tumor (SPT) and lymphoepithelial cyst (LEC). SPTs are rare epithelial neoplasms of the pancreas that occur predominantly in young women and are usually discovered incidentally [44,45]. Frequently obtaining large size before diagnosis, surgical resection is recommended as these indolent tumors do have malignant potential. They can appear solid, mixed solid and cystic, or purely cystic (Figure 16.5). Internal hemorrhagic necrosis is common, resulting in cystic spaces. Internal and peripheral wall calcifications can also be seen. EUS-FNA aspirate is generally bloody, however typical cytologic findings of monomorphic cells with round nuclei in a three-layered papillary architecture (central capillary, a middle layer of myxoid stroma and an outer layer of neoplastic cells) suggest the correct diagnosis [46,47]. Immunostains (vimentin, α-1-antitrypsin, beta-catenin, CD10, CD56) are also helpful in establishing the diagnosis [47,48].

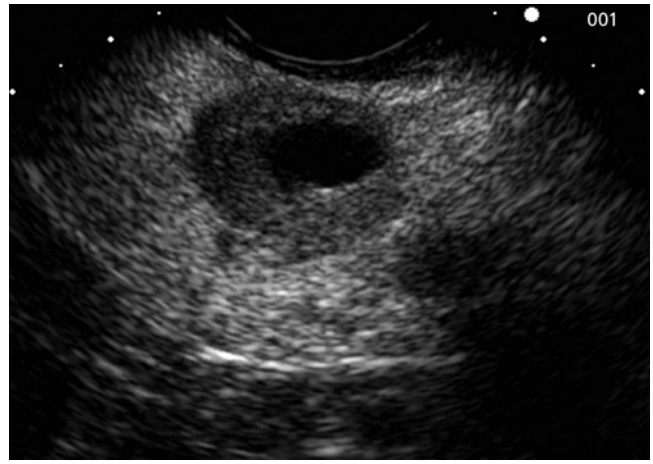

Figure 16.7 A 2 cm well-demarcated, round cystic islet cell tumor in the pancreatic body. This lesion has a "bulls-eye" appearance.

Lymphoepithelial cysts of the pancreas are extremely rare, benign, non-neoplastic cysts that can mimic solid tumors or cystic neoplasms both clinically and radiographically [49,50]. By EUS, they can appear predominantly solid, multilocular or microcystic (Figure 16.6). Middle-aged men are predominantly affected [51]. EUS-FNA, in our experience, reveals a thick milky, gray or frothy aspirate; this gross appearance should raise suspicion for LEC. Cytologic smears reveal anucleated squamous cells, amorphous debris, and lymphoid tissue [51]. Histologically, these lesions are lined by mature stratified squamous epithelium surrounded by dense lymphoid tissue with prominent follicles [49]. Given the benign nature, they should only be resected if symptomatic.

Cystic islet cell tumors are also very rare, comprising $< 10\%$ of pancreatic endocrine tumors in our experience. They can appear as unilocular simple cysts, or as a thick-walled "bulls-eye" lesion (Figure 16.7). The latter appearance should trigger the endosonographer to include islet cell tumor in the differential diagnosis. Previously thought to be a difficult preoperative diagnosis [52], EUS-FNA provides diagnostic samples.

Solid ductal adenocarcinomas can also undergo cystic degeneration and mimic true cystic lesions. There is generally a significant mass component surrounding the area of cystic degeneration, which may appear irregular (Figure 16.8). EUS-FNA should be directed at the solid component for diagnostic purposes.

A pseudocyst is the result of acute or chronic pancreatitis, or pancreatic trauma. A consequence of pancreatic duct disruption, it is a walled-off fluid collection comprised of pancreatic juice which can also contain variable amounts of necrotic debris (if occurring as a result of acute pancreatitis). It is not a true cyst as it lacks an epithelial lining; its "wall" of fibrous and granulation

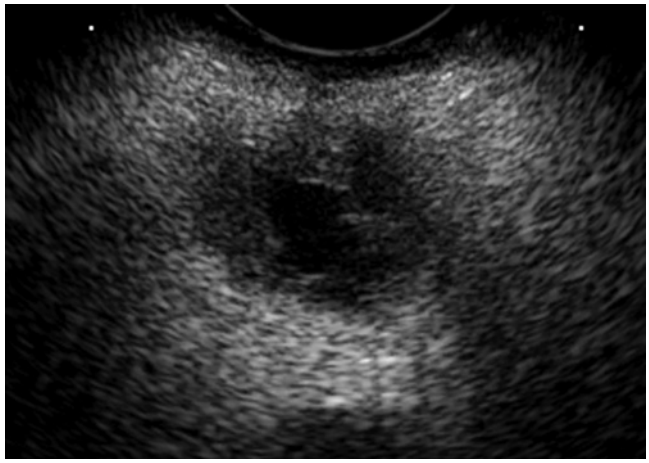

Figure 16.8 Adenocarcinoma with cystic degeneration. Note the poorly defined margins with an irregular cystic space.

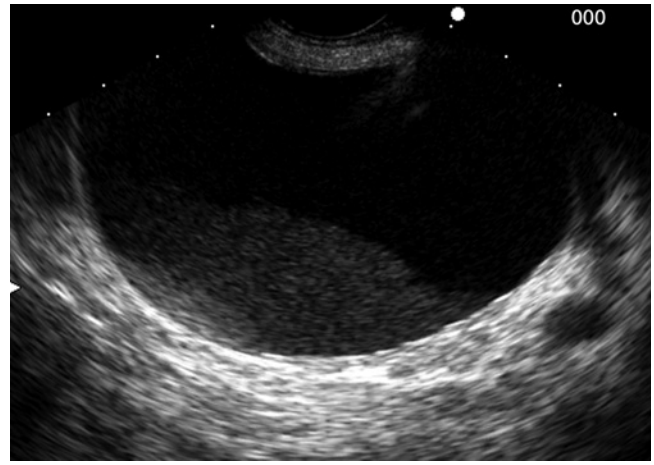

Figure 16.9 An 8 cm pseudocyst in the pancreatic tail with dependent, layering fine debris.

tissue generally takes approximately 6 weeks to mature. At EUS, pseudocysts usually lack septations and mural nodules, although internal debris is frequently seen (Figure16.9). We aspirate presumed pseudocysts under EUS guidance for diagnostic purpose as they can mimic MCN [53,54]. However, care must be taken to avoid contaminating an immature pseudocyst or phlegmon. Only those without debris or with a minimal amount of dependent layering debris should be aspirated.

When aspiration is undertaken, attempts should be made to evacuate the entire pseudocyst, as if it is not communicating with the pancreatic duct, the procedure may also be therapeutic. A 19-g needle is helpful when aspirating a large pseudocyst. The fluid is generally thin and brown; a purulent aspirate is diagnostic of an infected pseudocyst. The amylase content is elevated (>5000) [22]; however, mature non-communicating pseudocysts may lose amylase activity with time. Cyst fluid cytology frequently reveals a variable inflammatory component comprised of acute and chronic inflammatory cells, histiocytes, macrophages and granular debris [55]. CEA levels should be routinely sent to exclude MCN, as the EUS and gross fluid appearance of a hemorrhagic unilocular MCN can masquerade as a pseudocyst.

EUS-FNA technique

My approach to pancreatic cysts has evolved to evaluation solely with the curvilinear array (CLA) echoendoscope. It is my subjective opinion, concurrent with others, that the CLA echoendoscope provides better pancreatic imaging as compared to the mechanical rotating radial echoendoscope. This point may be increasingly debated in the future given the introduction of electronic radial echoendoscopes. Regardless, the CLA scope provides FNA capability and, in differentiating mucinous from nonmucinous lesions, tissue (or in this case cyst fluid) is the issue and aspiration is recommended [22]. Additionally, the use of only one echoendoscope to evaluate pancreatic cysts allows for a more efficient EUS practice through reduction in equipment set-up and procedural time.

A full, standard pancreatic examination should be performed with the CLA echoendoscope to evaluate for parenchymal changes, duct characteristics and number of cysts as these may provide clues to the cyst type. If a cystic lesion is identified, the patient is administered an intravenous antibiotic, generally a quinolone, in preparation for EUS-FNA. This is to reduce the incidence of infection as a nonsterile needle will be advanced into a sterile cystic lesion. Prior to FNA, the size of the cyst is measured and recorded, images are captured, and the location with reference to major vascular structures is noted. In particular, relationship to the portal vein is important, as those lesions to the left of the portal vein may be amenable to laparoscopic surgical resection if necessary. The cyst morphology is also noted, notably whether thick walls, septations, calcifications or mural nodules are present. The cyst is then positioned so as to minimize the amount of normal pancreatic tissue that will be traversed with the needle before entering the cyst. This is in hopes of minimizing FNA-related complications, notably pancreatitis. Pancreatic head and neck lesions are best imaged from the duodenal bulb; some lesions located in the uncinate process may require FNA approach from the second portion of the duodenum, which can prove more challenging. Body and tail lesions are imaged from the gastric lumen.

Once the lesion is positioned appropriately, Doppler analysis is employed to ensure the anticipated needle path is free of vascular structures. If not, the lesion may need to be repositioned to find an appropriate window for FNA. If present, a solid component or mural nodule should be first targeted, as these findings are harbingers of malignancy. In the absence of the above, the cyst is punctured with attempt to completely aspirate the contents. In doing so, the needle should be gently moved to and fro to contact any septations and/or the opposite wall of the cyst to increase the chance of a cellular yield (Figure 16.10). It is optimal

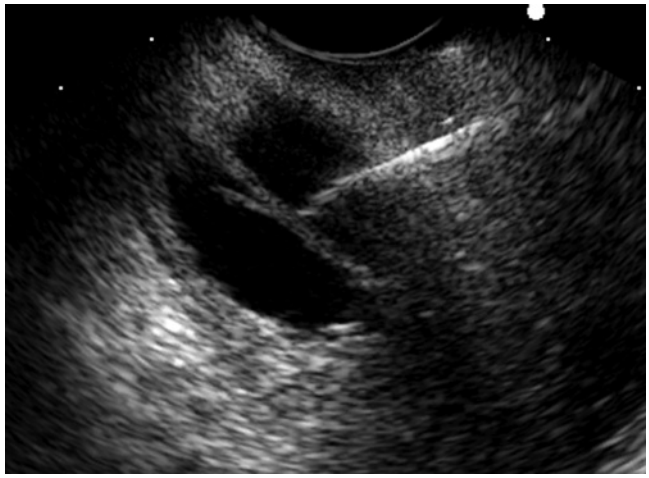

Figure 16.10 EUS-FNA of a septated mucinous cystadenoma. While aspirating fluid, the needle is moved to and fro to contact the septation to increase the cellular yield.

to make only one needle pass to theoretically decrease the complication rate. However, some cysts contain extremely viscous fluid which cannot be aspirated through the EUS needle, and therefore may require additional needle passes to obtain a suitable sample. The cyst fluid is sent for cytology, CEA and amylase levels. We place one drop of fluid on a glass slide to make a smear for cytology; note is also made of the gross viscosity of the fluid. We also flush the needle contents into alcohol or another appropriate medium for cell block analysis. If only a small amount of fluid is obtained, CEA level measurement is given priority as it has the proven accuracy for diagnosing mucinous cysts. A quantity of 0.5 to 1 mL of fluid is generally necessary to measure CEA. Amylase levels are also requested if there is sufficient fluid.

Cyst size that warrants EUS-FNA is debatable. Longitudinal radiologic studies suggest small cysts are indolent [56,57], however 20% of cysts <2 cm were malignant in the surgical series of Fernandez-del Castillo et al. [2]. The overwhelming majority of these small malignant cysts were symptomatic lesions. I avoid aspirating cysts smaller than 5 mm in size. I generally will aspirate cysts 5 to 10 mm in size for diagnostic purposes; if results are favorable, CT surveillance is employed with additional EUS-FNA reserved only for those that enlarge. For cysts larger than 10 mm, EUS-FNA is routinely employed, where aspirate results and surgical candidacy dictate management. Cysts >2 cm in size receive stronger consideration for surgical resection, however there is no definitive size criteria; the ultimate guiding factor for management is the operative candidacy of the patient. Cysts not undergoing resection are surveyed, be it by CT, MRI/MRCP or EUS. After initial EUS evaluation, I favor MRCP surveillance for small indolent branch duct IPMNs as it avoids cumulative radiation exposure.

Regarding EUS-FNA needles, all sizes have been used for cyst aspiration (19-g, 22-g, 25-g). I generally use a 22-g needle, however have subjectively achieved comparable results with a 25-g needle. It is unclear whether a smaller needle gauge translates to a lower complication rate.

It is recommended that patients receive an additional 3 days of antibiotics (oral quinolone) to prevent infection after cyst aspiration [52]. Fortunately, the risk of infection in the setting of antibiotic prophylaxis is rare ($<1\%$) [8,55]. A complication of pancreatitis is more common, with a rate of 1 to 2% [58]. It may be advisable to recommend a clear liquid diet for 24 hours following EUS-FNA to theoretically lower the risk of pancreatitis via pancreatic rest, however this practice is unproven. Personally, I allow a low-fat diet following the procedure, with advancement as tolerated.

Evolving approaches

Evolving methods to increase diagnostic yield for pancreatic cysts are being actively evaluated, and are directly coupled to EUS. EUS-guided Trucut biopsy (EUS-TCB) has been performed in the attempt to obtain a histologic core sample of the cyst wall. In a small study, EUS-TCB was performed in 10 patients without complication, providing a firm diagnosis in 7 patients; standard EUS-FNA cytology was nondiagnostic [59]. Additional studies evaluating TCB for cyst diagnosis are expected, with hopes for more user-friendly Trucut needle designs.

Attention has also turned to molecular analysis of cyst fluid aspirates obtained via EUS-FNA. It has been hypothesized that epithelial cells lining the cyst cavity shed their DNA into the fluid during cell turnover. As pancreatic carcinogenesis is characterized by the accumulation of genetic defects, mutations should be detectable through cyst fluid DNA analysis. As such, a malignant cyst should have a higher DNA content due to a higher cell turnover rate, with more mutations being present. If true, molecular analysis could serve as an adjunct test to predict the actual presence of malignancy. To test this hypothesis, molecular analysis of EUS-guided cyst fluid aspirates was performed via polymerase chain reaction (PCR) amplification of individual microsatellite markers associated with pancreatic carcinogenesis, along with direct sequencing of the *K-ras-2* gene [7]. The DNA amount within the fluid (optical density), quality of DNA, number of mutations and temporal sequence of mutations was shown to accurately predict the presence of malignancy. A first-hit *K-ras* mutation followed by an allelic loss was highly predictive of malignancy [7]. A multicenter trial, recently completed, confirmed these preliminary results [60]. Importantly, this molecular analysis can be performed on just a few drops of cyst fluid. Frequently, a sufficient quantity of fluid cannot be obtained for CEA measurement from a mucinous lesion, given the viscosity. Indeed, in the initial study evaluating molecular analysis, 25% of samples were of insufficient quantity for CEA measurement [7]. In the future, additional molecular applications are anticipated to increase diagnostic accuracy and determination of malignancy in mucinous cystic lesions.

Summary

Pancreatic cysts require further evaluation, as neoplastic mucinous cysts are most common [2]. Current recommendations (Table 16.3)

Table 16.3 EUS evaluation of cystic lesions of the pancreas. From Ref. 22 with permission from the American Society for Gastrointestinal Endoscopy

Recommendations for EUS evaluation
Morphologic analysis by EUS (microcystic, macrocystic, associated mass)
FNA and complete evacuation if possible
Cyst fluid analysis (cytology, CEA, amylase)
Interpretation of results in conjunction with history and results of CT scanning

call for cyst morphologic assessment by EUS coupled with FNA to send cyst fluid for cytology, CEA and amylase levels [22]. The cyst should be completely evacuated if possible to theoretically increase yield and decrease the risk of infection. An elevated CEA level offers the best diagnostic accuracy for mucinous cysts [6]. Molecular analysis may serve as an ancillary tool for detection of malignancy [7]. Interpretation of results must take into account the clinical presentation and results of cross-sectional imaging (CT), with ultimate management decisions dependent upon the surgical candidacy of the patient. Mucinous cystic lesions should be resected in appropriate candidates; however, as natural history is mostly unknown, surveillance is acceptable for questionable surgical candidates and/or small cystic lesions.

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17 Endoscopic Ultrasound for Pancreatitis

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Introduction

Endoscopic ultrasound (EUS) has proven to be an important technological advancement that provides detailed images of the pancreas. Placement of the transducer within the gastrointestinal lumen eliminates interference from both bowel gas and intervening fat that limit the visualization of abdominal ultrasonography. As detailed in Chapters 6 and 7, sonographic imaging of the normal pancreas is homogenous and characteristically described as "salt and pepper" in appearance. Due to a higher fat content, the pancreas appears more echogenic relative to the liver. EUS examination of the pancreas begins with placement of the endoscope in the third part of the duodenum (station 1) to visualize the uncinate process of the pancreas. Next, the transducer is pulled back to the second part of the duodenum and placed against the major papilla (station 2). In this position, the head of the pancreas is seen in cross-section, along with the distal bile duct and pancreatic duct converging together into the ampulla. The ventral anlage, which represents the embryological ventral bud, may be seen in this location as a triangular hypoechoic area in 45 to 75% of normal subjects [1]. In patients with pancreas divisum, the main (dorsal) pancreatic duct enters into the minor papilla and "the crossed duct sign" (crossing of the pancreatic duct and bile duct) may be seen. Upon further withdrawal of the transducer into the duodenal bulb (station 3), the remainder of the head of the pancreas, proximal common bile duct and gallbladder can be examined. The neck, body and tail of the pancreas are visualized by placement of the endoscope in the body and fundus of the stomach. The main pancreatic duct is visualized coursing through the pancreas as a linear anechoic, tubular structure. Normal accepted dimensions of the pancreatic duct are 3 mm in the head, 2 mm in the body and 1 mm in the tail. Side branches off the main pancreatic duct are generally not seen; however, one study reported the presence of side branches in 17 of 25 normal subjects [2].

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Due to the detailed imaging of the pancreas permitted by EUS, there has been great interest in its ability to diagnose inflammatory diseases of the pancreas. The aim of this chapter is to outline the use of EUS in the diagnosis and management of acute, chronic and autoimmune pancreatitis.

Acute pancreatitis

Acute pancreatitis is an acute inflammatory process of the pancreas which is caused by alcohol or obstructing common bile duct (CBD) stones in 80 to 85% of cases. The EUS appearance of the pancreas during acute pancreatitis is nonspecific. The anterior-to-posterior dimensions of the gland may be relatively normal but can also be diffusely swollen from edema. Some regions of the parenchyma can appear hypoechoic relative to other areas. Small cysts as well as dilated ductal side branches may also be noted. Except for intraductal stones and possibly parenchymal calcifications, all the sonographic features of chronic pancreatitis may be seen during imaging of acute pancreatitis [3]. Focal edema from pancreatitis may be indistinguishable from a true pancreatic mass, thus making the diagnosis of a tumor in this setting difficult. Currently, multidetector CT with intravenous contrast is the test of choice to stage the severity of acute pancreatitis and to assess for any gland necrosis. The use of diagnostic or contrast-enhanced EUS imaging has not been well studied in these patients and its use for this purpose is not recommended without further clinical investigation. In patients without chronic pancreatitis, it is presumed that the normal, preexisting sonographic appearance of the pancreas returns slowly after an index episode of acute pancreatitis. However, the exact time interval for this resolution is not known. Nevertheless, it appears reasonable to wait for 1 month after acute pancreatitis to perform EUS imaging of the pancreas if clinically indicated.

If acute biliary pancreatitis with persistent choledocholithiasis and obstruction is suspected, early ERCP and sphincterotomy is recommended in those with moderate to severe pancreatitis or evidence of cholangitis [4,5]. In some patients with a low

to moderate risk for retained bile duct stones, screening for choledocholithiasis with CT or transabdominal ultrasound (TUS) may be occasionally be used. However, TUS is insensitive for the detection of choledocholithiasis due to the ileus and subsequent overlying bowel gas that frequently accompanies acute pancreatitis [6–9]. Similarly, CT does not reliably identify small retained distal bile duct stones [10]. The reported sensitivity of helical CT for choledocholithiasis is 85 to 88%, specificity is 88 to 97%, and accuracy 86 to 94% [7,10]. Therefore, in patients with a low to moderate risk of choledocholithiasis and suspected biliary pancreatitis, alternative imaging including MRCP or EUS may be helpful prior to proceeding with ERCP and/or sphincterotomy. These methods have been independently compared to ERCP with encouraging results [11]. MRCP is a noninvasive sensitive and specific test [12], however it requires a high level of patient cooperation and is not tolerated in up to 5% of patients because of claustrophobia [13]. EUS permits detection of stones as small as 1 to 2 mm and EUS has been shown to identify smaller stones and sludge within the CBD which may be missed on MRCP [14]. The sensitivity of EUS for the identification of retained CBD stones has ranged from 88 to 97% with a specificity of 96 to 100% [15–24]. Despite the advantages of EUS for detection of small stones, the overall sensitivity and specificity of EUS for identification of choledocholithiasis is similar to MRCP and both are acceptable options for these patients with acute biliary pancreatitis. EUS remains an invasive procedure that requires conscious sedation and is only of diagnostic value [25].

Idiopathic pancreatitis

Acute pancreatitis without an identifiable cause is generally classified as idiopathic pancreatitis. Possible etiologies for idiopathic pancreatitis include: pancreas divisum, sphincter of Oddi dysfunction [26,27], microlithiasis [28,29], medications or viral infections.

For the detection of biliary microlithiasis, two trials have reported that diagnostic EUS is superior to duodenal aspiration for biliary microscopic examination [30,31]. These findings are in contrast to another study which found that duodenal bile aspirate could detect microlithiasis in 46% of patients after a negative EUS [32]. Hence, the best diagnostic method for biliary sludge and microlithiasis has yet to be determined and additional comparative trials are needed.

There have been several published studies that address the value of EUS for identifying the etiology of idiopathic pancreatitis (Table 17.1) [32–36]. As Table 17.1 illustrates, pertinent findings include identification of chronic pancreatitis, gallstones, gallbladder sludge, pancreatic tumors/cysts and pancreas divisum. These studies together [32–36], however, included heterogeneous populations with either a single, acute episode of idiopathic pancreatitis or recurrent idiopathic pancreatitis. Additionally, the exact time interval between the acute attack and EUS varied. Nevertheless, the above studies suggest that EUS is a useful study for the evaluation of patients with idiopathic pancreatitis, particularly when previous tests have failed to identify a cause. At Indiana University, EUS is performed after a single episode of idiopathic pancreatitis in all patients over 40 years of age, but we prefer to wait at least 1 month if possible after the acute episode to perform this test. For those under the age of 40 years, the use of EUS in these patients after one idiopathic acute attack is not routinely performed but may be used on a case-by-case basis.

It is uncertain whether EUS is indicated in patients under the age of 40 years of age after a single episode of idiopathic pancreatitis. For example, Ballinger et al. [37] found that only 1 of 32 patients with idiopathic pancreatitis had a recurrent attack after a median follow-up of 36 months. Other studies have revealed 20% to 50% of patients with acute pancreatitis will have a recurrence [38–40]. A recent systematic review [41] suggests that an invasive clinical evaluation is warranted following a second episode of idiopathic pancreatitis because a diagnosis can be established in 38 to 76% of these cases. Depending on the elapsed time since the index attack, these authors recommended that TUS should be repeated because serial examinations may be required to identify small gallbladder stones or sludge. Observations on the sensitivity of EUS for sludge suggest it may be ideal after a negative TUS to both identify gallbladder stones or sludge and to screen for choledocholithiasis.

Chronic pancreatitis

Chronic pancreatitis is a progressive inflammatory condition that may lead to permanent structural organ damage. Histopathologic assessment of the pancreas is the gold standard for the diagnosis of chronic pancreatitis. However, acquisition of pancreatic tissue for this purpose is usually impractical. Furthermore, chronic pancreatitis is a patchy disease and therefore a single biopsy sample may yield a false negative result [42]. In a patient with chronic pancreatitis, imaging studies such as plain abdominal films, TUS, CT and MRCP may show pancreatic calcifications, duct dilation or tortuosity, fluid collections and/or cystic lesions within the pancreas. However these four tests are generally considered useful only for identification of moderate to severe forms of the disease [43,44].

Secretin-stimulated collection of pancreatic juice from the duodenum or pancreatic duct is considered a sensitive measure of exocrine function. However, one study [45] reported the sensitivity of this test for the diagnosis of early pancreatitis was less than 40%. Recently there has been renewed interest in using duodenal bicarbonate to diagnose exocrine pancreatic insufficiency. Conwell et al. [46] evaluated symptoms of chronic abdominal pain in patients with and without risk factors for chronic pancreatitis and those with advanced chronic pancreatitis. All patients were administered secretin followed by endoscopic duodenal fluid collection at 0, 15, 30, 45 and 60 minutes and the aspirated

Table 17.1 Summary of studies evaluating the role of EUS in patients with idiopathic pancreatitis

Reference (year)	No. enrolled	Design	EUS criteria for chronic pancreatitis	Results	Comments
Yusoff et al. (2004) [32]	370	Consecutive patients with a single or recurrent episodes of idiopathic pancreatitis underwent EUS	>5 criteria	EUS identified potential cause of pancreatitis in 29.2%	Up to 120 g of alcohol used >14 days prior was included in the study
Frossard et al. (2000) [33]	168	Consecutive patients with acute pancreatitis and a nonrevealing ultrasound examination underwent EUS to evaluate the usefulness of EUS in the diagnosis of bile duct pathology or chronic pancreatitis	⩾3 criteria for chronic pancreatitis and 1–2 criteria for "early" chronic pancreatitis	EUS performed a mean of 18 days (range 10–180 after acute episode) EUS identified etiology in 80% of cases Biliary tract disease (61%) Chronic pancreatitis (7%) Pancreatic cancers (2%)	Done soon after the acute episode. Only single modality used to image and identify etiology of pancreatitis
Norton et al. (2000) [34]	44	Consecutive patients with idiopathic pancreatitis 18% had previous cholecystectomy 23% were recurrent Aim: To identify if EUS is able to detect unidentified gallstones in cases of idiopathic pancreatitis	Not stated	EUS 50% gallbladder stones 9% choledocholithiasis 2% pancreas divisum 2% pancreatic masses 9% chronic pancreatitis	Not mentioned time between episode and EUS not mentioned. Single modality used to image the pancreas
Liu et al. (2000) [35]	89	Consecutive patients with idiopathic pancreatitis EUS performed in those with idiopathic disease	Not stated	EUS confirmed gallstones in 14/18 patients with idiopathic acute pancreatitis	Time interval as short between acute episode and EUS
Coyle et al. (2002) [36]	90	Patients with unexplained acute (27%) and acute recurrent (63%) pancreatitis who underwent ERCP (99%) with bile analysis including CCK stimulation, EUS (62%) and sphincter of Oddi manometry (70%)	⩾3 criteria	Chronic pancreatitis 20% abnormal EUS and ERCP 10% abnormal EUS, normal ERCP 12% chronic changes on ERP alone EUS identified biliary tract disease only 17%	No details on type of pre-procedural imaging used

fluid was analyzed for bicarbonate concentration. These authors found that bicarbonate secretion was markedly reduced in patients with chronic pancreatitis and they concluded that this test may be valuable in patients with abdominal pain and normal radiographic imaging studies. The same group compared the endoscopic pancreatic function test (ePFT) to the traditional bicarbonate collection using the Dreiling tube and found a 100% agreement when a cutoff value of 80 mEq/L of bicarbonate was used [47]. Dual-timed duodenal fluid aspiration at 30 and 45 minutes appears to be useful to screen for pancreatic exocrine insufficiency in patients with abdominal pain. These ePFTs however are labor intensive and not widely utilized outside selected tertiary referral centers [48].

In the absence of histopathology or evidence of calcific pancreatitis by imaging studies, endoscopic retrograde pancreatogram (ERP) is the accepted gold standard for the minimally invasive diagnosis of chronic pancreatitis. The severity of chronic pancreatitis by ERP is most widely staged by the Cambridge classification [49]. This classification assigns a pancreatogram as normal, mild, moderate or severe chronic pancreatitis based on the abnormalities of the main pancreatic duct or its side branches. Although the Cambridge classification has been validated and confirmed in numerous studies, the use of diagnostic ERP for the diagnosis of early chronic pancreatitis is neither routinely used nor recommended. This is principally due to the risks of ERCP (including post-ERCP pancreatitis) and the advent of other safer tests such as EUS and MRCP. Secretin-stimulated abdominal MRCP can noninvasively provide high-quality pancreatogram images with little to no risk of pancreatitis. Additionally, normal pancreatograms are seen in symptomatic patients and amongst those with pancreatic exocrine dysfunction [50–52].

EUS features of chronic pancreatitis and reproducibility

The diagnosis of chronic pancreatitis by EUS utilizes abnormalities detected in both the pancreatic parenchyma (hyperechoic foci, hyperechoic foci with shadowing, hyperechoic strands, hypoechoic lobules and cysts) and ductal (main duct dilation, main duct irregularity, side branch dilation, hyperechoic duct walls and calculi) systems (Figures 17.1 to 17.4). It is hypothesized that as the severity of chronic pancreatitis progresses, the number of abnormalities detected by EUS and other tests should correspondingly increase. However, there are no histological studies to corroborate these assumptions.

The sonographic criteria for the diagnosis of chronic pancreatitis were first described by Jones et al. [53] and further developed by Wiersema et al. [54]. An international consensus [55] later defined the minimum standard terminology (MST) for identification of inflammation of the pancreas by EUS (Table 17.2) and this has been tested by subsequent studies. These sonographic criteria have also been evaluated by experienced endosonographers with moderately good overall agreement for the final diagnosis of chronic pancreatitis ($\kappa = 0.45$) [56]. Agreement was good for individual features of duct dilatation ($\kappa = 0.6$) and lobularity ($\kappa = 0.51$) but poor for the other seven features ($\kappa < 0.4$). The single most predictive criterion for the diagnosis of chronic pancreatitis was presence of stones. The frequency of sonographic changes of chronic pancreatitis (particularly hyperechoic stranding) appear to increase in the elderly (usually above 60 years of age) [57]. Therefore a higher number of threshold criteria may be needed in males and in elderly patients.

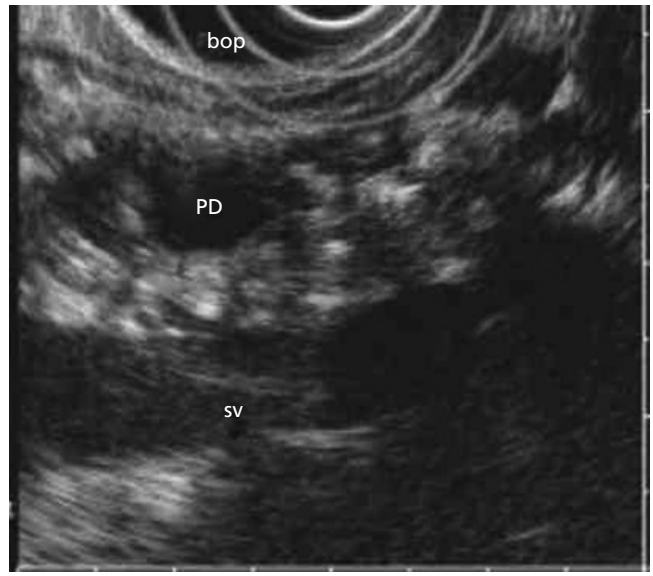

Figure 17.1 EUS image (7.5 MHz) of chronic calcific pancreatitis in the body of the pancreas using radial endosonography. Multiple hyperechoic foci are present with posterior acoustical shadowing. The pancreatic duct (PD) is dilated. The splenic vein (SV) is posterior to the pancreas.

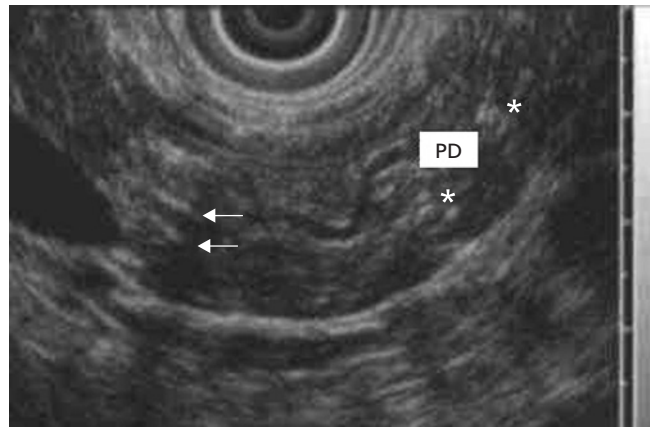

Figure 17.2 Radial EUS image of the body of the pancreas illustrating changes consistent with mild chronic pancreatitis. The nondilated pancreatic duct (PD) is tortuous with hyperechoic walls. There is no visible duct sidebranching. In the parenchyma, there is hyperechoic stranding (*white arrows*) and hyperechoic foci (*to left of each asterisk*).

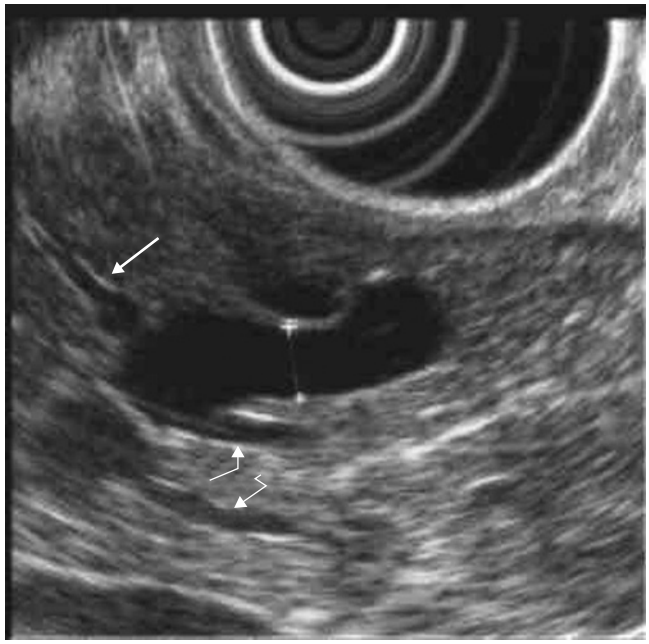

Figure 17.3 Radial EUS image (7.5 MHz) of the head of the pancreas demonstrating a dilated main pancreatic duct (*outlined by line between Xs*) measuring 4.7 mm. Sidebranches with hyperechoic walls are also visible (*curved white arrows*).

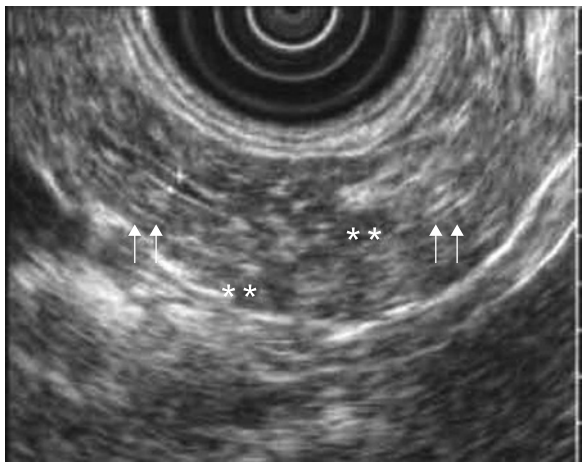

Figure 17.4 Radial EUS image (7.5 MHz) of the body of the pancreas showing mild chronic pancreatitis. The pancreatic duct is normal in dimension but both walls are hyperechoic. In the parenchyma, hyperechoic foci (*above two asterisks*) and stranding (*above white arrows*) form lobules. Pancreatogram during ERCP in this patient was normal. These findings illustrate the discrepancy between these tests that may occur in patients with suspected early chronic pancreatitis by EUS.

Comparison of EUS findings of chronic pancreatitis to histology

The accuracy of EUS for the diagnosis of chronic pancreatitis has been extensively compared to histology, secretin-stimulated duodenal aspiration and pancreatography (Table 17.3). Histologic studies suggest that a group of patients with symptoms suggestive of chronic pancreatitis but with normal pancreatogram and other imaging studies may in fact have EUS features of chronic pancreatitis and mild chronic pancreatic inflammation (Figure 17.4) [58–60]. Walsh et al. [58] studied 486 patients and identified 43 with symptoms of pancreatic disease but normal or equivocal ERCP, CT, or US. A total of 16 patients failed to respond to medical therapy and underwent pancreatic resection. The histological appearance of the resected pancreas showed subtle but distinct evidence of chronic pancreatitis. These changes were "focally" distributed throughout the gland and included lymphocytic cell infiltrates, intralobular and periductal fibrosis, and focal ductal dilatation with inspissated protein plugs. Early studies by Lees [59] compared EUS morphology to histology after pancreatic resection. In 6 of 7 patients with EUS changes, a diagnosis of chronic pancreatitis was confirmed by histology. Another study [60] (published only in abstract form) reviewed 34 patients who underwent EUS followed by either pancreatic resection or open surgical biopsy. Of these, 68% were found to have chronic pancreatitis based on histology. The authors concluded that four or more EUS criteria were optimal for the diagnosis of chronic pancreatitis. Furukawa et al. [61] compared intraductal ultrasound (IDUS) to histology in freshly excised pancreatic tissue in 15 patients with chronic pancreatitis. IDUS detected chronic pancreatitis changes in 11 of the 15 cases.

Two recent studies have re-examined the correlation of EUS findings with histology specimens in these patients. In a small, prospective cohort of 21 patients who underwent pancreatic resection after EUS examination, Varadarajulu [62] found that four or more EUS criteria optimized the diagnosis of non-calcific chronic pancreatitis. Parenchymal EUS features in this study that were significantly associated with histopathologic chronic pancreatitis included foci, stranding, and lobulations. Significantly associated ductal features included a dilated or irregular main pancreatic duct, side branches and hyperechoic duct margins. A larger nine-year retrospective study [63] evaluated 71 patients with a median histologic fibrosis score of 7 who underwent EUS followed by surgery. This study, which included patients with calcific chronic pancreatitis, concluded that three or more EUS criteria optimized sensitivity and specificity for the diagnosis of chronic pancreatitis. In addition, these authors found that EUS may identify calcifications missed by other imaging studies.

Comparison of EUS findings of chronic pancreatitis to other modalities

EUS has also been compared to ERP and secretin-stimulated duodenal aspiration. Sahai et al. [64] conducted a double-blinded prospective trial to evaluate the accuracy of EUS in 126 patients to diagnose, rule out, and establish the severity of chronic pancreatitis when compared to the gold standard of ERP. The sensitivity of EUS for the diagnosis of chronic pancreatitis was >85% when <3 criteria were required and specificity was >85% when >5 criteria were used. In a similar study, Catalano et al. [65] reviewed 80 consecutive patients with recurrent pancreatitis who

Table 17.2 Endosonographic criteria and definitions of chronic pancreatitis (CP) and presumed histological correlates: minimum standard terminology (MST) for identification of inflammation of the pancreas by EUS. From Ref. 55 with permission

EUS criteria for CP	MST definition	Histological correlate
Hyperechoic foci	Small distinct reflectors	Focal fibrosis
Hyperechoic strand	Small string-like hyperechoic structures	Bridging fibrosis
Lobular out gland margin	No MST definition	Fibrosis, glandular atrophy
Lobularity	Containing lobules-rounded homogeneous areas separated by strands of another echogenicity	Interlobular fibrosis
Cyst	Abnormal anechoic round or oval structure	Cysts/pseudocysts
Stone	Hyperechoic lesion with acoustic shadowing within a duct or gallbladder	Calcified stones
Calcification	Hyperechoic lesion with acoustic shadow within a parenchymal organ or a mass	Parenchymal calcification
Ductal dilation	No MST definition	$>$3 mm in head, $>$2 mm in body, $>$1 mm in tail
Side branch dilation	No MST definition	Side branch dilation
Duct irregularity	Coarse, uneven outline of the duct	Focal dilation/narrowing
Hyperechoic duct margins	No MST definition	Periductal fibrosis
Atrophy	No MST definition	Atrophy
Inhomogeneous echo pattern	No MST definition	Edema

Table 17.3 Summary of studies evaluating the role of EUS in patients with chronic pancreatitis

Reference (year)	n	Gold standard	Results of EUS for the diagnosis of chronic pancreatitis
Lees et al. (1986) [59]	7	Histology	Sensitivity 86%
Zimmerman et al. (1997) [60]	34	Histology	The sensitivity and specificity using $\geq$ 3 criteria were 87% and 64%, for $\geq$ 4 criteria 78% and 73%, for $\geq$ 5 criteria 60% and 83%, and for $\geq$ 6 criteria 43% and 91%
Furukawa et al. (1994) [61]	15	Histology	Sensitivity 73%
Sahai et al. (1998) [62]	126	ERP with duodenal aspiration	Sensitivity $>$ 85% when $<$ 3 criteria were present
			Specificity $>$ 85% when $>$ 5 criteria were present
			PPV $>$ 85% when $>$ 6 criteria were present
			NPV $>$ 85% when $<$ 3 criteria were present.
Catalano et al. (1998) [63]	80	ERCP, and secretin test	Secretin test and ERP had 100% agreement with EUS for those with normal exams or severe chronic pancreatitis ($>$ 5 EUS criteria)
			In moderate chronic pancreatitis (3–5 EUS criteria) the agreement was 92% with ERP and 50% with secretin testing.
			In patients with mild ($<$ 3 criteria) disease, the agreement was poor with both secretin (13%) and with ERP (17%)
Nattermann et al. (1993) [64]	114	ERCP	Abnormal EUS features in all patients with Cambridge grade 2 and 3 chronic pancreatitis. Abnormal EUS was seen in 88% of those with grade 1, and in 63% of cases with a normal ERP
Wiersema et al. (1993) [54]	89	ERCP	Sensitivity 80%, specificity 86% and accuracy 84% when $\geq$ 3 criteria used
Buscail et al. (1995) [65]	81	ERCP	Sensitivity 88%, specificity 100%
Varadarajulu et al. (2007) [62]	21	Histology	Sensitivity 91%, specificity 86% when $\geq$ 4 criteria used
Chong et al. (2007) [63]	71	Histology	Sensitivity 83%, specificity 80% when $\geq$ 3 criteria used
Hollerbach et al. (2001) [81]	37	ERCP	EUS-FNA increased the specificity and negative predictive value for the diagnosis of chronic pancreatitis compared to EUS imaging alone
DeWitt et al. (2005) [82]	18	Histology and ERCP	EUS-Trucut biopsy may demonstrate chronic pancreatitis but its use is limited due to potential complications and poor correlation with EUS imaging alone and ERCP

underwent EUS, followed by ERCP and secretin-stimulation test at least 6 weeks after the last episode of pancreatitis. The authors concluded that a normal EUS excludes chronic pancreatitis and >5 EUS criteria for chronic pancreatitis confirms the diagnosis. Additionally, even among those with <3 criteria chronic pancreatitis may be present.

Nattermann et al. [66] correlated parenchymal and ductal changes on EUS to ERP in 114 patients including 94 with acute or chronic pancreatitis and a control population of 20 with a normal ERP. These authors found that EUS showed inflammatory changes in almost all patients in whom ERP suggested chronic pancreatitis. Yet EUS was also abnormal in a considerable number of cases with normal ERP but who have a clinical evidence of pancreatic inflammation.

Wiersema et al. [54] studied 20 asymptomatic volunteers evaluated by EUS and subsequently 69 patients with chronic abdominal pain of suspected pancreaticobiliary origin that underwent EUS followed by ERP and in 16 had secretin stimulated intraductal pure pancreatic juice (PPJ) collection. Thirty patients were found to have chronic pancreatitis and EUS was abnormal in 24 of these individuals. All patients that had an abnormal pancreatogram had an abnormal EUS. Twenty-two of 30 patients with chronic pancreatitis had early disease (no or minimal changes on ERCP). In this subgroup of patients, the sensitivity of EUS was 86% versus 50% for ERCP ($P = 0.01$). For all patients, the sensitivity, specificity and accuracy of EUS in diagnosing chronic pancreatitis was 80, 86 and 84%, respectively. Receiver operating characteristic (ROC) curves demonstrated that optimal sensitivity and specificity were obtained when three or more abnormal parenchymal and/or ductular features were found.

The usefulness and accuracy rate of endoscopic ultrasonography (EUS) in the diagnosis of chronic pancreatitis were prospectively evaluated in 81 patients with suspected pancreatic disease by Buscail et al. [67]. All underwent EUS, abdominal ultrasonography (US), and computed tomography (CT). Of these patients 55 also underwent ERP. For the diagnosis of chronic pancreatitis, EUS and CT scan were identical and superior to TUS. Sensitivity for diagnosis of chronic pancreatitis was 88% for EUS, 58% for US, 74% for ERCP and 75% for CT, respectively. The specificity was 100% for ERCP and EUS, 95% for CT scan, and 75% for TUS. Limitations in this study include the lack of use of standardized EUS criteria and no mention of the actual number of criteria that were required to confidently diagnose chronic pancreatitis by EUS.

How many EUS criteria should be used and other controversies in diagnosing chronic pancreatitis

Since EUS appears to be more sensitive than other imaging tests for the diagnosis of chronic pancreatitis, some investigators have attempted to ascertain how many sonographic criteria are required to confidently make the diagnosis of chronic pancreatitis. It must be remembered that increasing the number of criteria required for the diagnosis decreases the sensitivity while increasing specificity of EUS [64] and the number chosen will reflect this tradeoff.

From the studies reviewed above, this number has reportedly varied between one and six. Using ROC curves, Wiersema [54] suggested that 3 or more criteria yielded a sensitivity of 100% and a specificity of 79%. Sahai [64] reported that one or two EUS criteria effectively rules out moderate to severe pancreatitis (Cambridge class 3 and 4) and presence of five or more criteria suggests chronic pancreatitis. Recent studies correlating histology to EUS findings suggest that three or four criteria optimize sensitivity and specificity [62–63]. Currently, at Indiana University, we consider EUS imaging of shadowing calcifications or intraductal stones as diagnostic for chronic pancreatitis. In their absence, we attempt to maximize specificity for the diagnosis by requiring at least four or more features to be present. Patients with one, two or three criteria are deemed equivocal for chronic pancreatitis. We consider mild and moderate chronic pancreatitis to be 4-5 and 6-7 criteria, respectively. Those with more than seven criteria or evidence of shadowing calcifications or intraductal stones are considered to have severe disease (Figures 17.1, 17.5, 17.6).

In addition to the number of features required, there are other controversies in the use of EUS for the diagnosis of chronic pancreatitis. First, there are no guidelines on what portion of the pancreas should be examined. Examination of the head of the pancreas alone is not recommended since a normal ventral anlage may manifest features (particularly hypoechoic, lobular parenchyma and hyperechoic stranding) similar to those seen in chronic pancreatitis. For these reasons, we utilize EUS features seen principally during imaging the body and tail of the pancreas in these patients. Second, there is no agreement about whether the radial or linear echoendoscope should be used. Finally, there are no defined guidelines on what minimal imaging features define each criteria routinely used by EUS for the diagnosis of chronic pancreatitis. For example, how long should a hyperechoic strand measure or should lobularity of the parenchyma be examined within the middle or outer margins of the gland?

Two recently presented studies (in abstract form) attempted to answer some of these dilemmas. First, a recent consensus meeting of 45 internationally recognized EUS experts was held in Rosemont, Illinois (USA) to attempt to unify widely accepted EUS criteria utilized for the diagnosis of chronic pancreatitis. The end result of this meeting was the new proposed "Rosemont Classification" (Table 17.4) [68]. The principal change this classification employs is that equal weight was not assigned to all EUS parenchymal and ductal features of chronic pancreatitis that were proposed in previously published classification schemes. Rather, major and minor criteria were proposed. The three major criteria included two Major A criteria [hyperechoic foci with shadowing and main pancreatic duct (PD) calculi] and one Major B criterion (parenchymal lobularity with honeycombing). Minor criteria are as follows: cysts, dilated PD $\geq$ 3.5 mm, irregular PD contour, dilated side branches $\geq$ 1 mm, hyperechoic duct wall, strands, non-shadowing hyperechoic foci, and lobularity with non-contiguous lobules. The diagnosis of chronic pancreatitis in the Rosemont Classification is labeled as "most consistent with", "suggestive of", "intedeterminate for" and "normal" depending

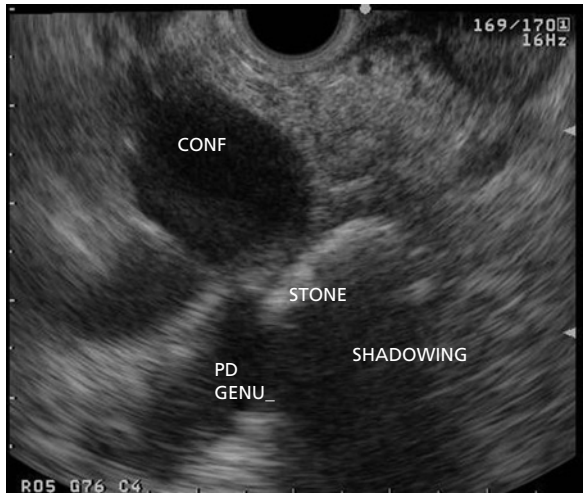

Figure 17.5 Transduodenal imaging of the head of the pancreas showing obstruction of the main pancreatic duct by a hyperechoic 20 mm stone. There is shadowing from the stone and upstream dilation of the genu of the pancreatic duct. The confluence (CONF) of the portal vein and splenic vein are shown.

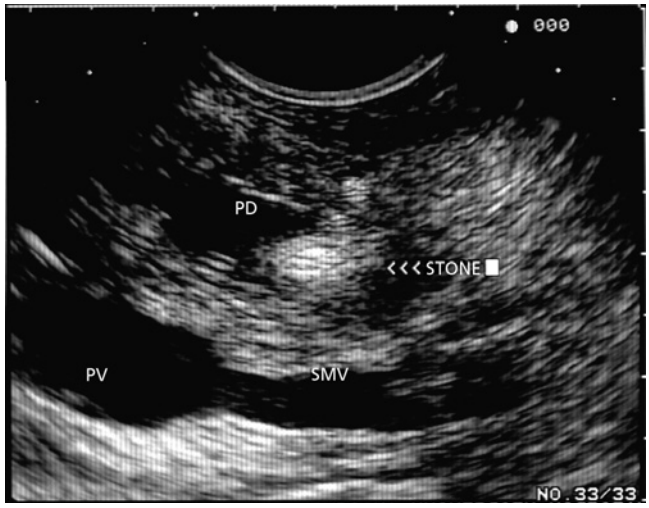

Figure 17.6 Pancreaticolithiasis in the head of the pancreas as imaged with a by a linear echoendoscope at 5 MHz. The pancreatic duct (PD) is dilated, measuring 7 mm. The superior mesenteric vein (SMV) and portal vein (PV) are also shown.

on the number of visualized major and minor features. These experts agreed that EUS examination is best performed via transgastric imaging of the body and tail of the pancreas. The second recently presented abstract [69] compared the agreement of linear and radial endosonography for the diagnosis of chronic pancreatitis using the Rosemont Criteria. This study concluded that these two endoscopes are comparable for the diagnosis of chronic pancreatitis, particularly for the parenchymal features where there was over 90% agreement. Agreement was less precise for ductal features.

Abnormal EUS but normal pancreatogram

Since patients with EUS features of chronic pancreatitis may have normal pancreatograms [58,70,71], it would be important to know the natural history of the clinical and imaging features of these patients. To answer this question, Kahl et al. [72] studied 130 patients with known ($n = 51$) or suspected ($n = 79$) chronic pancreatitis by ERCP and EUS using different endoscopists who were blinded to the results of the other test. These authors found 38 patients with normal pancreatograms, 32 of whom had one or more EUS feature of chronic pancreatitis. During a median follow-up of 18 months, 22 of 32 (68.8%) had a repeat ERP that confirmed chronic pancreatitis. Similarly, in a retrospective review (published in abstract form only) of 240 patients with suspected pancreatitis who had both EUS and ERCP, Mainie et al. [73] found that 55% of patients with a normal ERP but abnormal EUS progressed to a clinical diagnosis of chronic pancreatitis during a mean follow-up of 8.4 years. These studies further suggest that EUS is an essential test for the diagnosis of chronic pancreatitis in those with otherwise negative imaging studies and may demonstrate abnormalities before they become apparent on other imaging tests. Although many of these patients will subsequently develop clinical evidence of chronic pancreatitis, clearly this is not always the case, thus illustrating the EUS may occasionally be "too sensitive" for the diagnosis.

Table 17.4. The Rosemont classification of EUS features for chronic pancreatitis[a]

Option	Most consistent with chronic pancreatitis	Suggestive of chronic pancreatitis	Indeterminate for chronic pancreatitis	Normal
A	One MAJOR A feature plus >3 MINOR features	One MAJOR A feature plus >3 MINOR features	Between 2 and 5 MINOR features	⩽ 2 MINOR features
B	One MAJOR A feature plus MAJOR B feature	MAJOR B feature plus 3 MINOR features	MAJOR B alone	–
C	Two MAJOR A features	⩾ 5 MINOR features (any)	–	–

[a]The two Major A criteria are hyperechoic foci with shadowing and main pancreatic duct (PD) calculi. The one Major B criterion is parenchymal lobularity with honeycombing. Minor criteria are as follows: cysts, dilated ducts ⩾ 3.5 mm, irregular PD contour, dilated side branches ⩾ 1 mm, hyperechoic duct wall, strands, non-shadowing hyperechoic foci, and lobularity with non-contiguous lobules.

Use of EUS for pancreatic disease in patients with atypical or no symptoms

Physicians performing endosonography may identify features of chronic pancreatitis in patients without identifiable symptoms of pancreatic disease. Should these patients be labeled as having chronic pancreatitis? Hastier et al. [74] performed EUS and ERCP in 72 patients with alcoholic cirrhosis and compared both tests for the detection of chronic pancreatitis and other pancreatic lesions. Patients with minimal parenchymal changes at initial EUS underwent clinical follow-up and subsequent EUS and/or ERCP to document the occurrence, absence, or progression of these changes. Chronic pancreatitis was diagnosed in 14 patients (19%) by both methods independently. Isolated parenchymal lesions were observed in 18 patients by EUS alone and these did not change after a mean follow-up of 22 months. Ten of the 18 patients underwent follow-up ERCP which was normal in all cases. Hence, approximately 19% of patients with alcoholic cirrhosis were felt to have chronic pancreatitis and 25% had isolated pancreatic parenchymal changes at EUS that did not progress during the follow-up period.

Sahai et al. [75] enrolled 156 patients with dyspepsia and 27 control patients and compared the prevalence of endosonographic pancreatic abnormalities in both groups. The mean number of endosonographic abnormalities was higher in dyspeptic patients than in control patients. The strongest independent predictors of severe endosonographic abnormalities (defined as five or more abnormalities) were the presence of suspected pancreatic disease (odds ratio 7.29) and dyspepsia (odds ratio 7.21). Half of the dyspeptic patients had four or more EUS criteria and 39% had five or more criteria. In the control group, 34% had three or more abnormalities and 19% had four or more EUS criteria. These findings suggest that either that some patients were mislabeled as dyspeptic in a population with a high prevalence of chronic pancreatitis, or alternatively the EUS findings of chronic pancreatitis are nonspecific. These data also underscore the need to combine a patient's symptoms of "pancreatic-like" pain with EUS features to confidently diagnose chronic pancreatitis.

EUS-guided tissue sampling in suspected chronic pancreatitis

EUS-guided fine-needle aspiration (EUS-FNA) is a useful method for the diagnosis of pancreatic cancer with a sensitivity of 85 to 90% and a specificity of nearly 100% [76–78]. However, in the presence of chronic pancreatitis, sensitivity of EUS-FNA for the diagnosis of cancer decreases to 54 to 74% without a corresponding decrease in specificity [79,80]. However, more EUS-FNA passes may be required to obtain the diagnosis of malignancy in this setting. For patients with nonfocal chronic pancreatitis (i.e. without a pseudotumor or mass-like lesion), EUS imaging is subjective and therefore the diagnosis in early disease is often difficult. It has been postulated that the addition of tissue sampling may improve its detection. Hollerbach et al. [81] found that the addition of EUS-FNA to diagnostic EUS was relatively safe and increased the negative predictive value but not the specificity for the diagnosis of chronic pancreatitis (Plate 17.1). However, cytology provides only cellular material for microscopic examination, and its exact correlation with histopathology is unknown. Acquisition of pancreatic histology usually is impractical without surgery. Recently, a 19-gauge core biopsy device (Quick-Core®, Cook Endoscopy, Winston-Salem, NC) has been shown to be useful for histological sampling (EUSguided Trucut biopsy, EUS-TCB) of pancreatic masses. DeWitt et al. [82] found that EUS-TCB may permit histologic sampling of the pancreas in suspected nonfocal chronic pancreatitis. However, this study demonstrated histologic evidence of chronic pancreatitis in only one of nine patients with clinically suspected disease in whom pancreatic core biopsy specimens were obtained. Nondiagnostic biopsy specimens were found in six of fifteen patients with retrievable tissue. Because of potential complications and limited diagnostic yield, the authors concluded that technique is not currently recommended for use in the routine evaluation of these patients.

Autoimmune pancreatitis

The entity of autoimmune chronic pancreatitits (AICP) was first postulated by Sarles et al. [83] in 1961 but the term " autoimmune pancreatitis" was not introduced until 1995 by Yoshida et al. [84]. As implied by the name, AICP is thought to have an autoimmune origin. Supporting this idea is the frequent association of the disease with other autoimmune disorders, such as Sjögren's syndrome, primary sclerosing cholangitis (PSC) and inflammatory bowel disease [85–89]. Additionally, patients may have serologic markers of autoimmunity such as ANA, antibodies to carbonic anhydrase-II and lactoferrin, certain HLA haplotypes and elevated serum IgG4 levels [90–92]. Symptoms of AICP are often similar to those of pancreatic carcinoma, including jaundice, weight loss and nonspecific abdominal pain [85,86]. Thus, patients with AICP may undergo surgical resection for presumed malignancy. In previous surgical series, AICP accounted for about 2.5% of pancreaticoduodenectomy specimens in patients with presumed malignancy [93,94]. The histological hallmark of this disease in the pancreas is a collar-like periductal infiltrate composed of lymphocytes and plasma cells. Occasionally periductal necrotizing epithelioid cell granulomas may be seen [95,96]. There is increasing recognition that the IgG4-positive plasma cells seen in AICP are part of a systemic disease with extra pancreatic involvement in other sites including the bile duct, salivary gland, lung, gallbladder and kidney [97]. Treatment with oral corticosteroids usually leads to prompt, complete resolution of the pathological condition and reversal of any mass lesion, strictures and symptoms. Therefore nonoperative identification and medical treatment of patients with this condition may prevent unnecessary surgery. CT of the abdomen may show either diffuse "sausage-shaped" enlargement of the pancreas or a "halo" around the outer margins of the gland. In the head of the pancreas, there may be focal enlargement indistinguishable from malignancy. Classically, ERCP shows a stricture of both the pancreatic and bile ducts (Figure 17.7). In the main

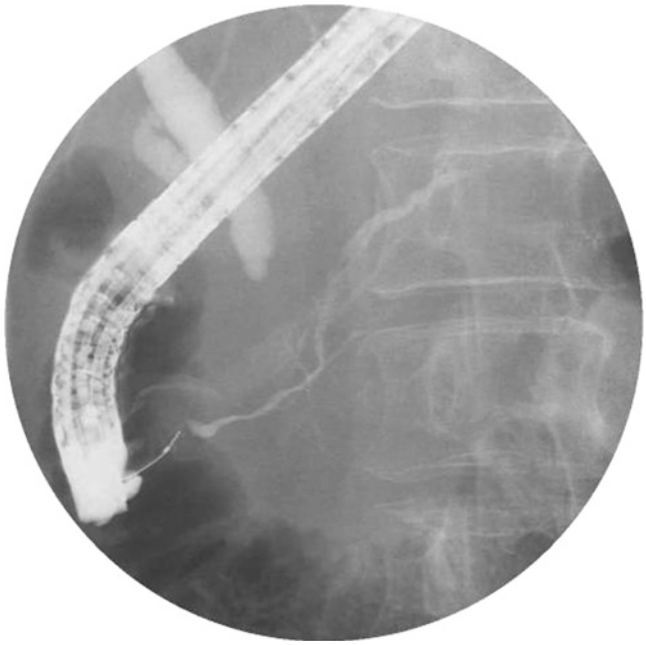

Figure 17.7 ERCP in a 54-year-old male with a 2-week history of abdominal pain and jaundice. Transabdominal ultrasound demonstrated a diffusely enlarged, hypoechoic pancreas without a discrete mass. Abdominal CT scan also demonstrated an enlargement of the entire pancreas without a mass. Cholangiogram shows a 2.5 cm stricture in the distal bile duct with upstream biliary dilation measuring 12 mm. The ventral pancreatic duct in the head also shows a long stricture in the head and only slight dilation of the duct in the body.

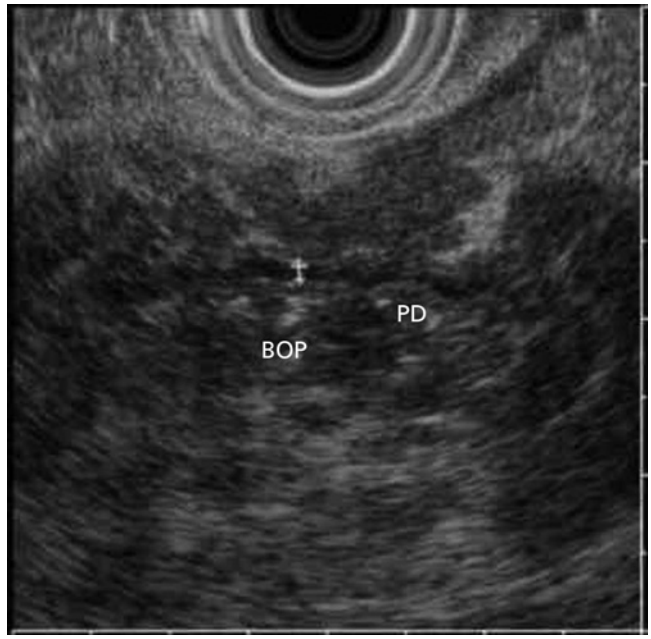

Figure 17.8 Radial EUS (7.5 MHz) imaging of the pancreatic body in the same patient as Figure 17.7. The parenchyma is enlarged and hypoechoic with hyperechoic foci, stranding and lobularity along the outer margins of the gland. The pancreatic duct (*outlined between Xs*) is tortuous with intermittent hyperchoic duct wall margins. Duct sidebranches are not visible.

pancreatic duct there are characteristically segmental strictures with minimal to no dilation upstream. The first diagnostic criteria for autoimmune pancreatitis required stricturing of the pancreatic duct on ERCP along with either elevated serologic autoantibodies or characteristic histologic changes [98]. However, these criteria may not identify all patients with AIP [99] and it is increasingly recognized that there a wide variety of imaging findings in these patients [100]. Therefore, another classification for the diagnosis of AIP has recently been proposed that (along with typical histologic, imaging and serologic features) adds the criterion of response of pancreatic/ extrapancreatic manifestations to steroid therapy [101].

EUS features of AICP usually include either a diffusely enlarged, hypoechoic pancreas (Figure 17.8) or a solitary hypoechoic focal mass (usually in the head) [102]. Pancreatic cysts and peripancreatic fluid collections do not appear to be common features of AIP. EUS may also show hypoechoic enlarged celiac and peripancreatic lymph nodes, a biliary stricture and suspected vascular invasion. EUS-guided FNA of the pancreas in these patients usually shows chronic inflammation. Desphande et al. [103] found that cytology from EUS-FNA in these patients shows a higher proportion of stromal fragments with embedded lymphocytes compared to those with adenocarcinoma and chronic pancreatitis. These authors however also reported a false positive cytologic diagnosis of adenocarcinoma ($n = 1$), solidpseudopapillary tumor ($n = 1$) and a mucinous neoplasm ($n = 1$) in these patients. Therefore, the routine use of cytomorphology alone from EUS-FNA of the pancreas cannot be recommended for the diagnosis of AIP. The use of molecular analysis of cytology specimens to differentiate malignancy from AIP or other benign conditions may improve the diagnostic accuracy of cytology alone [104]. However, these techniques are best considered experimental at this time.

To overcome limitations of cytology alone, Levy et al. [105] evaluated the role of EUS-guided Trucut biopsy (EUS-TCB) in three patients presenting with obstructive jaundice who were suspected of having autoimmune pancreatitis based on their clinical, laboratory and imaging studies (Plate 17.2). Histology from these biopsies established the diagnosis of AIP in two and identified nonspecific changes of chronic pancreatitis in the third. EUS-guided FNA was performed in two and failed to establish the diagnosis in either patient. One patient experienced transient abdominal pain. This data is intriguing but it remains to be seen whether or not the diagnosis of AIP may be made from pancreatic core biopsies alone. It is known that AIP is a patchy disease in the pancreas [106]. Therefore, sampling error from the often small core biopsies obtained by EUS-TCB may not be sufficient obtain the diagnosis.

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18 Endoscopic Ultrasound for Biliary Disease

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One of the most powerful applications of endoscopic ultrasound (EUS) is the evaluation and management of diseases of the biliary system. Over the last 15 years, EUS has contributed, along with magnetic resonance cholangiopancreatography (MRCP), to the diminishing role of diagnostic endoscopic retrograde cholangiopancreatography (ERCP) and has become an essential tool for the complete biliary endoscopist. The clinical situations that can be evaluated by EUS include biliary obstruction, suspected choledocholithiasis, indeterminate biliary strictures, idiopathic pancreatitis, unexplained right upper quadrant pain, and mass lesions within and adjacent to the biliary tree. EUS also plays a pivotal role in patients with documented malignancies because it is highly accurate for locoregional and lymph node staging. While dedicated echoendoscopes are the most commonly used instruments for biliary imaging, the use of catheter-based miniprobes for intraductal ultrasound (IDUS) via the endoscopic retrograde route has further expanded the impact of EUS. In addition to imaging alone, EUS-guided needle puncture enables transluminal aspiration of tissue and provides direct transluminal access to the bile ducts for diagnostic ductography and therapeutic interventions. The purpose of this chapter is to review the use of EUS for biliary diseases with an emphasis on practical advice and technical guidance.

Instruments

The currently available instruments for biliary EUS include radial and linear echoendoscopes and catheter-based IDUS probes. Both radial and linear echoendoscopes can be used to image the biliary tree. The radial scanning instruments may initially make orientation easier and electronic radial instruments with Doppler are now available to help distinguish small vessels from small ducts and to improve vascular staging. However, linear EUS technique, once mastered, is a powerful skill that provides detailed images and can direct fine needle puncture. The availability of high-frequency catheter-based ultrasound probes has made it possible to obtain ultrasound images from within the biliary tree with relative ease. IDUS probes are wire-guided and can be placed without sphincterotomy across the papilla into the common bile duct, the hilar region, the intrahepatic ducts, the gallbladder, and across biliary strictures.

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Technique

When compared to other endoscopic procedures, and even to EUS of the gastrointestinal tract wall, EUS of the biliary tree is difficult. The endoscopist must obtain the images by maneuvering the tip of the scope between the duodenal bulb and the second portion of the duodenum in a blinded fashion. The EUS image can also be used as a guide to supplement the endoscopist's "muscle memory" of how to maneuver the cumbersome echoendoscope upstream and downstream in this region. It is important to avoid compressing important structures or trapping multiple duodenal folds and/or air between the transducer and areas of interest. As a result, one needs both considerable endoscopic skill and a detailed understanding of the regional cross-sectional anatomy in order to obtain and interpret images of the biliary tree. The basic technical aspects of our approach to bile duct imaging are described below.

Radial imaging

There are two general approaches to examining the bile duct, depending on whether the imaging begins in the duodenal bulb or at the level of the papilla. To begin imaging from the bulb, advance the echoendoscope tip across the pylorus and bulb until it lodges in the superior duodenal angle and then tip the scope gently downward. Aspirate any air and partially fill the water balloon to improve acoustical contact. Overfilling the balloon will decrease the mobility of the tip of the endoscope. Addition of luminal water at this point is usually unnecessary and can make imaging worse by either introducing air bubbles

which impair the ultrasound signal or by stimulating duodenal motility. At this position the portal vein is usually easily identified running 1 or 2 cm deep to the transducer between the liver and the head of the pancreas. Once identified, it is advisable to electronically rotate the image so that the portal vein is along the left side of the screen with the liver on the top left of the screen and the pancreatic head in the lower aspect of the screen (Figure 18.1). The common bile duct and common hepatic duct are seen in their long axis alongside the portal vein and superficial to it. If the duct is dilated, recognition of this prominent structure is usually immediate. However, if it is not dilated, identification may be more difficult. One must be careful to avoid mistaking the gastroduodenal artery for the bile duct, which is a common mistake when imaging without Doppler. Once identified, the bile duct can be traced both upstream to the confluence of the right and left hepatic ducts and downstream to the papilla. In order to be sure that the entire extrahepatic biliary tree is visualized, try to identify these three duct confluences in every patient: left and right hepatic, cystic and common hepatic, and common bile duct with the pancreatic duct at the papilla of Vater. The gallbladder is usually easily identified from the bulb and may also be imaged from the antrum or occasionally from deeper in the duodenum.

When the bile ducts are not dilated, it may be best to begin imaging at the level of the papilla. In this position, the endoscopist can confirm visually that the EUS images represent the peripapillary pancreas and ducts, which may appear as small slits, ovals or circles in this region. Once the bile duct has been identified in the peripapillary pancreas, it can be traced upstream to the level of the liver hilum and gallbladder. In practice both of these methods are used in tandem as the bile duct is imaged repeatedly in the upstream and downstream directions in order to collect adequate information.

Linear imaging

As with radial EUS, the bile duct can be approached from the duodenal bulb in a long position or from the papilla using a short position. It is advisable to begin the examination in the bulb, because often the entire duct can be imaged from that position. To begin the examination, use endoscopic guidance to cross the pyloric channel and let the scope come to a gentle stop in the distal bulb. Using EUS, the bile duct can usually be identified as a Doppler-negative tubular or oval structure between the duodenal wall and the portal vein (Figure 18.2). Once the duct is identified, it is possible to follow the duct into the head of the pancreas using a combination of rightward torque, slight upward tip deflection, and gentle scope insertion. Trace the duct to the papilla and then, reversing the complex movement, return to base position where the mid duct is easily seen adjacent to the portal vein. To image the hilum, torque to the left, tip down, while carefully pulling back gently on the endoscope shaft. Starting from a long position keeps the scope from falling back into the stomach during this maneuver. From this position, the left and right hepatic confluence can be observed and the cystic duct can be identified and its course can be traced between the bile duct and the gallbladder.

Occasionally the duodenum is either long, tortuous, or both, and images of the distal duct cannot be reliably obtained from the deep bulb position described above. In that case, pass the

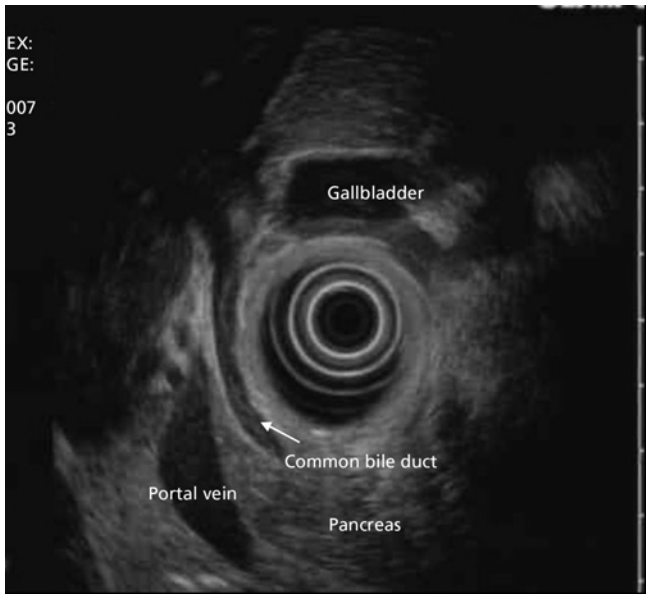

Figure 18.1 This radial EUS image using the Olympus (Olympus America, Incorporated (Olympus AI), Center Valley, PA) GFUM160 echoendoscope demonstrates normal anatomy. The relationship of the gallbladder, bile duct, portal vein, and pancreatic head can been easily seen.

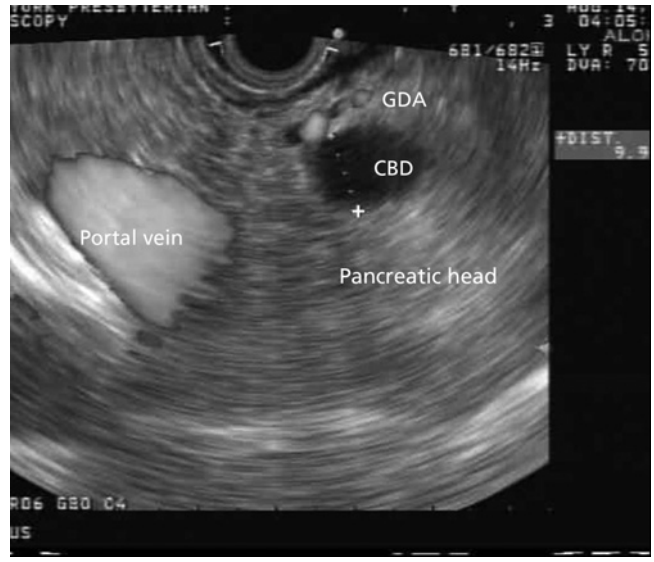

Figure 18.2 This linear EUS image using the Olympus (Olympus America, Inc, Center Valley, PA) GFUC140P echoendoscope shows a dilated common bile duct (CBD) adjacent to the gastroduodenal artery (GDA), which shows a positive Doppler signal. The GDA can be mistaken for a nondilated bile duct.

endoscope to the second portion of the duodenum using endoscopic visualization and shorten the scope to a short position similar to when performing ERCP. Inflate the balloon and make contact with the medial wall of the duodenum and identify the inferior pancreatic head and uncinate process. As you withdraw the scope slowly the pancreatic duct and bile duct will be seen as short black slits as they enter the papillary mound. Once identified, the bile duct can be followed with scope withdrawal up to the mid duct region. Overfilling the balloon with water may be required to control the scope during withdrawal from this position so that the bile duct can be traced slowly upstream. It is important to learn to obtain this view as it facilitates EUS needle puncture of the distal bile duct and/or associated masses. The optimal position for the imaging of the gallbladder is highly variable, but is most commonly seen from the duodenal bulb and antrum of the stomach. To image the body, fundus and the neck of the gallbladder, the transducer should be moved slowly and carefully along the entire course of the gallbladder using torque and tip deflection as needed.

Biliary strictures and malignancy

Diagnosis of malignancy using EUS

Differentiation between malignant and benign strictures is important, as 13 to 24% of patients with presumed hilar cholangiocarcinoma are found to have benign disease [1,2]. This can be a substantial problem, especially in proximal strictures involving the hilum. The typical endosonographic image of a bile duct tumor cancer shows a round or fusiform hypoechoic area arising from or surrounding the bile duct wall, but EUS alone (without FNA) may not be sufficiently sensitive to diagnose malignancy and a definitive diagnosis requires tissue. This was shown in a 2007 meta-analysis of nine studies (555 subjects) that measured EUS (without FNA) performance in diagnosing malignant biliary obstruction. The sensitivity was 78% (95% CI 69–85) and the specificity was 84% (95% CI 78–91) [3].

Tissue diagnosis requires EUS with FNA. In a retrospective series of 238 patients with suspected or known biliary strictures, EUS-guided FNA obtained a tissue diagnosis in 12/26 (46%) patients, all of whom previously had a negative cytology or an unsuccessful ERCP [4]. Although the role of EUS with FNA for biliary strictures is evolving, sensitivity has been reported as 43 to 86% for all biliary strictures, with 25 to 83% for proximal biliary strictures [5–10].

Staging using EUS

Endosonographic staging of bile duct tumors is based on the TNM system (Table 18.1). Qilian et al. [11] evaluated the use of EUS for the preoperative assessment of 18 patients with extrahepatic bile duct tumors. The overall accuracy for T stage was 72% and for N stage 61%. In an earlier study, Mukai et al. [12] reported the accuracy of EUS for determining the T and N stage of CBD tumors in 16 patients. All 16 patients underwent resection. The extent of malignant invasion (T stage) was accurately diagnosed by EUS in 81% of patients and the accuracy for lymph node staging was 81%.

Table 18.1 TNM staging of bile duct cancer

Primary tumor (T)			
TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
Tis	Carcinoma in situ		
T1	Tumor confined to the bile duct histologically		
T2	Tumor invades beyond the wall of the bile duct		
T3	Tumor invades the liver, gallbladder, pancreas, and/or unilateral branches of the portal vein (right or left) or hepatic artery (right or left)		
T4	Tumor invades any of the following: main portal vein or its branches bilaterally, common hepatic artery, or other adjacent structures such as the colon, stomach, duodenum, or abdominal wall.		
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		
Stage grouping			
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1-3	N1	M0
Stage III	T4	Any N	M0
Stage IV	Any T	Any N	M1

Tio et al. conducted an early and large volume of work on EUS for staging of proximal bile duct cancers. They found that the overall accuracy of EUS for T stage was 86% and for N stage was 64% [13]. Lymph node accuracy can be improved with EUS-guided fine-needle aspiration biopsy, which has an overall accuracy of about 91% [14].

For determining resectability of bile duct cancer, portal venous invasion remains a key factor. This particular aspect of staging was the subject of a comparative trial reported by Sugiyama et al. [15]. In their trial, EUS was prospectively compared to ultrasound, computed tomography and angiography for the detection of portal venous system invasion in 19 bile duct cancers. All of the 19 lesions were resected, with or without portal venous resection, and underwent careful histopathologic staging. The authors of this study separated the degree of apparent involvement of the portal vein by tumor, as imaged by EUS, into four grades. Using this system, they found that the accuracy for determining portal venous invasion was 93% for EUS, compared to 74% for US, 84% for CT and 89% for angiography.

Diagnosis of malignancy using IDUS

The usefulness of IDUS is based on its ability to detect early lesions, to determine the maximal longitudinal extent of the bile duct cancer, and to determine the presence of extension into other organs or major blood vessels when the tumor is not well defined by other imaging methods. IDUS criteria that suggest malignancy include eccentric wall thickening with an irregular surface, a hypoechoic mass, heterogeneity of the internal echo pattern, a papillary surface, disruption of the normal three-layer sonographic structure of the duct, and the presence of lymph nodes or vascular invasion [16–20]. By using these criteria, studies evaluating the performance of IDUS in patients with biliary strictures without an associated mass lesion have found the sensitivity and diagnostic accuracy to range from 83% to 89% and from 83% to 90%, respectively [18–20].

In contrast to EUS, IDUS is often better able to evaluate the proximal biliary system and surrounding structures, such as the right hepatic artery, portal vein and the hepatoduodenal ligament. The largest published series to comparatively assess the accuracy of IDUS and EUS in the diagnosis of biliary strictures was a prospective histopathologically controlled study in which 56 consecutive patients with obstructive jaundice due to bile duct strictures underwent both conventional EUS and IDUS [21]. IDUS was significantly more accurate than EUS (89% versus 76%) for determining the nature of bile duct strictures, with the advantage of IDUS being most pronounced in the proximal biliary tree.

IDUS is commonly used to improve the diagnostic accuracy of ERCP for biliary obstruction especially when there is no mass apparent on imaging. When used in conjunction with ERCP brushings, IDUS may increase the diagnostic accuracy of ERCP brushing to 58% to 90% [22,23], and thus supports IDUS to be a valuable adjunct to ERCP tissue sampling in the management of biliary strictures. In one recent large prospective study involving patients with painless jaundice but no mass lesion on abdominal CT, 45 patients with biliary strictures on ERCP underwent IDUS with a high-frequency (20 MHz) wire-guided probe [20,23]. The authors found that bile duct wall thickness $\leqslant$ 7 mm at the stricture site, in the absence of extrinsic compression, had a negative predictive value of 100% for excluding malignancy in this cohort.

Staging of malignancy using IDUS

IDUS can be used to assess the T stage of biliary tumors, but is not suitable for assessing lymph nodes, because of the limited depth of imaging with the miniprobe. On the other hand, IDUS is very useful in assessing tumor invasion to the portal vein, right hepatic artery, and pancreatic parenchyma. The comparative accuracy of EUS and IDUS to assess preoperative staging and prediction of tumor resectability was studied in a large prospective series in 56 patients with obstructive jaundice due to bile duct strictures [21]. IDUS was better able to determine the potential resectability of bile duct tumors (82% versus 76%) and T stage (78% versus 54%).

Common bile duct stones

Although studies are confounded by the lack of a true gold standard for the detection of choledocholithiasis, the diagnostic accuracy of EUS has been shown to be as good or better compared to ERCP [24–27] (Figure 18.3). ERCP has traditionally been considered the most accurate test for diagnosis of common bile duct stones, but it too can produce both false-negative and false-positive results.

Prat et al. [24] conducted one of the earliest and most elegant prospective studies comparing ERCP and EUS which stands out because the presence of common bile duct stones (CBDS) was confirmed by instrumental exploration (balloon and basket extraction) regardless of the EUS or ERCP findings. In a study population in which CBDS were strongly suspected, 119 patients (both pre- and post-cholecystectomy) underwent EUS and ERC. The study found 78 (66%) patients had choledocholithiasis, 17 (14%) had other bile duct diseases and 24 (20%) had a clear bile duct or did not require an additional invasive endoscopic therapeutic procedure. The sensitivity, specificity, PPV and NPV for EUS were 93%, 97%, 98% and 88% respectively. The corresponding values for ERCP were 89%, 100%, 100% and 83%. The authors concluded that EUS is at least as sensitive as ERCP for CBDS, and also concluded that EUS may prevent inappropriate invasive exploration of the common bile duct. Similar results on the comparison of ERCP and EUS have been supported by numerous other studies (Table 18.2) [25–27].

A 2007 meta-analysis supports EUS as a diagnostic modality for choledocholithiasis. In 31 studies (3075 subjects), most of them using ERCP as a gold standard, the sensitivity of EUS to diagnose choledocholithiasis was 89% (CI 87% to 91%) and

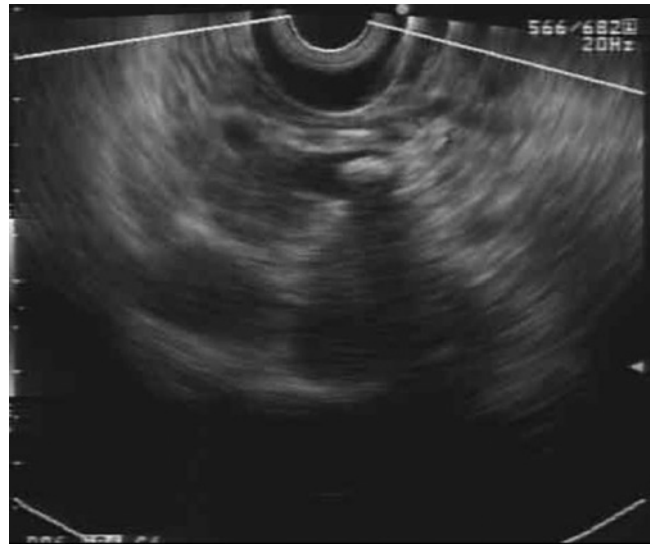

Figure 18.3 This linear EUS image using the Olympus (Olympus America, Inc, Center Valley, PA) GFUC140P echoendoscope shows a distal common bile duct stone with acoustic shadows.

Author	No. of patients	Frequency of choledocholithiasis	Sensitivity (%)	Specificity (%)	Diagnostic accuracy (%)
Denis [53]	60	25 (42%)	92	100	97
Amouyal [25]	62	32 (52%)	97	100	98
Napoleon [54]	58	26 (45%)	100	90	95
Salmeron [55]	211	133 (63%)	96	96	96
Shim [56]	132	28 (21%)	89	100	97
Palazzo [26]	422	152 (36%)	95	98	96
Prat [24]	119	78 (66%)	93	97	95
Sugiyama [57]	142	51 (36%)	96	100	99
Norton [58]	50	24 (48%)	88	96	92
Canto [59]	64	19 (30%)	84	95	92
Buscarini [60]	150	88 (59%)	95	96	94
Kohut [61]	134	98 (64%)	93	93	94

Table 18.2 Prospective and blinded studies comparing endoscopic ultrasound to endoscopic retrograde cholangiopancreatography

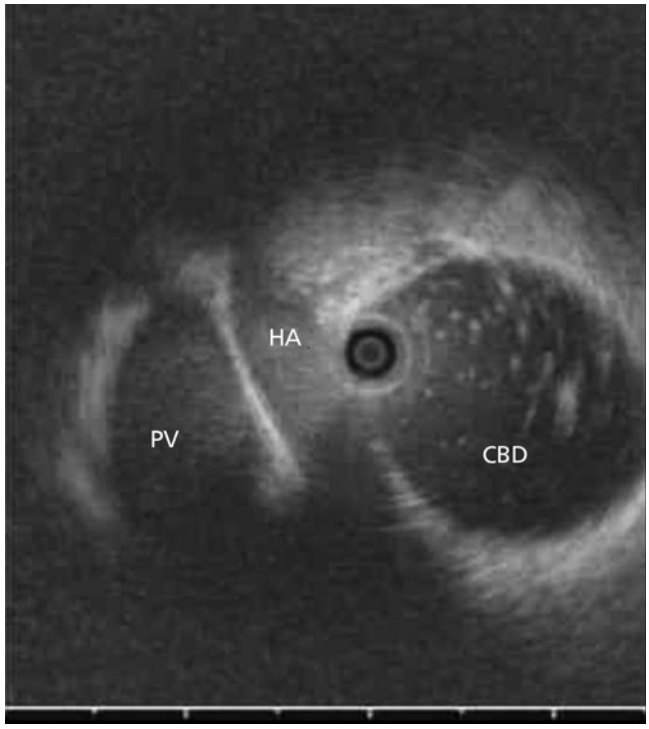

Figure 18.4 Intraductal ultrasound (Olympus America, Inc, Center Valley, PA) image showing suspended sludge in the dilated common bile duct (CBD) with a normal wall. Also seen are the hepatic artery (HA) and the portal vein (PV) to complete the portal triad.

the specificity was 94% (CI 91% to 96%) [3]. The authors found that while clinical context (malignant versus stone) appeared to affect EUS performance, other factors such as study quality, type of echoendoscope, EUS era and presence of pancreatitis were not significant confounders. When used as a triage tool, EUS can spare the costs and complications related to ERCP in a select patient population [28].

IDUS can detect small stones and sludge within the biliary tree that are missed on other imaging studies, including ERCP (Figure 18.4). Thus IDUS is suited to situations in which ERCP is indeterminate or negative for stones in the setting of high clinical suspicion. The diagnostic accuracy of IDUS for CBD stones is 93 to 97% [29–31], and can differentiate stones from air bubbles and prevent unnecessary sphincterotomies. One study of 35 patients with suspected CBD stones and negative or equivocal ERCP found that IDUS changed management in 37% (13/35) of cases [32], though the rate of residual stones in this study was high. In rare instances, IDUS may allow for performance of and therapeutics via ERCP without fluoroscopy [33].

EUS versus MRCP

MRCP has many advantages in biliary imaging. However, stones smaller than 3 to 6 mm may be missed by MRCP and EUS offers the distinct advantage of immediate sequential ERCP. Comparative studies between EUS and MRCP should be interpreted with caution, as they are limited due to the differences in MRI protocols and techniques, the operator-dependent nature of both modalities, the time interval between the different diagnostic modalities (thus not addressing the problem of stone migration), the pretest probability for CBDS, and finally, the choice of reference standard, i.e. ERCP versus intraoperative cholangiogram (IOC).

In studies directly comparing EUS to MRCP in patients with biliary obstruction, the sensitivity and specificity of MRCP range from 40 to 100% and 94 to 96.6%, respectively, and that for EUS range from 80 to 100% and 88 to 96.6%, respectively [34–39]. When the biliary tree is nondilated, the sensitivity may be lower [40]. The reported sensitivity and specificity of EUS compared to MRCP has varied significantly with the proportion of patients with a final diagnosis of CBDS. In one large prospective trial which focused on choledocholithiasis, 47 patients with a high suspicion for CBD stones underwent EUS and MRCP [38], followed by subsequent ERCP or IOC if results of the EUS/MRCP were abnormal or if cholecystectomy was performed. The sensitivity and specificity of MRCP and EUS were similar, and the accuracy did not significantly differ between the techniques (Table 18.3). In a recent meta-analysis of 46 trials (3592 individuals) comparing

Table 18.3 Prospective and blinded studies comparing diagnosis of choledocholithiasis by magnetic resonance cholangiopancreatography vs. endoscopic ultrasound

Author	No. of patients	Frequency of CBDS	EUS	MRCP	Reference standard
			Sensitivity	Specificity	
			Specificity	Dx Accuracy	
			Dx Accuracy		
Ainsworth [62]	163	60 (37%)	89%	90%	ERCP
			98%	92%	
			93%	91%	
De Lédinghen [34]	32	10 (31%)	100%	100%	ERCP
			94%	73%	
			96.9%	82.2%	
Kondo [35]	28	24 (86%)	100%	88%	ERCP with IDUS
			50%	75%	
			93%	86%	
Materne [37]	50	9 (18%)	97%	91%	ERCP or IOC
			88%	94%	
			94%	92%	
Aube [38]	45	16 (36%)	93.8%	87.5%	ERCP or IOC
			96.6%	96%	
Scheiman [36]	28	5 (18%)	80%	40%	ERCP
			96%	96%	
			89%	61%	
Schmidt [39]	57	18 (32%)	97.4%	94.9%	ERCP, IOC or clinical follow-up
			94.4%	94.4%	

CBDS, common bile duct stones; ERC, endoscopic retrograde cholangiopancreatography; IDUS, intraductal ultrasound; IOC, intraoperative cholangiogram.

MRCP to a gold standard there was a sensitivity of 92% (95% CI 80–97) and specificity of 97% (95% CI 90–99) [41]. There is only one study comparing MRCP to IDUS, which reported the sensitivity of MRCP and IDUS for CBDS as 80% and 95%, respectively [31]. The message from all these studies is that the choice of imaging should take into account local expertise and the specific clinical situation.

Microlithiasis

Biliary sludge or microlithiasis (stones less than 3 mm in diameter) is associated with biliary colic and acute cholecystitis and it may be responsible for up to 60% of cases of idiopathic pancreatitis [42–44]. These small stones are often unrecognized at ERCP. IDUS and EUS are sensitive in detecting biliary microlithiasis and may prevent unnecessary sphincterotomies [25,30,45,46] (Figures 18.5, 18.6).

Evaluation of gallbladder masses

The widespread use of transabdominal ultrasonography and CT has increased the detection rate for polypoid lesions in the

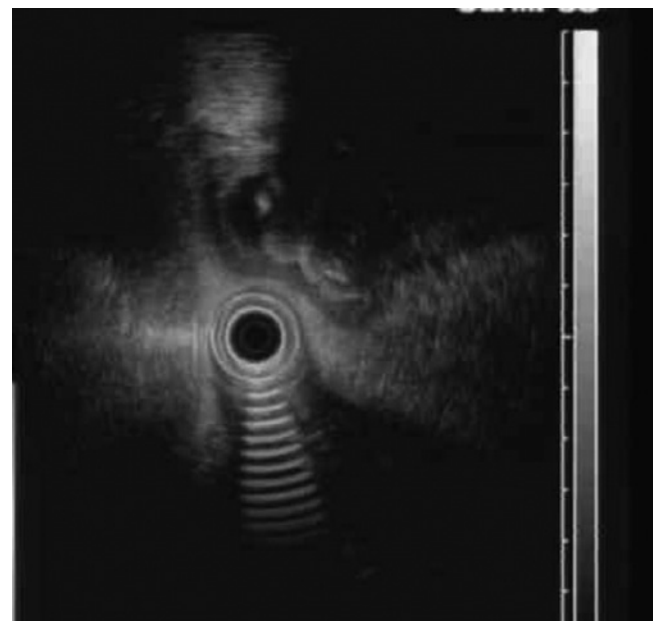

Figure 18.5 The radial EUS image using the Olympus (Olympus America, Inc, Center Valley, PA) GFUM160 echoendoscope shows the gallbladder with a thickened wall and multiple shadowing stones.

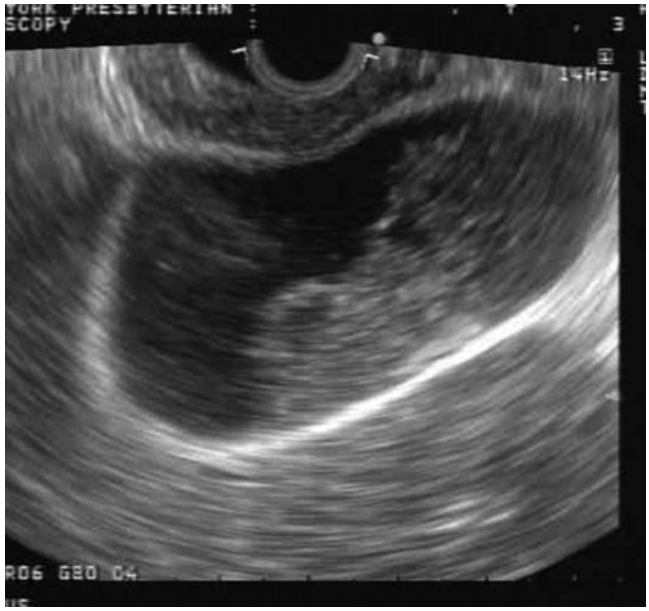

Figure 18.6 This linear EUS image using the Olympus (Olympus America, Inc, Center Valley, PA) GFUC140P echoendoscope demonstrates dependent and suspended sludge in the gallbladder with a normal wall

gallbladder. EUS is more accurate than US for visualizing the gallbladder because US uses a lower frequency (3.5 MHz) than EUS (7.5 MHz). In addition, the resolution of EUS is not limited by the presence of gas in the bowel. Carcinoma may be a pedunculated or sessile mass with a rounded shape which it retains even after becoming a large mass. The internal echo is hypoechoic to isoechoic and almost homogeneous, if not slightly heterogeneous [47,48]. As with transabdominal ultrasound, other EUS findings that are suggestive of gallbladder cancer include a fixed mass in the gallbladder wall, loss of interface between the gallbladder and liver, and direct liver infiltration. In a series of 89 patients with gallbladder polyps, the sensitivity, specificity, PPV and NPV for the diagnosis of gallbladder cancer by EUS were 92%, 88%, 76% and 97% respectively, compared with 54%, 54%, 54% and 95 %, respectively, for traditional ultrasound [48]. EUS may be useful for the staging of gallbladder cancer as well [49]. No recommendations or guidelines have been made regarding EUS characteristics or further screening with EUS. In order to prevent unnecessary surgery, EUS may be helpful to precisely distinguish benign lesions from malignancies.

Polyps less than 10 mm are rarely malignant and require only serial surveillance. Prevalence has been reported as 4 to 7% of healthy subjects [50–52]. The differential diagnosis of gallbladder polypoid lesions larger than 10 mm is difficult with conventional US, CT and MRI and includes cholesterol polyps, adenomyomatosis and carcinoma. In US as well as EUS, the echo image of polyp may be hypoechoic, isoechoic or hyperechoic that of the most lateral layer of the wall. Relatively large polyps more than 10 mm in diameter may not give the typical images and may have a spotty echo texture. A cholesterol polyp is a pedunculated lesion and shows a granular surface. The internal echo is hyperechoic to isoechoic with a tiny spotty echo pattern. Adenomyomatosis is a sessile polyp, which has an echo-free internal area and slightly irregular surface.

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19 Colorectal Endoscopic Ultrasound

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Instruments for colorectal endosonography

Rigid probes

Rigid probes do not incorporate fiberoptic bundles or video chips and thus do not provide a simultaneous endoscopic and ultrasound image. The use of rigid probes has been limited to the rectum. The most frequently used rigid probe is an instrument with a single element 7.5 MHz transducer that provides a 360-degree radial image at right angles to the long axis of the probe (Bruel & Kjaer; Naerum, Denmark; Marlborough, MA). A balloon around the transducer provides acoustic coupling with the gut wall. Rigid probes with linear array imaging are also available.

Echoendoscopes

Endoscopic ultrasound (EUS) is a technique where a high-frequency miniature ultrasound transducer is incorporated into the tip of a conventional endoscope. This results in enhanced resolution of the gastrointestinal wall and structures within close proximity of the gastrointestinal wall. The frequencies available for these instruments range from 5 MHz to 20 MHz. The lower frequencies in this 5 to 20 MHz spectrum have greater penetration and are suitable to image structures beyond the gut wall, while frequencies on the higher side have limited penetration but they provide superior resolution of various layers of the gastrointestinal wall. EUS of the gastrointestinal wall classically reveals five layers which correlate with mucosa (first and second layers), submucosa (third layer), muscularis propria (fourth layer), and serosa (fifth layer) or adventitia in the case of rectum. Radial echoendoscopes provide a scan in a direction that is perpendicular to the long axis of the echoendoscope. Linear echoendscopes provide an imaging plane that is parallel to the long axis of the endoscope. The scanning plane of radial instruments does not allow optimal visualization of a needle passed through the biopsy channel of the endoscope. Linear array echoendoscopes in contrast to a radial EUS instrument provide a sector scan parallel to the long axis of the echoendoscope. The linear array instruments are thus able to visualize a needle along its long axis as well as ultrasonically monitor its depth of penetration, allowing interventional techniques under EUS guidance. Small, high-frequency miniprobes are also available that can be passed through the biopsy channels of standard endoscopes. These miniprobes can then be applied to image the gastrointestinal wall and focal lesions by direct application of the miniprobe to the target lesion under endoscopic vision.

Examination technique

Preparation for colonic examination by endosonography is variable depending on the area to be imaged. Laxative enemas similar to the preparation for flexible sigmoidoscopy may be sufficient for anorectal and sigmoid lesions. However, we and many other groups prefer a standard colonoscopy preparation even for rectal and sigmoid lesions to avoid artifacts and optimize imaging. For colonic endosonography proximal to the sigmoid colon, a peroral lavage similar to pre-colonoscopy is definitely a prerequisite. A quick flexible sigmoidoscopy should be routinely performed prior to rectosigmoid EUS to ensure that the rectosigmoid lumen is free of stool debris as it can interfere with sonographic imaging and cause artifacts. An awareness of other potential artifacts during transrectal ultrasound is also desirable [1].

Endosonographic examination is then conducted with one of the available instruments. If one of the blind rectal probes is being used, it is lubricated and inserted into the anus and advanced into the rectal vault. A balloon at the tip of the rigid probe allows the creation of an acoustic interface between the rectum and the transducer. Regardless of the type of transducer, a familiarization of the normal rectal anatomy with that particular transducer is desirable prior to imaging pathological lesions. If the examination is being performed only of the anal sphincter, the instrument is withdrawn so that the transducer provides images of the internal and external anal sphincter.

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The side-viewing upper endoscopic ultrasound instruments can also be inserted into the rectum and then under endoscopic visualization advanced to the distal sigmoid. We have imaged sigmoid/left colonic lesions with this technique as far as 45 cm from the anal verge [2]. However, caution needs to be exercised when advancing the side-viewing echoendoscopes to the sigmoid colon and probably refrained from until considerable experience with use of the side-view echoendoscope. A front-viewing upper echoendoscope or a dedicated echocolonoscope that has front-viewing optics can of course be advanced under direct endoscopic vision to the level of the cecum if clinically necessary.

Colorectal cancer staging by endoscopic ultrasound

Tumor (T) stage

Malignant colorectal tumors appear as hypoechoic masses on EUS. 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 by EUS (Figure 19.1). A colorectal carcinoma invading into the muscularis propria (hypoechoic fourth EUS layer) but with an intact outer margin of the muscularis propria and with no penetration completely through the muscularis propria will be a T2 lesion by EUS (Figure 19.2). A T3 lesion by EUS penetrates completely through the rectal wall and all the EUS layers, has irregular outer margins or has tumorous pseudopodia extending beyond the five echo layers (Figures 19.2, 19.3a). A T4 lesion by EUS is a colorectal cancer that is locally invading into an adjacent organ, e.g. the prostate.

N stage

Lymph nodes during EUS may be seen as round, oval, or sometimes triangular structures that may be hypoechoic, echogenic, or with mixed echogenicity. Moving the ultrasound probe and following these structures to ensure that a round hypoechoic/anechoic area does not elongate into a long tubular structure helps differentiate vessels from lymph nodes. In addition, if a color Doppler is available on the echoendoscope it may further help in differentiating a vascular structure from a lymph node by observing color flow within a vessel (Figure 19.3b). When no lymph nodes are seen during EUS or if the lymph nodes visualized during EUS are considered reactive and not malignant the N stage is classified as N0. When lymph nodes visualized during EUS are believed to be malignant, N1 stage by EUS is diagnosed with one to three regional lymph nodes and N2 stage is diagnosed with four or more regional lymph nodes.

EUS is a highly useful technique for local staging of rectal cancer as preoperative staging determines the type of surgery performed and whether preoperative neoadjuvant chemoradiation is needed. Savides et al. [3] summarized the indications for EUS in rectal cancer after review of the literature and potential impact based on tumor stage. Indications for EUS in rectal cancer include:

(**a**) in a large polyp or small rectal cancer to determine suitability for endoscopic mucosal resection or transanal excision (if the lesion is T1 by EUS);

(**b**) in a large, rectal cancer to determine whether preoperative chemotherapy and radiation is needed or not (T2: radical resection, T3, T4 or N1: preoperative chemoradiation followed by radical resection);

(**c**) surveillance after surgery for rectal cancer.

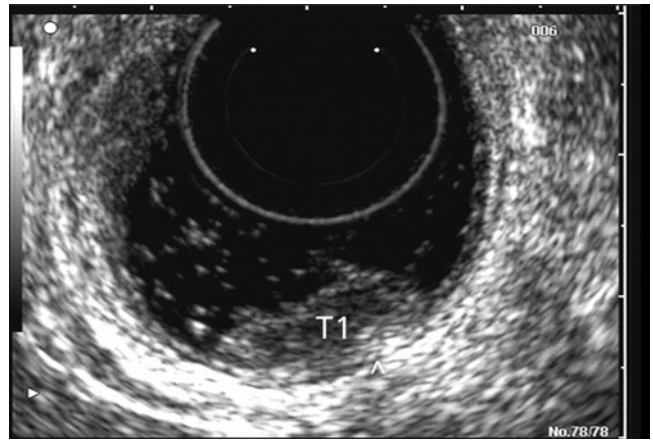

Figure 19.1 A T1 rectal adenocarcinoma (by radial EUS) arising in a villous adenoma with an intact submucosa and muscularis propria (*arrowhead*) underneath.

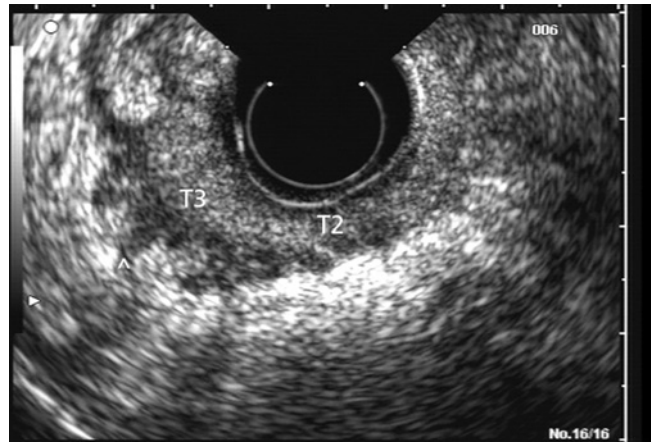

Figure 19.2 Radial EUS image of a rectal adenocarcinoma that appears to be T2 (penetration into muscularis propria) in one portion and T3 (penetration through muscularis propria into perirectal fat; *arrowhead*) in another.

Accuracy of T and N staging

The accuracy of EUS T-staging for colorectal carcinoma varies between 78 and 95% [2–11] though it has been as low as 60 to 69% in some studies [12,13]. In comparison CT and MRI accuracy in staging has been 75% to 85% [14–17]. Both overstaging

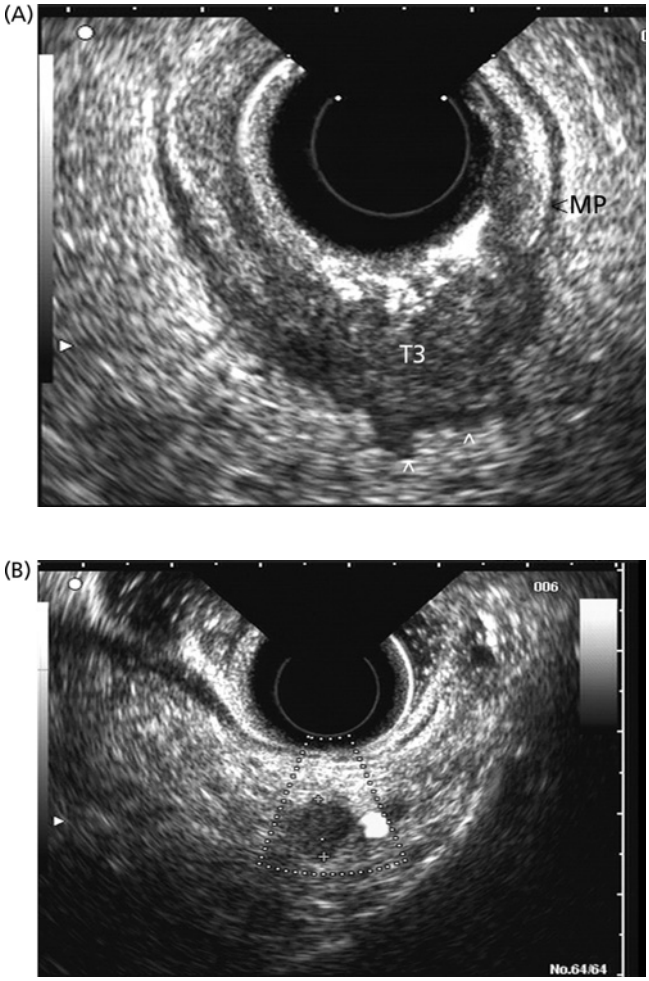

Figure 19.3 (A) Radial EUS of a T3 N1 lesion showing the primary rectal tumor penetration through the muscularis propria (MP) into perirectal fat (*arrowhead*). (B) Radial EUS of the patient in Figure 19.3A showing a 7 mm round, perirectal, hypoechoic lymph node with no flow on color Doppler with an adjoining vessel nearby with color flow.

and understaging may occur. Overstaging seems to be a greater problem than understaging. Overstaging has been attributed to the occurrence of peritumoral tissue reaction [18,19]. N-staging by EUS has been somewhat less accurate in the range of 73 to 83% [10]. This happens primarily due to the fact that all visualized lymph nodes are not necessarily malignant. Multiple echo features of the visualized lymph nodes have been studied including size, sharpness of margins, echogenicity, presence of a echogenic center, round or oval shape, and so on. Lymph nodes that are >10 mm, round, with distinct margins and hypoechoic have been considered to have a much greater chance of malignant invasion in upper gastrointestinal cancers such as the esophagus [20]. However, there is no universal agreement among endosonographers about the features most predictive of malignant invasion [21]. In rectal cancer, the size cut-off for lymph nodes considered as suspicious for malignant invasion is 5 mm instead of 10 mm. The application of EUS-guided FNA may be

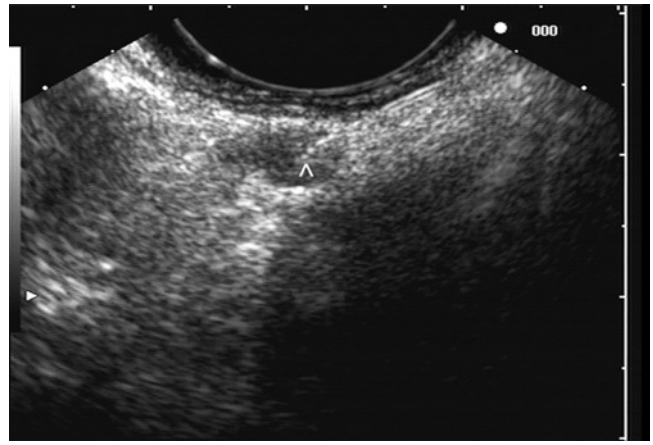

Figure 19.4 EUS guided fine needle aspiration of a perirectal lymph node. The tip of the needle is within the lymph node (*arrowhead*).

used as an adjunct to accurate lymph node assessment during EUS [21] and it has been applied in patients with rectal cancer [22] (Figure 19.4). EUS-guided FNA of lymph nodes is not an option for lymph nodes that are in the immediate vicinity of the primary tumor since traversing of the EUS-FNA needle through the primary will lead to false positive results [3,23].

Glancy et al. [24] performed a study to assess the accuracy of EUS for selection of 156 patients with rectal neoplasia suitable for local excision by transanal endoscopic microsurgery (TEM). EUS (uT stage) was compared to the postoperative histopathological stage of the resected specimens (pT stage). Of the 62 patients undergoing TEM the accuracy was 95% in this group. Among the other 94 patients undergoing an alternative procedure, accuracy of EUS at predicting advanced disease was 89% with an overall accuracy of 92%.

A recent study compared the ability of EUS and two MRI coils to locally stage rectal carcinoma before surgery [25]. Forty-nine patients with rectal carcinoma were staged by EUS and either body coil MRI or phased-array coil MRI. The EUS and MRI findings were compared with histologic findings on the surgical specimen. For local T-staging the accuracy of EUS was 70%, 43% for body coil MRI and 71% for phased-array coil MRI. For N stage, accuracy of EUS, body coil MRI and phased-array coil MRI was 63%, 64% and 76% respectively. For T-staging, EUS had the best sensitivity (80%) and the same specificity (67%) as phased-array coil MRI. For N stage, phased-array coil MRI had the best sensitivity (63%) and the same specificity (80%) as the other methods.

Interobserver variability in rectal cancer staging by EUS

Burtin et al. [26] studied interobserver variability in EUS for rectal cancer staging in 37 patients with rectal cancer. Agreement

was fair for uT1 tumors (k = 0.40) and poor for uT2 tumors (k = 0.20). Agreement was good (k = 0.58; CI 0.51 to 0.65) for uT3 tumors. There was a significant interobserver correlation for the exact measure of the extent of rectal fat invasion (ICC = 0.65). The agreement was also good (k = 0.54, CI 0.47 to 0.61) for metastatic lymph nodes. Roubein et al. [27] also performed a study on interobserver variability in the interpretation of EUS by three endoscopists in the staging of rectal carcinoma in 26 patients. There was agreement of T stage in 88% of patients, with the following kappa coefficients: T1 ($\kappa = 0.00$); T2 ($\kappa = -0.04$); T3 ($\kappa = -0.05$); T4 ($\kappa = 0.00$). N stage agreement was in 73% of patients ($\kappa = 0.42$).

Three-dimensional EUS for rectal cancer staging

Three-dimensional (3D) EUS image reconstruction may improve the accuracy of EUS and may help decrease errors in staging. Kim et al. [28] studied 33 patients using both 3D and conventional EUS for staging rectal cancer. Accuracy of 3D EUS was 90.9% for pT2 and 84.8% for pT3, whereas that of conventional EUS was 84.8% and 75.8%, respectively. Lymph node metastasis was accurately predicted by 3D EUS in 28 patients (84.8%) and in 22 patients (66.7%) by conventional EUS. Another study by Kim and colleagues [29] compared the efficacy of 3D EUS with that of two-dimensional (2D) EUS and computed tomography (CT) for staging of rectal cancer in 86 patients. The accuracy for T-staging was 78% for 3D EUS, 69% for 2D EUS and 57% for CT, with accuracy for lymph node metastases being 65%, 56% and 53%, respectively. Examiner errors were the most frequent cause of misinterpretation, occurring in 47% of 2D EUS examinations and in 65% of 3D EUS examinations [29].

Giovannini recently used a new software program [30] in 35 patients for staging of rectal cancer by 3D EUS that can be used with electronic radial or linear rectal probes. In six of 15 patients classified as having T3N0 lesions, 3D EUS revealed malignant lymph nodes, a finding that was confirmed surgically in five of the six cases. 3D EUS also made it possible to assess the degree of infiltration of the mesorectum precisely in all cases, demonstrating complete invasion of the mesorectum in eight cases. These findings were confirmed in all cases by surgery. 2D EUS accuracy for T and N staging was correct in 25 of 35 rectal tumors (71.4%) while the accuracy with 3D EUS was 31 of 35 (88.6%).

Clinical impact of T and N staging in colorectal cancer

In rectal cancer, preoperative T and N staging is important because sphincter-saving transanal excision of an early (T1N0) lesion can be performed rather than an abdominoperineal resection which can be reserved for more advanced lesions that have penetrated into the muscularis propria or beyond [10,31].

EUS may be useful in predicting malignant transformation in, for example, a rectal villous adenoma prior to surgical excision if invasion to the muscularis propria is seen, which should not happen in a benign adenoma. A simple transanal excision then may not be appropriate in such a case. However, determination of malignancy within a large adenoma at the level of the anal sphincters may be technically very difficult due to artifacts [32].

T and N staging by EUS in rectal cancer is important for T-stage dependent preoperative chemotherapy and radiation protocols. The role of EUS staging in colon cancers throughout the rest of the colon is less clear as these patients would undergo laparotomy and resection anyway, if there are no distant metastases. However EUS may become anportant staging modality for proximal colon cancers with the advent of minimally invasive laparoscopic and endoscopic mucosal resection [33–36] for early lesions.

Harewood and colleagues [11,37–40] have published multiple studies on the clinical impact of EUS in rectal cancer. In the study on cost effectiveness [39] for rectal tumors, evaluation with abdominal CT plus EUS was found to be the most cost-effective approach ($24,468/yr) compared with abdominal CT plus pelvic magnetic resonance imaging ($24,870) and CT alone ($26,076). In a study [40] on clinical impact in rectal cancer EUS staging information changed the surgeon's original treatment plan based on CT alone in 31% of patients. T-staging accuracy was 71% for CT and 91% for EUS ($P = 0.02$). N-staging accuracy was 76% (CT), 82% (EUS) and 76% (EUS FNA) (P = NS). The authors concluded that preoperative staging with EUS results in more frequent use of preoperative neoadjuvant therapy than if staging was performed with CT alone. The addition of FNA of lymph nodes only changed the management of one patient. The authors concluded that FNA seems to offer the most potential for impacting management in patients with early T stage disease. Harewood [11] reviewed all published estimates of EUS accuracy in staging rectal cancer between 1985 and 2003 in the English literature. Both T-staging and N-staging accuracy rates declined over time with the lowest rates reported in more recent literature. The author concluded that the performance of EUS in staging rectal cancer may be overestimated in the literature due to a publication bias, and an inflated estimate of the capability of EUS may lead to unrealistic expectations of this technology.

Although Harewood et al. [40] have suggested that EUS-FNA may have a negligible role in the initial management of rectal cancer, a recent study from the same institution by Levy et al. [41] studied the role of EUS-FNA in staging of rectal cancer by targeting and imaging for the presence of malignant iliac lymph nodes that are designated as M1 stage in rectal cancer. This may alter patient management in relation to surgical candidacy, extent of resection and/or radiation therapy field. Previously rectal EUS studies have not included evaluation of the iliac area for lymph nodes although this is an area accessible to flexible EUS probes in contrast to the rigid endoultrasound instruments.

Levy et al. prospectively studied 457 rectal cancer patients who underwent T, N and M staging by EUS. Suspicious nonperitumoral lymph nodes were sampled by FNA. EUS visualized suspicious

iliac lymph nodes in 32 of 457 rectal cancer patients (7.0%) of which 15/32 (47%) were found to be malignant by EUS-FNA. CT detected iliac lymph nodes in only 7/15 (47%) patients with confirmed malignant iliac lymph nodes. Discovery of malignant iliac lymph nodes by EUS-FNA indicated the need for expansion of the radiation field and extended lymphadenectomy in four patients, and expanded radiation field and palliative nonoperative therapy in 11 patients.

The authors concluded that these data support the routine assessment of iliac lymph node status among rectal cancer patients who undergo EUS. If these results are confirmed at other centers and clear impact of iliac lymph node imaging and FNA is shown by EUS in future studies, then flexible echoendoscopes with FNA capability may have a definite advantage over rigid rectal probes that cannot be advanced in the colon to the level of the iliac lymph nodes. More studies are clearly needed in this direction.

EUS for local recurrence of colorectal carcinoma

Local recurrence of colorectal cancer after attempted curative resection occurs in 2.6% to 32% of patients [42]. Endosonography may be useful in the diagnosis of suspected local recurrence when no lesions arising from the mucosa are seen during conventional endoscopy. EUS in such cases may reveal hypoechoic areas (or areas of mixed echogenicity) outside the colorectal wall. Endosonographic alterations due to the primary surgery need to be kept in mind. Fibrosis at the site of surgery appears hyperechoic. Surgical anastomosis is seen as an interruption of the five-layer echo structure [43]. If staples were used during surgery, they create a very bright localized echo [44]. The risk of recurrence after surgery for rectal cancer is greatest in the first 2 years after surgery. Detection of local recurrence in a resectable stage provides an opportunity for repeat surgery with curative intent. A number of studies have shown EUS to be accurate in detecting recurrent rectal cancer at or near the anastomotic site with EUS-FNA being able to provide tissue confirmation [45–48]. Lohnert et al. [45] performed a prospective study to assess the role of endorectal and endovaginal ultrasound to detect asymptomatic resectable local recurrence in 338 patients. Local recurrence was found in 116 patients (34.3%) which was suggested by EUS and proven by EUS-guided needle biopsy in all cases of unclear pararectal structures that could not be verified by endoscopic biopsy. In the study by Rotondano et al. [46] 62 patients operated on for rectal cancer were prospectively enrolled in a follow-up study including endorectal ultrasound (EUS), serial CEA levels, digital examination, colonoscopy and pelvic CT. Local recurrence occurred in 11 patients; in all cases this was suggested by EUS. In two patients (18%) other techniques had failed to detect recurrent disease, which was identified only by EUS. Hunerbein et al. [47] prospectively investigated the role of EUS with biopsy in the postoperative follow-up of rectal cancer in 312 patients. Local recurrence was found in 36 patients. Intraluminal recurrence was diagnosed by proctoscopy in 12. Transrectal EUS-guided biopsy showed pelvic recurrence in 22 of 68 patients with perirectal masses. There was a strong agreement between EUS-guided transrectal biopsy results and the final diagnosis (kappa = 0.84), the sensitivity and specificity being 91% and 93%, respectively. In comparison, clinical examination ($\kappa = 0.27$), CT ($\kappa = 0.47$), or EUS imaging alone ($\kappa = 0.42$) showed only a moderate level of agreement with the histopathologic diagnosis.

Although many studies have shown the value of EUS in detecting local recurrence in rectosigmoid cancer, the optimal interval for repeating EUS after surgical treatment of rectal cancer is unclear. Joint update [49] of guidelines by the American Cancer Society and the US Multi-Society Task Force on Colorectal Cancer addresses endoscopic (colonoscopy and EUS) surveillance of rectal cancer. This update does recognize that patients undergoing low anterior resection of rectal cancer generally have higher rates of local cancer recurrence compared with those with colon cancer. Although effectiveness is not proven, the joint update states that performance of endoscopic ultrasound or flexible sigmoidoscopy at 3- to 6-month intervals for the first 2 years after resection can be considered for the purpose of detecting a surgically curable recurrence of the original rectal cancer.

Restaging after chemotherapy and radiation

Neoadjuvant chemoradiation is often utilized for downstaging of a rectal cancer prior to surgical resection. Although EUS is very accurate in T and N staging for rectal cancer prior to initiating any treatment, restaging after chemoradiation is problematic. Inflammation and necrosis after chemoradiation appears hypoechoic and indistinguishable from malignant tissue. This results in the obvious problem of overstaging by EUS after radiation and chemotherapy [50,51].

Similarly, lymph nodes visualized prior to treatment may still be present but commenting on whether they are benign or malignant may not be accurate. In a recent study comparing digital rectal examination, CT, endorectal ultrasound and magnetic resonance imaging for predicting T1N0 disease after irradiation of rectal cancers, digital examination had the highest negative predictive value, which still detected only 24% of patients to be free of disease. Endoscopic ultrasound failed to detect the absence of disease in 83% of patients [51]. Similar problems with overstaging after chemoradiation occur in esophageal cancer [50]. Accuracy of EUS for staging rectal cancer after radiation therapy is decreased because of postradiation edema, inflammation, necrosis and fibrosis [3,52,53].

Vanagunas et al. [54] studied the accuracy of EUS in staging rectal cancer after neoadjuvant chemoradiation in a large cohort of patients. EUS staging was performed before and after concurrent 5-fluorouracil and radiotherapy in 82 patients with recently diagnosed locally advanced rectal cancer. All patients underwent subsequent surgical resection and complete pathologic staging. After chemoradiation, 16 patients (20%) had no residual

disease at pathologic staging (T0N0). Overall accuracy of EUS post-chemoradiation for pathologic T stage was only 48%, with 14% understaged and 38% overstaged. EUS accuracy for N stage was 77%. The T category was correctly staged before surgery in 23 of the 56 responders (41%) and in 16 of 24 nonresponders (67%). EUS was unable to accurately distinguish postradiation changes from residual tumor. Similarly another recent study [25] tried to compare the accuracy of EUS staging for rectal cancer before(group I) and following chemoradiation (group II). The accuracy of the T-staging for group I was 86% (57/66). Inaccurate staging was mainly associated with overstaging EUS T2 tumors. In group II, following chemoradiation, overstaging EUS T3 tumors accounted for most inaccurate staging. The EUS staging predicted post-chemoradiation T0N0 stage correctly in only 50% of cases.

Restaging with EUS after chemoradiation, if attempted, should be done with caution with understanding of limitations/pitfalls as well communication with oncologists and surgeons using the EUS information for possible therapeutic decisions. Romagnuolo et al. [55] using a novel brachytherapy protocol for downstaging and achieving high tumor sterilization rates in rectal cancer showed that the sensitivity, specificity and positive and negative predictive values of post-brachytherapy EUS in predicting residual tumor were 82%, 29%, 64% and 50%, respectively. The post-brachytherapy EUS accurately predicted the T stage in only 44% of patients. Most of the errors were due to overstaging.

Linitis plastica of the rectum

Linitis plastica of the rectum (RLP) is a rare phenomenon. It may be a primary rectal carcinoma or metastases from another primary such as gastric linitis plastica, breast carcinoma or prostate carcinoma. Endoscopy generally reveals rectal stenoses with induration and thickening of the folds and an endoscopic mucosal biopsy is positive in only a small number of these cases. EUS in RLP classically reveals circumferential thickening of the rectal wall with a mean thickness of 12 mm, with either a thickening of the submucosa/muscularis propria or disruption of the five-layer echo architecture [41,56–58]; perirectal fat infiltration, ascites, or lymph nodes may also be seen. However, EUS cannot differentiate between primary and secondary rectal linitis plastica. If these patients undergo chemotherapy, EUS may be used to monitor treatment [56].

Anal sphincter defects

Transrectal ultrasound has provided a unique method to image the external and internal anal sphincters [59]. The internal anal sphincter is seen as a thin hypoechoic zone surrounding the anal canal. The external anal sphincter is seen as a heterogeneous echogenic area lateral to the internal anal sphincter. Defects in the continuity of the external and internal anal sphincters can be visualized by transrectal sonography. Imaging of these defects is useful in evaluation of patients with fecal incontinence problems to anatomically define defects in their anal sphincter mechanism [60]. These sphincter defects visualized during anal sonography correlate with physiologic defects by anal needle electromyography [61–63]. Patients with anorectal inflammatory conditions such as Crohn's disease, ileoanal pouch with infectious complications, and radiation proctitis have increased thickness of the anal wall when studied by anal sonography [64].

Submucosal compression of the colorectal wall

It is difficult to predict the cause of an endoscopically visible bulge into the gastrointestinal lumen when the overlying mucosa is normal. Such submucosal compression can be due to an intramural lesion arising from the deeper layers of the gastrointestinal wall or due to an extramural compression by an intrinsic lesion or anatomic structure. Similar to submucosal compressions of the upper gastrointestinal tract, EUS is extremely useful in evaluating lower gastrointestinal submucosal lesions. In the American Endosonography Club study on the clinical utility of EUS, the subgroup where EUS had the greatest impact was patients with submucosal lesions [65]. A lipoma is characterized by a homogeneous, echogenic lesion that is contiguous with the third echo layer corresponding with the submucosa. Most lipomas are benign, and malignant transformation is a rare phenomenon. Thus, there is controversy about the need for endoscopic removal once a lipoma is diagnosed by EUS. However, EUS would be a prerequisite prior to contemplating an endoscopic removal of a lipoma. EUS may also help in monitoring this lesion if it is not removed.

A myogenic tumor appears as a hypoechoic mass that is contiguous with the fourth echo layer representing the muscularis propria (Plate 19.1, Figure 19.5). The differential diagnosis of a myogenic tumor includes a leiomyomia, leiomyosarcoma,

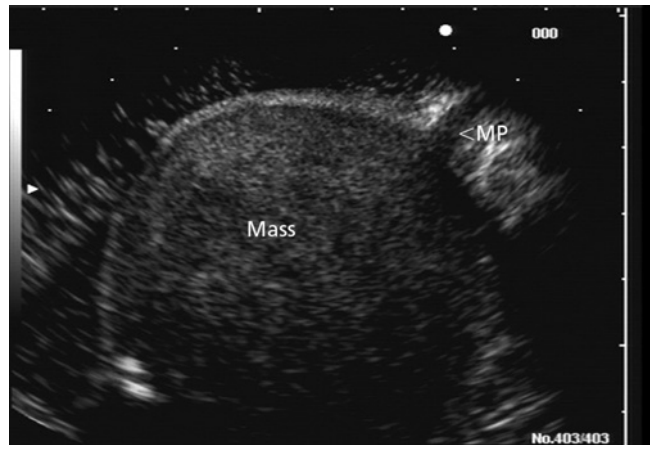

Figure 19.5 EUS of the mass in Plate 19.1 shows it to be to be a hypoechoic mass that is contiguous with the muscularis propria (MP). EUS FNA revealed it to be a gastrointestinal stromal tumor (GIST). air within the fistula.

leiomyoblastoma or a GIST (gastrointestinal stromal tumor). A myogenic tumor, which is >4 cm in diameter, has an irregular margin, with cystic or echogenic foci is more likely to be a malignant lesion [66]. However, there is overlap between benign and malignant myogenic or GIST lesions, and resection of the entire lesion is the surest way to ensure absence of malignancy [67]. If, however, a decision is made to monitor a myogenic lesion that appears benign, EUS may be useful. Any change in echo features such as size, echogenicity, margins or appearance of lymphadenopathy may then warrant a surgical resection.

Myogenic lesions and GISTs may also arise superficial to the muscularis propria from the muscularis mucosa of the colorectal mucosa. Such lesions, if limited to the second and third EUS layers and if small (<1 cm), may be removed by local excision. Enteric endometriosis also appears as a hypoechoic lesion arising from the muscularis propria – the fourth echo layer. However, enteric endometriosis is usually shaped like a spindle or a half moon while myogenic or GIST tumors may be lobulated, especially if the lesion is large [67].

Carcinoid tumors of the rectum are not uncommon [68,69]. They generally appear as a firm, small, submucosal nodule [70]. By endoscopic ultrasound a rectal carcinoid appears as a hypoechoic mass arising from the second echo layer and sometimes compressing or extending to the submucosa. Lesions that are <2 cm in size, with no extension beyond the submucosa by EUS, may be treated locally by endoscopic or transanal surgical excision [71–73]. A more aggressive surgical approach is necessary for rectal carcinoids that are >2 cm and/or reveal invasion into the muscularis propria or regional lymphadenopathy by EUS.

Colonic lymphangiomas can also produce a submucosal compression. By endosonography they appear as multiple, anechoic (cystic) lesions with echogenic septations located within the third echo layer corresponding with the submucosa [67,74–76]. These lesions are generally benign and are left alone unless they cause symptoms such as bleeding, intestinal obstruction or intussception [76]. The endosonographic image of a rectal lesion, colitis cystic profunda, is similar to echo features of colonic lymphangiomas [77,78]. There have also been isolated case reports of endosonography in colonic pneumatosis cystoids intestinalis [79] and polypoid prolapsing mucosal folds associated with colonic diverticular disease [80]. Recurrence of colorectal carcinoma, malignant lymphoma and appendical mucocele may also cause submucosal elevation in the colorectum [67]. Rectal varices may produce multiple submucosal elevations in the rectum. If there is a question about the diagnosis of rectal varices, EUS can reveal multiple anechoic tubular and circular structures in the submucosa and just outside the rectal wall which is the classical EUS image of varices [81].

Sasaki et al. [82] recently published their results on the use of EUS-guided fine needle aspiration for investigation of submucosal and extrinsic masses of the colon and rectum. The aim of this study was to evaluate the use of EUS-FNA for the diagnosis of lesions either within or adjacent to the wall of the colon and rectum. Sufficient tissue for evaluation was obtained from 21 of the 22 patients (95.5%). The overall rate of detection of malignant and benign masses was 95.5% (21/22) for EUS-FNA and 81.8% (18/22) for pre-EUS-FNA imaging investigations. There were no complications related to the EUS-FNA procedure. Some of the lesions that were diagnosed by EUS with FNA in this series included GIST, hemangioma, lymphoma, neuroendocrine carcinoma, lipoma, carcinoid tumor, recurrence of rectal carcinoma and recurrence of other distant malignancies such as gastric and ovarian carcinoma.

There have been a few recent reports [83–85] that suggest that EUS may have an important role in assessing rectosigmoid involvement in patients with endometriosis. EUS has not been extensively used for this condition in the past. Delpy et al. [83] wanted to assess the value of EUS in diagnosing rectal wall involvement by pelvic endometriosis. A prospective study was done in 30 patients who presented with suspected rectovaginal septal endometriosis and underwent anorectal EUS that showed the presence of endometriosis in the rectovaginal septum in 26 patients (88%), in the uterosacral ligaments in 10 patients (33%), and in the ovaries in two patients (6%). The sensitivity, specificity and positive and negative predictive value of anorectal endoscopic ultrasonography as a means of diagnosing endometriosis of the rectovaginal septum and infiltration of the rectal wall were high and found to be 96%, 100%, 100% and 83%, and 92%, 66%, 64% and 92%, respectively. EUS was somewhat less accurate for nodules located away from the EUS probe such as endometriosis in uterosacral ligaments and ovaries. The accuracy for detecting nodules in the uterosacral ligaments or in the ovaries was 56% and 53%, respectively.

In another small case series, the role of EUS and EUS-FNA in the diagnosis of rectosigmoid endometriosis in symptomatic patients was studied [84]. Five women with nonspecific gastrointestinal complaints underwent EUS examination of a rectosigmoid subepithelial mass found on colonoscopy. EUS revealed a hypoechoic lesion infiltrating the muscularis propria and the serosa of the rectal wall, and extending outside the rectal wall. These findings were consistent with rectosigmoid endometriosis. This diagnosis was confirmed in these patients by EUS-FNA, surgical exploration, and/or the patient's clinical course.

Peri-anorectal abscess and fistula

Endosonography is a unique modality to study peri-anorectal abscesses and fistulae [41,86,87]. A fistula during EUS will appear as an anechoic or hypoechoic track in the anorectal area. Air within the fistula can produce moving reverberation echoes confirming its presence. An abscess on the other hand appears as an irregular anechoic or hypoechoic area around the anorectum. Necrotic debris within the abscess cavity may create scattered echogenic foci. Endoluminal ultrasound was performed with rigid probes in 36 patients with Crohn's disease suspected of harboring an abscess and/or fistula. Thirty-two patients were found to have a fistula and an abscess associated with the fistula

was seen in 29 or 32 patients. Seventeen of 32 patients underwent surgery and the EUS presence of an abscess or a fistula was confirmed in all of them [86]. Endoluminal ultrasound is a reliable method for detecting and defining the course of a peri-anorectal fistula [59,88,89].

Interestingly, endoluminal ultrasound and digital examination have been found to be comparable in identifying intersphincteric and trans-sphincteric fistulous tracks [90]. However, a digital examination will not delineate the course of a fistula and is unable to reveal a communication of the fistula with an abscess or an adjacent organ. A comparison has also been made between pelvic CT scan and endoluminal ultrasound for detection of fistulae and abscesses. While endoluminal ultrasound and CT had an equal detection rate for abscesses, ultrasound detected the fistulae in 82% versus 24% by CT scan with surgical findings as the gold standard [91]. The advantages of endoluminal ultrasound in rectal and perirectal disease are its efficacy, safety, simplicity, low cost and lack of radiation.

Schwartz et al. [92] tried to determine accuracy of endoscopic ultrasound (EUS), examination under anesthesia (EUA) and magnetic resonance imaging (MRI) for evaluation of Crohn's disease perianal fistulas in 34 patients. The accuracy of all three modalities was $\geqslant$ 85%: EUS 91%, MRI 87%, EUA 91%. Accuracy was 100% when any two tests were combined. The authors concluded that EUS, MRI, and EUA are accurate tests for determining fistula anatomy in patients with perianal Crohn's disease. The optimal approach may be combining any two of the three methods. Another study by Schwartz et al. [93] suggested that using EUS to guide therapy for Crohn's perianal fistulae with an immunosuppressive (e.g. infliximab) and an antibiotic is associated with a high short- and long-term fistula response rate. EUS may identify a subset of patients who can discontinue infliximab without recurrence of fistula drainage.

EUS in IBD beyond imaging for perianal fistulas

Efforts to differentiate patterns of inflammation between ulcerative colitis and Crohn's disease have been made even by transabdominal ultrasound. The gut wall in ulcerative colitis was found to be thickened and with reduced echogenicity but the five-layer echo structure was maintained. Crohn's colitis, on the other hand, still revealed a thickened and echo-poor gut wall, but the five-layer stratification and differentiation was lost [94]. In vitro data by Kimmey revealed that ultrasound was able to differentiate normal (thickness $<$3 mm) colonic wall from an inflamed colon due to colitis which was thicker than 3 mm. However, differentiation between ulcerative colitis and Crohn's colitis was not very reliable [95]. Experience in endosonography for inflammatory bowel disease is limited, but Shimizu et al. [96] have performed endosonography in patients with ulcerative colitis and Crohn's colitis. They have found progressive thickening of the mucosa and the submucosa, and loss of distensibility of the colonic wall with increasing severity of ulcerative colitis. Five patterns of endosonographic findings in ulcerative colitis based on wall thickening and distensibility have been described [96]. The same group has found that in Crohn's colitis intestinal thickening is patchy and transmural, involving all layers [96].

In cases of indeterminate colitis; Hildebrandt et al. [97] have used EUS to determine whether the inflammation is mucosal or transmural, hypothesizing that patients with transmural disease are more likely to have Crohn's disease. They have then excluded these patients with transmural inflammation from surgical procedures requiring an ileal reservoir as there is a risk of recurrence of disease in the ileal pouch in patients who are on the Crohn's side in the spectrum of inflammatory bowel disease. Using this strategy, this group has found improved outcome in patients undergoing surgery for indeterminate colitis. However, despite the above data, EUS applications for inflammatory bowel disease are limited for lack of further data. However, EUS is a useful modality for evaluation of peri-anorectal fistulae and abscesses in inflammatory bowel disease, especially in Crohn's disease.

A number of studies have been performed on the role of EUS in imaging ulcerative colitis (UC), Crohn's colitis and indeterminate colitis [98–100]. Yoshizawa et al. [101] undertook a study to determine whether EUS is useful for evaluating the depth of intestinal inflammation, predicting the response to medical treatment, and determining the necessity for surgery in 42 patients with active UC. Intestinal inflammation was extended into the muscularis propria or deeper on preoperative EUS in a significantly higher percentage of patients who required surgery (67%, 10/15) than in patients in whom remission was induced by medical treatment (19%, 5/27; $P = 0.002$). The authors suggested that EUS can objectively evaluate the degree of vertical spread of intestinal inflammation in UC and that EUS is useful for predicting the response to medical treatment and for determining the necessity for surgery in active UC. However, the accompanying editorial by Maple and Edmundowicz [102], raised a number of questions that must be addressed in future studies to clarify the role of EUS in the management of inflammatory bowel disease such as: Are EUS findings reproducible? Which scoring system is the best? And what is the clinical impact in decision making? For the present time however they have suggested that the "the forecast is still cloudy" for routine application of EUS in UC and Crohn's disease for examination of the colonic wall by EUS.

EUS-guided drainage of perirectal abscesses

There are a few early reports of EUS-guided drainage of perirectal pelvic abscesses. Attwell et al. [103] reported a case of EUS-guided drainage of diverticular abscess as an adjunct to surgical therapy. In a series by Giovannini by colleagues [104] clinical efficacy of EUS-guided transrectal aspiration and drainage by plastic prosthesis of deep pelvic abscesses, using a therapeutic echoendoscope, was studied in 12 patients. No major complication occurred during this study. Transrectal stent insertion succeeded in nine patients. In three patients, only aspiration

was possible without the ability to insert a stent for drainage. The nine patients in whom a stent was successfully introduced into the fluid collection, complete drainage without relapse was achieved in eight patients at a mean follow-up of 10.6 months. The stent was removed via endoscopic means after 3 to 6 months. Drainage was incomplete in one patient who subsequently needed surgical drainage. Two of the three patients in whom aspiration alone was performed developed a recurrence of the abscess and required surgical treatment.

More recently, Varadarajulu et al. [105] reported a case series on EUS-guided transrectal catheter placement for pelvic abscess drainage. This was a prospective study of poor-risk surgical patients who underwent EUS-guided drainage of pelvic abscesses that were not amenable for drainage by ultrasound or CT guidance. After accessing the abscess cavity with a 19-gauge needle, guide wire was passed into the abscess cavity with dilation of the tract and placement of a 10 Fr transrectal single pigtail catheter. The catheter was flushed periodically with normal saline and discontinued when abscess resolution was documented on follow-up CT. Of six patients referred for EUS, two were excluded as one had a large rectocele and another a multiloculated fluid collection with immature walls. The remaining four patients underwent EUS-guided drainage. The procedure was technically successful in all patients. No procedure-related complications were encountered. The mean duration for abscess resolution was 6 days. The above studies in a limited number of patients show that EUS-guided drainage of deep pelvic abscesses may be considered in some carefully selected patients as adjunct or alternative treatment to surgery.

Conclusion

In conclusion, EUS continues to be useful for a variety of conditions of the colon and rectum. Recent developments in this technique in the colorectal area have been in the field of confirming and assessing the clinical impact of staging of rectal carcinoma, technological improvements (e.g. 3D EUS), assessing recurrence of rectal carcinoma with EUS becoming part of postrectal cancer surgery surveillance guidelines, evaluation of rectocolonic subepithelial lesions and development of techniques for EUS-guided therapy.

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20 Therapeutic Endoscopic Ultrasound

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Endoscopic ultrasound (EUS) combines two modalities, endoscopic visualization and high-frequency ultrasound, thereby permitting precise delineation of the individual layers of the gastrointestinal tract [1]. In comparison to computed tomography and magnetic resonance imaging, EUS appears to have a unique advantage of allowing placement of a biopsy needle into lesions that are often too small to be identified by imaging techniques or too well encased by surrounding vascular structures to allow safe percutaneous biopsy. Rapid strides have made EUS advance from a purely diagnostic procedure to an interventional modality. The aim of this chapter is to give an overview of the present status of EUS-guided therapy, suggestions on how to perform these procedures, and future perspectives.

Definitions

Interventional EUS may be defined as a procedure where EUS, directly or indirectly, is used for monitoring of an interventional procedure. An interventional EUS procedure can be either a diagnostic or a therapeutic procedure. Therefore, it seems reasonable to define two different ways of performing an EUS-guided intervention.

EUS-directed intervention: A procedure where the entire intervention or part of it is directly and simultaneously monitored by endoscopic ultrasound.

EUS-assisted intervention: A procedure that requires the aid of endosonography to be completed. EUS can be performed either immediately before or simultaneously with the interventional procedure. However, the EUS-assisted intervention is not directly monitored by ultrasound.

In order to perform an EUS-directed therapeutic intervention, an endoscope with linear transducer technology has to be used since this is the best way to monitor the intervention by ultrasound, whereas an EUS-assisted intervention can be performed with both radial and linear transducers.

A therapeutic EUS intervention may comprise EUS-guided injection for therapeutic purposes, EUS-guided drainage procedures, EUS-guided resection of various lesions or EUS-guided antitumor therapy.

EUS-guided injection

Since the first description of EUS-guided fine needle aspiration [2], the idea of EUS-guided injection in order to deliver substances into structures or lesions outlined by EUS has been an obvious challenge. The early reports of EUS-guided injections were injection of contrast media into dilated duct systems under fluoroscopy. Since then a growing number of case series, case reports and preliminary report has been published.

Celiac plexus neurolysis

Pancreatic cancer and chronic pancreatitis commonly produce pain that is difficult to control [3,4]. Although opioids effectively relieve pain, they are frequently associated with side effects. When conservative therapy fails to adequately control the patient's pain, celiac plexus neurolysis or block may provide significant relief. Celiac plexus block has traditionally been performed percutaneously under radiologic guidance [5]. Since the celiac ganglion is consistently located at the origin of the celiac artery from the aorta and is well visualized during EUS, celiac plexus neurolysis can be performed using a transgastric approach.

Technique

Linear EUS imaging from the posterior lesser curve of the gastric body allows identification of the aorta, which appears in a longitudinal plane. The aorta is traced distally to the celiac trunk, which is the first major branch below the diaphragm. Color Doppler can confirm the vascular landmarks. A 22-gauge needle is primed with saline solution and placed through the biopsy channel and affixed to the hub. The needle is inserted under

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EUS guidance immediately adjacent and anterior to the lateral aspect of the aorta at the level of the celiac trunk. The needle is flushed with 3 mL of normal saline solution to remove any tissue acquired during insertion. An aspiration test is performed to rule out vessel penetration before each injection. For celiac plexus neurolysis in pancreatic cancer patients, 10 mL (0.25%) of bupivacaine is injected, followed by 10 mL (98%) dehydrated alcohol. The alcohol, which produces an echogenic cloud, may lead to discomfort despite sedation. Before withdrawing the needle, it should be flushed with 3 mL of normal saline solution to prevent seeding of the needle track with alcohol. The entire process is then repeated on the opposite side of the aorta. Occasionally, altered anatomy resulting from significant lymphadenopathy and/or bulky tumors may necessitate injection of the entire solution into one site. The efficacy of unilateral versus bilateral injection has never been formally studied and many endosonographers only inject the solution directly on top of the celiac trunk. After the procedure, the vital signs are monitored for 2 hours. Before discharge, the blood pressure is checked in both a supine and erect position to assess for orthostasis. Celiac plexus neurolysis is routinely performed as an outpatient procedure.

For celiac plexus block in patients with chronic pancreatitis, some physicians substitute a steroid (triamcinolone suspension 40 mg bilateral, 80 mg unilateral; Fujisawa USA, Deerfield, IL) in place of alcohol. Although its use in patients with benign disease is controversial, the investigators administer a small volume of alcohol (4 mL bilateral, 8 mL unilateral) in addition to the steroid to increase the neurolysis. If alcohol, which is bactericidal, is not given along with the steroid, then the investigators recommend administering broad-spectrum antibiotics, particularly if the patient is receiving acid-suppressive therapy.

Results

Wiersema [6] published a large study of 58 patients evaluating EUS celiac plexus neurolysis for pain secondary to inoperable pancreatic cancer. Neurolysis was performed by injecting 3 to 6 mL (0.25%) bupivacaine and 10 mL (98%) alcohol into both sides of the celiac region. Pain scores were assessed using a standardized 11-point visual analogue scale. A total of 45 patients (78%) experienced a drop in pain score after EUS celiac plexus neurolysis. The overall pain scores were significantly lower ($P < 0.0001$) 2 weeks after the procedure. A multivariate analysis showed that patients found sustained pain relief for 24 weeks independent of morphine use or adjuvant therapy. However, patients who received chemotherapy alone or chemotherapy plus radiation had additional benefit. Pain relief resulting from adjuvant therapy increased over time and at 24 weeks was statistically significant ($P = 0.002$). Although opioid administration increased throughout the study, the increase was not statistically significant. There were no major complications. Minor complications were mild and transient and included postural hypotension (20%), diarrhea (17%) and pain exacerbation (9%).

While this study offers preliminary data suggesting the efficacy and safety of EUS celiac plexus neurolysis, the small sample size, the absence of a placebo control group, and no physician or patient blinding limits the strength of the conclusions. Despite 45 patients (78%) experiencing a drop in pain score, only 31 (54%) experienced a decline of greater than 2 points, which is a measure of improvement that some consider necessary to signify efficacy. The benefit of EUS celiac plexus neurolysis diminished at 8 to 12 weeks, after which pain scores in patients not receiving adjuvant therapy increased.

A small percentage of patients undergoing EUS-guided celiac plexus neurolysis or block may experience postural hypotension (1%) and diarrhea (4% to 15%), transient increases in pain (9%) [6]. These complications are due to the sympathetic blockade and are usually self limited and are easily treatable by saline infusion (postural hypotension) and anti-diarrheals. A single case of pseudoaneurysm of the splenic artery after EUS-guided celiac neurolysis using bupivacaine and alcohol has been reported [7]. There has also been a case report of an intra-abdominal abscess occurring after EUS-guided celiac plexus block in a patient with chronic pancreatitis using bupivacaine and steroids. The most dreaded complication of celiac plexus neurolysis is paraplegia. This complication is seen in about 1% of patients undergoing percutaneous radiology-guided celiac plexus neurolysis through a posterior approach. Since EUS-guided celiac plexus neurolysis is performed through an anterior approach with a short needle track it has been theorized that the chances of paraplegia may be less by using EUS as compared to a posterior percutaneous approach [5,8].

At this time, it is reasonable to conclude that EUS celiac plexus neurolysis, when performed by experienced endosonographers, is a safe and efficient procedure, but many additional studies are needed.

Botulinum injection in achalasia

Originally reported by Pasricha et al. [9], endoscopic injection of botulinum toxin into the lower esophageal sphincter in patients with achalasia is safe and widely used. The reported short-term symptomatic improvement is 90%, but with lower sustained response because the technique of delivery is "blind" [10]. The lower esophageal sphincter can be accurately visualized by EUS as an echo-poor structure in the lower esophageal wall, and using high-frequency transducers even the longitudinal and the circular anatomy of the muscle layer of the esophagus may be seen [11–16]. Several authors have reported on the use of EUS in patients with achalasia, and suggest that the lower esophageal sphincter may be thickened in these patients [10–16]. A few studies have described the use of EUS-directed injection of botulinum toxin selectively into the lower esophageal sphincter in patients with achalasia [10,11,15]. However, no large randomized and controlled series comparing the blind endoscopic method with the EUS-guided method have been reported.

Injection therapy in upper gastrointestinal bleeding

There has been considerable interest in the evaluation of varices by EUS. Catalano and his group [17] made some very interesting

observations when comparing EUS-assisted sclerotherapy with band ligation in esophageal varices; in a small study of 14 patients, EUS-assisted sclerotherapy required significantly fewer sessions to achieve variceal obliteration and it decreased the rate of rebleeding and mortality from recurrent variceal bleeding. Lahoti et al. [18] performed real-time EUS-guided sclerotherapy in five patients with nonbleeding esophageal varices. There were no complications, and varices were obliterated in 2.2 sessions on average. They concluded that the confirmation of obliteration of varices coupled with the ability to obliterate the perforating veins, which is not possible with standard sclerotherapy or banding techniques, might decrease the number of sessions and variceal recurrence. Whether secondary prevention of gastric or esophageal variceal bleeding by color flow and Doppler-assisted EUS-guided fine needle injection improves morbidity and mortality is unknown. Logistic problems with EUS-directed therapy in acute variceal bleeding are similar to those of acute ulcer bleeding and represent a significant handicap to the application of EUS in this area.

A few studies have shown EUS to be helpful in targeting therapy in patients with upper gastrointestinal bleeding. In a study by Lee et al. [19], patients with gastric variceal bleeding underwent bi-weekly EUS of gastric varices followed by injection of cyanoacrylate until gastric varix obliteration was documented by the absence of anechoic vascular structures in the gastric wall. They found a statistically significant reduction ($P = 0.0053$) in the rebleeding rate compared with their non-EUS control group ($n = 47$).

Steroid injection in refractory gastrointestinal tract strictures

Endoscopic ultrasound miniprobe-assisted steroid injection in patients with refractory esophageal strictures has been reported in a preliminary study [20]. In three patients not responding to dilation and subsequent blind injection of triamcinolone acetonide (40 mg/mL), a 12.5 MHz radial scanning miniprobe (Microvasive, Boston Scientific Corp.) was passed through a standard endoscope in order to examine the most thickened area for steroid injection. After dilatation of the stricture, 0.5 mL aliquots of steroid solution were injected in each of four quadrants at the thickest site of the stricture as judged by endosonography. All three patients had symptomatic improvement but no long-term results are yet available. There are at present no controlled studies demonstrating that steroid injection is of any benefit in patients with benign esophageal strictures.

EUS-guided pancreatic cyst ablation

EUS plays a very important role in the evaluation of pancreatic cystic neoplastic lesions. High-resolution ultrasound imaging provides a detailed evaluation and directs fine needle aspiration. Using principles of ethanol ablation, EUS-guided ethanol lavage may offer an alternative to surgical resection of cystic neoplasm. Currently the technique employed for the ablation of pancreatic cystic lesions involves lavage of 80% ethanol over a 5-minute period [21]. Only thin-walled unilocular lesions with a diameter between 1 and 5 cm are ideal, but a small number of septations are permitted. Intraductal lesions have not been treated, and cystic lesions that communicate with the main pancreatic duct are excluded from treatment. The most common complication is transient abdominal pain, which occurs in less than 10% of patients. A small percentage of patients have experienced transient pancreatitis. There are no reports of infections, bleeding, or thrombosis. In the fist step of lavage the cyst is aspirated with a 22-gauge needle. The cyst fluid is evacuated until the cyst collapses. With the needle in place, 80% ethanol is repeatedly injected and lavaged over a 5-minute period. At the conclusion of the treatment session, the cyst contents are completely evacuated.

In a further study [22], 25 patients with pancreatic cystic lesions of unknown subtype underwent FNA and subsequent injection of variable concentrations of ethanol (0% to 95%). The authors hypothesized that a one-time injection of ethanol would ablate the epithelial lining of the cyst, regardless of the histologic subtype. The results of the study were encouraging and resulted in no complications. Of the 25 patients 23 had complete follow-up by way of resection (5 patients) or repeat imaging. Eight of the 23 patients had complete radiologic resolution. Five patients underwent subsequent resection and showed variable degrees of epithelial ablation. A small number of patients have undergone repeated ethanol lavage with evidence of decreasing cyst fluid CEA concentration and gradual decrease in cyst diameter. Long-term studies will be required to determine whether ethanol lavage is capable of preventing the development of malignancy.

EUS-guided neuroendocrine tumor ablation

Surgical resection is currently considered to be the criterion standard for treatment of insulinomas. EUS-guided ethanol ablation of endocrine tumors has been reported [23] in a 78-year-old female. Because of severe complications during several hypoglycemic episodes, a poor general condition, and strict refusal of surgical resection, the decision was made to ablate the insulinoma by EUS-guided alcohol injection. A total of 8 mL 95% ethanol was injected into the tumor. The patient was discharged and exhibited no further hypoglycemic episodes, and her general condition improved rapidly. EUS-guided ablation may become a minimally invasive alternative for patients with insulinomas in whom surgery is not feasible.

EUS-guided drainage procedures

A growing number of EUS-guided drainage procedures have been reported alongside the introduction of EUS endoscopes with working channels large enough to allow introduction of catheters and stents. These procedures may be entirely monitored on ultrasound but many of these require both monitoring by ultrasound and endoscopic visualization either with the EUS endoscope itself or after exchange with a second endoscope. A variety of procedures have been described ranging from pancreatic pseudocyst drainage, bile duct drainage, pancreatic

duct drainage, abscess drainage, drainage of fluids and percutaneous EUS-guided gastrostomy.

Pseudocyst drainage

Endoscopic drainage of pancreatic pseudocysts, either transgastric or transduodenal, has become an established alternative to surgical treatment. Endoscopic pseudocyst drainage has some limitations due to the potential risk of puncture of vessels interposed between the cyst and the gastric wall with the risk of hemorrhage being 6%. Endoscopic transmural drainage of pancreatic pseudocysts is a relatively "blind" approach. The risk of perforation is particularly high when endoscopically visible intraluminal bulging is absent [24,25].

EUS allows precise assessment of the cyst anatomy, including its location, possible feeding duct, and content, as well as the shortest path between the gastric or duodenal wall and the cyst. Thus the most optimal puncture site can be selected and puncture of interposed vessels avoided [26–36]. The initial endosonographic evaluation can be done using either a radial or curved array echoendoscope. Three slightly different ways of endosonographically guided cystogastrostomy have been described.

Cyst drainage can be EUS assisted, where the EUS-guided forceps marks the mucosa [33]. The subsequent stent placement is then performed "semi-blindly" using the standard endoscopic approach.

In the two-step method the pancreatic pseudocyst is punctured under direct endosonographic guidance (EUS-directed puncture) using a diathermy needle housed in a plastic catheter or a 19-gauge needle [27,29]. Once inside the pseudocyst, the diathermy needle inside the catheter or the stylet inside the needle is replaced with a guidewire. The echoendoscope is then withdrawn and a large channel duodenoscope is inserted to perform an over-the-wire insertion of the endoprosthesis after dilatation of the tract. A major drawback of both techniques is the need to exchange the ultrasound endoscope with a standard endoscope to allow introduction of an endoprosthesis.

In the single-step method the EUS-guided pseudocyst drainage procedure is entirely performed through the echoendoscope. The first step of the procedure is to puncture the cyst under EUS direction using either a 19-gauge needle and a 0.035″ or 0.038″ guidewire, or to puncture the cyst with a needle wire with electrocautery followed by guidewire insertion. This procedure is entirely monitored by ultrasound. The second step is to dilate the tract using either a dilator catheter or a TTS balloon and finally to deliver the stent. The latest technology linear EUS endoscopes have instrument channels of 3.8 mm diameter and allow the introduction of a 10 Fr endoprosthesis. It is recommended to insert two or three stents depending on the size of the cyst.

Technique

The following technique is our own preferred method. We start by localizing the cyst by EUS and evaluate the contact zone between the gastric or duodenal wall and the cyst wall. Doppler assessment of the stomach or duodenal wall for interposed vessels should always be carried out. Having determined the optimal site for puncture, the pancreatic pseudocysts is punctured using a 19-gauge FNA needle or a needle knife, and a sample of the cyst contents is aspirated and submitted for biochemical, cytological and tumor marker (e.g. CEA) analysis. If infection is suspected, a sample should be sent for gram stain, culture and sensitivity.

Contrast filling of the pancreatic pseudocyst may be performed under fluoroscopy to document the size and anatomical boundaries of the cyst but this is not mandatory and we do not do this in our own practice. Communication of the cyst with the pancreatic duct may be seen. Filling of the cyst can also be verified by EUS seen as a visible streamline effect. A guidewire is coiled up inside the cyst via the 19-gauge needle or the needle knife. The tract is dilated using an 8 to 10 mm balloon over the wire. Even this dilatation procedure may be fully monitored during EUS. A nasocystic drain or stent is placed to drain the pancreatic pseudocyst or pancreatic abscess. The choice between a nasocystic catheter or a stent for drainage will depend on the appearance of the cyst contents. A chronic cyst with clear liquid contents can be drained with stents alone. An infected cyst mandates irrigation by a nasocystic catheter. The nasocystic catheter can be removed after 7 days and exchanged for a large-bore stent. Pancreatic cysts complicating necrotizing pancreatitis can be managed endoscopically but require aggressive irrigation and drainage over an extended time period.

Results

A relatively large number of publications, mainly case series, has been published. There are no randomized or controlled studies comparing different methods at present.

Giovannini et al. [37] drained 35 pancreatic cysts under EUS guidance, of which 15 were pseudocysts and 20 were pancreatic abscesses. Of the 33 transgastrically drained cysts, in only one patient was an extrinsic compression seen using a forward-viewing gastroscope. No major complications occurred except a pneumoperitoneum in one patient, which was successfully managed conservatively. No bleeding was encountered. A 7 Fr nasocystic drain was placed in 18/20 cases of pancreatic abscess. Surgery was performed in the other two patients. In the pseudocyst group, placement of an 8.5 Fr stent was successful in 10 patients and a nasocystic drain in five. In one case, only cyst puncture and aspiration was performed. Over a mean follow-up of 27 months (6 to 48 months) one recurrence among the 15 pancreatic pseudocysts and two relapses of the 18 pancreatic abscesses have been observed. The EUS-guided drainage success rate was 88.5% (31/35); only four patients with pancreatic abscesses underwent surgery.

Seifert et al. [38] evaluated a new one-step stenting device using a large channel echoendoscope (3.2 mm) for pseudocyst drainage in 6 patients. One of them had a pancreatic abscess. Transmural drainage was successful using modified 7 Fr stents. There were no complications encountered with the endoscopic interventions. One patient with necrotizing pancreatitis, who refused surgery, died secondary to sepsis. At follow-up after

3 to 13 months the cysts had completely resolved in four patients. This study confirmed the feasibility and effectiveness of EUS-guided one-step technique in draining various cystic lesions; however, larger studies are needed. In a subsequent study and using the one-step device through a 3.7 mm channel echoendoscope, the same group was able to place a 10 Fr stent in three patients and a 7 Fr in one patient, all with peripancreatic cystic lesions. One of the cysts had persisted for more than 3 months and was found to be a ganglioneuroma after surgical enucleation.

Binmoeller et al. [27] reported EUS-guided pseudocyst drainage in 27 patients with a mean cyst diameter of 11 cm. Pseudocyst puncture and drainage was successful in 25 patients and failed in 2 patients due to procedure-related bleeding. The primary late complication was cyst infection, which occurred in 13 patients due to stent clogging. These patients were treated by stent drainage alone. Pseudocysts resolved in 21 patients, giving an overall success rate for EUS-guided pseudocyst drainage of 78%.

Bile duct drainage

Endoscopic biliary stenting is the most common method of treating obstructive jaundice [39,40]. But in 3% to 12% of cases, selective cannulation of the major papilla fails and surgery or percutaneous biliary drainage is required [41]. Percutaneous transhepatic drainage requires dilated intrahepatic biliary ducts and the reported rate of complications reach 20% including intraperitoneal bleeding and bile peritonitis [42,43]. A new technique of biliary drainage using EUS-guided puncture of the intrahepatic bile ducts or the common bile duct is now possible. The procedure may either be performed directed by EUS or partly directed and assisted by EUS. Several approaches have been described either via the duodenum or the stomach into the common bile duct, hepatic duct or intrahepatic duct system. Stent insertion may be performed via the echoendoscope, by exchange of endoscopes or as a rendezvous procedure with ERCP.

Transcholedochal approach

The echoendoscope is placed in the distal antrum or duodenum, permitting imaging of the dilated choledochus. Color Doppler is used to identify regional vasculature. Bile duct punctures with a 19-gauge needle is then performed under fluoroscopic and endosonographic control. After successful biliary access, bile is aspirated through the needle, and contrast is instilled under fluoroscopy to demonstrate biliary opacification. A guidewire is introduced through the EUS needle and advanced in an antegrade fashion, to cross the biliary obstruction and advance the guidewire into duodenum. In some cases, the obstruction can only be transversed by impaction of a bougie into the stricture to create an anchoring point from which the guidewire can be forced across the obstruction. In cases where the guidewire cannot be advanced across the obstruction, a transenteric fistula is created in an attempt to decompress the biliary tree.

If the guidewire has successfully been advanced into the duodenum, either a rendezvous procedure with ERCP is performed or the procedure is completed in an antegrade fashion. The choice between the two alternatives depends on the accessibility to the ampullary orifice, the anatomy of the patient, and the ease of stent deployment.

Transhepatic approach

The echoendoscope is placed at the cardia or lesser curve and oriented to visualize the intrahepatic biliary system. Color Doppler is used to identify regional vasculature. Bile duct puncture is performed with a 19-gauge EUS needle and a guidewire is advanced in an antegrade fashion through the EUS needle, in order to cross the biliary obstruction and advance the guidewire into the duodenum. The rest of the procedure and its restrictions are similar to the previous approach.

Hepaticogastrostomy

This method was first described in 2003 by Giovannini et al. [44] and can be seen as a variation of the intrahepatic approach, but without selective drainage through the Ampulla. A 19-gauge needle is inserted transgastrically into the distal part of the left hepatic duct and contrast medium is then injected. The needle is exchanged over a guidewire for a 6.5 Fr cystoenterostome (EndoFlex, Voerde, Germany) which is used to enlarge the channel between the stomach and the left hepatic duct with the application of cutting current. A plastic hepaticogastric stent or a covered metallic expandable stent can then be inserted. To prevent bile leakage, Giovannini et al. recommend placement of a 6 Fr or 7 Fr nasobiliary drain inside the metallic stent for 48 hours.

Results

Burmester et al. [45] performed endoscopic ultrasound-guided cholangio drainage (ECD) in four patients, with successful 8.5 Fr stent placement in three, and one bile leak as a complication. In two cases Mallery et al. [46] performed ECD by cannulation adjacent to an EUS-placed wire, with a minor complication of wire passage outside the bile duct lumen. Puspok et al. [47] reported a total of six successful ECDs with no immediate complications. Another bile leak was reported by Ponnudurai et al. [48] in a patient with malignant biliary obstruction treated with EUS-guided hepaticogastrostomy followed by the deployment of a covered Wallstent.

Kahaleh et al. [49] performed ECD in 23 patients. Of these patients 17 presented with malignant strictures while 6 had benign conditions. Intrahepatic cholangiography was performed in 18 of the patients with conversion to an extrehepatic intervention in 5 (27%). Of the 13 patients who therefore underwent intrahepatic intervention, 11 had a stent placed across the major papilla. In one patient, a cholangiogastric fistula was created with placement of a double pigtail stent. Resolution of obstruction occurred in 12 or 13 patients, giving a success rate of 92%. The individual in whom no intervention was successful had primary sclerosing cholangitis with tortuous ducts and multiple strictures through which a guidewire could not be advanced. This patient was referred for surgery. One patient had minor bleeding during the procedure that was noted as filling defects within the

bile duct during cholangiography. The bleeding spontaneously resolved and the patient was monitored for 24 hours with no appreciable drop in hematocrit.

A total of 10 patients underwent an extrahepatic approach, this includes the five in whom an intrahepatic approach was initially attempted. Of these patients, nine underwent successful placement of a biliary stent with decompression. In two individuals, either a choledochoduodenal fistula or a choledochogastric fistula was created, with improvement of jaundice. One failure occurred in a patient with an impacted common bile duct stone; this patient required a percutaneous transhepatic drain with subsequent internalization of the drain. One significant and two minor complications occurred with the extrahepatic approach. One patient developed a bile leak which was diagnosed 48 hours after the procedure, requiring percutaneous drainage. Other minor complications were two cases of self-limiting pneumoperitoneum. The overall reported success rate of ECD was 89% with an overall rate of complication of 18% that included three major complications.

Pancreaticogastrostomy

Endoscopic ultrasonography may be used to access a dilated pancreatic duct which cannot be drained by conventional ERCP due to complete obstruction. By using an interventional echoendoscope, the dilated main pancreatic duct can be visualized from the stomach. EUS-directed puncture with a 19-gauge needle can then be performed under combined fluoroscopic and ultrasound guidance. The procedure can be completed either as a drainage procedure with insertion of a stent over a guidewire between the duct and the stomach after dilatation of the tract, or as a rendezvous procedure after passing the obstruction with a guidewire, and completing the procedure with a duodenoscope from the duodenum. Only a few case series using this procedure have been described.

Abscess drainage

A number of publications have reported on EUS-guided abscess drainage. Most series have dealt with pelvic abscess drainage but small case series or case studies have been reported with abscesses located in the mediastinum, the subphrenic region, the peripancreatic region, and within the liver [50]. Pelvic abscesses frequently occur after obstetric surgery and after colorectal resection for cancer [51]. As an alternative to traditional surgical, transrectal and transgluteal drainage, transrectal and transvaginal ultrasonographically guided aspiration and catheter drainage of gynecologic pelvic abscesses have been reported in the literature with a high rate of success [51–54]. Giovannini et al. [55] reported this method in 12 patients using a EUS-guided technique for a perirectal or a pelvic abscess. The drainage of these collections was performed under EUS guidance using therapeutic EUS scopes with a large working channel. Transrectal stent insertion succeeded in nine patients. In five patients a 8.5 Fr straight endoprosthesis was inserted into the collection, in three patients a 10 Fr double pigtail stent was placed into the suppurate cavity, and one patient received two stents (8.5 Fr and 10 Fr) for a large perirectal abscess. Concerning the nine patients in whom a stent was placed into the collection, a complete drainage without relapse occurred in eight patients (mean follow-up 10.6 months; range 6 to 14 months). The stents were removed endoscopically after 3 to 6 months (mean 4.3 months). Drainage was incomplete in one case (large abscess >8 cm in diameter) and the patient underwent a surgical drainage. This study showed that EUS-guided drainage of postoperative perirectal abscess is possible using stents of 8.5 Fr or 10 Fr placed into a collection through the rectal wall. Stenting is more accurate than simple aspiration of the collection.

Percutaneous endoscopic gastrostomy

Endoscopic ultrasound-assisted placement of a percutaneous endoscopic gastrostomy tube (PEG) in an obese patients has been described where transillumination of the abdominal wall by a standard endoscope could not be achieved [56]. A radial scanning ultrasound endoscope was used to image the anterior abdominal wall from the stomach. The anatomy of the stomach wall layers and the echogenic abdominal wall adipose tissue were clearly seen. The optimal position for placement of the PEG tube was confirmed by both the visual and EUS appearance of the proposed tract. The ultrasound image of a finger depressing the abdominal wall from outside the patient was demonstrated. No intervening bowel loops or liver parenchyma were seen, and this site was used for endoscopic PEG placement. Whether this technique may avoid the feared complication of perforation of interposed intestines is an open question.

EUS-guided resection

Endoscopic resection of an elevated mucosal or submucosal lesion in the upper gastrointestinal tract has become an attractive alternative to open surgery. Immediate recovery from an inexpensive and complete endoscopic procedure is highly cost effective compared to surgery and has obvious acceptability for the patient. However, problems with perforation and bleeding, and in cancer patients the crucial question of radicality, have reduced the initial enthusiasm. Following the introduction of dedicated endoscopes and EUS miniprobes, endoscopic resection gained favor. At least theoretically, EUS might outline the lesions in question, and thereby aid the clinical decision as to whether endoscopic resection is possible or not based on size, intramural location and the location of interposed small-caliber vessels. EUS can monitor the endoscopic resection procedure by guiding the submucosal injection prior to resection (or decide that this is not necessary) and monitor the resection itself and the immediate follow-up after resection. Sun et al. [57] reported the results of 16 patients with submucosal tumors in which endoscopic mucosal resection was aided by EUS-guided saline injection. The 16 patients had lesions that were mucosal ($n = 1$), submucosal ($n = 6$), or invading the muscularis propria ($n = 9$). They had no perforations and no recurrences at 12 to 17 months of

follow-up. Whether EUS-guided injection is safer or necessary is unknown. In our own experience submucosal tumors up to 3 cm can be resected endoscopically if the proper muscle layer can be seen intact underneath the lesion [58].

EUS-guided tumor therapy

EUS has focused attention on the large group of patients with upper gastrointestinal tract malignancy who either have disseminated disease or in whom therapeutic options are limited due to concurrent disease. The search for more effective treatment strategies, include new methods for directed tumor destruction, have intensified, and following the introduction of EUS-FNA, EUS-directed tumor therapy seems to be, at least in theory, a new option for more intensive and accurate targeted therapy. EUS-directed tumor therapy can be applied to the primary tumor (e.g. liver, pancreas, stomach), to malignant lymph nodes, or to metastases within the liver parenchyma.

Chang et al. [59] in 2000 published their preliminary data from a phase I clinical trial using EUS-directed immunotherapy. They examined the feasibility and safety of direct injection of cytoimplant under EUS guidance in eight patients with unresectable pancreatic adenocarcinoma, The median survival was 13.2 months. Major complications including bone marrow toxicity, hemorrhagic, infectious, renal or cardiopulmonary toxicity were absent. This study showed that local immunotherapy is feasible and safe.

The technique of EUS-guided fine needle injection (EUS-FNI) has been applied to deliver antitumor viral therapy [60]. ONYX-015 (dll520) is an EIB-55-kDa gene-deleted-replication-selective adenovirus that preferentially replicates in and kills malignant cells. A total of 21 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 gemcitabine (IV, 1000 mg/m^2). After combination therapy, two patients had partial regressions of the injected tumor, two had minor responses, six had stable disease, and 11 had progressive disease.

The most recent EUS-guided antitumor therapy involves a novel gene therapy [61]. TNFerade is a replication-deficient adenovector containing human TNFa gene, regulated by a radiation-inducible promoter Egr-1. The study design consisted of a 5-week treatment of weekly intratumoral injections of TNFerade ($4 \times 10^{9-11}$ particle units (pu) in 2 mL). EUS-guided FNI was compared with percutaneous approaches (CT or US). TNFerade was combined with continuous intravenous 5-FU (200 mg/m^2/day administered on 5 days per week) and radiation (50.4 Gy). Four patients underwent resection, and one of these patients had a complete pathologic response. The report covering 50 patients was presented at Digestive Disease Week 2006 [62].

EUS-guided injection of TNFerade has also been applied to locally advanced esophageal cancer [63]. This may represent a new treatment paradigm in esophageal cancer, with the endoscopist administering the local antitumor agent under real-time guidance and assessment of tumor response and local toxicity.

Percutaneous ultrasound-guided injection of absolute alcohol into hepatic carcinomas less than 50 mm in diameter has demonstrated increased patient survival when compared with surgery, but EUS-guided alcohol therapy for malignant disease has not yet been tested. For large lesions, EUS would probably be inferior to the percutaneous route. A case report tested the feasibility of this approach. One patient was treated with EUS-guided alcohol injection of a solitary hepatic metastasis [64].

Ultrasound-guided radiotherapy by implantation of radioactive seeds has been used for treatment of prostate cancer, but if this technique were adapted for EUS-directed tumor therapy it would require the development of a shielded delivery system.

Placement of radiographic markers

EUS has been used to place radiographic markers (fiducials) in patients with intrathoracic and abdominal malignancies, enabling precise guidance of the CyberKnife frameless image-guided stereotactic radiosurgery system for delivery of radiation doses to tumors. In this study [65] EUS-guided fiducial placement was successful in a total of 11 of 13 patients (84.6%). The locations of the tumors were as follows: retrocrural area at the dome of the diaphragm, porta hepatis, gastroesophageal junction, mediastinum, thoracic paraspinal area, and pancreas. A total of three to six fiducials were placed in each patient. An infectious complication developed in one patient within 30 days of the procedure. This new application of interventional EUS further expands the role of EUS in the multidisciplinary approach to the oncology patient [65].

Radiofrequency energy and photodynamic therapy

Radiofrequency ablation (RFA) causes a relatively predictable zone of coagulation necrosis by intense tissue heating. Accurate and precise targeting of the tumor is important to maximize the yield and minimize morbidity to the patient. RFA is performed routinely by surgeons (laparoscopically or open) or percutaneously by ultrasound, MRI or CT-guided methods in patients with primary, recurrent, or metastatic liver cancers. Depending on the site of the lesion, EUS may be the safest and easiest method to deliver RFA therapy. In 1999 Goldberg et al. [66] published a study on the feasibility and effectiveness of radiofrequency ablation under EUS-guidance in 13 pigs, confirmed by necroscopy. Potential applications for EUS-guided RFA may include poorly accessible liver lesions, small functional pancreatic endocrine tumors, or submucosal gastrinomas.

Photodynamic therapy of pancreatic cancer by using percutaneously placed light catheters has been reported in a group of 16 patients with advanced pancreatic cancer [67]. All patients had substantial tumor necrosis without evidence of pancreatitis. The same Boston group [68] subsequently reported another animal experiment using EUS-guided activation of photodynamic therapy to the pancreas. Localized tissue necrosis was achieved in all organs, without significant complication.

Brachytherapy

Brachytherapy has been shown to have benefit in treating primary esophageal tumors. A potential advantage over the more traditional external beam radiotherapy (EBRT) is its ability to limit radiation toxicity to the normal tissues surrounding the cancer. EUS-guided brachytherapy for a primary tumor has been reported in one small series of patients with head and neck malignancy [69]. A case of EUS-guided brachytherapy in a patient with recurrent esophageal cancer with perigastric lymph nodes has also been reported [70]. For temporary brachytherapy where the seeds are only present for a limited period of time, iridium (^{192}Ir) is the most common isotope used. Permanent seed brachytherapy can be done as an outpatient procedure, with little radiation safety risks. Iodine (^{125}I) may be preferable because of its relatively slower dose delivery rate (half-life of 60 days for ^{125}I. This theoretically would result in less adjacent tissue damage, in a previously irradiated area. Another group in Shanghai, China, has published a report of 10 patients with pancreatic cancer who underwent EUS-guided brachytherapy using ^{125}I. CT follow-up examinations were performed 1 month after the therapy. Their results reported relief of pain in nine patients after 1 to 3 days. There were no complications reported, including pancreatitis. This report show promising preliminary data that malignant tumors in the pancreas as well as metastatic or recurrent lymph nodes can be treated safely with EUS-guided brachytherapy.

Future perspectives

EUS-guided tissue apposition and suturing

Since EUS allows visual access to organs adjacent to the gastrointestinal tract, endoscopic surgical procedures are being developed (natural orifice transgastric surgery, NOTES) to treat conditions that would otherwise require open or laparoscopic surgery. The first step in performing such procedures is to create a transluminal access with a needle knife and then pass with the entire endoscope into the peritoneal cavity to perform intra-abdominal procedures. Whichever way or whichever procedure is wanted, the desired organ or structures need to be apposed to the gut wall. To achieve this and to sew the two viscera together or close the possibly necessary gut incision, a new and rather simple sewing method has been developed [71]. Tissue apposition and sewing is performed using a commercially available flexible, 19-gauge EUS needle procedure for routine use. A custom-made 6 to 8 mm long metallic anchor, attached to a thread, can be loaded into its hollow inner part. The anchor thread runs within the accessory channel of the enchoendoscope. Once the needle has been directed into the target, the stylet is advanced to eject the anchor. Following ejection the examiner can pull on the anchor thread from outside the endoscope, which will enable the anchor to pull the target organ toward the gut wall. Any such manipulations can be seen in real-time imaging on the ultrasound screen. If necessary the threads can be locked to the accessible inner gut wall or be kept outside the patient for further manipulation. Specifically for this device, a locking and cutting mechanism was designed to either lock one thread against a stricture or two or more threads together to form a stitch. The needle can be removed following the deployment of the anchor or it can be used to provide additional access to the target site by exchanging the stylet for devices such as guidewires. The tissue apposition system or suture system represents a basic kit for future EUS-guided interventions and also for NOTES [71–74].

EUS-guided anastomosis

Under EUS vision the anchor and thread method was used to target a small bowel loop exclusively from the inside of the stomach and appose the small bowel to the serosal aspect of the gastric wall [75,76]. Several methods were attempted to achieve nonsurgical anastomotic access between the gastric and intestinal lumen, deploying one device on the small bowel side and yet another on the gastric luminal aspect to compress the apposed tissues causing initial ischemia-controlled necrosis with subsequent fistula formation concluding in the formation of a stoma [75,76].

The best option to date has been a balloon system, which can be passed over a guidewire deployed into the small bowel lumen under EUS guidance [77]. It can then be inflated and filled with water to provide counter-pressure from the nonaccessible small bowel side against a second balloon, or compression button, inflated on the gastric aspect. This will force the two walls (small bowel and stomach) together with a pressure higher than 200 mmHg which in general is high enough to cause ischemia. The remaining catheter is cut and the system stays in place for a few days to form an opening between the small bowel and the gastric wall.

EUS-guided antireflux therapy

The EUS-guided gastropexy utilizes the suturing system described earlier [71,72]. Using EUS as a guide, two separate anchors are deployed through the gastric wall, one into the median arcuate ligament and the other just beyond the wall of the lower esophageal sphincter. After ejection of the anchors, both the connecting threads, now appearing on the luminal aspect, are locked together endoscopically against the gastric wall using the above-mentioned locking device. To achieve sufficient traction on the threads fixed to the cardia, esophageal manometry has to be performed before, during and after the procedure, measuring the alterations of the pressure in the lower esophageal sphincter. In experimental studies performed in more than 20 survival procedures in smaller pigs, the median sphincter pressure increased significantly from 11.2 mmHg to 21 mmHg ($P < .05$) [78]. The median length of the lower esophageal sphincter increased from 2.8 to 3.5 cm. Even 4 weeks after the procedure, these data were reproducible. Human trials are still pending.

EUS-guided lymphadenectomy

Although high-grade dysplasia and early cancers are amenable to endoscopic mucosal resection, presence of locoregional lymph

nodes raises concerns regarding possible metastasis. EUS helps detection of small (<1 cm) periesophageal or perigastric lymph nodes and also facilities selection of "suspicious" nodes by their echo-morphology. Until now there was no way of removing these potentially affected nodes without surgery. A combined approach using EUS guidance and transgastric manipulations now seems feasible. After an initial EUS evaluation and selection of a target lymph node, EUS-guided deployment of a custom-made anchor and thread into or just beyond the lymph node under real-time visualization was performed in an animal model. When traction was applied on the thread, the lymph node could be pulled closer to the stomach, indenting the gastric wall [73]. Endoscopic incision of the gastric wall using a needle knife around the thread provided transgastric access through a full thickness opening in the gastric wall. The node was removed by endoscopic dissection while pulling on the thread along with the anchor in the node. Once the specimen was retrieved, the gastric laceration was closed endoscopically using the anchor and thread suturing system [71–73]. Further and larger animal studies are needed before embarking on studies in human.

EUS-guided cardiac interventions

The proximity of cardiac structures to the wall of the esophagus might allow transesophageal interventions under EUS guidance. This method of access might open a variety of possibilities for procedures such as myocardial biopsies, injections or abalations. To investigate the feasibility and safety of a variety of interventional transesophageal cardiac procedures, experimental studies in five live pigs were undertaken [79,80]. Excellent EUS views could be obtained of the left atrium, aortic valve [79], pulmonary trunk and left coronary artery. It was possible to pace the heart through the EUS scope under direct ECG and vital function control. Diathermy could be applied to the aortic valve. Using the smaller-size needle electrodes, ECG traces could be obtained directly from the surface of the heart and also from intracardiac sites. Experimental procedures studied included needle biopsies, contrast injections into the atrium and the coronary arteries, passage of a guidewire into the atrium and ventricle, direct intracardiac recording of ECG, cardiac conductive tissue ablation and direct cardiac pacing [79]. There were no complications. These preliminary studies suggest that a variety of transesophageal intracardiac procedures are feasible and that extension of these preliminary experiments and experiences may be valuable.

EUS-guided vascular interventions

A concurrent color and power Doppler evaluation facilitates both the morphological and functional examination of the periluminal vasculature such as azygos vein, splenic vein and superior mesenteric vein (for portal venous hemodynamics), celiac and superior mesenteric arteries (to look for possible mesenteric ischemia), and renal vessels (in the context of renal artery stenosis or renal vein thrombosis). Magno et al. [81] described preliminary studies in porcine model performing EUS-guided angiography using different needles. Brugge et al. [82,83] have performed EUS-guided portal vein catheterization and pressure measurement as well as portal vein embolization with Enteryx in animal experiments.

Conclusion

Many of the techniques described in this chapter are still experimental. Larger trials are essential to provide evidence of their potential superiority when compared to other diagnostic and treatment modalities. Some of the techniques reported will fade into oblivion when faced with better imaging techniques or superior treatment modalities, but rapid strides are being made to overcome some of the technical limitations of EUS. A large working channel is essential for the future development of interventional EUS, since it will enable the use of larger and more sophisticated treatment and drug delivery systems. Much work lies ahead, especially regarding further development of accessories for specific interventional EUS procedures.

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21 Training in Endoscopic Ultrasound

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Endoscopic ultrasound (EUS) is among the most challenging of endoscopic techniques to learn, requiring a practitioner to understand ultrasound physics, recognize three-dimensional anatomy from an internal perspective, and master additional fine motor skills. The learning curve for EUS is steep and continues beyond training programs into practice [1]. EUS is now an established tool in the management of gastrointestinal tract malignancies as well as benign and malignant pancreaticobiliary diseases. EUS was initially embraced as a tool for diagnostic imaging because it provided the most detailed mucosal and submucosal detail in the gastrointestinal tract and was proven to be superior to other diagnostic modalities such as computed tomography (CT), magnetic resonance imaging (MRI) and angiography in the staging of early gastric cancers, esophageal cancer, and rectal and pancreatic cancer [1–3]. EUS fine needle aspiration and injection has illuminated new options for more invasive diagnostic and therapeutic applications. Moreover, in the next stage of EUS development, the technology has been applied to extraintestinal diseases such as lung cancer staging [4] and has served as a technology platform for endoscopic interventions outside of the gastrointestinal tract lumen [5].

This chapter will describe how an endoscopist can learn EUS and identify the key studies that have shaped training guidelines. The role of live courses, animal laboratories, simulators and computer media for EUS training will be explained and some of the more novel EUS simulators will be highlighted.

While the majority of EUS procedural volume occurs at academic and tertiary care centers, the equipment has also been installed in many community hospitals across the US. In addition to the expense of the equipment and the relatively lower reimbursement, a key barrier to the dissemination of EUS into the community has been inadequate training resources. Many gastroenterologists in practice have had to devise self-teaching curricula for EUS that can become a long and tedious process. Guidelines for minimal number of EUS procedures required for competency have been articulated by professional societies such as the American Society for Gastrointestinal Endoscopy. Yet recent surveys of training programs revealed that most general gastrointestinal fellows and indeed many advanced endoscopy trainees are not performing the prescribed number of procedures before entering practice [6]. Indeed, new therapeutic, endoscopic technologies are straining conventional training programs, leading at least one expert endoscopist to propose a new training standard beyond gastroenterology fellowship, "the minimally invasive gastrointestinal specialist" [7]. Thus there is a hypothetical risk that the promise of EUS technology and its advantages in clinical practice could be lost due to the combined effects of inadequately trained gastroenterologists, capital expense as well as physician and facility reimbursement issues. Improving the availability of EUS technology will in part depend on how well EUS is taught to gastroenterology trainees and how readily accessible and viable the options are for gastroenterologists in practice to become competent and credentialed in EUS.

EUS is difficult to learn for several reasons. For one, EUS scopes utilize forward oblique optics and they are more difficult to pass and maneuver than forward-viewing endoscopes. In addition to learning how to handle the instruments and position them, trainees must also acquire expertise with the fine adjustments in scope position necessary to bring the ultrasound image into focus. Perhaps the most difficult aspect, however, is interpretation of the images. Experienced endosonographers typically recommend a strategy of pattern recognition obtained through a high volume of examinations. Examining many patients with normal anatomy or with focal abnormalities but preserved anatomy at other examining stations can help build an endoscopist's experience so that he or she can more easily recognize abnormal anatomy when it is encountered. Clearly, however, some of the education in pattern recognition can be done without hands-on experience by observing an experienced endosonographer or through self-instruction with atlases and digital media.

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Training options

The best way to learn EUS is through an intensive and immersive training experience that combines a period of didactic lectures, book learning, and observation of an experienced endosonographer with an intensive hands-on period solving clinical problems under the guidance of an experienced teacher. This type of experience could be created for a third-year gastrointestinal fellow or could be the focus of a fourth year of gastrointestinal training. These elements might also be replicated outside a formal training program by a practicing endoscopist in a self-study curriculum. Such an initiative could involve reviewing EUS videotape, observation of transabdominal ultrasound imaging to become familiar with gray-scale imaging, shadowing a busy, experienced endosonographer and participating in intensive hands-on EUS courses that typically utilize hands-on porcine models.

The goal of the principal stage of training is to familiarize the trainee with the technology of ultrasound and how images are generated and how to "fine tune" a gray-scale image. The various types of artifact also need to be taught. Simultaneously, at this stage of learning, a trainee should learn the history of the development of EUS and review the early literature that established the foundation for the clinical applications that followed such as the research that correlated the sonographic wall layers to the histologic components of the gastrointestinal tract wall: mucosa, deep mucosa, submucosa, muscularis propria and serosa. From this literature review, a consideration of the research that demonstrates the efficacy of EUS in gastrointestinal malignancy and pancreaticobiliary imaging should follow.

In the subsequent stage, the trainee observes EUS examinations and reviews each patient's clinical indication and outcome. After observing a large volume of cases, the trainee can progress to hands-on instruction, either with a live model or with a patient under the guidance of a preceptor.

Two- and three-day hands-on courses that utilize a swine model have been sponsored in the past by the American Society for Gastrointestinal Endoscopy and other gastrointestinal societies and by academic institutions that have a strong EUS foundation. The swine model has been successful because its internal anatomy, specifically that of the pancreas and biliary tree, resembles that of the human. These live animal model courses can be highly educational but their exact role in the credentialing process is still unclear. Clearly, a single weekend in a live course is insufficient for an endoscopist to become competent in EUS.

Telemedicine is an exciting area with possible applications to EUS training. By sharing digital EUS images electronically, a trainee can obtain feedback from a mentor, during a procedure or afterwards, thereby improving accuracy or facilitating credentialing. There are a growing number of clinical examples where telemedicine is being utilized, for example teleconferencing for tumor board meetings has become popular at some academic centers.

Quality indicators in EUS training

Because EUS training has not been standardized, a few have questioned whether EUS interpretation varies among individual endosonographers based on the type of training or experience obtained. Reports on interobserver and intraobserver variation and the reproducibility of endoscopic ultrasonography results suggests that three major factors influence the interpretation of EUS. These are operator subjectivity, operator experience and machine-dependent factors which produce artifacts that can interfere with image interpretation [8,9]. This data suggests that the operator's duration of experience, in performing EUS procedures, is important for obtaining competency for evaluating lesions of the gastrointestinal tract.

Because EUS is used frequently to diagnose and stage gastrointestinal malignancies, there is hope that EUS findings will be consistent from one endosonographer to another. A study published in 1996 investigating the interobserver agreement for EUS staging of esophageal and cardia cancer reported that interobserver agreement was generally good, especially for T1 and T4 tumors. Overall agreement for T2 lesions was poor. Unfortunately, the authors did not look at specific factors that might affect agreement such as the type of EUS training, number of EUS procedures performed and overall length of experience with EUS [10]. In a study on submucosal masses, we evaluated each endosonographer by his/her overall training experience (formal fellowship versus self-teaching), total EUS procedures performed, total esophageal EUS cases performed, and the number of years of EUS experience for each endosonographer. We observed that endosonographers with the most years of experience were more likely to correctly identify submucosal lesions (with higher agreement) [9].

A retrospective multicenter study of the diagnostic accuracy of FNA of solid pancreatic masses found that EUS-FNA was diagnostic of malignancy in 71% of cases. The authors suggested that endoscopists with a final cytologic diagnosis rate of malignancy that was less than 52% were in the lowest quartile and should evaluate reasons for their low yield [11].

Other studies have enlightened us on the learning curve and training parameters for obtaining competency in general endoscopic procedures. Cass reported on the skills and experience required for obtaining competence in performing upper endoscopy and colonoscopy [12]. Marshall et al. also provided us with similar important information for colonoscopy [13]. In 1996, some data on the experience and procedural volume necessary to perform endoscopic retrograde cholangiopancreatography (ERCP), an advanced endoscopic procedure, was reported [14]. We have reported on the role of EUS experience in the staging of pancreatic cancer [15]. In this study we noted that an endosonographer's experience appeared to improve significantly after performing 100 EUS cases for pancreatic cancer staging. In another study published in 2005 there was a documented, slight drop in the complication rate of one endosonographer performing

EUS-guided FNA of the pancreas. Throughout the course of the 300 procedures performed in the study, the median number of needle passes required to obtain a diagnostic specimen fell from four to three. This case series suggests that the EUS learning curve continues well beyond fellowship [16].

Since there is limited data available on the parameters necessary for obtaining competency in EUS, this chapter attempts to provide useful information from available sources; including previously published experience data for other endoscopic procedures, learning theory, the learning experiences from other fields of medicine, and personal experience. We hope this material can provide the framework of reference necessary for those who want to learn EUS.

Learning endoscopic ultrasound

Motivation

Physicians are experts in self-directed learning. Fox et al. have tried to organize possible motivations for self-study into ten broad categories [17]:

- curiosity
- personal well-being
- financial well-being
- stage of career
- competence
- the clinical environment
- relationships with medical institutions
- relating to others in the profession
- regulation
- family and community

This is a useful list to contemplate before learning EUS and it can be applied to the acquisition of a new skill in any career. Curiosity is defined as a need to pursue, expand or develop an often pre-existing interest. Applied to EUS this could mean, as an example, that an "interest" in imaging, in general, may be evidenced by regularly reviewing CT scans of one's patients with the radiologist, because it is "interesting." Financial aspects are important in EUS; the training period itself involves a significant opportunity cost. In addition, the purchase price for both linear array and radial scanning equipment can be out of reach for some hospitals and group practices. Furthermore, although reimbursement is evolving, the current RVUs (relative value units) assigned to EUS procedures do not provide a marginal reward for the endoscopist that is commensurate with the investment required to learn EUS.

For most physicians who have started to learn EUS or are considering it, enhanced clinical competence is the major motivational factor. However, competitive forces in the clinical environment need to be assessed closely. To become highly skilled, an endosonographer ideally should be kept busy and an endoscopist would be wise to consider if his or her community will be able to generate adequate referrals for EUS procedures. This leads to two other important considerations: relationships with institutions and others in the profession. Is EUS really useful for my community? It makes very little sense to try to establish EUS in an environment without the support of medical and surgical oncologists, interventional radiologists and pancreaticobiliary endoscopists. How motivated are my colleagues, referral sources and my primary hospital to support this endeavor? Here motivation and commitment is not a one-way street. In other words, if the physician learning EUS cannot communicate his long-term commitment to EUS, he will not be able to engender the support, trust and feedback necessary to get started and develop his skills. And finally, the hospital administration must be supportive of the EUS program. In other words, there must be a genuine interest in EUS, shared among many individuals, that is the driving force behind those endoscopists' pursuit of training in endosonography.

Dimensions for learning EUS

A rapid and wide diffusion of EUS through the gastroenterology community will only become a reality if increased training options become available and self-trained individuals continue to supplement the fellowship-trained practitioners, until more of the latter become available. The value and competence of individuals without formal training in this transition period is evident from the earlier examples of ERCP, cardiac echography and laparoscopic cholecystectomy. Each of these examples has some similarities with EUS, but differs from it in other important aspects. In contrast, the skill of maneuvering the echoendoscope into the desired position for accurate imaging is complicated by the experience that is also needed for interpretation of the resultant images. This cognitive component of the procedure is exceedingly difficult to learn. Only constant repetitive practice can improve the pattern recognition necessary to differentiate normal from abnormal findings and ultimately perform and interpret EUS competently.

Visual perception and reality

> "During the act of knowledge itself, the objective and subjective are so instantly united, that we cannot determine to which of the two the priority belongs." (Samuel Taylor Coleridge 1772–1834)

This statement is very true for EUS. Sensory stimulation from an ultrasound image, consisting of gray-scale pixels, is translated into a description in the mind that is meaningful and not cluttered with useless information. We create an image based on what we "see." For example, the novice endosonographer cannot at first discriminate one simple shape from another. One must first create meaningful objects, such as the splenic vein, the pancreas and the common bile duct, from a flickering ultrasound image; which at first, appears not unlike the radar image of a snowstorm (white noise). Gestalt theorists have worked out principles of visual organization of which the most general is referred to as *Prägnanz*. Implicit in the concept is that, given a complex visual stimulus, whenever possible, some figure or pattern will

be perceived. Thus, the novice endosonographer will gradually learn to differentiate images of anatomical structures from those of ultrasound artifacts.

There are two major theories of perceptional learning. According to *enrichment theory*, perceptual learning consists of enriching sensory experience with specific associations and rules for its interpretation that is derived from past experience. The proponents of the *discovery theory* interpret perceptual learning as a process of discovering how to transform previously "overlooked potentials for sensory information" into effective information. Therefore, one discovers new aspects of the sensory stimulus and creates new "realities." Clearly, both theories are not mutually exclusive and both are valuable in conceptualizing what happens when one begins to learn EUS [18].

Perpetual styles differ among individuals. A person who resists contextual influences and perceives the world as highly differentiated is said to be "field-independent." Field-independent people are superior in locating a simple visual figure embedded in a complex pattern (i.e. hidden figure tests). Field-independent individuals are able to counteract optical illusions more readily than field-dependent persons. It would seem that this is a desirable trait in the acquisition of EUS skills. Field dependence appears to decline with increasing age as does the closely related susceptibility to optical illusions.

Learning curves

Most of the research associated with learning curves has been reported in the area of psychomotor skills acquisition. The dependent variable is a fairly simple and easy-to-observe parameter such as reaction time, number of errors, etc., whereas the independent variable is the number of trials. These curves can be described by second-order polynomials and show no stepwise plateaus of proficiency but obey the law of diminishing returns. In other words, the learning curve is initially steep (large and rapid gains) and flattens with time (small and slow gains).

It appears that results from these experiments are most appropriate for the acquisition of the specific task studied, and may have limited relevance to perceptual visual learning, which is paramount for learning EUS. With this caveat, it may be useful to summarize some of the findings of this research: practice alone does not make perfect, and relevant feedback is necessary. Feedback is most helpful when it is *simultaneous* with continuous, frequent and specific skill acquisition tasks. The result of unreinforced practice is extinction of the correct response and a proliferation of errors [19]. Therefore, it would seem that EUS training in a formal training program under the direction of a mentor would be the preferred method for learning EUS.

Adult learning theory

Earlier theories of psychomotor learning yielded significant insights but are limited in scope. In addition, they have the advantage that they can be studied rigorously in the laboratory. This is not the case with more complex theories of human learning. One non-reductionist approach, Kolb's *experiential learning theory*, seems to be particularly useful for our purposes [20]. Learning is a cycle that begins with experience, continues with reflection and later leads to action. Kolb refined the concept into the stages of action: concrete experience, critical reflection, active experimentation and abstraction (Figure 21.1) which continues in a spiral fashion. This model seems to describe the interaction between the EUS trainee, the echoendoscope, the EUS images obtained and the preceptor/mentor in a meaningful way.

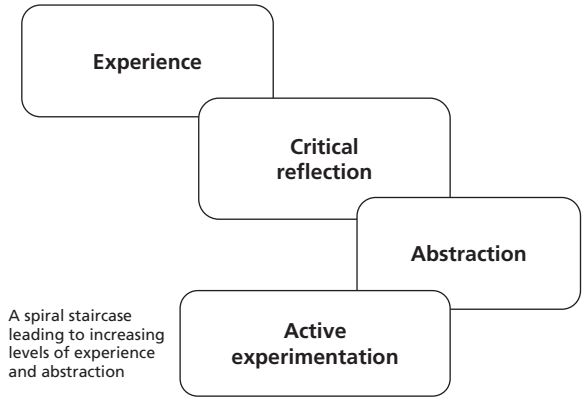

Figure 21.1 Kolb's experiential learning model.

Learning, as a process, has been divided into stages by others, which is more consistent with what adult learners and, especially, physicians, know from introspection [21]. The growth of development is stimulated by prior learning experiences and becomes incremental where eventually a comfort zone is reached. A new learning challenge can cause apprehension and creates tension. Learning a new task as complex as EUS can be very stressful. This can manifest as a dip in the learning curve, or performance regression. One gets through this period by coping with the stress, for example, by letting go of short-term expectations in favor of more long-term learning. By accepting the fact that it will take a large number of cases before being able to discriminate EUS images confidently, one should be able to overcome the apprehensions and stress of learning this demanding endoscopic procedure.

Published data on learning experiences

Schueneman et al. tested 120 general surgery residents with a neuropsychologic battery and then rated them by attending surgeons, on surgical skills exhibited during the course of 1,445 surgical procedures [22]. Analysis of the neuropsychological battery resulted in three factors (complex visuospatial organization, stress tolerance and psychomotor abilities) that were statistically unrelated to traditional measures, such as the Medical College Admission Test and National Board scores. Multiple regression analyses indicated that academic predictors, taken alone, either did not correlate (National Board scores) or correlated negatively (Medical College Admission Test scores) with the surgery ratings. Conversely, neuropsychologic test scores showed significant positive correlation ($r = 0.68$) with the ratings. When both sets of

predictor variables are combined, a multiple regression coefficient of 0.80 is found with the ratings, with more than two-thirds of the predictive power attributable to the neuropsychologic test scores.

The relationship between a specialized form of spatial ability known as "field articulation" and technical surgical skill was investigated by Gibbons et al. [23]. This form of spatial ability was discussed above under perceptual styles and field dependence. The latter can be defined as the ability to differentiate a simple figure from a complex configuration background. The relationship between hidden figure test scores and average ratings of technical surgical skill made by 17 academic surgical faculty members in two independent institutions was highly significant.

Of course, the results of these studies are not directly applicable to the learning of EUS. However, parallels can be drawn. Individuals who start to learn EUS clearly have different visuospatial abilities; which are probably relevant to the speed with which they will be able to acquire the skills to perform EUS competently. There is very little data on the factors affecting individuals' ability to learn and perform the EUS procedure competently.

Nevertheless, some interesting published data relating to the acquisition of general endoscopic skills does exist. Cass reported on findings from a prospective multicenter study evaluating competence parameters for upper endoscopy and colonoscopy [12]. This study showed that certain criteria must be achieved before an individual can competently and independently perform these general procedures. Furthermore, they showed that a certain number of procedures for upper endoscopy and colonoscopy are necessary in order to achieve these milestones or competency criteria. Marshall et al. also showed similar findings, reporting a minimum number of colonoscopies were necessary to achieve overall competence [13]. Data from Duke University Medical Center reported on the minimum number of ERCP procedures necessary for a gastrointestinal fellow to achieve competence in therapeutic ERCP, a technically advanced endoscopic procedure [14]. Unfortunately, such important data is not yet available for EUS. However, there are several reports exploring training issues pertaining to EUS.

Catalano et al. studied interobserver variation and reproducibility of EUS staging of esophageal cancer [8]. They reported that experienced endosonographers were more accurate than inexperienced endosonographers at staging esophageal tumors. Fockens et al. reported that after completing 100 total EUS procedures for esophageal cancer staging, T-staging accuracy for esophageal tumors with surgical correlation increased from 58% for the first 36 patients to 83% for the following 35. This significant study shows that a learning curve exists for EUS staging of esophageal cancer with a minimum of 100 EUS examinations being required for this indication to achieve an acceptable level of accuracy [24]. A similar study for pancreatic cancer staging was also performed by Gress et al. who reported that after 92 total EUS procedures for pancreatic cancer staging, T-staging accuracy for pancreatic tumors improved significantly [15].

Currently, there are no prospective, multicenter trials indicating the number of EUS procedures an individual has to perform before he or she can be considered competent. Furthermore, endoscopy societies both in Europe and the United States have been unable to decide on a minimum number of procedures recommended for assessing competency. According to the European Society of Gastrointestinal Endoscopy, "it is difficult to assess how many procedures are required in order to achieve sufficient skill and expertise, since this is dependent on many variables." This makes the task of hospital credentialing committees difficult, a subject which we will return to later.

In a survey of endoscopic ultrasonographers reported by Boyce et al., the consensus was that approximately 150 procedures for staging luminal gastrointestinal tumors are needed to acquire technical competence, defined as the ability to position the echoendoscope to obtain accurate imaging [25]. They noted that more procedures are necessary for "interpretative" competence. It is not clear whether the acquisition of technical and interpretative competence is different for a third-year fellowship trainee compared to a seasoned endoscopist or an experienced biliary endoscopist. These are additional issues which deserve further study. In the mean time, we have to continue to teach and learn EUS without the benefit of multicenter training studies.

Practical aspects of EUS learning

Ideally, formal fellowship training in EUS will provide all aspects necessary for obtaining competence in this procedure. This section is dedicated to those interested in exploring their interest in EUS and those wishing to acquire these skills in a self-teaching program. However, these suggestions can be applied to anyone interested in learning EUS. The first step in learning EUS is to immerse oneself in the subject. This includes utilizing all available educational materials. Trainees are urged to read a textbook on the subject from cover to cover. A list of useful resources is given at the end of this section. Second, it is imperative that the student conduct a thorough review of anatomy, both cross-sectional and traditional. There are excellent CT correlated anatomy texts available, that provide a basic foundation for developing the conceptual thinking necessary for interpreting EUS. We recommend the text edited by Han and Kim which provides superb CT anatomical imaging. The trainee should also be constantly applying the anatomical subject matter to EUS by continuously asking: How does this apply to EUS? Intense mental imagery is necessary to become oriented with the numerous complex anatomical relationships. Important questions to ask are: how would this relationship look from behind, below or above?

At this stage, the trainee should try to learn and absorb as much as possible and observe actual EUS procedures whenever possible. Observational practice means watching frequent and repetitive EUS procedures. If this is not practical, then a review of available EUS teaching videotapes and DVDs is essential. Some videotapes and DVDs are commercially available and many more are in the teaching collections of accomplished endosonographers. In addition, observing transabdominal ultrasound procedures may be a

useful way for some to become familiar with gray-scale imaging, its peculiarities and pitfalls, and to condition the mind for EUS.

Observational practice can be a useful adjunct to learning EUS and there is empirical evidence in other areas to validate this. The observation period allows the learner to concentrate fully on perceiving the generated images, to process this information mentally, enrich his concept about the structures seen and discover new aspects of the structures and/or their ultrasound representation. This observational experience will allow for reflection by sending the trainee back to the drawing board (i.e. the anatomy atlas and the EUS textbook) for further refinement and consolidation of the learning experience. This process is repetitive until a new level of awareness has been reached.

After an extended observation or self-study period the student will naturally seek out hands-on experience. There can be little doubt that the best learning environment is found in a one-to-one preceptor-trainee relationship, ideally in a formal training program. However, other less equal alternatives exist. The student can make personal arrangements with an EUS expert to observe procedures one day a week for a period of time. Eventually, the student will advance to a level where he can intelligently discuss or even anticipate the findings of the expert. At this stage, the learner can consider performing his/her own EUS examinations. I have personally worked with some trainees, typically individuals who have experience with ERCP and have been practicing for several years beyond their gastrointestinal fellowship, and found that this approach can work in select individuals.

Additionally, two- or three-day hands-on-courses are periodically sponsored by the American Society of Gastrointestinal Endoscopy and other gastrointestinal societies and some institutions. Although "hands-on" involves animal models, it is a reasonable way to get started. The swine model for teaching EUS is considered the model that best resembles the human anatomy of the gastrointestinal tract, pancreas and bile ducts [26].

We are also aware that some programs exist outside the US, mainly in Canada and Europe, that offer short, hands-on learning experiences on a fee basis. We must mention however, that taking a hands-on EUS course in no way certifies an endoscopist for privileging in endoscopic ultrasound. Credentialing can only be granted to those who can demonstrate acceptable competence in EUS. For example, one must be able to stage gastrointestinal tumors using EUS, with the same accuracy as that reported in the literature (see Tables 21.1 to 21.5) [25–58]. We believe that this can only be done over an extended period of time, after adequate cases with surgical correlation have been achieved.

At the same time, the student will need to keep up to date with current developments in the field by reading endoscopic and clinical gastrointestinal journals and textbooks, and viewing educational videos or DVDs.

Table 21.1 Reported accuracy of EUS compared to histopathology in local staging of esophageal carcinoma

Reference	*n*	T stage	N stage
Murata [27]*	173	88%	88%
Tio [28]	102	89%	81%
Dittler [29]	97	85%	75%
Vilgrain [30]	51	73%	50%
Botet [31]	50	92%	88%
Grimm [32]	49	89%	90%
Rösch [33]	44	82%	70%
Ziegler [34]**	37	89%	69%
Sugimachi [35]	33	90%	—
Rice [36]	22	59%	69%
Schlick [37]*	22	77%	86%
Date [38]***	20	85%	—
Takemoto [39]	18	72%	79%
Total	718	82%	70%

*Only traversable tumors included.
**Linear scaning echoendoscope.
***Only adventitial and organ involvement (T3/4) was assessed.

Table 21.2 Reported accuracy of EUS compared to histopathology in determining the T and N stages of patients with gastric carcinoma

Reference	*n*	T stage	N stage
Caletti [40]	34	88%	58%
Murata [27]	146	79%	—
Grimm [41]	118	80%	88%
Akahoshi [42]	74	81%	50%
Tio [43]	72	84%	68%
Ziegler [44]	71	80%	80%
Aibe [45]	67	73%	69%
Rosch [1]	41	71%	75%
Botet [31]	50	92%	78%
Saito [46]	110	81%	—
Schlick [37]	19	79%	72%
Ohashi [47]	174	67%	—
Total	976	80%	71%

Simulators for EUS learning

Several simulators have been developed for EUS that either utilize video to simulate three-dimensional anatomical views or provide a hands-on experience in vital or inanimate tissue. The goal of their use is to replicate the visual and tactile experiences involved in performing EUS and to serve as a key step in training between didactic learning and hands-on experience on patients.

The video simulators include a few educational CD-ROMs produced through industry-supported grants and software package adaptations for conventional video endoscopy simulators. These interactive programs show three-dimensional anatomy and corresponding EUS video clips. A collection of CDs and DVDs are available from the ASGE or at the ASGE Learning Center during Digestive Diseases Week (DDW) [59,60].

Table 21.3 Reported accuracy of EUS in the assessment of vascular invasion of the portal venous system by pancreatic carcinoma

Reference	*n*	Accuracy (%)
Yasuda [48]	37	81
Rösch [1]	40	95
Snady [49]	30	97
Gress [15]	81	93
Total	198	92

Only surgically confirmed cases are included. Data express the correct prediction of the presence or absence of vascular involvement.

Table 21.4 Reported accuracy of EUS in the correct determination of depth of tumor invasion (T stage) and lymph node metastases (N stage) in ampullary carcinoma

Reference	*n*	T stage	N stage
Rosch [1]	12	83%	75%
Mitake [50]	28	89%	69%
Tio [51]	24	88%	54%
Total	64	87%	66%

Table 21.5 Reported accuracy of EUS in the local staging of rectal carcinoma

Reference	*n*	T stage EUS	N stage EUS
Akasu [53]	41	80%	78%
Pappalardo [54]	14	93%	86%
Rotte [55]	25	84%	—
Ruf [25]	49	88%	—
Rifkin [26]	81	67%	80%
Waizer [56]	48	77%	—
Goldman [57]	32	81%	—
Beynon [52]	44	91%	—
Strunk [58]	10	70%	—
Total	344	81%	81%

There are similar internet-based EUS learning experiences available via the DAVE Project (http://dave1.mgh.harvard.edu/) and the *Visible Human Journal of Endoscopy* (http://www.VHJOE.com) where EUS clips are correlated with normal anatomic views derived from the Visible Human Database (VHD) at the University of Colorado Health Sciences Center. In 2001, a three-dimensional computer simulator of EUS images based on the VHD was described by Gumustop et al. [61]. This program sharpens the visual margins around tissues with different ultrasound conductivity. The computer also does not allow the image to penetrate bone or air, adding authenticity to the experience.

One corporation with endoscopy simulator experience (Symbionix Corporation, Cleveland, OH) offers an EUS package for its upper endoscopy mannequin simulator. The EUS images are derived from cross-sectional CT scan and MRI images that the computer correlates to the position and direction of the echoendoscope inside the mannequin.

An EUS-FNA phantom has been constructed that generates images through a linear EUS scope that is passed through a rectangular box (Olympus America, Melville, NY). The phantom experience strives to show the echogenicity of normal human tissue as well as the contrast seen in solid and cystic lesions. The phantom is particularly useful for demonstrating scope maneuvers during fine needle aspiration, but it does not provide an optical endoscopic experience nor does it challenge the trainee to maneuver the scope in a lumen that resembles the gastrointestinal tract.

An inexpensive, nonvital EUS simulator was described in 2003 as a method for teaching fine needle aspiration [62]. This simulator involved a modified barium enema bag filled with agar and vegetables, macaroni and latex spheres and pierced by a circuit of tubing to recreate blood flow. The bag was surrounded by water to allow acoustic coupling. The inventors said that the model could be built for less than $50 and could be used for 200 fine needle aspirations over a 4-month period.

Currently, only live animal laboratory courses allow trainees to develop a "feel" for maneuvering an EUS scope while receiving optical and EUS image feedback. These vital simulators come the closest to recreating a real-time EUS examination.

While several research articles have described the practicality and utility of simulators for training in conventional video endoscopy [63,64], to date none of the described EUS simulators has been validated as a training tool.

Internet resources

Internet websites have a short life and, even if they continue to exist, they may not have been updated for a long time. Everybody who is familiar with "the Net" will know how to help themselves. Nevertheless, a few suggestions may be helpful. First of all, it is well worth periodically checking for EUS-related resources by using general-purpose search engines, especially those which automatically perform simultaneous searches on several different search engines and combine the results (meta-searches). Relevant search terms are: endoscopic ultrasound, EUS, endosonography and endoscopic ultrasonography.

The American Society for Gastrointestinal Endoscopy (ASGE) maintains a website (www.ASGE.org) which has links to other useful sites including the acclaimed DAVE Project created by the Gastrointestinal Unit at Massachusetts General Hospital. The ASGE website is a rich resource for EUS materials and provides important guidelines and other documents relating to training and competence in EUS as well as access to the EUS Special Interest Group. This may also in the future remain a good starting point for web-related research.

Telemedicine

Another area which will certainly capture our attention is telemedicine. Telemedicine is currently in its infancy, but a variety of parties are expressing great interest in this area, and generous research

funds seem to be available. The necessary infrastructure, basically the Internet, is already in place and regularly teleconferenced tumor board meetings, etc., are a reality in some areas of the US.

How telemedicine could apply to EUS remains to be seen. However, an example of what is possible has been demonstrated by the Cardiology Division at the University of California, Irvine, who installed a telecommunications system in the cardiac catheterization laboratory at Kaiser Hospital, Los Angeles [56]. Cineangiograms, live fluoroscopy, *intravascular ultrasound studies* and images of the catheterization laboratory were transmitted in real-time over a dedicated T1 (high-speed business broadband) line to the core laboratory at the UCI University Hospital. The hook-up worked in 39 of 40 cases. The use of this system had a significant impact on the management of 58% of patients.

It is possible that similar arrangements could be used to solidify the tumor staging accuracy of a novice endosonographer by teleconferencing with a previously arranged mentor who observes the critical portions of an EUS examination and grades the EUS trainee. Moreover, most of the new generation teleconferencing devices are portable and need not be purchased for the endosonographer alone. Many institutions have such devices in place and they are used across disciplines.

Terminology

> "The limits of language are the limits of thought." (Ludwig Wittgenstein 1889–1951)

One of the characteristics of a new branch of learning is that it develops its own terminology. The use of a relatively standardized nomenclature in reporting EUS findings is important for a variety of reasons. In contrast to transabdominal ultrasound or echocardiography, where an ultrasound technician can obtain a series of standardized images that are later "read" by a radiologist or a cardiologist, obtaining and interpreting EUS images is done simultaneously. The written report should be dictated immediately after completion of the study, summarizing all relevant observations, and is as important if not more important than image documentation.

EUS is a very dynamic and operator-dependent procedure. Therefore, information obtained needs to be recorded in a way that is meaningful to other endosonographers, even if the referring physician is only interested in the overall impression. Accurate and comprehensive reporting is also an instrument of quality assurance and leads to an increasing refinement of what is "seen." Furthermore, the use of standardized terms is a prerequisite for database creation and text-based searches and supports the ability to do research in EUS.

We think that there is a direct relationship between the number of terms correctly understood and correctly used and the overall quality of the EUS report and the quality of examinations. The use of standard terminology should not stifle the creativity of the endosonographer in using a more individualized text description of the findings, if appropriate. Personal or individualized descriptions should, however, be used alongside and not instead of the accepted terminology. We recommend using standard terminology for EUS. This standard is best reflected in the *Minimal Standard Terminology in Endoscopic Ultrasonography, Version 1.0* developed by the International Working Group in January 1998.

Hospital privileges

Few hospitals have currently defined criteria for privileging physicians in EUS. Presently, privileging depends mostly on a letter from a recognized expert, stating that a certain level of competence has been achieved by the individual seeking privileges. This can be a thorny issue because the individual issuing such a letter puts his personal reputation at stake by doing so. Be that as it may, the lack of data and established criteria for assessing competency in EUS is a serious drawback.

The ASGE Training Committee developed the first guidelines for obtaining competence in EUS [13]. These guidelines were the first to recommend the use of specific performance criteria for assessing competence in EUS. Demonstrating competency in EUS is complex as it must take into consideration both the endoscopic skills required for obtaining the EUS images as well as the cognitive or interpretive aspects of the procedure. For example, in tumor staging, these guidelines use the important criteria of correlating a trainee's EUS staging ability to the gold standard measure of surgical pathology, or in the case of a lack of this standard, the staging of the trainee's mentor. The trainee's accuracy rate is being compared to what has been reported in the literature (Tables 21.1 to 21.5). Self-taught individuals would unfortunately be at some loss, since they would only have the surgical pathology of their own cases, assuming the patients all went to the operating room and none received preoperative chemotherapy and/or radiation. Given the complexity of the procedure, a substantial experience is required in order to obtain competency for each EUS indication (Tables 21.1 to 21.5) and before an individual could be credentialed in the procedure. Furthermore, EUS-guided fine needle aspiration and other "therapeutic" EUS procedures (e.g. celiac plexus block) will require far more additional experience and training than diagnostic or tumor staging.

The ASGE guideline for obtaining training and competency in EUS is an important document that addresses some of the training issues which we have mentioned. Credentialing criteria for EUS have to be formulated in such a way that incompetent practitioners are excluded. At the same time, the hurdles must not be set too high to preclude reasonably trained individuals from getting started. One approach to this dilemma could consist of creating different levels of privileging as outlined in Table 21.6. This would permit some individuals, who are mainly self-taught, to gradually acquire competency in EUS in a succession of stepwise levels starting with basic staging.

As we enter the third decade of using the EUS procedure for patient care, there still remain important issues in training that

Table 21.6 Proposed experience for endoscopic ultrasound (EUS)

Level 1
Diagnostic luminal EUS of esophageal, gastric and rectal lesions Requires: Privileges for diagnostic and therapeutic endoscopy of the upper and lower gastrointestinal tract and at least 100 EUS procedures performed under the supervision of an experienced endosonographer
Level 2
Diagnostic EUS of pancreatic, biliary and retroperitoneal lesions Requires: Level 1 privileges and at least 100 EUS procedures with pancreatic, biliary or retroperitoneal indications performed under the supervision of an experienced endosonographer
Level 3
Interventional EUS, including, but not limited to, fine needle aspiration, celiac plexus block, and pseudocyst puncture/cystgastrostomy, etc., should be acquired ideally in a formal training program Requires: Level 1 and 2 privileges and the successful completion of a dedicated therapeutic endoscopic ultrasound training period under the supervision of an experienced endosonographer performing EUS-guided fine needle aspiration biopsies, celiac plexus blocks, EUS-guided pseudocyst cystgastrostomy, etc.

need to be overcome; however, as simulation becomes more mainstream and more trained endosonographers disseminate the EUS technology, we are optimistic that the quality and availability of EUS will improve significantly.

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22 The Future of Endoscopic Ultrasound

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Endoscopic ultrasound (EUS) has become an essential tool in gastrointestinal endoscopy. Although EUS was originally designed as an imaging tool, the procedure has evolved into a means of guiding tissue acquisition from the gastrointestinal tract and adjacent organs. The development of EUS has occurred over a relatively short period of time and the pace of development will most likely continue for at least the next decade. In the past, EUS was used primarily as a diagnostic test and in the next decade we will see the development of a variety of therapeutic applications.

Instrumentation

The pace of instrument design and manufacture is one of the major drivers for the expansion of EUS in gastrointestinal endoscopy. The EUS instrumentation development will continue in radial and linear endosonoscopes as well as EUS accessories.

The most important recent development in EUS has been in linear endosonoscopes. The widespread dissemination of electronic linear instruments has dramatically increased the use of EUS-guided fine needle aspiration (FNA) in the diagnosis and staging of gastrointestinal malignancies. The quality of the linear instruments has steadily increased in terms of image quality, maneuverability, and shaft diameter. These improvements have also been made possible with dramatic improvements in ultrasound processors. The enhanced sensitivity of color and flow Doppler real-time imaging has improved the ability of clinicians to detect small lesions and avoid vascular structures during FNA and injection therapy.

In the future, it is likely that the use of linear EUS instruments will become widespread in the community. The small size of the instruments will continue to improve the ease of use in upper gastrointestinal endoscopy.

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Linear EUS instruments

Ultimately, linear EUS will become the dominant procedure, overtaking radial endosonography. Small-diameter linear devices will be marketed in the near future for bronchoscopy. Endobronchial ultrasonography (EBUS) will make it possible to perform transbronchial FNA. These instruments will also find uses in gastrointestinal endoscopy for the evaluation of highly stenotic tumors and small-diameter lumens compressed by tumors or benign lesions. These instruments will allow gastroenterologists to safely perform transgastric FNA in the setting of a highly stenotic esophageal cancer. As the instruments become smaller, so will the ultrasound processors. Simple ultrasound processors will become available in laptop size components that can be readily linked to endoscopic processors. These developments will further enhance the widespread dissemination of the ultrasound instruments in endoscopy units.

Since linear EUS devices have many similar characteristics to ERCP instruments, it is possible that the design features of these instruments will begin to merge. Large-channel EUS instruments with accessory channel elevators could be adapted for use in ERCP procedures. Ultrasound imaging with ERCP instruments could be used to detect bile duct stones and pancreatic-biliary malignancy throughout an ERCP procedure. Furthermore, ultrasound imaging could aid in the guidance of wire and stent placement [1].

Radial EUS instruments

Radial instruments have also improved dramatically over the past five years with the introduction of electronic image processing and Doppler capability. The elimination of the mechanical drives for the radial probes has improved the quality of images and most importantly has decreased the frequency of repair of endosonoscopes. Color Doppler capability improves the identification of normal and abnormal structures by providing ready differentiation between fluid collections, cysts and vascular structures (veins and arteries). This type of instrumentation has lagged behind linear endosonoscopes in terms of shaft size, length of the rigid tip, and flexibility. Ideally, hybrid instruments will be designed that can provide both linear and radial imaging

from the same probe and processor. This development remains many years ahead.

High-frequency probes

The pace of development of high-frequency probes has not been comparable to radial and linear EUS. Although the probes provide high-resolution images of mucosal structures, the mechanical design makes Doppler imaging impossible. The major advantage of probe endosonography is the ease of use, but the recent development in three-dimensional imaging provides a unique functionality. One of the major clinical applications of 3D imaging is the determination of tumor volume and assessment of tumor response to therapy. Probe endosonography will continue to play an essential role in providing EUS imaging of right colon lesions since traditional endosonoscopes do not have sufficient length to image the right colon.

EUS accessories

Just as important as developments in endosonoscopes are the developments in EUS accessories. The ability to provide a tissue diagnosis using FNA has revolutionized the indications for EUS. FNA needles have continued to evolve and offer greater ease of use and improved tissue acquisition. The dependence upon FNA cytology, however, has limited the diagnostic range of EUS. This has become particularly evident in the evaluation of pancreatic lesions. Although the yield of FNA cytology in the evaluation of malignant masses has steadily increased to over 90%, FNA cytology of benign pancreatic lesions has lagged. As a consequence, there are increasing efforts to provide EUS accessories that can acquire sufficient tissue for a histologic diagnosis of benign pancreatic lesions. Trucut needles have been developed that are capable of obtaining a core of tissue from the pancreas or subepithelial gastric masses. In the future, we will see more of these devices and more widespread application in the diagnosis of pancreatic disease. Tissue cores from the pancreas will not only make it possible to secure a diagnosis of chronic pancreatitis, but it might be possible to diagnose autoimmune pancreatitis and other infiltrative diseases of the pancreas [2]. Similar applications will become evident in the diagnosis of subepithelial lesions of the upper gastrointestinal tract as well as malignancies of the gastric wall.

Along similar lines, it is possible that endoscopic mucosal resection could become EUS-guided [3]. Currently, the endoscope resection cap is placed only on endoscopes, but it might be possible to design a resection cap that could be placed on the tip of the endosonoscope. This development would enable gastroenterologists to perform real-time ultrasound imaging during mucosal resection. Ultrasound imaging during endoscopic mucosal resection might guide the depth and breadth of resection of superficial mucosal malignancies.

Therapeutic accessory devices

In addition to developments in FNA cytology devices, there will be developments in therapeutic devices. Currently, the most important therapeutic application of EUS is in the drainage of pancreatic pseudocysts [4]. Several accessories have been introduced that aid in the performance of endoscopic cyst-gastrostomies and transgastric stent placement. Many of these accessories have been principally designed for ERCP or upper gastrointestinal endoscopes [5]. In the future, we can anticipate EUS devices that will allow for wire-guided cyst-gastrostomies, cautery, and balloon dilation of cyst-gastrostomies. It seems likely that pseudocyst drainage will become predominantly an EUS procedure because of the inherent ability to image the cystic structure and the wall surrounding the pseudocyst. The design of transgastric pseudocyst stents will allow for the development of removable self-expanding stents that will greatly increase the capacity for drainage of large and complex pseudocysts.

Tissue ablation

The delivery of ablative agents and devices to localized malignancies will become increasingly important as investigations demonstrate the ability to provide local control of neuroendocrine lesions of the pancreas and duodenum. The accessories that could be used for these therapeutics currently consist only of FNA needles. In the future, it is possible that more specific devices will be designed for the delivery of heat, cold, radiation and ablative chemicals into focal malignancies. For example, radiofrequency devices could be designed for EUS that could be used to provide transgastric ablation of liver, pancreatic and perigastric lesions. Recently, EUS-guided brachytherapy has been described in animal models [6]. This type of therapy could be applied to the therapy of unresectable pancreatic malignancy. Along similar lines, EUS can help guide the outlines of malignancy with the use of EUS-guided placement of fiducials [7]. Well-delineated pancreatic malignancies could be treated with highly focused radiation or ultrasound energy.

Recently, the possibility of injection of a chemotherapeutic agent into the pancreas was demonstrated. A gel containing a Taxol derivative was injected into normal pancreatic tissue using EUS guidance. This type of agent could provide adjunctive therapy for pancreatic cancer or primary therapy of adenomas, particularly cystadenomas [8].

Nongastrointestinal applications

A broadening of applications in EUS will continue with the introduction of transbronchial and laparoscopic instruments. Transbronchial EUS will become an important tool in the evaluation of chest masses, adenopathy and bronchial lesions [9]. Although gastroenterologists may not be called on to perform the procedure, it is likely that thoracic surgeons and pulmonologists will adopt this new procedure. A similar situation may exist with laparoscopic EUS [10] (Figure 22.1). While gastroenterologists may not be the primary providers, the procedure will be disseminated to surgeons and laparoscopists. The major indication for the procedure may be the evaluation of retroperitoneal lesions

Figure 22.1 Laparoscopic EUS instrument.

such as adenopathy, pancreatic masses and adrenal lesions. If the device could be equipped with FNA capability, the procedure might enable endoscopists to provide a tissue diagnosis for inaccessible lesions.

One of the newer procedures that is possible with the use of an FNA needle is intravenous pressure measurement. EUS-guided needle placement into venous structures is technically similar to FNA. The portal venous system is particularly amenable to EUS needle access. EUS-guided portal venous pressure measurements could provide a relatively noninvasive method for the diagnosis of portal hypertension, portal venous thrombosis and malignant portal vein invasion [11]. Therapeutic applications might include injections of thrombolytic agents, chemotherapeutic drugs and thrombotic material. However, the safety of EUS portal vein needle access has not been described in humans.

Expansion of EUS indications

In addition to changes in instrumentation, we can expect continued expansion of clinical indications in EUS. The major driver and indication will be abnormalities seen in CT and MRI scanning as well as endoscopy. The most compelling indication will be the presence of cystic or solid lesions of the pancreas. Since these lesions may represent a benign, premalignant, or malignant lesion, a biopsy is often required for the optimal management. Since many of the lesions are relatively small, CT-guided biopsies are often not possible. The use of preoperative biopsies is relatively important because surgical excision is often not necessary in benign or inflammatory lesions. EUS-guided FNA is ideally suited for imaging and tissue acquisition from the pancreas and its use will become more widespread.

Tissue analysis and management

Advances in tissue management will improve the diagnostic power of EUS cytology. One of the major improvements in tissue analysis has been the introduction of molecular analysis based on loss of heterozygosity (LOH) [12]. Originally designed to evaluate the cytologic material aspirated from solid lesions in the pancreas or biliary tree, LOH analysis has the potential to improve the diagnostic accuracy of aspiration cytology and further refine the biologic nature of lesions. These principles have been applied to pancreatic cystic lesions because of the low cellular content of cyst fluid. It appears that cystic lesions are a rich source of DNA, particularly mucinous lesions. Relatively small amounts of fluid can be used to provide evidence of malignancy and risk of the development of malignancy. Similar approaches have been described in the EUS-FNA diagnosis of pancreatic neuroendocrine lesions [13]. In addition to isolation of DNA for LOH analysis, other investigations have described gene expression profiles in pancreatic cancer [14]. In the future, it seems likely that molecular analysis of tissue specimens will become more routine with tailored LOH analysis for various lesions. This type of mutational analysis would be welcomed for the diagnosis and risk determination for gastrointestinal stromal cell tumors.

Injection therapy

EUS injection therapy has been described for nearly 10 years [15]. Since guidance with EUS allows for precise tumor localization, particularly in the pancreas, EUS holds great potential for injection and ablative therapy. Traditionally, ethanol injection has been used to provide neurolysis as a form of pain relief in pancreatic cancer. In the future, this therapy will become targeted specifically to ganglia that contain nerves for pain sensation from the pancreas.

Along similar lines, EUS-guided ethanol injection could be used to ablate pancreatic tissue [16] (Plate 22.1). Thus far we have seen ethanol used for ablation of cystic neoplasms of the pancreas [17]. Given the widespread availability of injection ethanol and its ability to penetrate multiple small cystic cavities, it seems that ethanol will have a promising role as an ablative agent. However, the concerns over toxicity and induction of pancreatitis will dampen its widespread use. Recently, animal studies have demonstrated the ability of ethanol injection to produce localized pancreatic tissue ablation. Future studies will need to examine the use of ethanol for solid tumor ablation. These principles of tissue ablation could be applied to a large variety of lesions such as gastrointestinal stromal cell tumors, carcinoids and granular cell tumors [18,19].

Other EUS ablative therapies will most likely be developed for pancreatic tumor ablation. Radiofrequency ablation has been examined for use in the pancreas. Radiofrequency ablation appears to provide focal pancreatic tissue ablation without evidence of pancreatitis. Future studies will need to examine the use of radiofrequency ablation in solid pancreatic neoplasia. Another promising technique is photodynamic therapy [20]. This approach to tissue ablation with the use of photosensitizers may prove to be more selective than RFA or ethanol injection.

Summary

The future of EUS is bright. With the close cooperation of academia, the endoscopic industry and accessory companies, a large number of therapeutic applications for EUS will be developed.

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