Sun-Whe Kim
Hiroki Yamaue
Editors

Pancreatic Cancer

With Special Focus on Topical Issues and Surgical Techniques

Springer

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Preface

Why is publishing a textbook so important? While people in younger ages want to keep what they know to themselves, seniors tend to think otherwise. Seniors want to give out and share their knowledge and experiences accumulated over the decades with others. For experts and senior professionals, just wanting to do so is not enough. These people with invaluable ideas, knowledge, and experiences have the obligation to pass and share them with others. Publication of a textbook is one of the means to fulfill this obligation. And what better ways than a textbook? A textbook can hold knowledge and experiences of many experts and can be passed to anyone who can get a hold of it.

Pancreatic cancer is one of the most dreaded cancers worldwide. Pancreatic cancer continues to demonstrate dismal outcomes, despite all the efforts poured in by many competent clinicians and scientists throughout the world. But we dare say that these efforts were not all in vain, and that we have been making progresses: slow and not so dramatic but gradual. Therefore, we feel that it is the right time to put current insights of the pancreatic cancer formed over decades by many dedicated experts into a textbook. In addition, the case volume of pancreatic cancer is restricted and this limits the number of pancreatic cancer experts globally. This is another very important reason to bring the experts' insights together into a single textbook. This will allow the experts' knowledge and experiences to diffuse to many growing minds. These growing minds will build upon them and advance our knowledge of pancreatic cancer, and ultimately stand on high ground in the battle against pancreatic cancer.

To make a firm foothold for the future pancreatologists, we are very happy and honored to have world-renowned pancreatic cancer experts of various fields from all over the world to participate in making this textbook. We are certain that this textbook contains current guidelines to help understand different aspects of pancreatic cancer, and it will greatly influence many young and emerging pancreatologists and pancreatic surgeons.

The editors would like to express gratitude to Drs. Ho-Seong Han, Jin-Young Jang, Manabu Kawai, Mee Joo Kang, and Wooil Kwon for their tremendous efforts and dedication to make the publication of this textbook possible.

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Part I

Pathology and Tumor Biology

Epidemiology

1

Young-Joo Won

1.1 Epidemiology of Pancreatic Cancer

Around 95%of pancreatic tumors are adenocarcinomas originating from the exocrine (digestive enzyme-producing) region of the pancreas. Nearly all of these are ductal adenocarcinomas. Endocrine tumors of the pancreas also exist, arising from the islets of Langerhans (which produce several hormones including insulin); however, endocrine tumors are rare. The disease is difficult to diagnose, especially in its early stages. Most pancreatic tumors arise in the head of the pancreas, often causing bile duct obstruction that results in clinically evident jaundice.

1.1.1 Incidence

Pancreatic cancer is the 12th most common cancer worldwide, with around 338,000 new cases diagnosed with the disease in 2012 (2% of the total number cases). The overall ASR of pancreatic cancer increases with age (Table 1.1). Most patients are between 60 and 80 years of age. Pancreatic cancer incidence rates are the highest in Northern America and lowest in Middle Africa; however, this partly reflects the varying quality of data worldwide [1]. A total of 479,436 new pancreatic cancer cases are anticipated in 2025, with more male ($n = 254,874$) than female ($n = 224,562$) cancer patients expected (Figs. 1.1 and 1.2).

In the United States of America, pancreatic cancer is the 2nd most common malignant tumor of the gastrointestinal tract and the 4th leading cause of cancer-related death in adults. In Europe, pancreatic cancer is the 8th most common cancer, with around 104,000 new cases diagnosed with the disease in 2012 (3% of the total number of cases). The highest age-standardized incidence rates for pancreatic cancer worldwide are in the Czech Republic for both men and women; the lowest rates are in Bosnia and Herzegovina for both men and women. The United Kingdom (UK) pancreatic cancer incidence rates are estimated to be the 8th lowest for male patients in Europe and the 20th highest for female patients [1]. These data are broadly in line with Europe-specific data available elsewhere [2].

The highest rates of pancreatic ductal adenocarcinoma are recorded among African Americans (about 12 per 100,000 men and 10 per 100,000 women) and among the indigenous population in Oceania. The lowest rates (<2 per 100,000 men and 1 per 100,000 women), which may be partly attributable to underdiagnosis, are recorded in India, Northern and Central Africa, and Southeast Asia.

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Table 1.1 Estimated pancreatic incidence by age

	Total	0–14	15–39	40–44	45–49	50–54	55–59	60–64	65–69	70–74	75+	Crude	ASR(W)
Both	337,872	0.0	0.2	1.3	3.1	6.1	10.4	16.5	24.0	32.5	55.7	4.8	4.2
Men	178,161	0.0	0.2	1.6	3.9	7.5	12.8	20.1	28.5	37.2	60.6	5.0	4.9
Women	159,711	0.0	0.2	1.0	2.4	4.7	8.0	13.2	20.0	28.6	52.4	4.6	3.6

Crude and age-standardized rates per 100,000

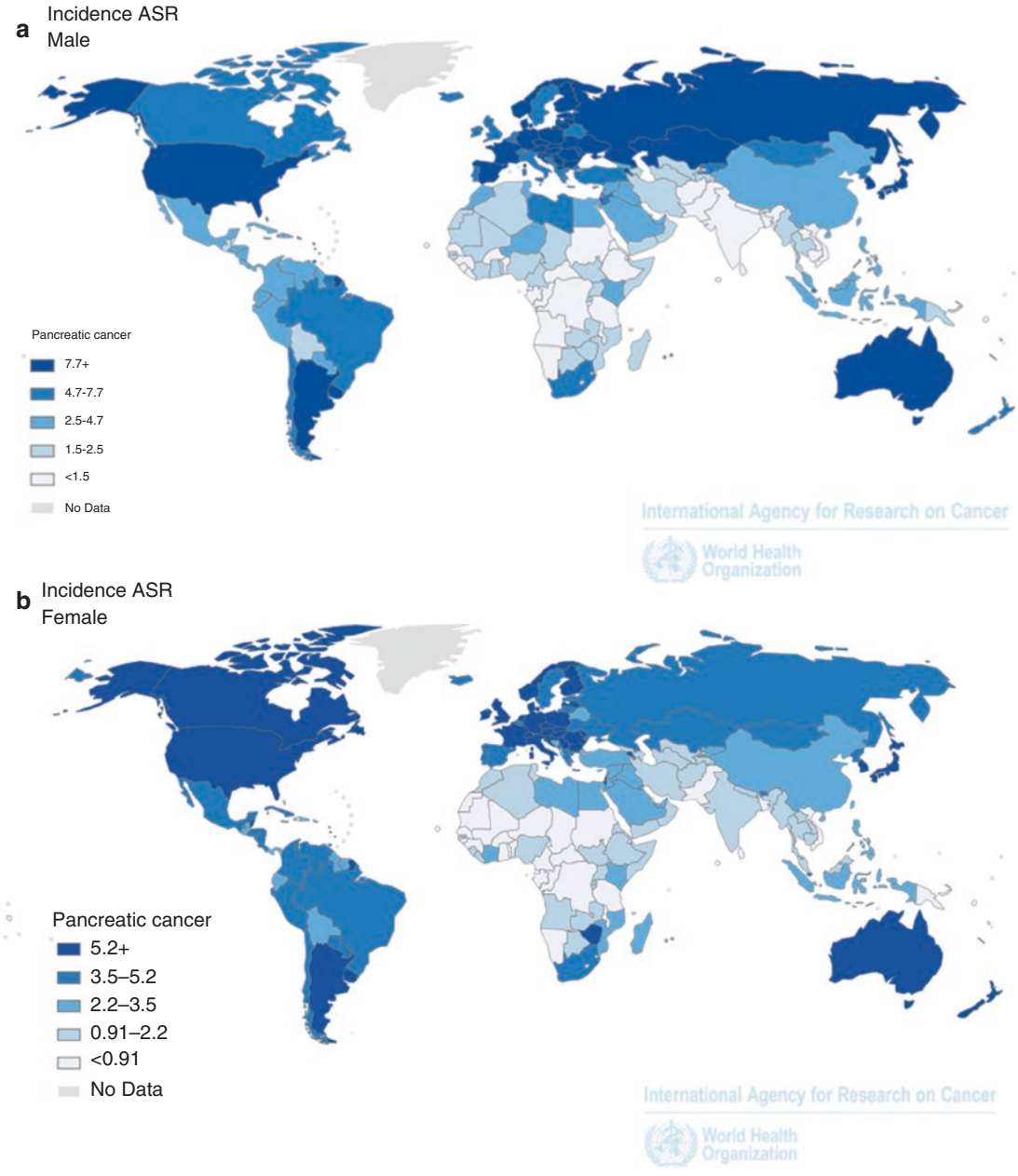
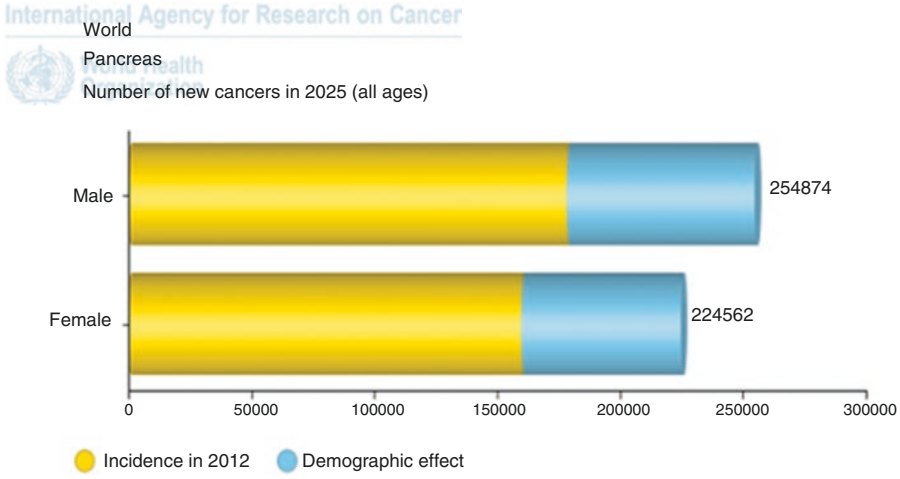


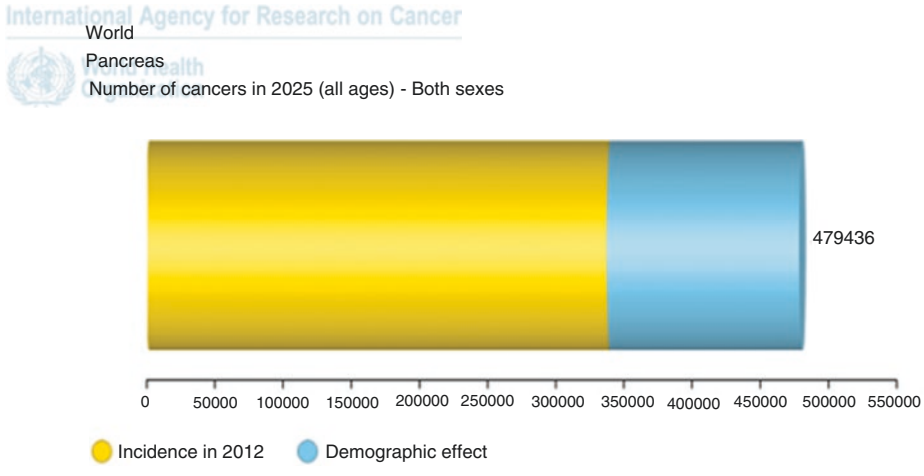
Fig. 1.1 (**a**) Incidence of pancreatic cancer in men. (**b**) Incidence of pancreatic cancer in women

World
Pancreas

Year	Estimated number of new cancers (all ages)	Male	Female	Both sexes
2012		178161	159711	337872
	ages < 65	74063	49149	123212
	ages > = 65	104098	110562	214660
2025		254874	224562	479436
	ages < 65	96391	63849	160240
	ages > = 65	158483	160713	319196
	Demographic change	76713	64851	141564
	ages < 65	22328	14700	37028
	ages > = 65	54385	50151	104536

GLOBOCAN 2012 (IARC) - 19.2.2016





GLOBOCAN 2012 (IARC) (19.2.2016)

Fig. 1.2 Incidence prediction of pancreatic cancer in 2025 (Population forecasts were extracted from the United Nations, World Population prospects, the 2012 revision. The numbers were computed using age-specific rates and corresponding populations for 10 age-groups)

1.1.2 Mortality

Pancreatic cancer is the 7th most common cause of cancer death worldwide, with 330,391 deaths from pancreatic cancer in 2012 (4% of the total number of deaths).

It is the 5th most common cause of cancer death in Europe overall, with more than 104,000 deaths from pancreatic cancer in 2012 (6% of the total number of deaths). In Europe in 2012, the highest age-standardized mortality rates for pancreatic cancer are in Macedonia for men and in Slovakia for women; the lowest rates are in Iceland for men and Belarus for women. The UK pancreatic cancer mortality rates are estimated to be the 5th lowest for males in Europe and 17th lowest for females [1]. These data are broadly in line with Europe-specific data available elsewhere [2] (Figs. 1.3 and 1.4, Table 1.2).

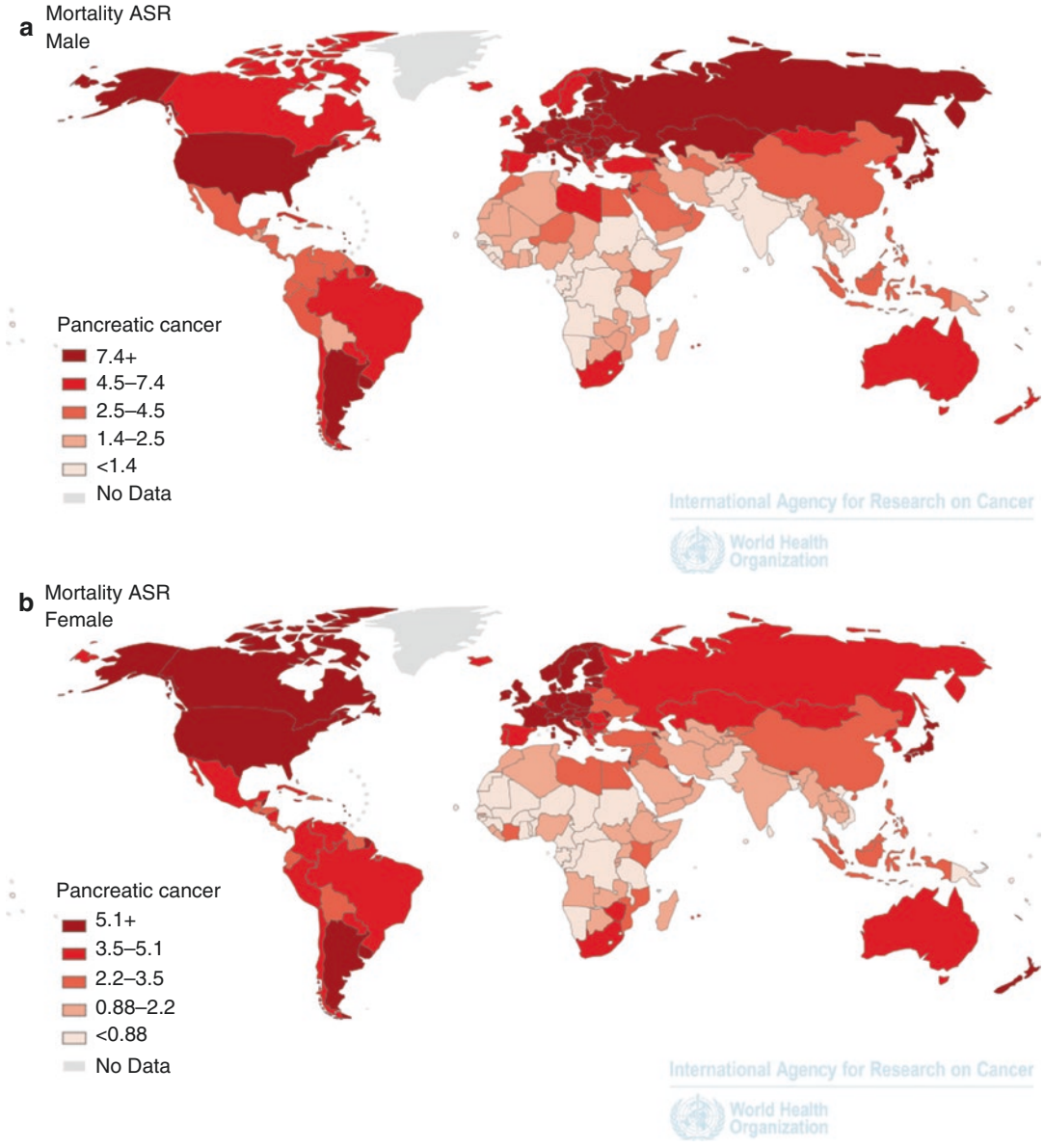
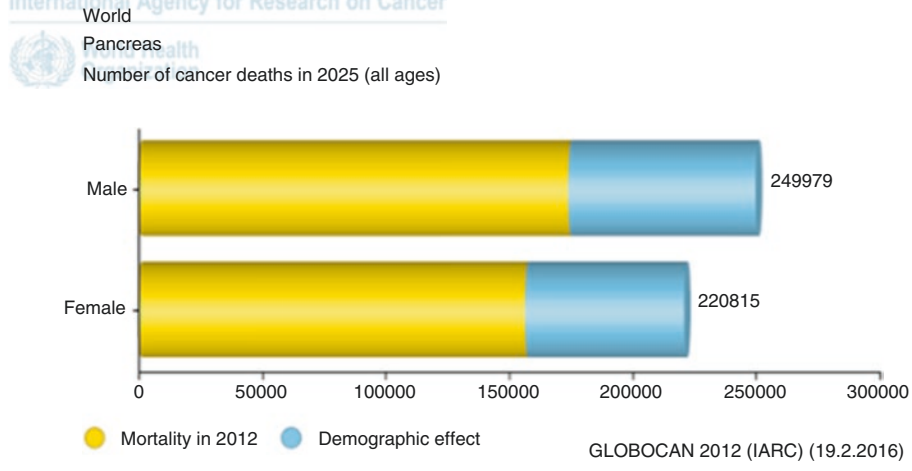


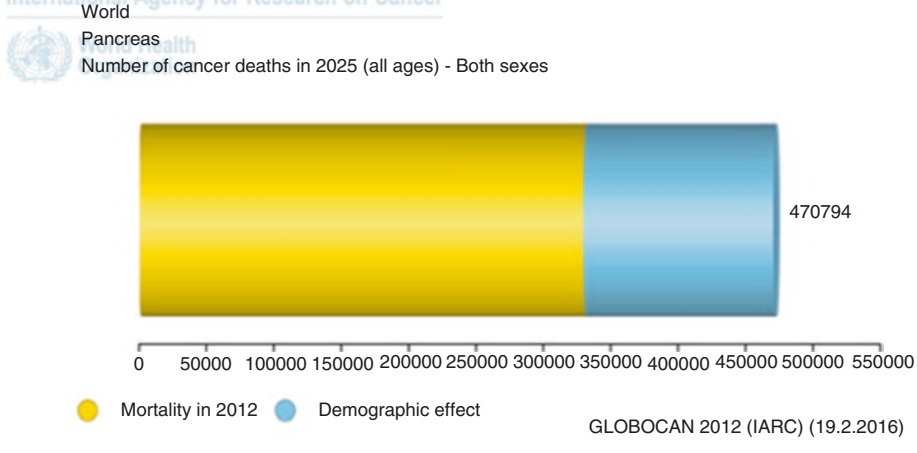
Fig. 1.3 (**a**) Mortality of pancreatic cancer in men. (**b**) Mortality of pancreatic cancer in women

World
Pancreas

Year	Estimated number of cancer deaths (all ages)	Male	Female	Both sexes
2012		173827	156564	330391
	ages < 65	66117	42108	108225
	ages > = 65	107710	114456	222166
2025		249979	220815	470794
	ages < 65	86427	54994	141421
	ages > = 65	163552	165821	329373
	Demographic change	76152	64251	140403
	ages < 65	20310	12886	33196
	ages > = 65	55842	51365	107207

GLOBOCAN 2012 (IARC) - 19.2.2016





Population forecasts were extracted from the United Nations, World Population prospects, the 2012 revision.
The numbers were computed using age-specific rates and corresponding populations for 10 age-groups.

Fig. 1.4 Mortality prediction of pancreatic cancer in 2025 (Population forecasts were extracted from the United Nations, World Population prospects, the 2012 revision. The numbers were computed using age-specific rates and corresponding populations for 10 age-groups)

Table 1.2 Estimated pancreatic mortality by age

	Total	0–14	15–39	40–44	45–49	50–54	55–59	60–64	65–69	70–74	75+	Crude	ASR(W)
Both	330,391	0.0	0.1	1.0	2.6	5.3	9.3	15.3	22.8	32.2	60.4	4.7	4.0
Men	173,827	0.0	0.2	1.2	3.2	6.5	11.6	18.9	27.3	37.1	66.0	4.9	4.7
Women	156,564	0.0	0.1	0.7	1.9	4.0	7.0	11.9	18.8	28.2	56.6	4.5	3.4

Crude and age-standardized rates per 100,000

1.1.3 Survival

It is difficult to perform comparisons of pancreatic cancer survival between countries due to differences in methodologies and criteria for including patients in analyses. Nevertheless, survival rates following surgical resection for pancreatic cancer range from 11 to 20 months. The 5-year survival ranges from 7% to 25% [3]. Patients with unresectable locally advanced disease (stage III) have a median survival of 6–11 months [4]. Patients who have metastatic disease have a median survival of only 2–6 months [5].

In the USA, there has been a steady increase in the survival rate for most cancers, whereas very slow advances have been observed for pancreatic cancer, for which the 5-year relative survival is currently 7%. These low rates ensue in part because more than one-half of cases are diagnosed at a distant stage for which the 5-year survival is 2%. The distribution of pancreatic cancer by stage is localized, 9%; regional, 28%; and distant, 53% [6].

In general, patients who can be treated with surgery tend to live longer than those not treated with surgery. Information from the National Cancer Database based on individuals diagnosed with exocrine pancreatic cancer between 1992 and 1998 shows that the 5-year survival rate for those with stage IA pancreatic cancer is about 14%. For stage IB cancer, the 5-year survival rate is about 12%. For stage IIA pancreatic cancer, the 5-year survival rate is about 7%. For stage IIB cancer, the 5-year survival rate is about 5%. The 5-year survival rate for stage III pancreatic cancer is about 3%. Patients with stage IV pancreatic cancer have a 5-year survival rate of about 1%.

Among men with pancreatic cancer, 22% survive for at least 1 year, and a previous study on the age-standardized net survival for patients diagnosed with pancreatic cancer during 2010–2011 in England and Wales predicted that this value may decrease to 4% for patients surviving for 5 years or more [7]. Survival rates for women are similar, with 20% surviving for 1 year or more and 3% predicted to survive for at least 5 years. Survival rates of pancreatic cancer patients continue to decline gradually beyond 5 years after diagnosis. Just 1% of both men and women are predicted to survive their disease for 10 years or more, as shown by age-standardized net survival for patients diagnosed with pancreatic cancer during 2010–2011 in England and Wales [7].

1.1.4 Risk Factors

An individual's risk of developing pancreatic cancer depends on many factors, including age, genetics, and exposure to risk factors (including some potentially avoidable lifestyle factors).

Increase risk ("sufficient" or "convincing" evidence)	May increase risk ("limited" or "probable" evidence)	Decreases risk ("sufficient" or "convincing" evidence)	May decrease risk ("limited" or "probable" evidence)
Tobacco, smokeless Tobacco smoking Body fatness	Alcohol Thorium-232 and its decay products X-radiation Gamma radiation Abdominal fatness Adult-attained height Red meat		Foods containing folate Fruits Physical activity

International Agency for Research on Cancer (IARC) and The World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) classifications. Find out more about IARC and WCRF/AICR classifications

Pancreatic cancer is associated with a number of risk factors. Smoking is the main risk factor for pancreatic cancer. Smokeless tobacco also causes pancreatic cancer. Physical activity, fruits, and foods containing folate may be associated with a lower pancreatic cancer risk; however, the evidence is unclear. Alcohol, red meat, ionizing radiation, and certain medical conditions and infections may relate to higher pancreatic cancer risk; however, the evidence is unclear.

Research from the UK presented that 37% of pancreatic cancer cases each year are linked to major lifestyle and other risk factors [8]. Smoking is the main avoidable risk factor for pancreatic cancer, linked to an estimated 29% of pancreatic cancer cases in the UK. An estimated 37% of pancreatic cancer cases in the UK are linked to lifestyle factors including smoking and overweight and obesity (12%).

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Molecular Alterations in Pancreatic Cancer

2

Toru Furukawa

2.1 Introduction

Cancer has somatically mutated genes that contribute to outdrive cellular proliferation and formation of a tumor. To know what genes are mutated, DNA sequencing is necessary; however until recently, only a limited number of genes or portions of genes could have been analyzed in a routine laboratory practice because of a limited ability of DNA sequencing in time and cost. However, there emerged a game changer, the next-generation sequencer (NGS), in 2009, which brought a paradigm shift in a way of genetic studies of diseases [1]. When the human genome project was conducted, 1987–2003, the automated Sanger sequencer was a main tool for analyzing DNA sequence. While the Sanger sequencer, still considered to be the most accurate sequencer, can output ~250 k bases per day, NGS can output 750G bases/3 days, in which the difference between them is one million times. The human genome is consisted of 3G base pairs of DNA; therefore, the output of NGS corresponds to 250 times of the human haploid genome. Despite this enormous output, NGS is an error-prone sequencer that needs redundant reads, usually 100 times, to get accurate sequencing. Nevertheless, NGS has given a revolutionary impact on sequencing studies primarily because it enables to sequence individual human genome in an affordable cost in a few days in a single laboratory. Alterations in protein-coding genes can be analyzed by exome that sequences every exon of human genes. Exons span 45M bases in total in the human genome, so that the exome analysis enables much cost- and time-saving studies than the whole-genome analysis. Moreover, base alterations in exomes can be interpreted directly as nonsynonymous or synonymous mutations, which is much more straightforward than interpreting variations in noncoding regions of the genome. For analysis of somatic mutations in cancer cells, comparison of sequencing data between cancer cells and normal cells is necessary; therefore, careful sampling with distinguishing between cancer cells and normal cells is needed.

An exome analysis of the pancreatic cancer has firstly reported by Jones et al. in 2008 [2]. Although this study was by means of Sanger sequencing, they analyzed 24 cases of pancreatic ductal adenocarcinoma (PDA). By NGS, Biankin et al., a team of international collaboration under International Cancer Genome Consortium, published a result of exome combined with a copy number variation (CNV) analysis of 142 PDAs in 2012 [3]. Later they published a result of whole-genome analysis of 100 PDAs in 2015 [4], and a result of integrated analysis consisted of whole-genome, CNV, transcriptome, and methylome

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analysis of 456 PDAs in 2016 [5]. There also are some independent studies published elsewhere including one by Wang et al. regarding exome analyses of 15 PDA cell lines in 2012 [6] and the other by Witkiewicz et al. regarding exome analysis of 109 PDAs in 2015 [7].

2.2 Genetic Alterations in PDAs

Exome analyses of PDAs indicate that one PDA has approximately 60 nonsynonymous mutations in average [3, 4]. PDAs with microsatellite instability that is caused by mismatch repair deficiency have more than 100 mutations/case, often 500 [4]. Spectra of mutations show that C:G>T:A transition is enriched in PDAs, especially CpG>TpG mutations are common, which indicates that an aberrant methylation may be a major cause of the mutations [4]. Smokers usually show enrichment of C:G>A:T transversion, which is observed in a fraction of PDAs. On the other hand, enrichment of C>T transition in TpCpW site, which is caused by apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like (APOBEC), a cytidine deaminase, is not common in PDAs [4].

Through the exome and CNV analyses, four commonly altered genes in PDAs, namely, *KRAS*, *TP53*, *CDKN2A*, and *SMAD4*, have reemerged [2–4, 7]. These four genes are altered frequently, 90% of PDAs harbor gain-of-function mutations in *KRAS*, 90% harbor mutations or loss of *CDKN2A*, 75% harbor *TP53* mutations, and 50% harbor mutations or loss of *SMAD4*, which has been well known since the late 1980s; hence, NGS analyses have reconfirmed alterations of these "Big 4" genes in PDAs. Next commonly altered genes are those encoding proteins involved in chromatin regulation, i.e., *KDM6A*, *KMT2C/MLL3*, *KMT2D/MLL2*, *ARID1A*, *ARID2*, and *PBRM1*, which are altered in ~25% of PDAs [4, 5]. Other genes each altered in ~10% of PDAs are those functioning in DNA repair system including *BRCA1*, *BRCA2*, *PALB2*, and *ATM*; those functioning in RNA processing and/or splicing including *SF3A1*, *SF3B1*, *U2AF1*, *U2AF2*, *RBM6*, and *RBM10*; those functioning in wingless-type MMTV integration site (Wnt) pathway including *CTNNB1*; those functioning in transforming growth factor beta (TGFb) pathway including *SMAD3*, *TGFBR1*, *TFGBR2*, *ACVR1B*, and *ACVR2A*; and those functioning in phosphatidylinositol 3-kinase (PI3K) pathway including *PIK3CA* and *PTEN* [4, 5].

2.3 *KRAS* and the Mitogen-Activated Protein Kinase Pathway

KRAS encodes Kirsten rat sarcoma viral oncogene homologue (KRAS) that is a small guanosine triphosphate (GTP)-binding protein and one of three members of rat sarcoma viral oncogene homologues (RAS) [8]. *KRAS* is mutated in 90% of PDAs, and mutations are commonly observed in codon 12, 13, and 61 as missense mutations, in which G12D and G12V are most common [5, 9]. G12C mutations that are known to be common in lung cancer and recently shown as a specific druggable target [10] are not common in PDAs. RAS plays a central role in controlling of activities of numerous signal transduction pathways, most notably of the mitogen-activated protein kinase (MAPK) pathway. In the RAS-MAPK pathway, a membrane-bound enzyme-linked receptor, e.g., the epidermal growth factor receptor or the platelet-derived growth factor receptor, activated by ligand binding activates a guanine nucleotide exchanging factor that facilitates exchanging guanosine diphosphate (GDP) bound to RAS with GTP, which makes RAS activated. The GTP-bound RAS activates the MAPK cascade consisted of the mitogen-activated protein kinase kinase kinase (MAP3K)/V-Raf oncogene homologue (RAF), the mitogen-activated protein kinase kinase (MAP2K)/MAP kinase-ERK kinase (MEK), and the mitogen-activated protein kinase 1 (MAPK1)/extracellular signal-regulated kinase (ERK), in which an activated signal is passed on by sequential phosphorylating reactions. RAS has an intrinsic hydrolase activity that turns bound GTP to GDP, which inactivates itself; however, the mutations in *KRAS* cause decreasing of the hydrolase activity and, hence, protracting activity of itself as well as downstream signal transduction pathways. Active

MAPK1/ERK translocates into nucleus and activates transcription factors that induce expression of effector genes functioning in DNA replication, RNA maintenance, transcription and translation, cell cycle and mitosis, transporting, and cell proliferation [11]. Activity of MAPK1/ERK is negatively regulated by dual specificity phosphatases (DUSPs), most directly by DUSP6 [12]. DUSP6 forms a negative feedback loop with MAPK1/ERK, i.e., an activation of MAPK1/ERK induces expression of DUSP6 that inactivates MAPK1/ERK; therefore, MAPK1/ERK activity is tightly regulated through this negative feedback loop [13]. However in some PDAs, expression of DUSP6 is downregulated mostly by aberrant methylation; hence, the negative feedback loop between MAPK1/ERK and DUSP6 is abrogated, which results in constitutive activation of MAPK1/ERK and expression of genes implicated in malignant phenotypes of PDAs [14].

BRAF encodes B-Raf proto-oncogene, serine/threonine kinase that functions as a MAP3K in MAPK pathway. *BRAF* is mutated in some of PDAs that harbor the wild-type *KRAS*; therefore, mutations in *BRAF* and *KRAS* are mutually exclusive in PDAs [15]. Most mutations of *BRAF* in human cancers including PDAs are observed as a V600E mutation, which turns the kinase constitutively active [16]. Vemurafenib is developed to target cancers with the $BRAF^{V600E}$ mutation [17].

2.4 TP53

TP53 encodes p53, a transcription factor involved in DNA damage response [18]. DNA damage provoked by irradiation and/or reactive oxygen species is sensed by and activates the ataxia telangiectasia mutated (ATM), a serine/threonine protein kinase, that phosphorylates p53. The phosphorylated p53 dissociates from the mouse double minute 2 homologue (MDM2), an E3-ubiquitin ligase, and binds DNA to induce expression of target genes that have a consensus binding sequence in their promoters. Most of these target genes of p53 encode proteins involved in cell cycle arrest, DNA repair, and apoptosis including p21, p27, BAX, PUMA, etc., which plays an important role in determining cells' fate whether they survive through DNA repair or die by apoptosis to avoid accumulation of mutations caused by DNA damage [19]. Mutations in *TP53* are found in 60–75% of PDAs. Mutations in *TP53* are either frameshift mutations or missense mutations within a DNA-binding domain of p53. The missense mutation in p53 abrogates DNA-binding activity, which results in dysfunction of its transcription-activating activity. These mutations have been thought as loss-of-function mutations, which definitely is the case in frameshift mutations; however, a recent investigation indicates that missense mutations in p53, at least some of them, can modulate functions of chromatin remodeling proteins and then enhance transcriptions of certain genes that promote malignant phenotypes of cancer, which indeed are gain-of-function mutations [20]. p53 proteins with missense mutations are refractory to MDM2-mediated proteasomal destruction and, therefore, accumulate in the nucleus and appeared as overexpressed by immunohistochemistry [21].

2.5 CDKN2A

CDKN2A encodes the cyclin-dependent kinase inhibitor 2A (CDKN2A)/p16. CDKN2A/p16 plays a role in attenuation of cell cycle progression from G1 phase to S phase. For progression of the cell cycle, the cyclin-dependent kinase 4 (CDK4) is activated by binding with cyclin D; subsequently the activated CDK4 phosphorylates retinoblastoma protein (RB), and then, the phosphorylated RB dissociates from the E2F transcription factor 1 (E2F1), which facilitates nuclear translocation of E2F1 and expression of target genes necessary for the cell cycle progression [22]. CDKN2A inhibits the activation of CDK4 by hampering its binding to cyclin D and, therefore, attenuates cell cycle progression. *CDKN2A* is mutated and deleted homozygously in 25% and 10% of PDAs, respectively [4]. Moreover, *CDKN2A* is epigenetically silenced by aberrant hypermethylation in 50–60% of PDAs; hence, *CDKN2A* is functionally disrupted in almost all PDAs, which presumably contributes to uncontrolled cell cycle progression [23].

2.6 SMAD4

SMAD4 encodes the Sma and Mad protein homologue 4 (SMAD4). SMAD4 plays a role in signal transduction of the transforming growth factor β (TGFβ) pathway. TGFβ, a ligand, binds and facilitates formation of a heterodimer between TGFβ receptor (TGFBR) type 1 and TGFBR type 2 and, then, induces phosphorylation of the receptors at each other. The phosphorylated TGFBR type 1 recruits and phosphorylates the Sma and Mad protein homologue 2 (SMAD2) or the Sma and Mad protein homologue 3 (SMAD3). The phosphorylated SMAD2/SMAD3 oligomerizes with SMAD4, and the SMAD2/SMAD3-SMAD4 oligomer translocates into nucleus and activates transcription factors, which induces expression of target genes that harbor TGFβ-responsive element in their promoters. The target genes include *MMP3* and *ADAM19*, which encode matrix metalloproteinases; *ARHGAP5* and *ARHGAP10*, which encode Rho-GTPase-activating proteins; *CSNK1A1*, *DKK1*, and *FRAT1*, which encode proteins associated with Wnt pathway; *CASP8* that encodes a caspase; *HDAC9* that encodes a histone deacetylase; and *CAMK2D* that encodes a protein associated with calcium signaling [24]. *SMAD4* is mutated and homozygously deleted in around 20% and 10% of PDAs, respectively [4, 25]. Many of the mutations are nonsense or frameshift mutations, which indicates that *SMAD4* alterations in PDAs are virtually loss-of-function alterations. *SMAD4* alterations in PDAs can be detected by immunohistochemistry as complete loss of its protein product in cancer cells [21].

2.7 Chromatin Modification Genes

Chromatin remodeling genes, *KDM6A*, *KMT2C/MLL3*, *KMT2D/MLL2*, *ARID1A*, *ARID2*, and *PBRM1*, are altered in ~25% of PDAs. *KDM6A/UTX* encodes the lysine-specific demethylase 6A (KDM6A) that contains a Jumonji C domain and catalyzes the demethylation of tri-/dimethylated histone H3 [26]. *KMT2C/MLL3* and *KMT2D/MLL2* encode the lysine-specific histone methyltransferase 2C (KMT2C) and the lysine-specific histone methyltransferase 2D (KMT2D), respectively, which are members of the ASC-2/NCOA6 complex (ASCOM) that are involved in transcriptional coactivation [27, 28]. Because KDM6A is associated with KMT2C and KMT2D, alterations of *KDM6A*, *KMT2C*, and *KMT2D* are mutually exclusive [5]. *ARID1A* encodes the AT-rich interactive domain 1A (SWI-like), a member of the SWI/SNF family, whose members have helicase and ATPase activities and are able to restructure the nucleosome to make its DNA accessible during transcription, replication, and DNA repair [29]. *ARID2* encodes the AT-rich interactive domain 2/BAF200, an integral component of the polybromo-associated BAF (PBAF) chromatin remodeling complex of the SWI/SNF family, which facilitates a ligand-dependent transcriptional activation by nuclear receptors [30]. *PBRM1* encodes the polybromo 1/BAF180 that is another subunit of PBAF complex [31]. ARID2/BAF200 and PBRM1/BAF180 are mutually exclusive in constitution of the PBAF complex, which contributes to distinct selection of remodeled genetic elements [30]. Mutations of these genes are largely loss-of-function mutations, which is thought to cause dysfunction of chromatin regulation and aberrant expression of target genes although detail of dysfunction of these molecules in PDA is waited to be elucidated [5].

2.8 DNA Repair-Associated Genes

DNA repair-associated genes including *BRCA1*, *BRCA2*, *PALB2*, and *ATM* are altered in ~10% of PDAs. *BRCA1* and *BRCA2* encode the breast cancer 1 (BRCA1) and the breast cancer 2 (BRCA2), respectively, both of which are involved in repair of a double-strand break of DNA by homologous recombination. When DNA suffers from a double-strand break caused by ionizing radiation and/or reactive oxygen species, BACA1 associates with a broken end and helps to process the end being ready for the homologous recombination [32]. BRCA2 binds a single-strand DNA and

helps to bring RAD51, a RecA homologue in eukaryotes, and plays a vital role in strand invasion in the homologous recombination, to damaging sites in DNA for its proper function [33]. *ATM* encodes the ataxia telangiectasia mutated (ATM) that is a kinase and functions in sensing of a DNA damage. ATM associates with a damaged site and phosphorylates some proteins including the checkpoint kinase 1 (CHK1) and the checkpoint kinase 2 (CHK2), which eventually results in cell cycle arrest for DNA repair. *PALB2* encodes the partner and localizer of BRCA2 (PALB2) that, as this name suggests, is co-expressed with BRCA2 in nuclear foci when cells are irradiated, which indicates that PALB2 also participats in DNA repair [34]. Since most of mutations of these genes are loss-of-function mutations, a proper repair of DNA cannot be pursued, and, therefore, secondary mutations accumulate in cells with mutations of these genes.

2.9 RNA Processing Genes

Genes encoding RNA processing and/or splicing factors including *SF3A1*, *SF3B1*, *U2AF1*, *U2AF2*, *RBM6*, and *RBM10* are mutated in ~16% of PDAs [5]. *SF3A1*, *SF3B1*, *U2AF1*, and *U2AF2* encode components of U2AF, a small nuclear ribonucleoprotein (snRNP) essential for proper splicing of pre-messenger RNA. Most of mutations in these genes are missense mutations in a functional domain and are demonstrated to function as a dominant negative protein that facilitates immature splicing [35]. *RBM6* and *RBM10* encode RNA-binding molecules implicated in alternative splicing. Mutations of these genes are mostly loss-of-function mutations, which is demonstrated to be implicated in dysfunction of alternative splicing of some key molecules for oncogenesis like *NUMB* [36].

2.10 Wnt Pathway Genes

Wnt pathway is an important signaling pathway in development of multicellular organisms. One of important mediators in Wnt pathway implicated in pancreatic cancer is beta catenin. The gene encoding beta catenin is *CTNNB1*, which is mutated in ~10% of PDAs. Beta catenin is a cadherin-associated protein in the adherence complex that mediates cell-cell junction. Beta catenin is also a cytoplasmic protein that can function as a signal mediator, which is tightly regulated through formation of a complex with axin and the adenomatous polyposis coli (APC) protein. The complex of beta catenin-axin-APC associates with glycogen synthase kinases that phosphorylate and render beta catenin for ubiquitin-proteosomal destruction. Wnt signaling suppresses the complex formation and facilitates free beta catenin. The free beta catenin translocates into the nucleus and functions as a transcriptional coactivator [37]. Mutations in *CTNNB1* cause to generate a protein refractory to the ubiquitin-mediated destruction, which results in facilitation of the transcriptional coactivator activity of beta catenin [38]. By immunohistochemistry, a mutated beta catenin is often found as an overexpressed protein in the nucleus.

2.11 Phosphatidylinositol 3-Kinase (PI3K) Pathway Genes

Genes encoding molecules implicated in PI3K pathway including *PIK3CA* and *PTEN* are mutated in ~5% of PDAs. PI3K pathway plays a fundamental role in cell growth. Phosphatidylinositol (PI) is a glycerophospholipid molecule sitting in the cell membrane. PI is phosphorylated by kinases on specific hydroxyl groups, PI-3, PI-4, and PI-5, and functions as a signal mediator. *PIK3CA* encodes the phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha. Mutations in *PIK3CA* mostly affect codon 545 or 1047, which causes upregulation of kinase activity of its protein product. *PTEN* encodes the phosphatase and tensin homologue, a phosphatase specific for PI-3. Mutations in *PTEN* are mostly frameshift or nonsense mutations that result in loss of function of its product.

2.12 Molecular Mechanism of Development of PDA

Pancreatic cancer has been hypothesized to develop from ductal cells, in which normal ductal cells would give rise to full-brown cancer cells via gradual dysplastic changes of themselves. PDA tissues usually have dysplastic ductal lesions in close vicinity of invasive carcinoma [39, 40], and studies on these dysplastic lesions have elucidated that dysplastic cells have varying grades of atypia, from low-grade to high-grade, and the high-grade lesions can be found frequently in a pancreatic tissue specimen with invasive cancer while extremely infrequently in that without invasive cancer [40]. Molecular studies have uncovered that low-grade dysplastic cells harbor *KRAS* mutations and *CDKN2A* inactivation, while high-grade dysplastic cells have aberrations of *TP53* and *SMAD4* in addition to the *KRAS* mutation and *CDKN2A* inactivation [21]. These results indicate that molecular aberrations indeed accumulate along with the progression of dysplastic grade of ductal cells. Now these dysplastic lesions are termed pancreatic intraepithelial neoplasia (PanIN) [41], i.e., PanIN is a noninvasive proliferative lesion of dysplastic ductal cells, which develops as a low-grade lesion and progresses to a high-grade lesion with an association with molecular alterations. This multistep hypothesis is known as the progression model for the pancreatic cancer [42].

The progression model for the pancreatic cancer seems to be further endorsed by studies of genetically engineered mouse models (GEMM) of pancreatic cancer. GEMM with *lox-Stop-lox (LSL)-Kras*^{G12D} and *Pdx1-Cre* induces the mutant *Kras, Kras*^{G12D}, the most common type of mutant *KRAS* in human PDAs, in a pancreas-specific manner during development. This mouse is born without any abnormality; however, it gradually develops microscopic proliferative lesions in the pancreatic duct that closely mimic PanIN and, eventually, although rarely, invasive ductal carcinoma in the pancreas in 2 years [43]. Detailed examinations of this model indicate that PanINs in early phase are with low-grade dysplasia, while those in late phase harbor high-grade dysplasia. GEMM with pancreas-specific expression of *Kras*^{G12D} and *Trp53*^{R172H} (mutant *p53)* shows facilitation of development of invasive ductal carcinoma with frequent metastasis, which indicates that an accumulation of genetic alterations, the mutated *Kras* and the mutated *Trp53* in this case, accelerates pancreatic cancer development [44]. Moreover, GEMM with pancreas-specific expression of *Kras*^{G12D} and *Trp53*^{R172H} and complete loss of *Smad4* develops a rapidly growing pancreatic tumor with metastasis and shows shorter survival than a mouse with *Kras*^{G12D} and *Trp53*^{R172H}, in which overexpression of *Runx3* is associated with the metastatic phenotype [45].

2.13 Genetic Alterations in Intraductal Papillary Mucinous Neoplasms

Intraductal papillary mucinous neoplasms (IPMNs) are characterized by manifestation of dilated duct filled with mucin. The dilated duct is lined with neoplastic cells growing in papillae with varying grades of atypia [46]. The papillae show diverse architectural variations termed gastric, intestinal, pancreatobiliary, and oncocytic subtypes [47]. The atypia ranges from low-grade to high-grade, which often intermingles with each other. Occasionally the neoplastic cells invade into parenchyma, which forms invasive mucinous colloid carcinoma or invasive ductal adenocarcinoma [48]. These features of IPMNs are quite distinctive from PDAs, a conventional type of pancreatic cancer; however, molecular alterations specific for IPMNs had been unknown until just recently. In 2011, two groups of researchers independently reported that IPMNs exclusively harbored somatic mutations in *GNAS*, which has uncovered a specific molecular pathway implicated in IPMNs [49, 50]. Somatic mutations in *GNAS* are observed in 50–70% of IPMNs while, strikingly, none of PDAs examined. *GNAS* encodes the guanine nucleotide-binding protein (G protein) stimulating alpha subunit (Gsα) that functions as a mediator in the G protein-coupled receptor (GPCR) pathway. GDP-bound Gsα forms a heterotrimeric G protein

complex with β and γ subunits in its inactive state. A ligand binding to GPCR activates the guanine nucleotide exchanging factor that mediates exchange of GDP with GTP-bound Gsα. GTP-bound Gsα turns into an active form, dissociates from β and γ subunits, and subsequently associates with and activates adenylyl cyclase. The adenylyl cyclase mediates production of cyclic AMP, which leads to activation of the cyclic AMP-dependent protein kinase (PKA). PKA translocates into the nucleus and phosphorylates downstream molecules implicated in gene expression. Gsα has an intrinsic hydrolase activity that catalyzes the hydrolysis of the bound GTP to GDP, which inactivates itself. Mutations in *GNAS* observed in IPMNs almost always involve codon 201, which commonly are R201H or R201C. These mutations abrogate the intrinsic hydrolase activity, which results in constitutive activation of Gsα, hence, gain-of-function mutations [51]. An in vitro experiment to examine an effect of the mutant Gsα shows that transfection of mutated *GNAS* in pancreatic ductal cells induces elevation of cyclic AMP and marked alteration of gene expression including upregulation of mucin genes, which indicates that the mutated *GNAS* is strongly associated with production of excess mucin in IPMNs [52]. To examine an in vivo effect of the mutated *GNAS*, a genetically engineered mouse model that harbors *LSL-GNAS*^{R201H} under *CAG* promoter (Tg(*CAG-LSL-GNAS*^{R201H})) was generated [53]. When this mouse crosses with *Ptf1a*$^{Cre/+}$ and *LSL-Kras*^{G12D} mice, synergistic expression of *GNAS*^{R201H} and *Kras*^{G12D} is induced in a pancreas-specific manner, and, as a result, a multicystic tumor develops in the pancreas within 5 weeks. The multicystic tumor is consisted of dilated ducts lined with papillary neoplastic epithelia, which closely mimics human IPMNs. This result indicates that the mutated *GNAS* indeed causes development of IPMN in vivo. *GNAS* mutations are observed in low-grade IPMNs as well as high-grade IPMNs [50]. In IPMN variations, intestinal-type IPMNs are more likely to harbor *GNAS* mutations than other types of IPMNs [54]. The pyloric gland variant of gastric-type IPMNs also commonly harbors *GNAS* mutations [55]. By immunohistochemistry, IPMN cells show strong expression of Gsα and phosphorylated substrates of PKA [50]. *GNAS* mutations are not associated with patients' survival [54]. These observations indicate that the *GNAS* mutation strongly contributes to development and manifestation of characteristic phenotypes of IPMNs.

Some IPMNs, 14% of them, harbor somatic mutations in *RNF43* [56, 57]. *RNF43* encodes ring finger protein 43 (RNF43), an E3-ubiquitin ligase associated with Frizzled receptor [58]. RNF43 mediates destruction of internalized Frizzled receptor whose ligand is Wnt, which contributes to control activity of the Wnt signaling pathway. Mutations in *RNF43* are protein-truncating mutations or missense mutations in the ring finger domain, which mostly are regarded as loss-of-function mutations that presumably induce hyperactivation of the Wnt pathway.

2.14 Familial Pancreatic Cancer

Some patients with PDAs have a strong family history, in which individuals suffering from PDA cluster within the first- or second-degree relatives. This familial predisposition to pancreatic cancer is known as familial pancreatic cancer, which is now precisely defined as a kindred with a pair of first-degree relatives with pancreatic cancer [59]. The risk of pancreatic cancer in the familial pancreatic cancer kindred is estimated to be 6.79-fold compared with the general population in the USA [60]. Moreover, kindred with three individuals with pancreatic cancer in the first-degree relatives have 32-fold risk of pancreatic cancer [61]. These results suggest a significant role for genetic factors in the familial pancreatic cancer kindred. Genes known to be associated with familial pancreatic cancer kindred are *BRCA2, PALB2, ATM, STK11, CDKN2A, PRSS1,* and *SPINK1*. *BRCA2, PALB2,* and *ATM* are DNA repair-associated genes whose functions are described in the previous section. Germline mutations in *BRCA2, PALB, and ATM* are found in 6%, 3%, and 3.5% of the familial pancreatic cancer kindred, respectively [62, 63]. *STK11* is a predisposed gene for Peutz-Jeghers

syndrome (PJS), an autosomal dominant disorder characterized by growth of polyps in the gastrointestinal tract and pigmented macules on the skin and mouth. *STK11* encodes the serine/threonine kinase 11 that regulates the AMP-activated protein kinase and plays a role in cell metabolism, cell polarity, apoptosis, and DNA damage response. The cumulative risk of pancreatic cancer is reported to be 11 in PJS compared with 0.5 in general population in age 60s [64]. *PRSS1* and *SPINK1* are known to be predisposed genes for a hereditary pancreatitis [65, 66]. *PRSS1* encodes a trypsinogen and *SPINK1* encodes a trypsin inhibitor. Individuals with hereditary pancreatitis yield the standardized incidence ratio, which is the ratio of observed pancreatic cancer cases in the cohort to the expected pancreatic cancers in the background population, of 53 [67].

2.15 Implication of Molecular Alterations in Clinical Practice

KRAS is mutated in 90% of PDAs, which indicates that an activation of RAS-MAPK pathway is nearly an essential molecular event for development or progression of PDAs. Several studies have been conducted whether *KRAS* mutation could be used as a specific molecular marker for PDA. Detection of *KRAS* mutation was tested in duodenal fluid [68], pancreatic juice [69], and feces [70], and, as expected, these studies showed justifiable sensitivities, however, questionable specificities, possibly because of prevailing occurrence of *KRAS* mutation in precursor lesions like PanINs [71] or IPMNs [72]. Recently, thanks to NGS power, detection of *KRAS* mutation in circulating tumor cells or free DNA in peripheral blood as "liquid biopsy" is being emerged as an alternative method of tissue biopsy [73]. Circulating tumor DNA (ctDNA) is free DNA identified in plasma. CtDNA is reported to be detectable by assessing tumor-specific mutations in 60–90% of metastatic PDAs and 20–50% in localized PDAs [73–75]. Increasing of ctDNA is associated with poor survival [74, 75].

Molecular alterations are associated with patients' prognosis. Aberrations of *CDKN2A/p16* are associated with poor survival [76, 77]. Loss of SMAD4 expression is associated with metastasis and poor survival [78, 79]. A recent report indicates that patients with mutations in *KRAS* at codon 61 (Q61), although a fraction of such patients is usually less than 10%, show better survival compared with those with *KRAS* codon 12 mutations [7]. *ROBO2* encodes the roundabout guidance receptor 2 that functions in axon guidance and cell migration, which is recently uncovered as a mutated gene in pancreatic cancer. *ROBO2* is mutated or deleted in ~15% of PDAs, and lower expression of ROBO2 is associated with poor survival of patients with PDAs [3].

Aberrations in DNA repair pathway are associated with sensitivity for chemotherapy. Mutations in *BRCA1*, *BRCA2*, or *PALB2* lead to dysfunction of BRCA pathway of DNA double-strand break repair. This dysfunction may cause additional mutations of genes implicated in progression of pancreatic cancer; however simultaneously, it also potentially causes cell death by devastation of genome integrity. Therefore, PDAs with defective BRCA pathway are sensitive to drugs, e.g., mitomycin C and cisplatin, or irradiation that induces extensive DNA double-strand breaks [4]. Poly ADP-ribose polymerase (PARP) is an enzyme that alternatively functions in DNA repair, and this alternative pathway is activated compensatory in cancers defective for BRCA pathway; therefore, a PARP inhibitor, e.g., olaparib, is effective in such PDAs [80].

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Pathological Classification

3

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The pancreas has distinct exocrine and endocrine components [1]. The *exocrine pancreas* constitutes 80–85% of the organ and is composed of acinar cells, arranged in small, rosette-like clusters packed back to back to form compact lobules separated by thin, fibrous septa and containing membrane-bound granules rich in proenzymes (zymogens), including trypsinogen, chymotrypsinogen, and prophospholipase A and B [1]. Upon secretion, these proenzymes and enzymes are carried by the ductal system to the duodenum, where they are activated by proteolytic cleavage in the gastrointestinal tract. The ductal component starts with the centroacinar cells, and through intralobar and interlobar ducts, the enzymatic secretions are carried to the main pancreatic duct and eventually to the duodenum through the ampulla of Vater [1]. The *endocrine pancreas* is composed of a million distinct clusters of cells, the islets of Langerhans, scattered throughout the gland. The islet cells secrete insulin, glucagon, and somatostatin and other hormones and overall constitute only 1–2% of the organ [1]. Pancreatic neoplasms are classified based on the degree to which they recapitulate one of the cellular components of the pancreas [2]. This section reviews the pathological characteristics of pancreatic neoplasms.

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3.1 Ductal Neoplasms

Despite being the least sophisticated component of the organ, by far the most common tumors of this organ are of ductal origin. Whether this is due to the regeneration ability of the ductal cells or whether it is related to their exposure to the external milieu or both remains to be analyzed. The most common neoplasm of ductal origin that is of clinical significance is "ductal adenocarcinoma" (also called pancreatobiliary-type adenocarcinoma). Pancreatic intraepithelial neoplasms, as defined currently, are perhaps even more common but seldom come to clinical attention. Intraductal neoplasms (intraductal papillary mucinous neoplasms and intraductal tubulopapillary neoplasms) are also fairly common, lesser examples commonly presenting as incidental cysts in the pancreas. There are also malignant neoplasms of ductal origin that are closely related to ductal adenocarcinomas but are classified separately such as adenosquamous, osteoclastic giant cell, and others. In the ensuing section, these neoplasms will be discussed in detail.

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3.1.1 Invasive Ductal Adenocarcinoma

Invasive ductal adenocarcinoma affects mainly the middle-aged to elderly. There does not seem to be significant gender predilection [3]. It has a remarkable tendency for rapid dissemination and insidious infiltration [3]. Typically, it spreads in the abdomen in a military fashion (intra-abdominal carcinomatosis) or is already widely metastatic by the time the primary tumor grows to 5–6 cm in size [3]. They typically invade the local nerves by the time of diagnosis and thus many patients have back pain. Despite the high frequency of distant metastases, some ductal carcinomas cause death of the patient as a result of predominantly local growth [3].

Most ductal adenocarcinomas are located in the head of the pancreas and infiltrate the neighboring structures, especially the common bile duct, and obstructive jaundice is a common finding at presentation. For this reason, it is often difficult to distinguish pancreatic carcinoma from a carcinoma of the distal common bile duct, especially given that the two are microscopically similar. Some pancreatic ductal adenocarcinomas infiltrate and ulcerate the duodenum or ampulla of Vater and may mimic a primary duodenal or ampullary neoplasm, and the classification of such cases may have to be based on arbitrary criteria such as the epicenter of the mass which requires careful grossing of the specimens.

Grossly, most ductal adenocarcinomas are scirrhous type of carcinomas; they are associated with abundant desmoplastic stroma, in which the neoplastic glands are widely scattered. This creates a challenge in the diagnosis of ductal adenocarcinoma, not only because often only a few cancer cells are present, if any, for evaluation in biopsy specimens but also it can be extremely difficult to distinguish from fibrosis of chronic pancreatitis radiologically and grossly. This is also a problem for cancer researchers, because most procured "tumor" specimens may in fact contain much more host tissue than the true carcinoma cells. The characteristics that distinguish ductal adenocarcinoma are its firm, gray, and gritty cut surface rather than the rubbery, milky white appearance of benign fibrotic lesions.

Microscopically, ductal adenocarcinoma is characterized by infiltrating tubular glands, often widely scattered, embedded in a desmoplastic stroma of variable cellularity (Fig. 3.1). These

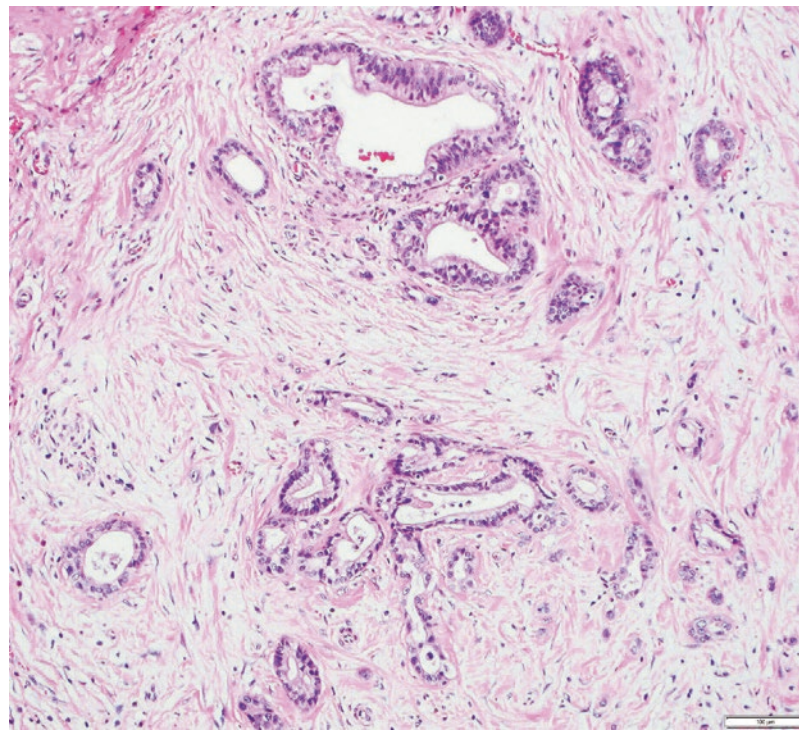

Fig. 3.1 Conventional pancreatic ductal adenocarcinoma: variably sized well-formed glands surrounded by abundant desmoplastic stroma

neoplasms vary from well-differentiated, duct-forming carcinomas, which may be so well-differentiated as to mimic nonneoplastic glands, to poorly differentiated carcinomas with epithelial differentiation demonstrable only on immunolabeling. In the vast majority, however, some degree of tubule formation is identifiable in thorough sampling. Ductal adenocarcinomas typically elicit an intense stromal reaction, and this reaction has been postulated to serve as a barrier to chemotherapy and facilitator of growth [4] although in some cases it may represent an attempt of the host to contain the tumor as well. Neoadjuvant therapy seems to cause substantial alterations in the morphology of the tumor cells. Also, residual foci of previously treated ductal adenocarcinoma may be patchy and may require more careful examination. Recently, scoring systems have been devised in an attempt to evaluate the efficacy of chemotherapy, and the one we advocate is the one proposed by H. Wang and colleagues from MD Anderson [5]; however, the relevance of these proposals requires further study.

The difficulty in distinguishing ductal adenocarcinoma from chronic pancreatitis also applies to the microscopic diagnosis and is regarded to be one of the most difficult distinctions in diagnostic pathology [6, 7]. Chronic pancreatitis may be associated with epithelial atypia, both architectural and cytologic, in pancreatic tissue; conversely, ductal adenocarcinoma is notorious for its deceptively bland appearance. Features favoring a malignant diagnosis include abnormal location of glands (adjacent to muscular arteries, within the duodenal muscularis, adjacent to adipocytes in the peripancreatic tissue, or around nerves), architectural abnormalities in the shape of the glands (cribriforming, angulation, or incomplete gland formation), and nuclear abnormalities (variation in the shape and size of nuclei by more than four to one, known as the *4-to-1 rule* among the cells within an individual gland) [6, 7]. Diagnostic difficulty also extends to the differential diagnosis of ductal adenocarcinoma in metastatic sites, because ductal adenocarcinoma often retains its well-differentiated appearance and mimics benign or low-grade neoplasms of these sites. Common pitfalls include misinterpretation of metastatic ductal adenocarcinoma in the ovary as a primary borderline ovarian tumor [8]; in the lung, as bronchioloalveolar carcinoma; and in the liver, as bile duct adenoma. In the last instance, the converse – misinterpretation of bile duct adenoma as metastatic ductal adenocarcinoma – seems to be more common.

No uniformly applied pathologic grading system exists for ductal adenocarcinoma. Schemes advocated by Western and Asian experts show major philosophical differences in principle and results. The current American Joint Commission on Cancer-endorsed tumor-node-metastasis (TNM) grading system [9] is similar to the grading of other adenocarcinomas of the gastrointestinal tract: *well differentiated* means 95% or more composed of glandular structures; *moderately differentiated,* 50–95% glandular in pattern; and *poorly differentiated,* with more than 50% solid nest and individual cells. The World Health Organization (WHO) has adopted the complex grading scheme proposed by Klöppel and colleagues, which is difficult to employ and not widely used in daily practice [10]. Intratumoral heterogeneity seems to be an important problem in the grading of ductal adenocarcinoma, and for this reason, a simpler, more practical, and more clinically relevant grading scheme that accounts for this heterogeneity by scoring the patterns of infiltration has been proposed [11].

The pathologic evaluation of a pancreatectomy specimen is important both for staging and in determining the adequacy of resection. Recent studies have highlighted that, with more careful grossing protocols in pathology laboratories, in the vast majority of resected pancreatic ductal adenocarcinomas, there often are insidious carcinoma units that involve the surfaces and the margins which are not visible grossly or clinically [10–17]. In one study, in >90% of the cases, there were carcinomatous foci in the peripancreatic adipose surfaces of pancreatoduodenectomy specimens [18] which renders the current AJCC T-stage protocol inapplicable [9], and for this reason a size based staging protocol has been proposed [13, 19]. Metastasis to lymph nodes is considered one of the most important predictors of outcome in resected ductal adenocarcinomas. Generally, at least 12 lymph nodes should be identified in a simple pancreatoduodenectomy specimen [20]. Most of these lymph nodes are embedded in the surfaces of the

pancreas or in the groove between the pancreas and duodenum. When careful harvesting of the lymph nodes is performed [12, 20], lymph node metastasis is detected in close to 80% of the resected pancreatic ductal adenocarcinomas [21].

Proper identification of margins and their adequate sampling are important components in the pathologic evaluation of a pancreatoduodenectomy specimen [12–17, 22]; however, what constitutes a margin remains controversial [12]. For example, the anterior surfaces are regarded as "margin" by some but not others. Similarly, whether to consider the posterior free surfaces of the pancreas as a "margin" or not has also been highly controversial, with vastly different views by different authors.

As expected, ductal adenocarcinoma shows immunohistochemical evidence of ductal differentiation. Briefly, most ductal adenocarcinomas express cytokeratins (7, 8, 18, 19, and variably 20), mucin (MUC1, MUC4, and MUC5AC), general adenocarcinoma markers (CEA, B72.3, CA125, and CA19-9), and some pancreatic cancer-specific markers (mesothelin, S-100A4, etc.) [23–25]. In addition, immunolabeling for antigens that function as surrogate markers for genetic changes can also be altered in ductal adenocarcinomas. Most ductal adenocarcinomas have abnormal nuclear labeling with antibodies to p53, and 55% show a loss of SMAD4 expression [26].

The genomes or exomes of a large number of ductal adenocarcinomas have been sequenced, significantly increasing our understanding of the molecular drivers of pancreatic cancer. Although the genetic changes identified are complex, the key to understanding pancreatic tumorigenesis lies in the recognition and appreciation that these mutations target a core set of pathways and processes. Mutation in codon 12 of the *KRAS* oncogene is found in more than 95% of ductal adenocarcinoma and seems to be an early event [27]. Mutation of *P16* or methylation of the promoter is common (>80%) and represents the pathogenetic link with the familial atypical multiple mole melanoma syndrome [28] and thus have clinical implications for patient and family screening. Overexpression of *p53* [29, 30] and loss of *SMAD4/DPC4* are detected in about half of cases [26]. *BRCA2* and Peutz–Jeghers gene mutations have been implicated in about 5% of ductal adenocarcinoma cases [27]. BRCA has been the subject of much discussion recently, because of the potential targeting agents in the treatment of such cases [31]. Fanconi anemia gene alterations also have been identified [32]. Abnormalities in mismatch repair proteins and microsatellite instability are uncommon, although pancreatic ductal adenocarcinomas can occur as one of the less common manifestations of Lynch syndrome [33].

3.1.2 Pancreatic Intraepithelial Neoplasia (PanIN)

The vast majority of pancreatic ductal adenocarcinomas are believed to arise from precursor intraductal proliferations termed pancreatic intraepithelial neoplasia (PanIN) [34]. PanINs are small microscopic intraductal lesions that are less than 5 mm in size. They are composed of a flat or papillary neoplastic epithelium. The spectrum of changes, originally classified in three grades [35], is now being modified into a two-tier system as low versus high-grade PanIN [36]. Replacement of the normal cuboidal, nonmucinous ductal epithelium with columnar cells that contain abundant apical mucin, but without architectural complexity (e.g., papilla formation) or cytologic atypia (previously called mucinous metaplasia, mucinous hypertrophy, and more recently, PanIN-1A), is regarded as the earliest form of neoplastic transformation in the pancreatic ductal system (Fig. 3.2a). As the intraductal neoplasm progresses, it acquires more papillary architecture and cytologic atypia. When irregular papillary architecture is present with tufting, severe cytologic atypia, necrosis, suprabasal mitoses, and loss of cell polarity, it is regarded as high-grade PanIN (previously called *PanIN3; high-grade dysplasia)*, which is equivalent to "carcinoma in situ" (Fig. 3.2b).

A progressive accumulation of molecular alterations is reported from low-grade PanIN to invasive carcinoma [27]. Some alterations, such as *KRAS* mutations, are early events; while others, such as *p53* overexpression, occur at the more advanced end of this spectrum. Low-grade PanINs are very common incidental findings in the normal population [37, 38]; therefore, they are generally believed to not to require any fur-

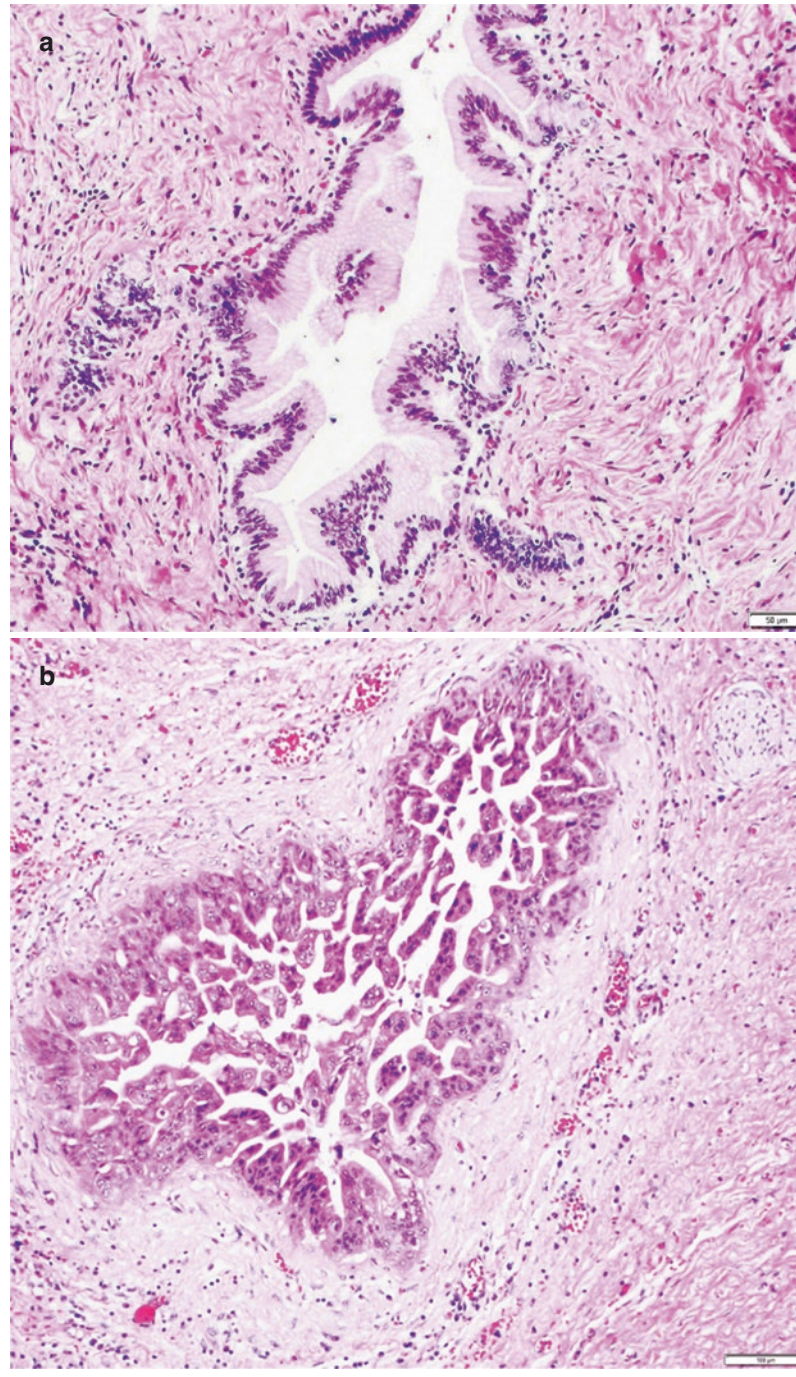

Fig. 3.2 (**a**) Pancreatic intraepithelial neoplasia, low grade; (**b**) pancreatic intraepithelial neoplasia, high grade

ther clinical attention, if encountered in isolation or at resection margins. In fact, it is not required to even record it in the surgical pathology report [36]. High-grade PanIN (previously PanIN3/CIS), on the other hand, is seldom seen in the absence of an invasive carcinoma [37], and for this reason, if high-grade PanIN (CIS) is encountered in a pancreas, the likelihood of carcinoma elsewhere in the gland is very high. In fact, one of the biggest challenges is to define and distinguish high-grade PanINs from colonization (cancerization: intraductal spread of invasive carcinoma),

i.e., invasive carcinoma cells that retrogradely infiltrate into the native ducts and "colonize" them and grow "pagetoidly" within the duct epithelium (cancerization), versus true precursor.

3.1.3 Other Carcinomas of Ductal Origin

There are other malignant neoplasms of ductal origin/lineage (i.e., carcinoma types) that may be related to ductal adenocarcinoma (and some also associated with ordinary ductal adenocarcinoma component) but are classified separately because of their distinctive clinical and molecular characteristics. In the following section, the salient features of these tumor types are discussed.

Colloid carcinoma is characterized by the production of copious amounts of extracellular mucin [39–41] (Fig. 3.3), and these distinctive neoplasms almost always arise in association with an intestinal-type intraductal papillary mucinous neoplasm (IPMN). The majority of intestinal-type IPMNs (as well as their associated carcinomas) harbors GNAS gene mutations, and, of interest, colloid carcinomas have a different biology with an unusually protracted clinical course [24, 42]. Overall, they have an incomparably better prognosis than ductal adenocarcinomas, with 5-year survival of >55% [39–41]. Since colloid carcinomas arise mostly from "intestinal-type" IPMNs, and since both show diffuse expression of intestinal lineage markers of CDX2/MUC2 which are otherwise practically nonexistent in other tumor types of this organ, it is being speculated that colloid carcinomas may have to be managed like an intestinal-type cancer (with the intestinal chemotherapy protocols) rather than pancreatic.

The medullary variant of pancreatic cancer is a poorly differentiated pancreatic cancer (Fig. 3.4). Syncytial nodules of large, poorly differentiated epithelial cells with a pushing pattern of invasion characterize medullary carcinomas. In our experience, these are significantly more common in the ampulla and duodenum than in the pancreas, and therefore, before a case can be classified as a pancreatic origin, these possibilities ought to be excluded. In fact, most of the cases advertised as pancreatic medullary carcinoma prove to be of ampullary origin in careful inspection. Medullary carcinoma can occur sporadically or in patients with Lynch syndrome [43]. Many but not all tumors are microsatellite instable, and immunostaining for mismatch repair proteins is lost in some of these cancers [44, 45]. The diagnosis of medullary carcinoma of the pancreas may be a clue to an inherited cancer syndrome, including Lynch syndrome, and may justify genetic counseling of the patient. In one study [44], these tumors were found to have a more protracted

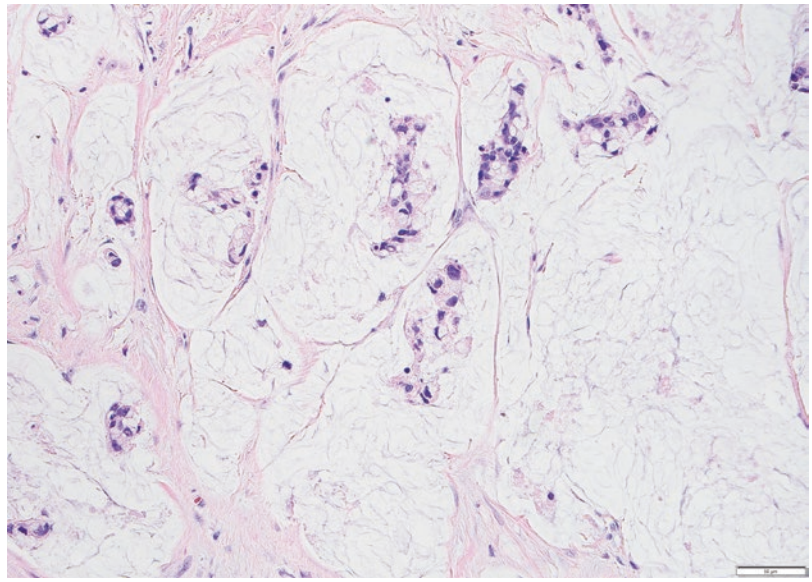

Fig. 3.3 Colloid carcinoma is a distinct indolent form of adenocarcinoma characterized by mucin lakes with malignant glands floating within. It is speculated that protracted clinical course of this type of carcinoma is attributable to the containing effect of the mucin

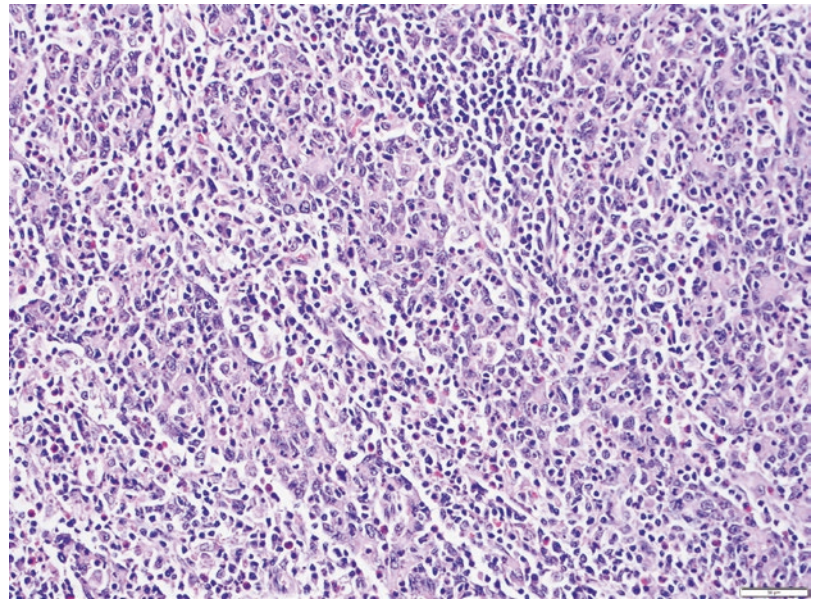

Fig. 3.4 Medullary carcinoma is a poorly differentiated carcinoma that mostly lacks gland formation and is characterized by syncytial growth of large atypical cells accompanied by a lymphocytic infiltrate

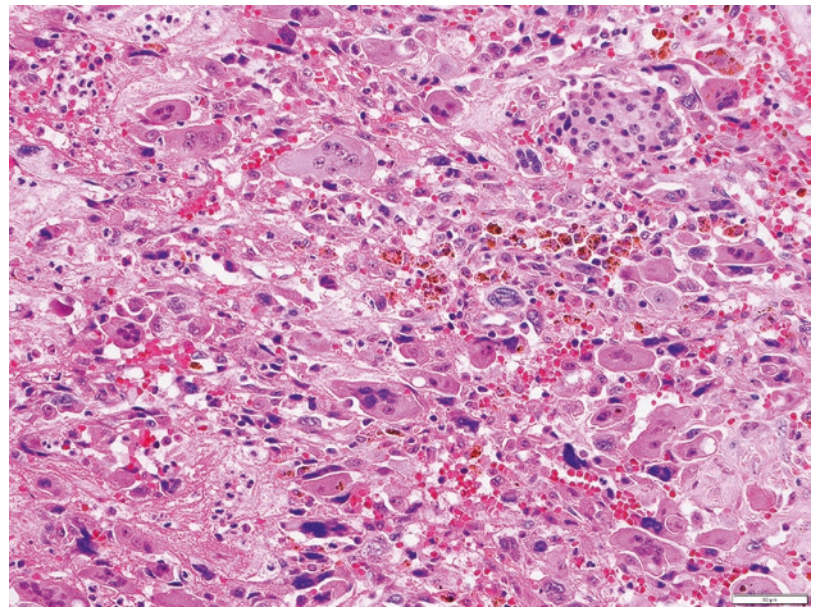

Fig. 3.5 Undifferentiated carcinoma with osteoclast-like giant cells: it is characterized by osteoclasts (benign multinucleated giant cells of osteoclastic type) admixed with pleomorphic sarcomatoid carcinoma cells and often accompanied by hemorrhage and hemosiderin in the tumor nodules

clinical course, but further data are necessary to define the prognosis of these rare tumors.

Undifferentiated carcinoma can be regarded as the least differentiated form of ductal adenocarcinoma, in which characteristic tubule formation is no longer evident or only focal. This term is unfortunately applied for ordinary ductal adenocarcinomas with significant nonglandular (poorly differentiated) component. Defined more stringently, undifferentiated carcinomas appear to occur in two different types. One is characterized by rhabdoid phenotype and common INI-1 loss, which is very uncommon [46], and the other is osteoclastic giant cell carcinoma [47]. The latter undifferentiated carcinoma with osteoclast-like giant cells (also known as osteoclastic giant cell carcinoma) is a distinctive tumor characterized by an abundance of osteoclasts in the background of a sarcomatoid carcinoma [47–49] (Fig. 3.5). Studies have shown

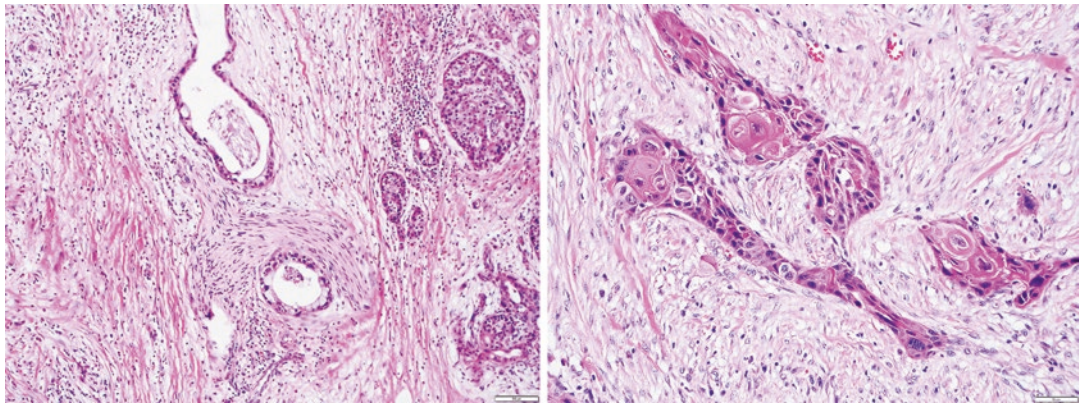

Fig. 3.6 Adenosquamous carcinoma: *left*, invasive adenocarcinoma component; *right*, large nests of cells with squamous differentiation including keratinization (pearl formation)

that the osteoclastic giant cells are nonneoplastic histiocytic cells [49], and the true neoplastic cells in this tumor are the sarcomatoid mononuclear cells. An adenocarcinoma component or, in some cases, high-grade PanIN or mucinous cystic neoplasm precursors may be present. Undifferentiated carcinomas with osteoclast-like giant cells are characterized by a well demarcated and a large solitary mass and exhibit nodular/pushing-border infiltration [47]. If examined carefully, many such tumors appear to have substantial intraductal growth. These are clearly malignant neoplasms; however, careful reappraisal of the literature elucidates that their prognosis is significantly better than that of ordinary ductal adenocaricnomas. In fact, in our experience, many of these patients experience unexpectedly long survival, with an overall 5 years of 42% [47], but more studies are needed to verify this impression.

Squamous differentiation is seen in some conventional ductal adenocarcinomas (i.e., adenosquamous carcinomas (Fig. 3.6), but rare pure examples of squamous cell carcinoma without any glandular components also may be seen [50] though exceedingly uncommon. They may have variable degrees of keratinization. Squamous cell carcinoma and adenosquamous carcinoma of this region are highly aggressive tumors [50] with a prognosis that is even worse than that of ordinary ductal adenocarcinoma.

3.1.4 Intraductal Neoplasms

Intraductal neoplasms are the generic category designation for the tumors that fundamentally arise in the main pancreatic duct or its branches. There are three types of pancreatic neoplasms that predominantly have an intraductal growth pattern: the common, usually cystic, intraductal papillary mucinous neoplasms; the rare, usually solid intraductal tubulopapillary neoplasms; and the rare "intraductal tubular pyloric gland-type adenoma," which is mostly regarded as a subset of one of the former entities [51]. In addition to these three tumor types, pancreatic neoplasms with a usually solid growth pattern such as acinar cell carcinomas [52, 53], neuroendocrine tumors, metastatic tumors, and undifferentiated carcinomas [47] may present, though very rarely, as predominantly intraductally growing neoplasms.

3.1.4.1 Intraductal Papillary Mucinous Neoplasms

Intraductal papillary mucinous neoplasms (IPMNs) account for at least 25–30% of all neoplastic cystic lesions [3]. By definition, IPMNs are mucin-producing epithelial neoplasms that involve the duct system and are equal to or larger than 1 cm in size. These neoplasms are noninvasive and can harbor varying degrees of dysplasia. Most arise in the head of the pancreas;

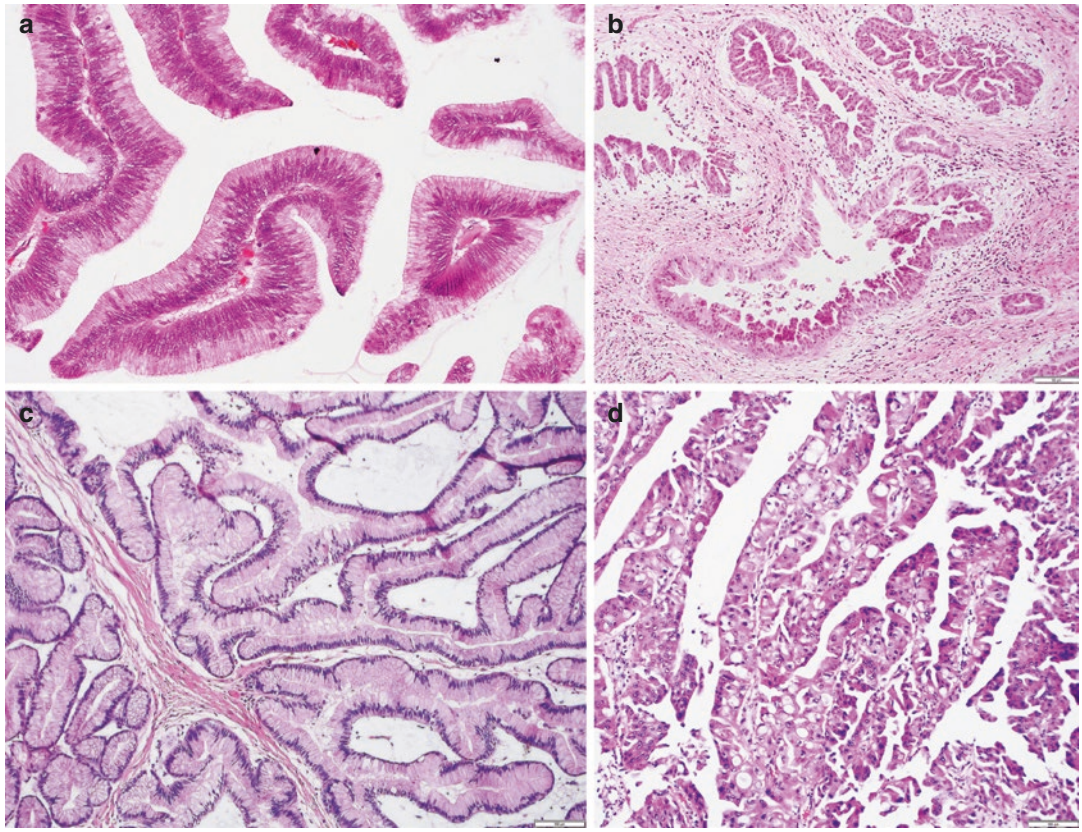

Fig. 3.7 Intraductal papillary mucinous neoplasm: (**a**) intestinal type resembling colonic villous adenoma; (**b**) pancreatobiliary type (with cuboidal cells and round nuclei); (**c**) gastric type (identical to gastric foveolar epithelium); (**d**) intraductal oncocytic papillary neoplasm (aka oncocytic variant of IPMN showing markedly complex papillae forming cribriform and/or solid areas; the tumor cells exhibit intracellular lumina and contain abundant eosinophilic granular cytoplasm and single prominent eccentric nucleoli)

however, they may also arise in the tail, and some even involve the entire pancreas [54–56]. The mucin produced by these tumors may exude from the ampulla of Vater, a finding that is virtually diagnostic of an IPMN. Radiographic findings of ductal dilatation with irregularities are often diagnostic as well. IPMNs may be multicentric, and therefore the presence of one lesion should heighten the clinical suspicion for additional lesions and mandate careful follow-up. Macroscopically, IPMNs are characterized by dilatation of the main or branch pancreatic ducts. Papillary fronds of neoplastic epithelium and tenacious luminal mucin are often present. Microscopically, the neoplastic epithelium can be papillary or flat and can show one of four directions of differentiation: intestinal, gastric, pancreatobiliary, or oncocytic [57–59]. In *intestinal-type IPMNs,* the papillary nodules are morphologically identical to colonic villous adenomas (Fig. 3.7a), and the invasive carcinomas that develop in these tend to be of the relatively indolent colloid type [39]. Intestinal-type IPMNs and colloid carcinomas typically express intestinal differentiation markers (MUC2 and CDX2) not found in ductal adenocarcinomas or in the nonintestinal subtypes of IPMNs discussed below, indicating that they represent a distinct "intestinal pathway" of carcinogenesis in the pancreas [57]. This is highly pertinent to the management of these tumors, because colloid carcinomas not only behave in a much more protracted clinical course but also may be closer in biology to the intestinal than pancreatic

adenocarcinomas and may have to be treated as such. The pancreatobiliary-type IPMNs, which are least well characterized, typically have complex arborizing and interconnecting papillary configuration with delicate fibrovascular cores and are composed of cuboidal cells with enlarged nuclei and little mucin production (Fig. 3.7b). This subtype tends to be associated with tubular-type invasive carcinoma (conventional ductal adenocarcinoma) and appears to have more aggressive behavior [60]. The gastric-type IPMNs are the most common type since most "incidentaloma cysts" of the pancreas prove to be this group. It is characterized by relatively simple and typically short papillae and often has pyloric-like glandular elements at their base in the cyst wall. The epithelial lining is identical to gastric foveolar epithelium (Fig. 3.7c). When high-grade dysplasia ensues on gastric-type IPMN, it typically starts to show more complex architecture and cuboidal cells with enlarged nuclei and less mucinous cytoplasm, which are also characteristics of the pancreatobiliary-type IPMN mentioned above. For this reason, some authors believe the pancreatobiliary type is a high-grade version of the gastric type [51]. What is currently classified as oncocytic type IPMN, which had been originally described as *intraductal oncocytic papillary neoplasm*, is now proving to be different not only morphologically but also by clinical behavior from other IPMN types and thus deserves to be recognized as a distinct entity [59, 61–63]. This entity is characterized not only by the oncocytic nature of the cells but also by the complexity of the papillary nodules, which have an arborizing pattern (Fig. 3.7d). Oncocytic IPMNs are often large and very floridly proliferative tumors and clinically they typically get diagnosed as "cancers" with cystic component [63]; whereas, the carcinomas arising from them tend to be small, the incidence of metastasis is very low, and the overall prognosis appears to be very favorable [59, 61, 62]. In fact, despite their large size and complexity, very little mortality has been attributed to this tumor type, if any. On the other hand, they also have a tendency to recur. Overall, clinicopathologic and behavioral characteristics of these oncocytic lesions are so distinctive and different from other IPMNs that they need to be regarded as a separate category [59, 61–63]. Recent molecular studies demonstrate that *GNAS* mutations are more prevalent in intestinal compared with pancreatobiliary and gastric subtypes [64–66] and oncocytic IPMNs have different molecular changes from other IPMNs, with a much lower incidence of *KRAS* mutation and frequent expression of MUC6, suggesting a pyloropancreatic lineage [23, 62].

Thus, these different histologic subtypes of IPMNs not only have different progression rates and different associations with biologically distinct invasive carcinoma types, but also are representing distinct pathways of carcinogenesis. Although IPMNs are typically classified into a histological subtype, more than one epithelial subtype can be present within the same IPMN. The degree of dysplasia in IPMNs is now grade in a two-tiered system as low grade (encompassing the previous low- and intermediate-grade dysplasia categories) versus high grade (which is reserved for the cases that used to be qualified as "carcinoma in situ" [36, 55]. Among patients with IPMNs who go to pancreatic resection, about 30% will have IPMNs that have an associated invasive adenocarcinoma [51] although this figure may be changing with earlier detection and better selection of cases for surgery. Patients with an invasive carcinoma arising in an IPMN have a better prognosis than do patients with a conventional ductal adenocarcinoma not arising in an IPMN, but some of this improved prognosis is lost when one controls for stage [51]. Invasive carcinomas that arise in IPMNs are recognized separately and are graded and staged like other ductal-type carcinomas [36, 55].

3.1.4.2 Intraductal Tubulopapillary Neoplasms

Intraductal tubulopapillary neoplasm (ITPN) [56, 57, 67–69] is a recently recognized category of mass-forming (>1.0 cm) intraductal neoplasm that is fairly similar to an IPMN, from which it is distinguished microscopically by its mucin-poor nature and distinctive tubular architecture. First reported by Tajiri and colleagues [67] under the

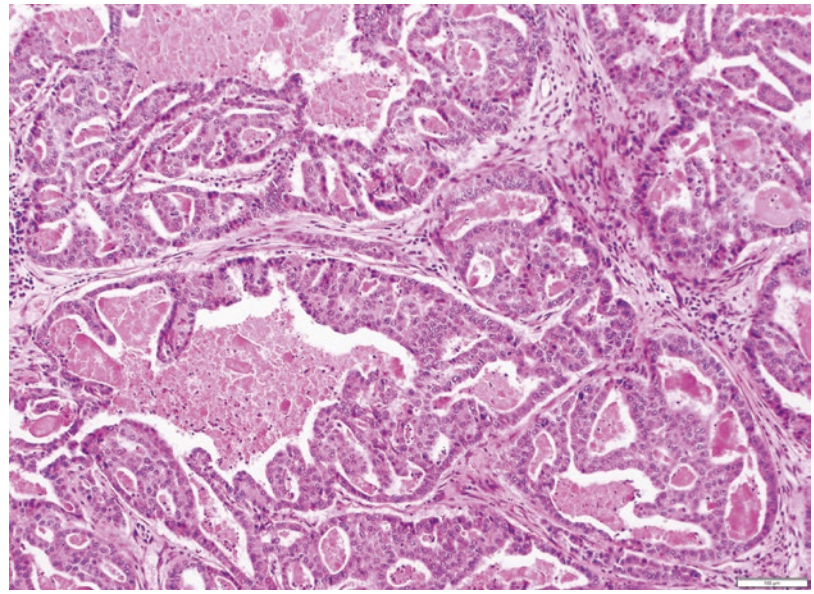

Fig. 3.8 Intraductal tubulopapillary neoplasm: it is composed of irregular tubules forming a large and cribriform mass

heading of *intraductal tubular adenocarcinoma,* the entity is now being designated *intraductal tubulopapillary neoplasm* in the WHO 2010 classification. It is a rare tumor seen at an average age of 53 years, and it presents with nonspecific symptoms [56]. The clinical findings are similar to those of IPMNs but generally forming more complex nodular tumors on imaging as well as macroscopic examination [56]. Cystic change is often less appreciable. ITPN occurs predominantly in the head of the pancreas but may involve any part. It is often large (mean, 7 cm; range, ≤15 cm) [56].

Histologically, ITPNs are characterized by densely packed cuboidal eosinophilic epithelial cells forming intraductal tubular proliferations, usually with moderate nuclear atypia, increased mitotic activity, and without overt mucus production (Fig. 3.8). Occasionally the glands form a tubulopapillary pattern and some cases have comedo-like necrosis or desmoplastic stroma. The tumor cells are positive for the ductal CKs [7, 8, 18, 19] and, in more than 60% of cases, for MUC1 and MUC6. MUC5AC and MUC2 are negative [56]. In about 40%, there is an invasive carcinoma component, which may be difficult to recognize but is usually limited in extent [56]. The prognosis is significantly better than that of PDACs. More than a third of the patients survive beyond 5 years, and a protracted clinical course may be even seen in those patients with recurrence and metastasis to lymph nodes or to the liver [56]. Molecular pathways involved in this tumor appear to be very different than those of ordinary ductal adenocarcinomas or IPMNs [70].

3.1.5 Mucinous Cystic Neoplasms

Mucinous cystic neoplasms (MCNs) of the pancreas are cystic mucin-producing neoplasms. Now defined by the presence of ovarian-type stroma, this entity has highly distinctive characteristics. The vast majority occur in perimenopausal women (98% female; mean age, 48 years) [71–73] with only few male patients with convincing ovarian stroma on record. Most (>98%) occur in the body/tail; they are very uncommon in the head. They form a relatively distinct (demarcated) lesion. In contrast to IPMNs, the cysts of MCN do not communicate with the larger pancreatic ducts. The cysts are most frequently multiloculated and distended with tenacious mucin, which is rich in glycoproteins and oncoproteins, such as CEA [74–77]. This feature may help distinguish these tumors from other cystic lesions. Grossly, the inner surfaces of the cyst walls may be smooth, they

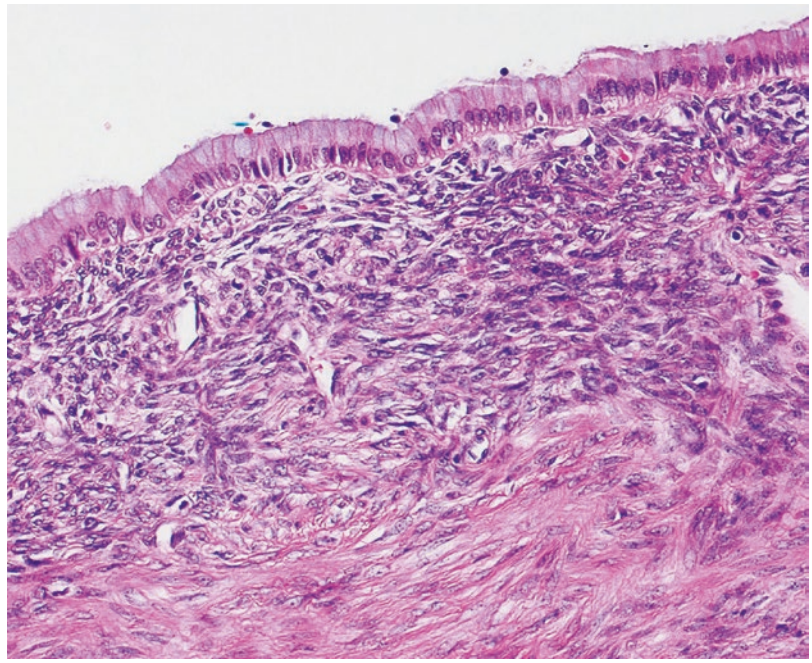

Fig. 3.9 Mucinous cystic neoplasm: tall-columnar mucinous epithelium is surrounded by an ovarian-type stroma

may have papillary excrescences, or they may have isolated intracystic solid nodules. Microscopic examination shows two characteristic components: variable lining, from low-cuboidal/nonmucinous to tall-columnar/mucinous arranged in a flat or papillary architecture, and distinctive ovarian-type stroma, the cells of which may express estrogen receptors [4] and also some progesterone receptors (Fig. 3.9). Based on the degree of cytoarchitectural abnormalities on the most atypical region, these neoplasms are now graded into two groups: low grade (previously called low- or intermediate-grade dysplasia) or high grade (previously called high-grade dysplasia and also corresponding to "in situ carcinoma") [36]. Invasive carcinoma is seen in about 15% of the cases, typically in larger and more complex examples that show florid papillary nodules in the cysts; invasion is seldom seen in tumors that are small (<3 cm) and noncomplex [73], raising the question of whether these may be amenable for watchful waiting in select patients as in IPMNs. Most invasive carcinomas are tubular (ductal) type and morphologically indistinguishable from ordinary ductal adenocarcinomas. A few are sarcomatoid carcinomas, some with osteoclastic giant cells [47, 73]. Recent literature indicates that if invasion has been ruled out by total sampling and thorough examination of the tumor, then noninvasive MCNs behave in a benign fashion [72, 73]. In contrast, those with invasive carcinoma appear to exhibit fairly aggressive clinical course, even when they are small. Having said that, in one recent study, those with "minimal invasion," defined as carcinoma limited to microscopic foci within the septa of the cysts, were found to have a fairly benevolent behavior [78]. Recently, the exomes of a series of well-characterized MCNs have been sequenced, and the *KRAS, p16, p53, RNF43, and SMAD4* genes have been reported to be targeted in MCNs [4].

3.1.6 Serous Cystic Tumors

Serous cystadenomas are rare benign neoplasms that can form relatively large masses (up to 25 cm) that tend to be well demarcated, predominantly in women and in the age group of 50s–60s [79]. Typically, they are composed of innumerable back-to-back tubules of variable size and shape creating the diagnostic macroscopic

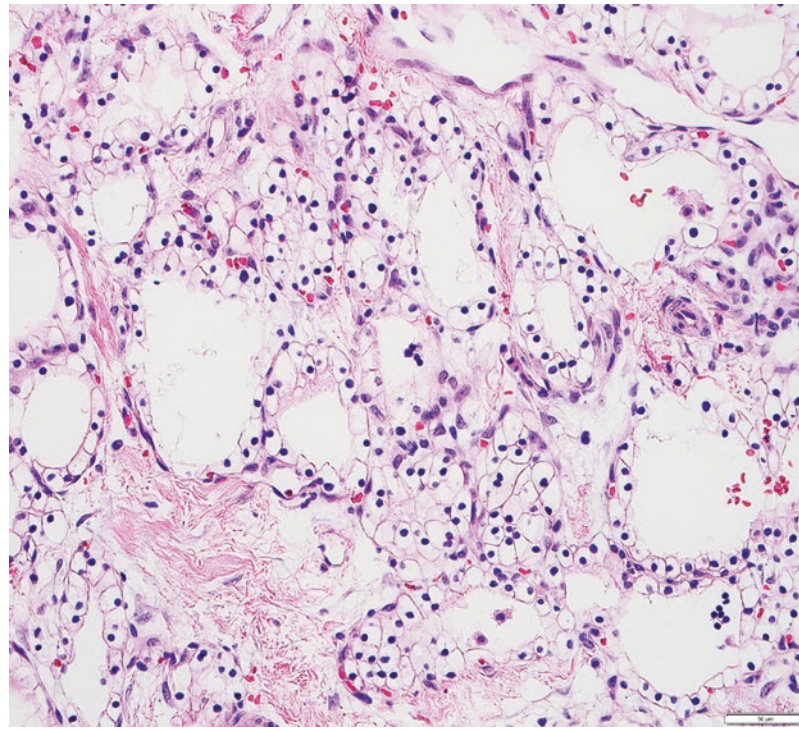

Fig. 3.10 Microcystic serous cystadenoma: each small cyst is lined by a flattened layer of epithelium; cytologically, the lining cells show clear cytoplasm and small, uniform, hyperchromatic nuclei. Intimately intermixed with the epithelium is a continuous layer of capillary-sized vessels

appearance of a spongelike configuration – characteristic *microcystic adenoma* (Fig. 3.10). Rare macrocystic (oligocystic), unicystic, and solid examples occur, and recent studies have shown that these do not significantly differ from the more common microcystic variant perhaps with the exception of their higher propensity to mimic (and be misdiagnosed as) other megacystic tumors or neuroendocrine neoplasms [79]. Microcystic serous cystadenomas often have a central stellate scar. Microscopically, they are characterized by distinctive glycogen-rich epithelial cells with uniform round nuclei; dense, homogenous chromatin; and a prominent epithelium-associated microvascular meshwork [80] (Fig. 3.10). Serous cystic tumors are one of the few ductal neoplasms of the pancreas that do not produce mucin, possibly reflecting a recapitulation of the centroacinar cells that are nonmucinous. Along the same lines, the cyst contents are devoid of the mucin-related glycoproteins and oncoproteins that typically are found in mucinous pancreatic tumors, a feature that may help in the preoperative diagnosis [81]. Instead, they appear to produce a fair amount of vascular endothelial growth factor (VEGF) and secrete it to the cyst fluid, which may be helpful in the preoperative diagnosis [80, 82]. Microscopically, these lesions are similar to the cysts seen in von Hippel–Lindau (VHL) disease, and some serous cystadenomas do show *VHL* gene alterations. Serous cystadenomas often are reported to coexist or "collide" with other pancreatic neoplasms (especially neuroendocrine neoplasms) and with congenital pathologic conditions [79, 82].

Convincing examples of malignant serous tumors (serous cystadenocarcinomas or carcinomas-ex-microcystic adenoma) are exceedingly rare [83] and are in fact dubious as to whether they really represent a malignant counterpart of serous neoplasm. Most of the cases reported in the literature as "malignant" serous cystic neoplasm (SCN) however appear not to qualify for the current WHO definition of malignancy for these tumors [79]. For example, SCNs that radiologically about the large vessels have been designated as "malignant." Also, larger SCNs can show adhesion to the neighboring organs [79, 84] such as

lymph nodes, spleen, stomach, and colon, which may not necessarily be a sign of true malignant behavior. Similarly occasional recurrences exhibited by SCNs may be a simple persistence of tumor that can be seen in some benign neoplasms, rather than true malignant behavior. Even the cases with synchronous liver involvement may in fact represent simultaneous independent involvement similar to what is seen in VHL cases. There has not been any documentation of metastatic SCN in distant organs other than the liver-involving cases (many of which may merely be synchronous disease) and there has not been any example with widely disseminated disease. We are aware of cases in the liver that were designated as "serous cystadenocarcinoma" who are alive without disease many years after the resection. And in critical review of the literature, most such cases appear to be like that. Thus, for practical purposes, serous cystadenomas limited to the pancreas are regarded as uniformly benign [79].

3.1.7 Pancreatic Neuroendocrine Tumors

Pancreatic neuroendocrine tumors (PanNETs) are the second most common malignancy of the pancreas [3]. Most neuroendocrine-type tumors of the pancreas are well-differentiated (low- to intermediate-grade) neuroendocrine tumors, previously referred to as *islet cell tumors/carcinomas* and now designated as *pancreatic neuroendocrine tumors* (PanNETs) by the 2010 WHO [85, 86], with low-grade malignant behavior [87]. Grossly, PanNETs are usually solid, circumscribed, and fleshy tumors, although multinodular and sclerotic examples occur [85, 86]. Rarely, cystic degeneration may be seen [75, 88–90], with a central unilocular cyst lined by a cuff of viable tumor; this occurs more often in the setting of multiple endocrine neoplasia (MEN) syndrome type I. These cystic examples may be more benevolent [75, 88–90]. PanNETs recapitulate the morphologic features of islet cells by forming nested, gyriform, trabecular, or rarely acinar or glandular patterns (Fig. 3.11). The cells have characteristic neuroendocrine features, including round, monotonous nuclei with a coarsely stippled chromatin pattern and moderate amounts of cytoplasm (Fig. 3.11).

Almost half of PanNETs are clinically functional, and functional PanNETs can be further subclassified based on the clinical syndrome they produce (not based on immunohistochemical hormone expression). The most common functional PanNETs are *insulinomas, while gastrinomas, glucagonomas, somatostatinomas,* and *VIPomas* (vasoactive intestinal peptide tumor) are rarer. Most insulinomas follow a benign

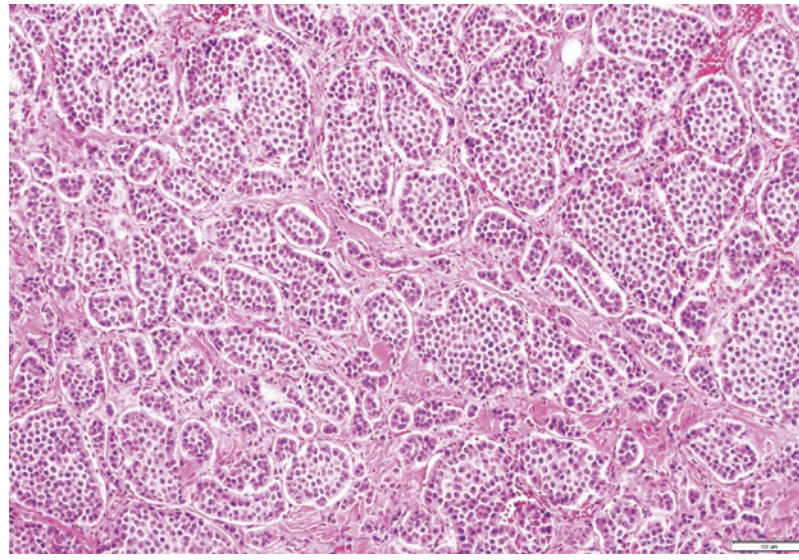

Fig. 3.11 Pancreatic well-differentiated neuroendocrine tumor: it shows nests and/or trabecular pattern of relatively round uniform epithelial cells with a fair amount of cytoplasm and salt-and-pepper chromatin

clinical course, likely because insulinomas typically are highly symptomatic, even when they are small, which leads to their early detection. Glucagonomas, on the other hand, tend to be large at diagnosis and have a more aggressive course. Nonfunctional PanNETs constitute an ever-enlarging proportion of PanNETs because they are being detected more commonly as incidental findings on abdominal imaging studies [91, 92]. PanNETs associated with MEN type I or other syndromes tend to be multifocal and less aggressive [93–95]. In addition to grossly evident and usually functional PanNETs, patients with MEN type I have numerous neuroendocrine microadenomas, defined as PanNETs (<0.5 cm). Most sporadically occurring functional and nonfunctional PanNETs are clinically low-grade malignancies. More than half of patients have recurrence or metastasis after resection, and many patients come to attention only after the development of metastatic disease. Nonetheless, there may be a relatively protracted clinical course even in patients with metastatic disease. It has been difficult, as in neuroendocrine tumors of other organs, to determine which PanNETs are more likely to metastasize and which metastatic cases are likely to progress most rapidly [96, 97]. Findings associated with more aggressive behavior include a size greater than 3 cm, a functional PanNET other than insulinoma, extrapancreatic or vascular invasion, high mitotic activity, high proliferation index (based on immunohistochemical staining for Ki-67) [98–100], CK19 expression [101], and c-KIT expression [102]; however, some PanNETs lacking all of these features may still metastasize. The genes targeted in neuroendocrine tumors, which differ significantly from those targeted in ductal adenocarcinomas, include *MEN1, DAXX and ATRX*, and genes coding for members of the mammalian target of rapamycin (mTOR) pathway [4].

Recently, a multidisciplinary group of international experts have proposed a set of parameters to be included in pathology reports [103]. It was emphasized that PanNETs ought to be evaluated by the approach used for any other malignancy, and accordingly, the grade and stage should be reported separately [85, 104]. For grading, the 2010 WHO adopted the system originally devised and tested by the European Neuroendocrine Tumor Society (ENETS), which grades PanNETs based on the mitotic count and Ki-67 labeling index. It is *grade 1* if the mitotic rate is 0–1/10 HPFs *or* the Ki-67 index is below 3%, *grade 2* if the mitotic rate is 2–20/10 HPFs *or* the Ki-67 index is 3–20%, and *grade 3* if *either* is above 20. Recent studies have shown that the G3 category actually includes at least two different tumor types with different morphological, genetic, and clinical features: histologically uniform NETs with an elevated proliferative rate and poorly differentiated NEC with small cell or large cell morphology [4, 105, 106]. For staging, the AJCC has adapted the TNM-based staging system used for adenocarcinomas, but the ENETS system is somewhat different [107].

3.1.8 Acinar Neoplasms

Although acinar tissue constitutes most of the pancreas, acinar neoplasms are rare, most being acinar cell carcinomas. Acinar neoplasms are characterized by the production of pancreatic enzymes, such as trypsin, chymotrypsin, and lipase. Solid acinar cell neoplasms are carcinomas; although a benign cystic variant exists, known as *acinar cell cystadenoma*, no solid acinar cell adenoma has been defined in the pancreas.

Acinar cell carcinomas form relatively large tumors (mean, 10 cm), usually in older men (mean age, 63 years) [108–110], although some occur in children [111]. In a small percentage of cases (10%), patients experience a "lipase hypersecretion syndrome" [112] characterized by subcutaneous fat necrosis, polyarthralgia, and peripheral eosinophilia. Serum α-fetoprotein (AFP) levels may be elevated in some cases [113]. Half of acinar cell carcinomas have metastases at the time of diagnosis, usually in the liver and/or regional lymph nodes [114]. Once believed to be almost as aggressive clinically as ductal adenocarcinomas with a 5-year survival of 10% [114], more recent studies place acinar cell carcinomas in a somewhat more indolent category [115] with some

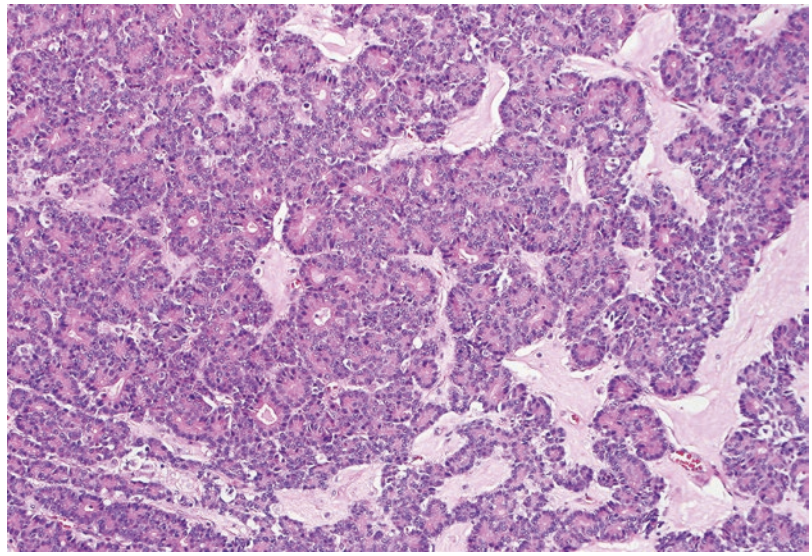

Fig. 3.12 Acinar cell carcinoma: it commonly exhibits a solid growth pattern, with sheets and nests of cells with moderate amount of amphophilic cytoplasm and minimal lumen formation

studies reporting a 5-year survival over 40% [108, 110]. In contrast to ductal adenocarcinomas, acinar cell carcinomas are stroma-poor cellular neoplasms with acinar cell differentiation, based on morphology and immunohistochemical staining for acinar enzymes, especially trypsin and chymotrypsin [115]. The cyanophilic acinar-appearing cells typically exhibit granular cytoplasm and centrally located nucleus with a prominent nucleolus. The cells are arranged in sheets and trabecular pattern [116] (Fig. 3.12). A subset of acinar cell carcinomas is characterized by prominent intraductal growth; such cases appear to be associated with a more protracted clinical course [52, 53]. Molecular genetic findings of acinar cell carcinomas markedly differ from those of ductal adenocarcinomas [117], with absence of the common alterations of ductal adenocarcinoma in genes such as *KRAS, TP53, P16,* or *SMAD4.*

Immunohistochemistry discloses scattered neuroendocrine cells in 30–40% of acinar cell carcinomas. Some cases have a significant neuroendocrine component that may be evident microscopically [115]. If the latter constitutes more than 25% of the tumor, it is classified as *mixed acinar-neuroendocrine carcinoma*, a tumor that seems to be biologically similar to pure acinar cell carcinoma [118, 119]. Similarly, acinar cell carcinomas with more than 25% ductal differentiation are classified as *mixed acinar-ductal carcinoma* [120]. Rarely, acinar cell carcinomas may show a grossly cystic pattern and are designated *acinar cell cystadenocarcinoma* [121, 122].

Acinar cell cystadenoma, also referred to as *acinar cystic transformation,* is a rare entity [123, 124]. They are usually small, incidental cysts lined by benign-appearing acinar cells, although some may form a mass that measures a few centimeters. The cysts may be patchily distributed amidst pancreatic parenchyma. Typically, the lining cells are often nondescript and intermixed with other cell types including nonmucinous ductal-type cells. In fact, acinar cells may be a relatively smaller population in the process. Some cases show nodular growth of proliferating acinar cells [125]. They are benign, non-clonal processes [125].

3.1.9 Solid Pseudopapillary Neoplasm

Solid-pseudopapillary neoplasms (SPNs) are rare solid neoplasms of the pancreas and typically occur in young women (mean age, 25 years; >80% female) [126–129] although they can be encountered at any age and in men as well. It is a peculiar neoplasm of unknown origin, and its obscure nature is reflected in the various descriptive names

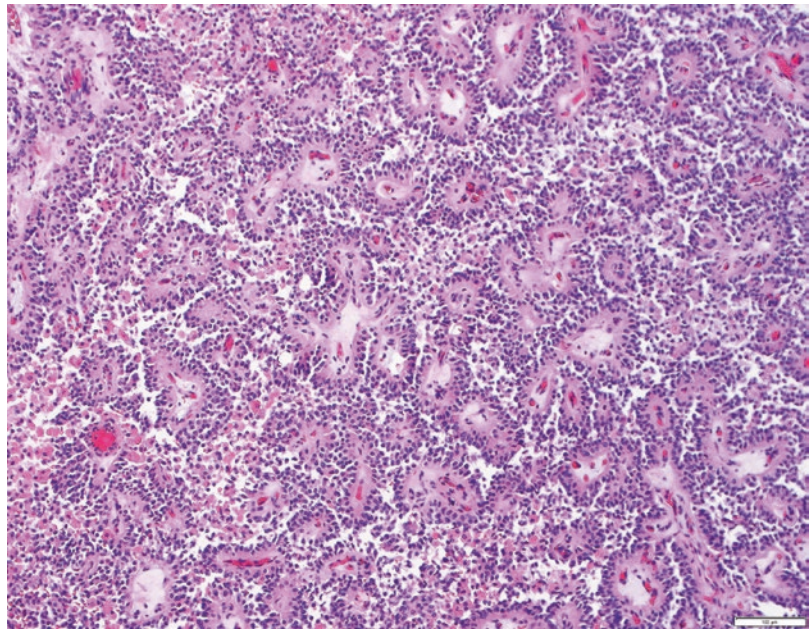

Fig. 3.13 Solid-pseudopapillary neoplasm: it shows sheets of cells punctuated by abundant small blood vessels; the tumor cells are dyscohesive and have degenerated, resulting in the formation of pseudopapillary configuration

assigned to this tumor in the past, including *papillary cystic tumor, solid and papillary tumor, solid and cystic tumor,* and *Frantz tumor* [130–133]. It is a very indolent "malignant" neoplasm for which complete resection is curative in most cases. Metastases are very uncommon, usually to liver or peritoneum and often at the time of diagnosis [129, 134]. Even patients with metastases appear to have a protracted clinical course, and death as a result of this tumor is rare [134]; however, very rare examples of high-grade sarcomatoid malignant transformation form a conventional solid pseudopapillary neoplasm [129].

Grossly SPNs are demarcated with solid (cellular) and cystic (degenerative) areas. Microscopically, SPNs are often found to send projections into the neighboring pancreas and entrap normal pancreatic tissue at their edge. The tumor is composed of bland-appearing cells with clear cell features and uniform nuclear morphology arranged in sheets and a pseudopapillary configuration (Fig. 3.13). Characteristic pseudopapillae are acquired due to degenerative changes and loss of cellular cohesion, which leaves a thin layer of neoplastic cells lining delicate vessels. Degenerative features include foam cells, hyalinization, cholesterol clefts, microcystic change, and hemorrhage. Hyaline globules are frequently present. Overall, the histologic picture may resemble closely that of PanNETs. The immunophenotype of this tumor is quite distinctive but fails to disclose the line of differentiation of the cells. The tumor typically expresses vimentin, progesterone receptors, CD10, and some of the neuroendocrine markers, in particular, CD56 and synaptophysin very commonly [126, 127, 135]. Chromogranin, the most specific neuroendocrine marker, is negative, which is important for the differential diagnosis with PanNETs, and pancreatic enzymes are not expressed. β-Catenin and cyclin D1 expression have been found in these tumors, suggesting an alteration in the *WNT* signaling pathway. E-cadherin and N-cadherin expressions are also abnormal [136, 137]. Paucity of keratins, chromogranin, and positivity of β-Catenin are helpful in distinguishing SPNs from PanNETs.

3.1.10 Pancreatoblastoma

Pancreatoblastoma is an extremely rare childhood tumor of the pancreas (mean age of 4 years, with a second small peak in the third decade) [111, 138, 139]. Pancreatoblastomas are usually

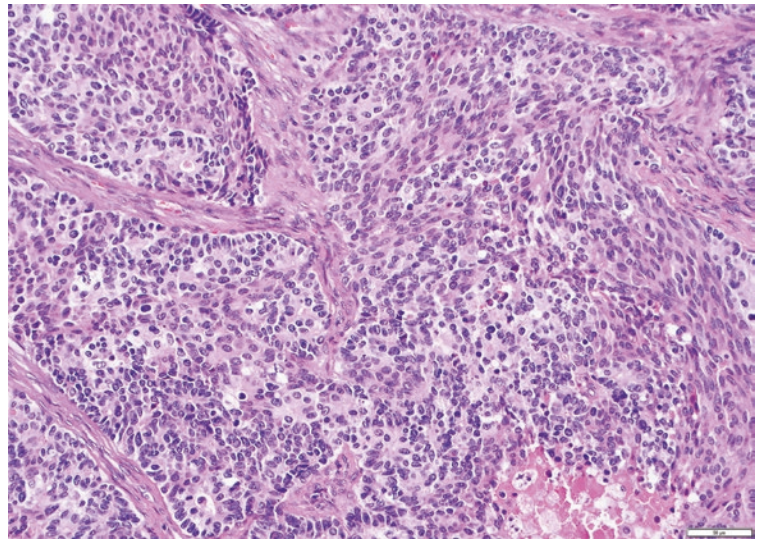

Fig. 3.14 Pancreatoblastoma: it shows solid nests with acinar lumen formation; focal clusters of spindle cells in whorled pattern (squamoid corpuscle formation) is pathognomonic

large (7–8 cm). Some cases are associated with elevated serum AFP levels, and occasional cases are seen in association with the Beckwith–Wiedemann syndrome [140, 141] or familial adenomatous polyposis (FAP) syndrome [142] or its relatives such as Gardner. Pancreatoblastomas are malignant tumors with a 5-year survival of about 25%, although children diagnosed before the development of metastases have been cured [111, 138, 139]. Typically, pancreatoblastomas exhibit all three lines of pancreatic differentiation – *acinar, neuroendocrine,* and *ductal* – although acinar elements are the most consistently present and most abundant [139]. Microscopically, they have sheets of primitive-appearing epithelial cells and acinar formations. A characteristic and peculiar microscopic finding is the so-called squamoid corpuscles, which are small morular arrangement of squamoid/meningothelial-like cells specific for this tumor type in the pancreas (Fig. 3.14). Molecular genetic findings of pancreatoblastomas are associated with β-catenin pathway alterations [117]. The so-called squamoid corpuscles can be very subtle in some cases appearing as zones of pallor in the sea of monotonous blue cells but can be highlighted by nuclear β-catenin expression immunohistochemically.

3.1.11 Miscellaneous Cystic Pancreatic Lesions

The most common cystic lesion in the pancreas, accounting for 80% of all cystic lesions, is the pseudocyst [143]. It most commonly occurs in adult men as a complication of alcoholic pancreatitis, although it can rarely follow other types of pancreatitis as well (biliary, traumatic, etc.). They are most often single but have been seen to be multiple [144]. Most often, pseudocysts are round or oval; however, they have been reported to be multilocular and irregular in shape [144]. Pathologically pseudocysts are fundamentally postnecrotic resorption of peripancreatic/intrapancreatic adipose tissue and typically do not affect the ducts unless the inflammation fistulizes into the ducts. The microscopic features vary by stage and often consist of fibrosis and inflammatory tissue with resorbing fat necrosis. Most are caused from large or small leaks of the ductal system and persist because of the constant filling by pancreatic secretions.

In addition to pseudocysts, other uncommon cystic lesions can also occur in the pancreas. Lymphoepithelial cysts are usually peripancreatic rather than intrapancreatic, and they occur predominantly in men (mean age, 52 years; male/female ratio, 3: 1) [145]. In contrast to their salivary gland counterparts, pancreatic lymphoepithelial cysts do

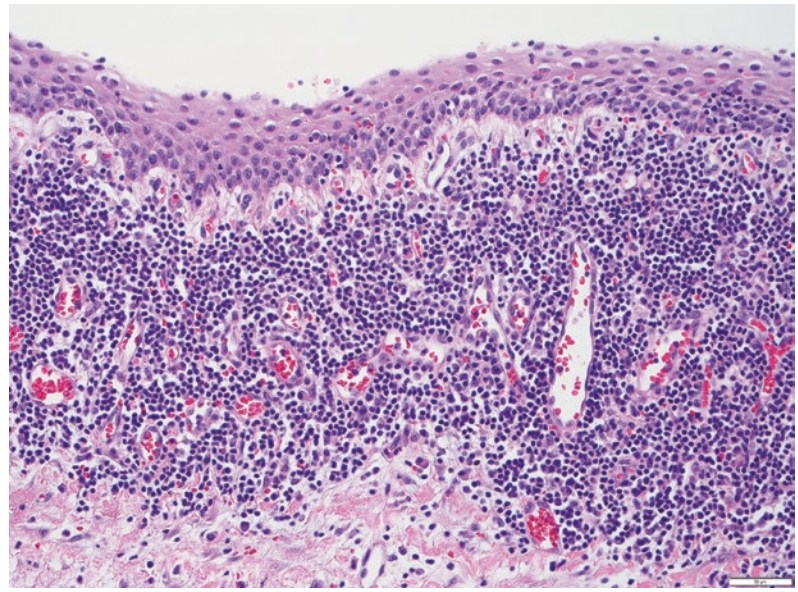

Fig. 3.15 Lymphoepithelial cyst: the wall is lined by squamous epithelium; underlying the epithelium is a dense band of lymphocytes

not show associations with autoimmune syndromes, human immunodeficiency virus, or lymphoma [145]. Lymphoepithelial cysts may occur in any part of the pancreas and may be unilocular or multilocular. They are characterized by variably keratinized, squamous-lined cysts immediately surrounded by a rim of lymphoid tissue, some with lymphoid follicles and a capsule (Fig. 3.15). The cyst contents may extrude into the cyst wall and cause an inflammatory reaction, including granulomas. Dermoid cysts are very uncommon, are similar to lymphoepithelial cysts but lack the lymphoid tissue and show skin adnexal elements, including sebaceous glands. Lymphangiomas are seen in young women (mean age, 29 years; male/female ratio, 1:3) [146] and form endothelial-lined cysts surrounded by a rim of lymphoid tissue. Congenital cysts and intestinal duplications may also form cystic lesions in the vicinity of the pancreas and periampullary region. These may have a variable lining, including respiratory type, intestinal, squamous, or transitional.

3.1.12 Pseudotumors

As discussed in the section on ductal adenocarcinoma, benign chronic inflammatory and fibrosing conditions of the pancreas may be difficult to distinguish from carcinomas both clinically and pathologically. Chronic pancreatitis of any cause – including alcohol, obstruction, and even causes with granulomatous inflammation – may lead to segmental fibrosis and a tumorous mass [147, 148]. However, certain subtypes of chronic pancreatitis are especially prone to form pseudotumors and mimic carcinomas [147–149].

In our experience, close to 8% of pancreatectomies performed with the clinical conviction of solid pancreas cancer prove to be pseudotumoral pancreatitis [150, 151]. About 40% of these prove to be nonspecific pancreatitis, often alcohol related, and are often <2 cm. The second most common source of pseudotumoral pancreatitis in our experience in the USA is paraduodenal pancreatitis, followed by autoimmune pancreatitis.

Autoimmune pancreatitis (AIP), also called lymphoplasmacytic sclerosing pancreatitis [152], is often misdiagnosed as carcinoma preoperatively. AIP typically is seen in patients in their 30s–50s, and high serum immunoglobulin G4 (IgG4) levels are helpful in the preoperative diagnosis [153–156]. It may be associated with extrapancreatic manifestations of IgG4 related diseases, such as sclerosing cholangitis, sclerosing sialadenitis, and retroperitoneal fibrosis [157]. Microscopically, dense periductal lymphoplasmacytic infiltrates, interstitial fibrosis with abundant

myofibroblasts arranged in a storiform pattern, and obliterative venulitis are characteristic.

Recently, a variant of AIP has been recognized [158] and termed variably as type 2 autoimmune pancreatitis or pancreatitis with granulocytic epithelial lesions (GELs). This type is more commonly seen in patients with ulcerative colitis and does not seem to be associated with IgG4-producing plasma cells but rather shows neutrophilic destruction of the duct epithelium [158]. This variant is difficult to define and is extremely uncommon in our experience.

Paraduodenal pancreatitis [159, 160] is the name recently proposed for a distinct but poorly recognized subset of chronic pancreatitis that creates a clinical picture often indistinguishable from pancreatic or periampullary carcinoma. This entity is also known as groove pancreatitis [149, 161–164] or cystic dystrophy of heterotopic pancreas [165, 166]. Affected patients are predominantly men in their 50s with a history of alcohol abuse. Endoscopically, in the second portion of the duodenum, proximal to the ampulla, mucosal nodularities are present that microscopically reveal inflamed mucosa, Brunner gland hyperplasia, or myoid spindle cell proliferation in the submucosa that can also extend to the mucosa. These pseudotumors are typically centered around the minor papilla or accessory duct and thus invade into the region between the common bile duct, duodenum, and pancreas (i.e., the "groove" region) [149, 161–164]. The process often exhibits a dense myofibroblastic proliferation within which lobules of pancreatic tissue are scattered, and cystic ducts contain inspissated enzymatic secretions. In some cases, cystic change in the duodenal wall can be prominent (cystic dystrophy of the duodenum) and may become large (paraduodenal wall cyst) [165, 166], mimicking pseudocysts, congenital cysts, or intestinal duplication. Some of the cysts are lined by granulation tissue without any epithelium.

Some developmental abnormalities also may lead to pseudotumors. A solid and cystic hamartoma and a cellular hamartoma [167, 168] have been reported to present as pancreatic tumors in adults. Lipomatous pseudohypertrophy [169] of the pancreas also may lead to a mass that could be mistaken for carcinoma. Adenomyomatous hyperplasia [170] of the ampulla – a common finding in the general population, reported in 40% of autopsies – has been implicated as a cause of biliary obstruction that mimics a periampullary carcinoma.

3.1.13 Mesenchymal Tumors

Primary mesenchymal tumors of the pancreas are rare [171, 172], but mesenchymal tumors from neighboring sites may secondarily involve the pancreas. In particular, gastrointestinal stromal tumors and retroperitoneal sarcomas may appear to be centered in the pancreas. A variety of benign mesenchymal tumors, including fibromatosis (desmoid tumor), solitary fibrous tumor [173], and schwannoma [146], have been reported in the pancreas. Schwannomas in this region are often cystic. Primary sarcomas include primitive neuroectodermal tumor [174], synovial sarcoma, desmoplastic small round-cell tumor, leiomyosarcoma, and malignant fibrous histiocytoma, all of which are largely documented in single case reports.

3.1.14 Secondary Tumors

A widely metastatic malignant neoplasm commonly may involve the pancreas; however, most of these are clinically undetected lesions identified only at autopsy [175]. Autopsy studies have shown that most secondary tumors involving the pancreas are of pulmonary origin, followed by gastrointestinal; however, a few metastatic tumors are prone to involve the pancreas in the absence of other metastatic foci, mimicking a primary carcinoma. Lymphomas and renal cell carcinomas [175, 176] seem to be the most common tumor types responsible for such cases. Renal cell carcinomas in particular are known to form polypoid ampullary nodules or even to grow within the ducts [175].

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Controversial Issues in Pathological Diagnosis

4

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Of all types of pancreatic cancer, invasive ductal carcinomas, even those that are ≤1 cm in size, carry the poorest prognosis. To improve the prognosis, it is necessary to make the diagnosis of ductal carcinoma as early as at the stage of carcinoma in situ. In recent years, with advances in diagnostic imaging, it has become possible to perform surgery even after detection of subtle changes in the pancreatic duct by imaging [1, 2]. Resected specimens from such patients sometimes reveal no evidence of invasive ductal carcinoma, but only histologically recognizable atypical epithelial lesions in the pancreatic duct. To allow carcinoma in situ to be detected in clinical settings, it is important to make an accurate pathological diagnosis of such intraductal atypical epithelial lesions [2, 3]. To date, there are few data on the clinical course and treatment of intraductal epithelial atypia diagnosed thus. The diagnostic criteria vary among pathologists [4–6]. In addition, many studies are ongoing, in which the genes involved in intraepithelial neoplasia are being sought, so as to identify genes useful for the diagnosis of carcinoma in situ [7, 8]. Twenty years ago, studies were conducted to investigate the possibility of diagnosing carcinoma in situ based on the presence of mutations in the Ki-ras gene, which was discovered as an oncogene [9]. This investigation revealed that Ki-ras mutations are also found histopathologically in epithelial mucous cell hyperplasia. Thus, it was established that detection of mutations of the Ki-ras oncogene is not sufficient for the diagnosis of carcinoma in situ. Thereafter, while extensive gene searches have been conducted to identify genes useful for the diagnosis of carcinoma in situ, no gene mutations contributing to the histological diagnosis have been identified yet. At present, there are no specific genes that can allow the diagnosis of carcinoma in situ to be reliably established.

As described above, the histopathological diagnosis of carcinoma in situ is controversial. The author has investigated carcinoma in situ lesions adjacent to invasive carcinomas using numerous resected specimens and established criteria for the histopathological diagnosis of carcinoma in situ.

In this chapter, we present histological images of our actual histopathological diagnosis of carcinoma in situ to show the characteristics

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of the atypia useful for the diagnosis of carcinoma in situ.

These histological images are presented in different scales to allow reasonable comparisons of the cells and lesions. Please note the scale of each image for comparison of size (Figs. 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 4.10, and 4.11).

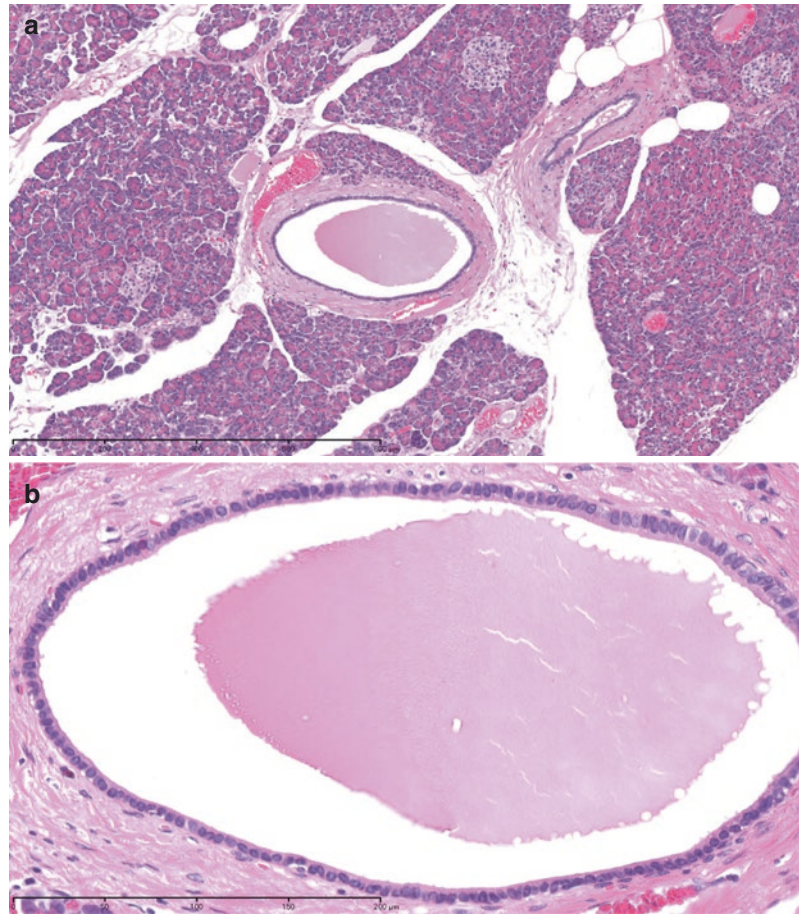

Fig. 4.1 (**a**, **b**) Normal pancreatic duct epithelium. (**b**) A magnified image. Epithelial lining composed of a single layer of cuboidal cells

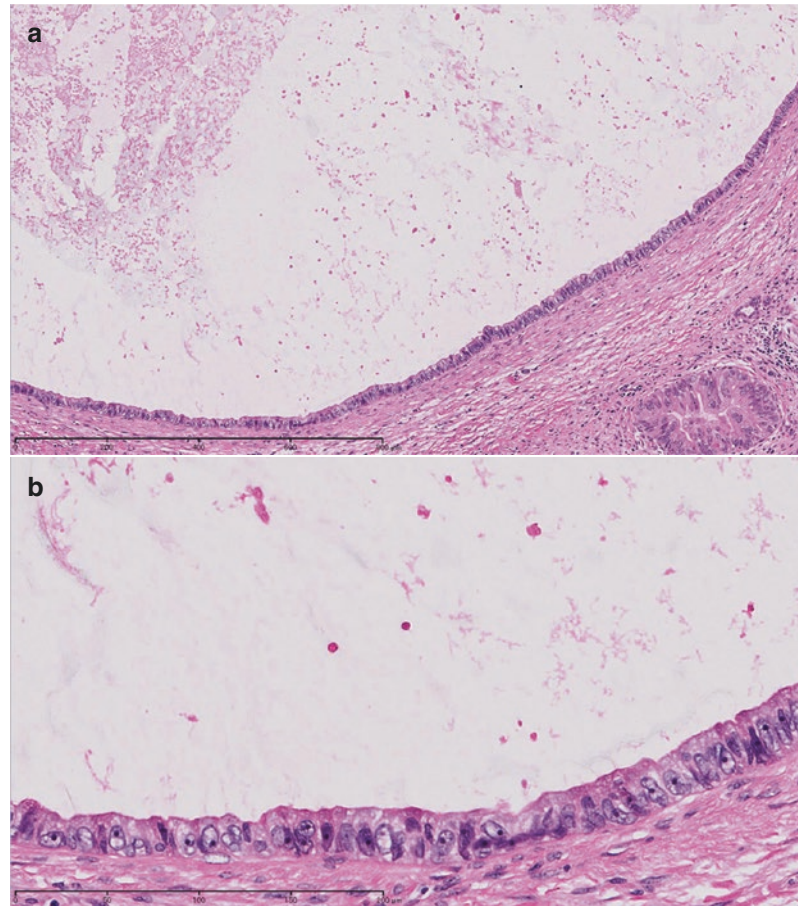

Fig. 4.2 (**a**) Carcinoma in situ composed of a single cell layer. (**b**) A magnified image. Epithelial lining composed of a single layer of cuboidal cells. The case was diagnosed as carcinoma in situ, because the cells composing the epithelium are larger in size than those shown in Fig. 4.1a. The normal epithelial cell count (Fig. 4.1b) is about 20 cells/100 μm. However, the epithelial cell count in this image is about 10 cells/100 μm, with the cell size being about twofold larger. The nuclear shape is irregular

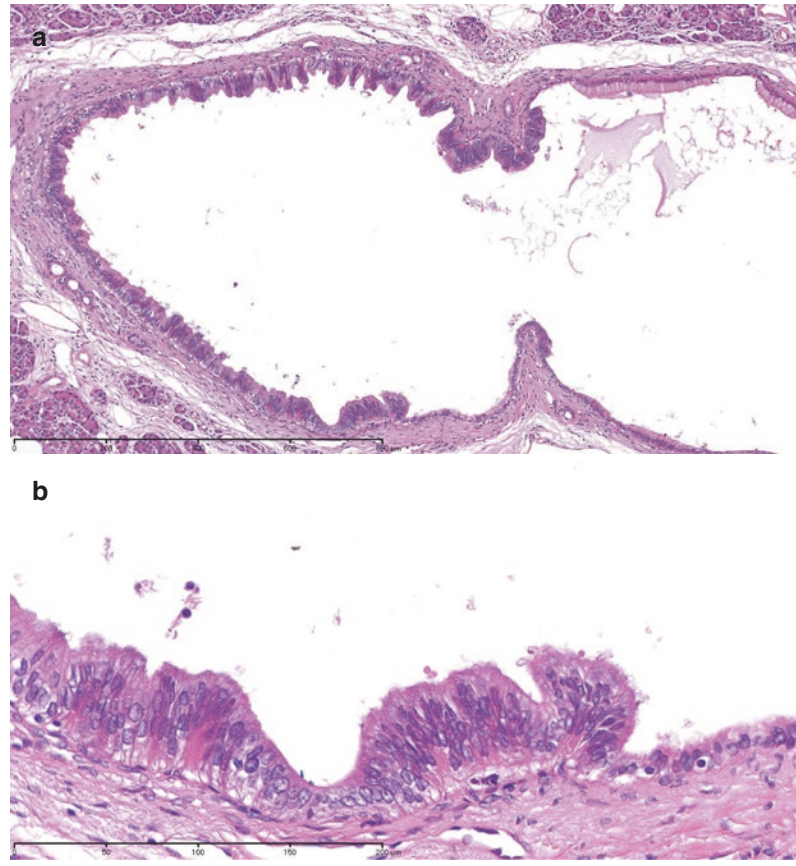

Fig. 4.3 (**a**) Carcinoma in situ in a single layer of tall columnar cells. (**b**) The cells have spindle-shaped nuclei and show milder nuclear atypia than that observed in Fig. 4.2. However, the case was diagnosed as carcinoma in situ based on the following findings: a clear border was seen between the nonneoplastic epithelium and atypical cells, and the cell density was high, with the nuclei located away from the base of the cells and spaced irregularly

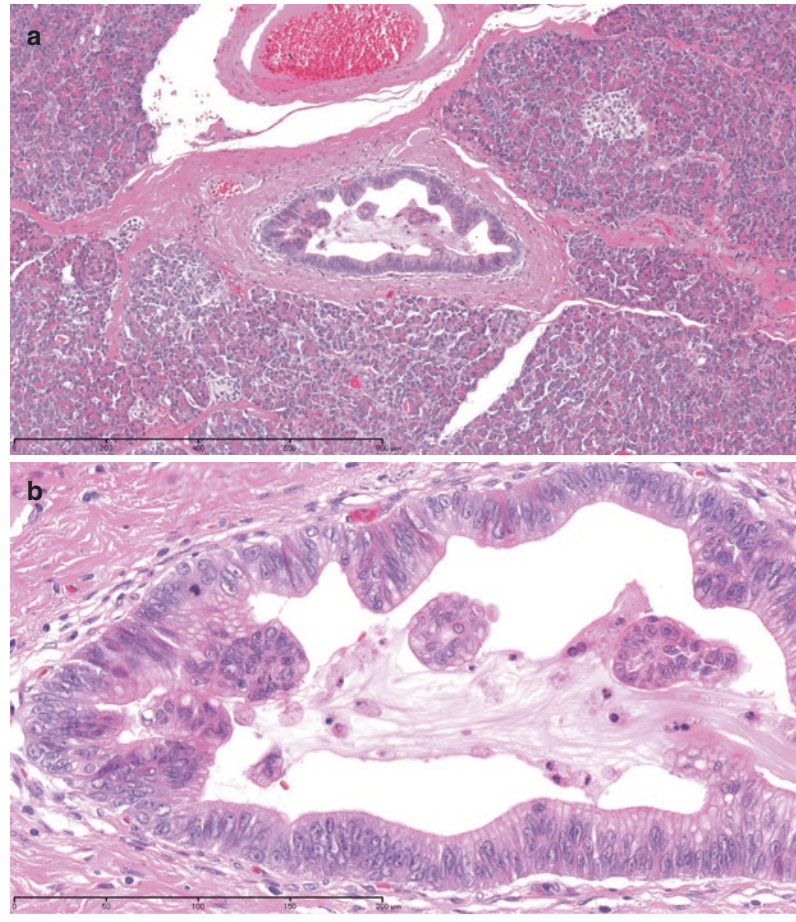

Fig. 4.4 (**a**) Carcinoma in situ in a single layer of cells, partly showing *low-papillary growth*. (b) It is difficult to differentiate between carcinoma and epithelium with atypia, because in a single layer of cells, the cells are relatively small in size and show less severe atypia. The area showing *papillary growth was diagnosed as carcinoma based on the presence of cellular and structural atypia. Since the cells in the single cell layer are similar to the cells in the area showing papillary growth, the lesion was diagnosed as* carcinoma in situ

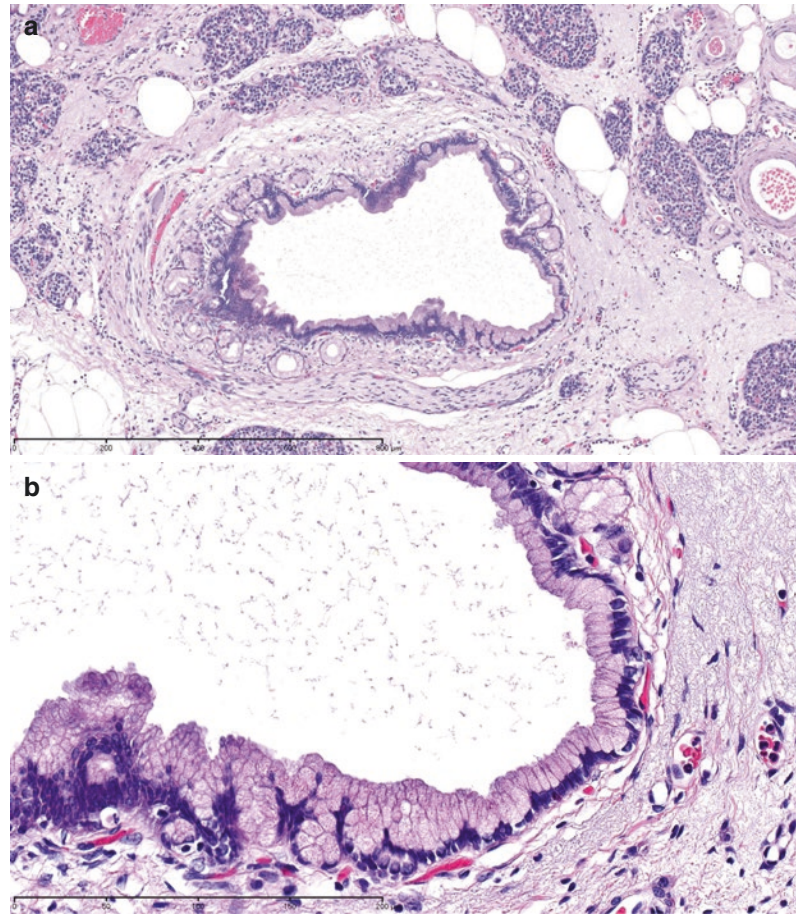

Fig. 4.5 (**a**, **b**) Epithelial mucous cell hyperplasia. Cells in mucous cell hyperplasia show a high frequency of point mutations in the Ki-ras oncogene and therefore are determined to be neoplastic by genetic analysis. However, clinically, even over long-term observation, these cells remain unchanged in morphology, being neither invasive nor metastatic. Therefore, histopathologically, such cells are diagnosed as mucous cell hyperplasia, which is regarded as a benign lesion

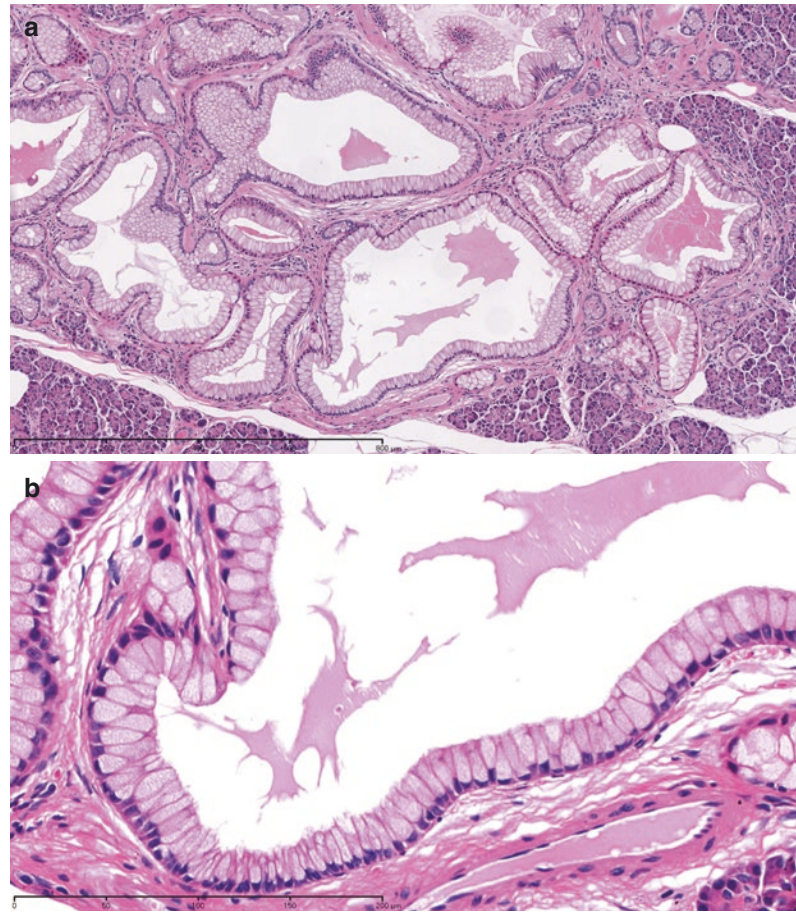

Fig. 4.6 (**a**) Glandular hyperplasia: proliferation of glandular ducts composed of epithelial mucous cell hyperplasia. (**b**) Proliferation of glandular ducts composed of cells similar to those shown in Fig. 4.5 is observed

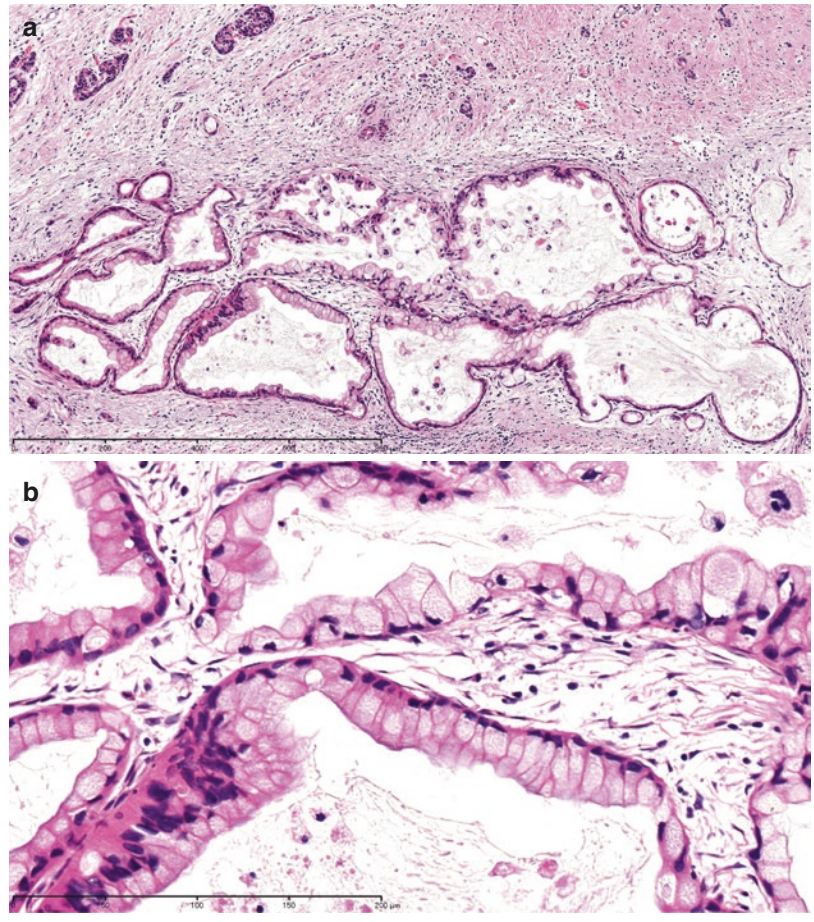

Fig. 4.7 (**a**) Carcinoma in situ showing proliferation of glandular ducts composed of cells containing abundant mucus in the cytoplasm, similar to the cells shown in Fig. 4.6. (**b**) Proliferation of glandular ducts composed of a single layer of cells containing abundant mucus in the cytoplasm is observed, as shown in Figs. 4.5 and 4.6. The lesion was diagnosed as carcinoma in situ, because the sizes of the cells composing the glandular epithelium are not uniform, and the nuclei are spaced irregularly, as compared to the regularly spaced nuclei located in the basal portion of the cells shown in Figs. 4.5 and 4.6

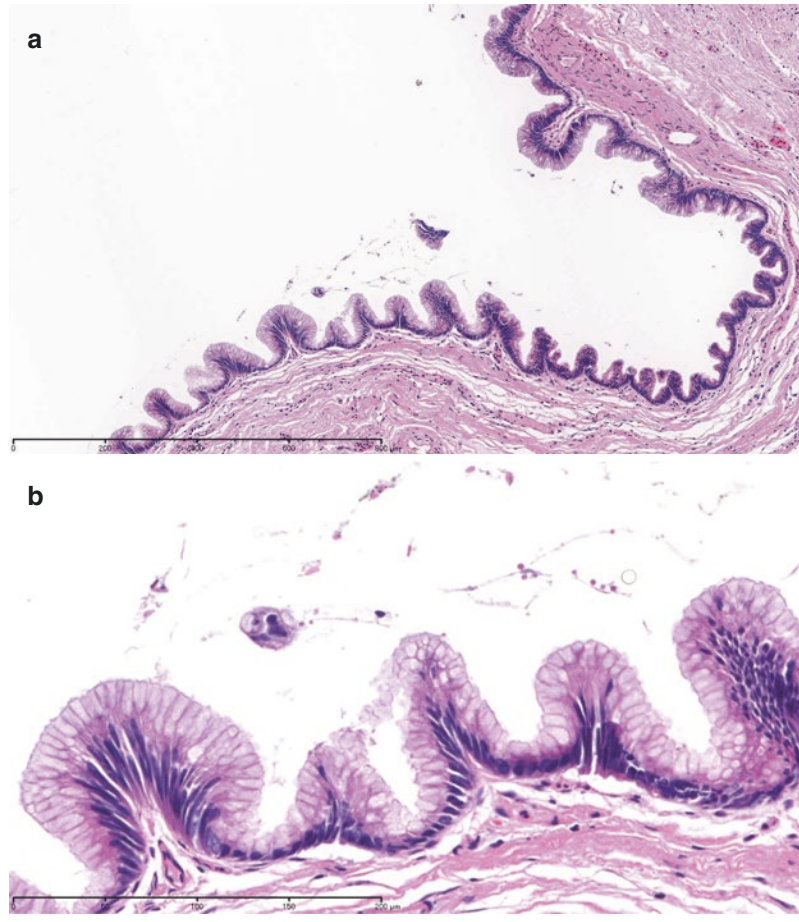

Fig. 4.8 (**a**) A benign lesion with a low-papillary pattern. (**b**) The *low-papillary lesion* with stroma in the central area shows mild structural atypia. Cells composing the *low-papillary lesion are similar to those* containing abundant mucus in the cytoplasm shown in Fig. 4.5. Nuclei are spaced regularly and located in the basal portion of the cells. A benign lesion was diagnosed *based on the absence of cellular and structural atypia*

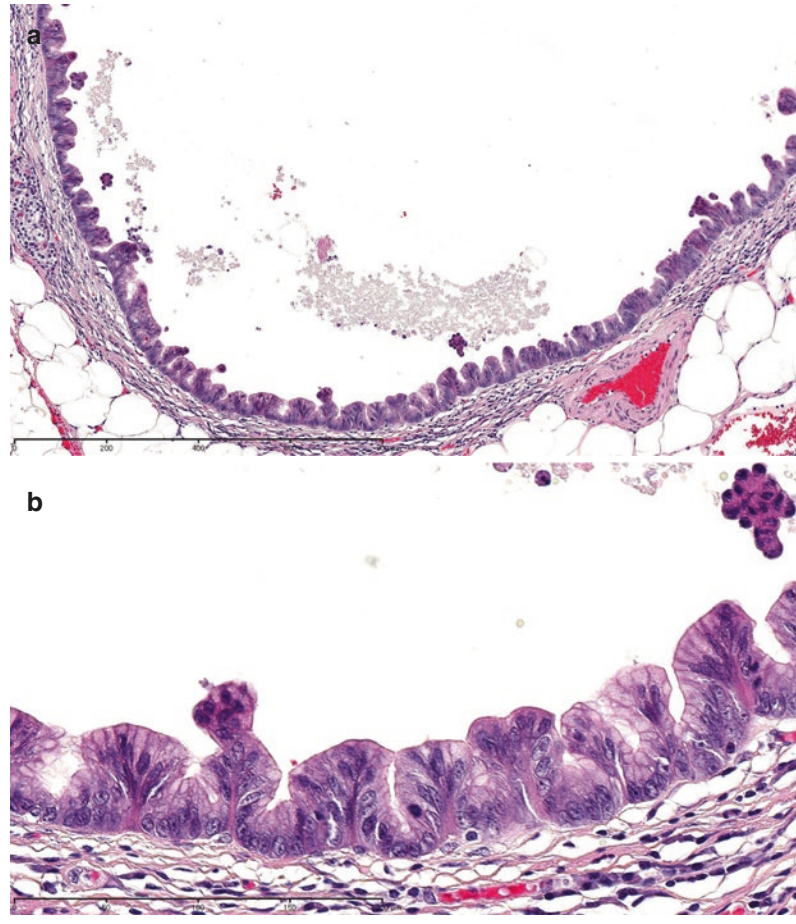

Fig. 4.9 (**a**) Carcinoma in situ composed of *low-papillary lesions*. (**b**) This is a lesion that needs to be differentiated as to whether it is a carcinoma or noncancerous epithelium. It was diagnosed with carcinoma in situ. The lesion was diagnosed as carcinoma because there is very little stroma in the center of the low-papillary lesion, and the cells show severe structural atypia. In addition, the cells composing the low-papillary lesion are arranged in the basal layer and show marked anisonucleosis, irregular nuclear shapes, and severe *cellular* atypia

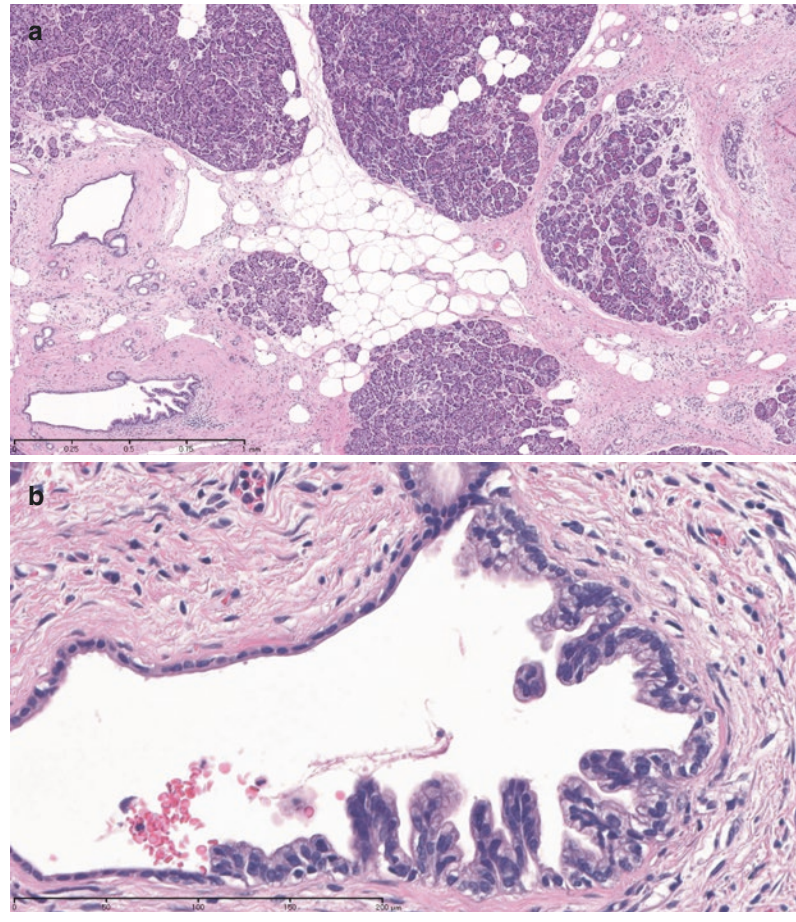

Fig. 4.10 (**a**) Carcinoma in situ composed of low-papillary proliferative lesions. (**b**) Similar to the case shown in Fig. 4.9, this is also a lesion that needs to be differentiated as to whether it is a carcinoma or noncancerous epithelium. It was diagnosed with carcinoma in situ, because the cells composing the lesion were smaller in size than those composing the lesion shown in Fig. 4.8 but showed marked anisonucleosis. In addition, the cells were arranged irregularly, and there was very little stroma *in the center of the* papillary proliferative lesion

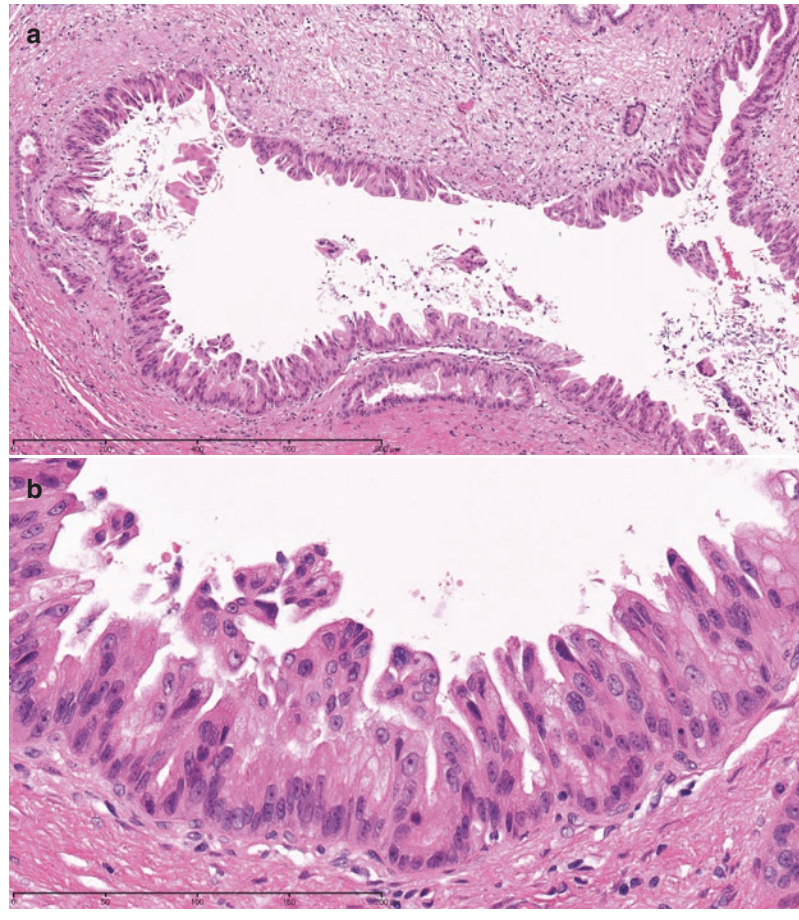

Fig. 4.11 (**a**) Carcinoma in situ composed of *low-papillary proliferative lesions*. (**b**) Carcinoma in situ with *low-papillary growth. The* carcinoma in situ was detected at the cut surface at the time of the surgical resection. About 10 months after the surgery, recurrence at the cut surface was detected as advanced cancer

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5 Operative Specimen Handling and Evaluation of Resection Margins

Caroline Sophie Verbeke

5.1 Introduction

Specimen dissection is the first step in the pathology reporting process. It is an important determinant of the overall quality of the pathology examination of a pancreatic cancer specimen, because suboptimal macroscopic examination and tissue sampling will significantly limit the accuracy of reporting on key data items such as tumour size and stage, lymph node and resection margin status and cancer origin. Unfortunately, a lack of consensus regarding specimen grossing has resulted in divergence of reported results and limited comparability of data from different studies and pancreatic centres [1–4].

This chapter provides a detailed account of the handling and examination of surgical pancreatic cancer specimens with, where appropriate, reference to (inter-)national recommendations and guidelines. Evaluation of the resection margins will be described at the various stages of the specimen grossing procedure, and an in-depth discussion follows in Sect. 5.9.

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5.2 Specimen Orientation and External Inspection

Various surgical resection procedures result in a variety of specimens. By far, the most common are pancreatoduodenectomy and distal pancreatectomy specimens, which will be discussed in this chapter.

5.2.1 Pancreatoduodenectomy Specimens

5.2.1.1 Specimen Orientation

Correct specimen orientation is the prerequisite for accurate macroscopic examination. Due to the complexity of the local anatomy, orientation of pancreatoduodenectomy specimens – resulting from a classical Whipple's procedure or a pylorus-preserving approach – may be difficult for the less experienced pathologist. Therefore, several national guidelines recommend that the surgeon marks one or multiple surfaces of the pancreatic head with a suture or with ink, according to a locally agreed protocol [5–8]. If inking is preferred, it is advisable that this is limited to only one surface of the pancreatic head, such that external specimen inspection by the pathologist is minimally interfered with. Usually, the surface facing the superior

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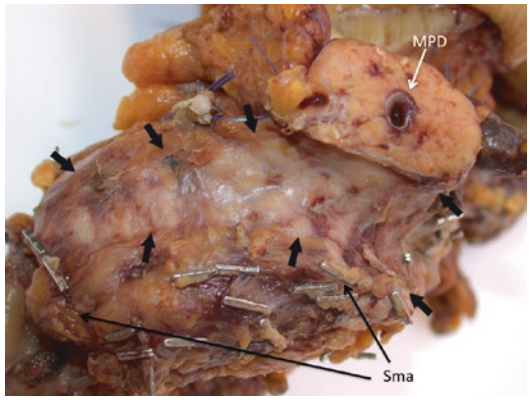

Fig. 5.1 View onto the medial aspect of a pancreatoduodenectomy specimen. Note the ovoid-shaped pancreatic transection margin with a dilated main pancreatic duct (*MPD*). The groove of the superior mesenteric vein (*black arrows*) is slightly curved and has a shiny surface. In contrast, the surface facing the superior mesenteric artery (*Sma*) is rough and fibrous

mesenteric vein (SMV) or superior mesenteric artery (SMA) is inked, because this allows unequivocal identification of the other surfaces.

For the identification of the various surfaces of the pancreatic head, it is best to start with the *transection margin of the pancreatic neck*, which is easily recognizable by its characteristic ovoid shape and the more or less centrally placed and often dilated main pancreatic duct (Fig. 5.1). Once this structure is identified, the surface facing the SMV is found immediately posterior to the transection margin of the pancreatic neck. It runs along the medial aspect of the pancreatic head and has the shape of a slightly curved groove, the so-called *SMV groove* (Fig. 5.1). It has a smooth, often slightly shiny surface and is usually slightly deeper at the level of the pancreatic neck and flattens out in its more caudal part. Following the SMV groove up to its cranial end will lead to the *transection margin of the common bile duct*. The extrapancreatic bile duct stump is usually short – up to approximately 10–15 mm in length – and may be closed with a suture. Located medial and slightly posterior to the SMV groove lies the surface that faces the SMA. As this is the area where the surgeon sharply dissects the peripancreatic soft tissue from the artery, the *SMA surface* has a rougher texture (Fig. 5.1). At the back of the pancreatic head, between the SMA surface and the posterior aspect of the duodenum lies the *posterior surface*, which is usually flat and slightly fibrous. The *anterior surface* of the pancreatic head is located between the anterior aspect of the duodenum and the SMV groove. It is usually smooth and shiny and can be covered with a variable amount of adipose tissue that blends in with the peripyloric adipose tissue and transverse mesocolon.

5.2.1.2 External Examination

In many instances, the presence of a pancreatic cancer may not be visible on external inspection of a pancreatoduodenectomy specimen. Occasionally, however, the tumour may cause bulging of a surface or irregularity of the duodenal mucosa or papilla of Vater. In particular, narrowing of the SMV groove or irregularity of its surface may indicate the presence of a tumour. In a similar way, the presence of an adherent segment or sleeve resection of a vein (SMV or portal vein) or artery (e.g. the hepatic artery) indicates tumour infiltration. Palpation will usually confirm the presence of an indurated tumour mass.

External examination can also reveal a variety of other pathological conditions, such as a tumour of the papilla or ampulla of Vater, dilatation of the papilla with oozing of mucus in case of intraductal papillary mucinous neoplasia or a rare annular pancreas that surrounds the entire duodenal circumference.

5.2.2 Distal Pancreatectomy Specimens

Orientation of distal pancreatectomy specimens is straightforward, especially as cancer specimens always include the spleen. Further helpful with specimen orientation is the presence of the splenic vessels, which run along the superior border of the pancreatic body and tail (Fig. 5.2).

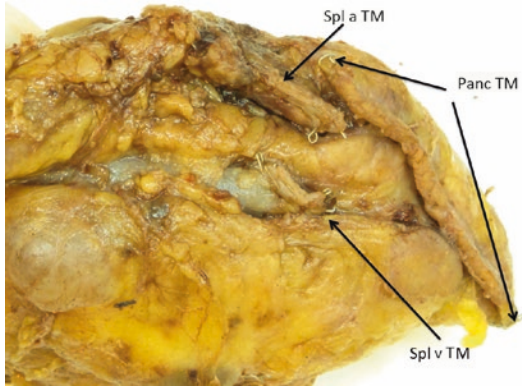

Fig. 5.2 View onto the posterior aspect of a distal pancreatectomy specimen following laparoscopic procedure. Note the staple lines on the pancreatic transection margin (*Panc TM*) and the transection margins of the splenic artery (*Spl a TM*) and vein (*Spl v TM*)

5.3 Specimen Fixation

5.3.1 Specimen Handling Prior to Fixation

To allow biobanking of fresh tissue samples, pancreatic resection specimens must be received unfixed, on ice, transported directly from surgical theatres (see also Sect. 5.10). The distal stomach and/or duodenum are opened longitudinally with scissors and rinsed. To avoid transection of a periampullary tumour, the duodenum should be opened along its antimesenteric aspect after careful probing with a finger. The gallbladder is opened longitudinally and rinsed. The specimen should not be pinned on a cork plate, as this is unnecessary and delays fixation.

5.3.2 Specimen Fixation

Fixation in buffered formalin should be approximately 48 h. The centre of the pancreatic head may not be fully fixed after 48 h; however, longer fixation of the specimen risks extensive autolytic change. Therefore, it is better to dissect the specimen after 48 h and leave the cassetted tissue samples in formalin for a few hours, which will complete the fixation process swiftly. Focal opening of a large cystic lesion, allowing the cyst content to drain and formalin to enter the cavity, will expedite fixation and ensure better preservation of the cavity-lining tissue.

5.4 Inking of the Specimen Surface

Inking of the specimen surfaces serves a dual purpose. It helps with orientation during macroscopic and microscopic examination, and it allows unequivocal microscopic identification of the true specimen surface, which is important for accurate margin assessment.

Inking is easiest done after specimen fixation, because inks stick better to fixed than fresh tissue surfaces. So-called bleeding of colours can be reduced by spraying 10% acetic acid onto the freshly applied ink. Should inking of a fresh specimen be required, the use of ground dry pigment dissolved in acetone may be considered. The use of acetone as a dissolvent ensures rapid drying of the dye, which reduces bleeding of colours.

The various specimen surfaces should be inked in different colours according to a locally agreed colour code. In pancreatoduodenectomy specimens, five different surfaces are discerned, whose identification and examination is part of the margin status assessment (Fig. 5.3) [9–11]. The surfaces of the pancreatic head are – as outlined in

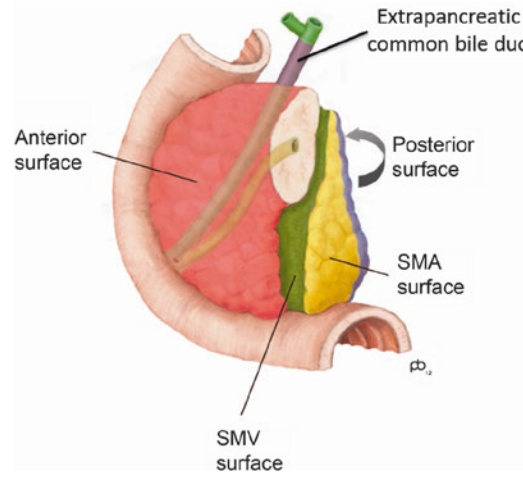

Fig. 5.3 Circumferential resection margins of pancreatoduodenectomy specimens are inked in different colours: *red*, anterior; *green*, facing the superior mesenteric vein (SMV); *yellow*, facing the superior mesenteric artery (SMA); *blue*, posterior; *purple*, around the extrapancreatic common bile duct (With permission of Springer, Pathology of the pancreas – a practical approach, [10], Fig. 3. 4, p. 31)

Sect. 5.2.1.1 – the anterior and posterior surface, the SMV groove and the SMA surface. Although the anterior surface is not a true resection margin but an anatomical surface that faces the lesser sac, inclusion of this surface in the assessment is important, as involvement of this surface increases the risk of cancer recurrence [12]. A further margin consists of the circumferential surface of the extrapancreatic common bile duct. Examination of the various specimen surfaces and resection margins is discussed in detail in Sect. 5.9.

In distal pancreatectomy specimens, two surfaces are discerned and inked: the anterior and posterior surface [10, 11]. If the transection margin of the splenic vessels is of particular concern (Fig. 5.2), this small area may also be inked in a separate colour, such that it can be easily identified during specimen dissection, tissue sampling and microscopic examination.

Pancreatic specimens resulting from an extended resection include one or more additional structures or organs, e.g. a part of the SMV, (meso-)colon or small bowel in extended pancreatoduodenectomy specimens, and the left adrenal gland, part of the stomach or left colon in extended distal pancreatectomy specimens. In such instances, additional surfaces or resection margins must be inked, depending on the individual case.

For practical purposes, it is best to carefully remove without tissue disruption any surgical sutures, clips or staples prior to inking, as the presence of these may render specimen dissection difficult.

5.5 Specimen Dissection

Specimen dissection takes a central place in the macroscopic examination process. Its purpose is to reveal lesions and display them in a way that is conducive to accurate description and assessment as well as optimal tissue sampling. Currently, three dissection techniques are being used worldwide: the bi- or multivalving technique, the bread loaf slicing approach and the axial slicing technique [9, 10]. The principal difference between these three dissection techniques is the plane of sectioning. In the bi- or multivalving technique, the specimen is sliced along the plane that is defined by probes inserted in the main pancreatic duct and common bile duct (Fig. 5.4). According to the bread loaf slicing technique, the specimen is sliced along a plane that is parallel to the transection margin of the pancreatic neck (Fig. 5.5). With the axial slicing technique, pancreatoduodenectomy specimens are serially sliced in the axial plane, i.e. along the plane that is perpendicular to the longitudinal axis of the descending part of the duodenum (Fig. 5.6). It is the same plane as the one that is used for computerized tomography (CT) imaging of the pancreas. The following sections will provide a detailed description of the axial slicing technique for pancreatoduodenectomy specimens and discuss the advantages of this technique compared to other approaches. Dissection of distal, total and extended pancreatectomy specimens will be discussed separately.

5.5.1 Axial Slicing of Pancreatoduodenectomy Specimens

Dissection according to this technique does not require any further specimen preparation, and, in particular, the main pancreatic duct or distal common bile duct should not be probed or opened. If a metal stent is present in the common bile duct and it cannot be removed by gentle pulling, the metal mesh should be opened by cutting several wires, following which wires can be extracted individually using small pliers. Plastic stents can remain in situ as they do not hinder specimen dissection. Slicing of a fixed specimen in the axial plane is technically easy; hence, specimen slices can be thin (3 mm), and a pancreatoduodenectomy specimen will result in at least 10, often 12–14 or more slices. Using a long dissection knife and pulling it steadily across the specimen with long violin bow strokes ensure that the cut surface of the specimen will be smooth and even. Specimen slices are laid out in sequential order, the inferior side facing upward (as on CT imaging), as illustrated in Fig. 5.7.

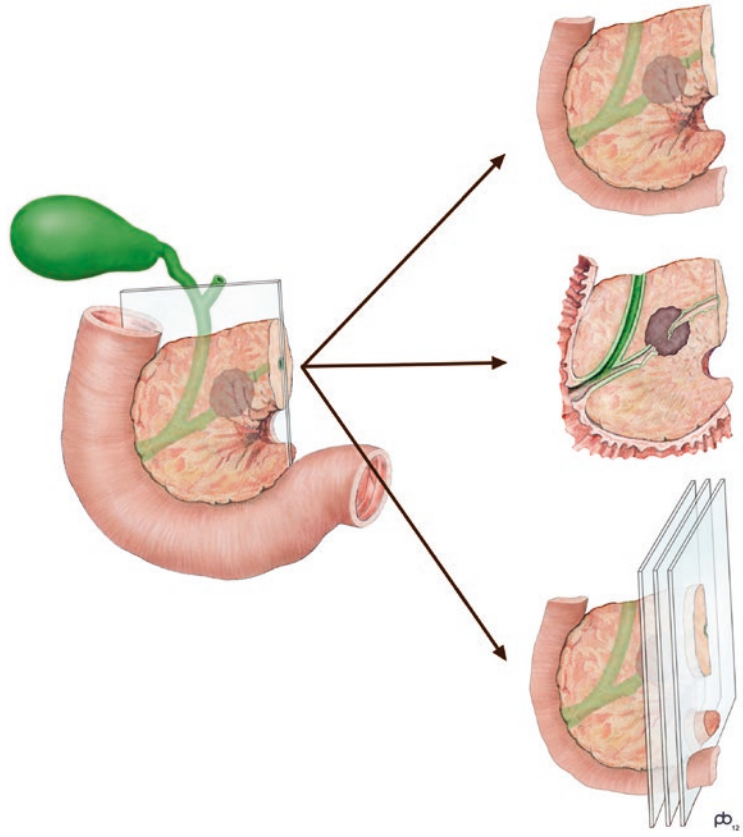

Fig. 5.4 Bi- or multivalving of pancreatoduodenectomy specimens. The specimen is sliced along the plane defined by the pancreatic and common bile duct. The resulting specimen slices are large and usually require further dissection, e.g. in a plane parallel to the pancreatic transection margin (With permission of Elsevier, from: Verbeke [9], Fig. 2)

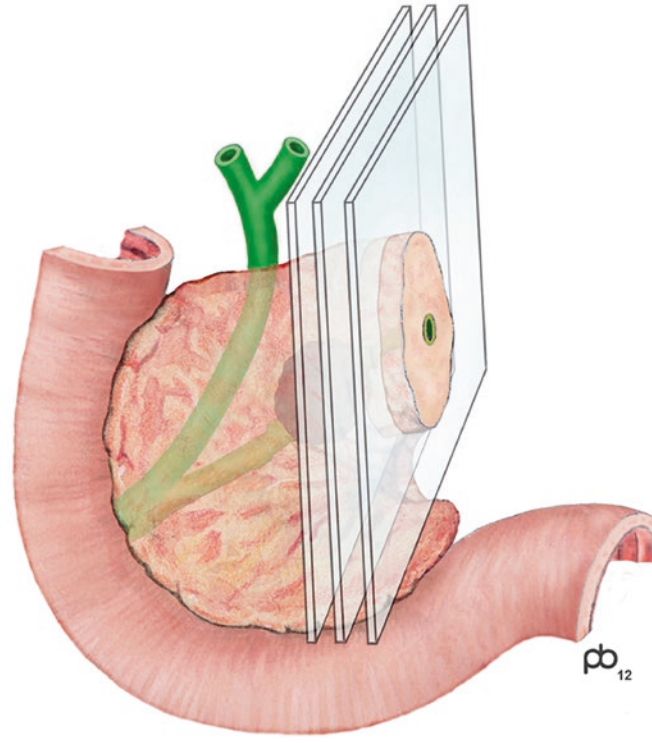

Fig. 5.5 Bread loaf slicing technique of pancreatoduodenectomy specimens. The specimen is serially sliced along the plane that is parallel to the transection margin of the pancreatic neck (With permission of Elsevier, from: Verbeke [9], Fig. 3)

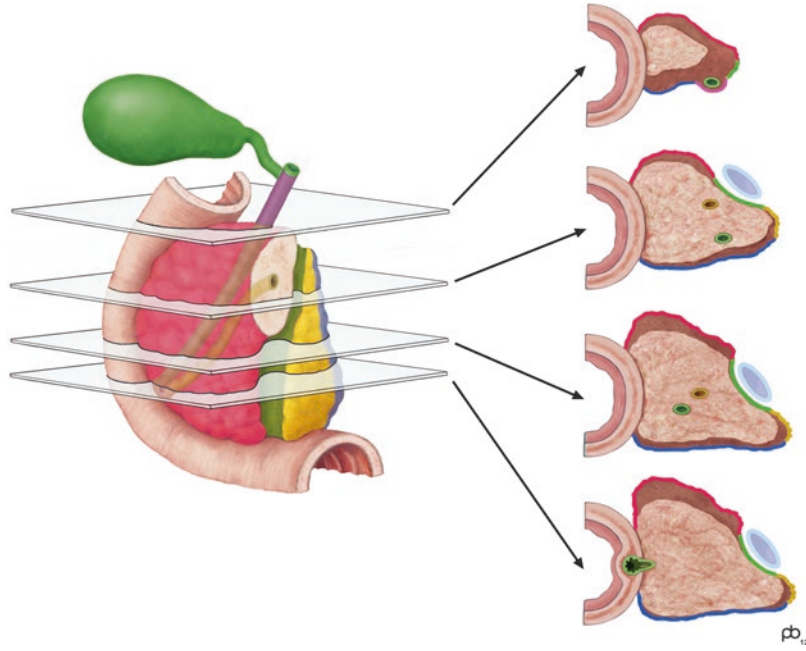

Fig. 5.6 Axial specimen dissection of pancreatoduodenectomy specimens. The specimen is serially sliced in a plane perpendicular to the longitudinal axis of the descending duodenum. The resulting specimen slices at various levels have a characteristic configuration (With permission of Elsevier, from: Verbeke [9], Fig. 4)

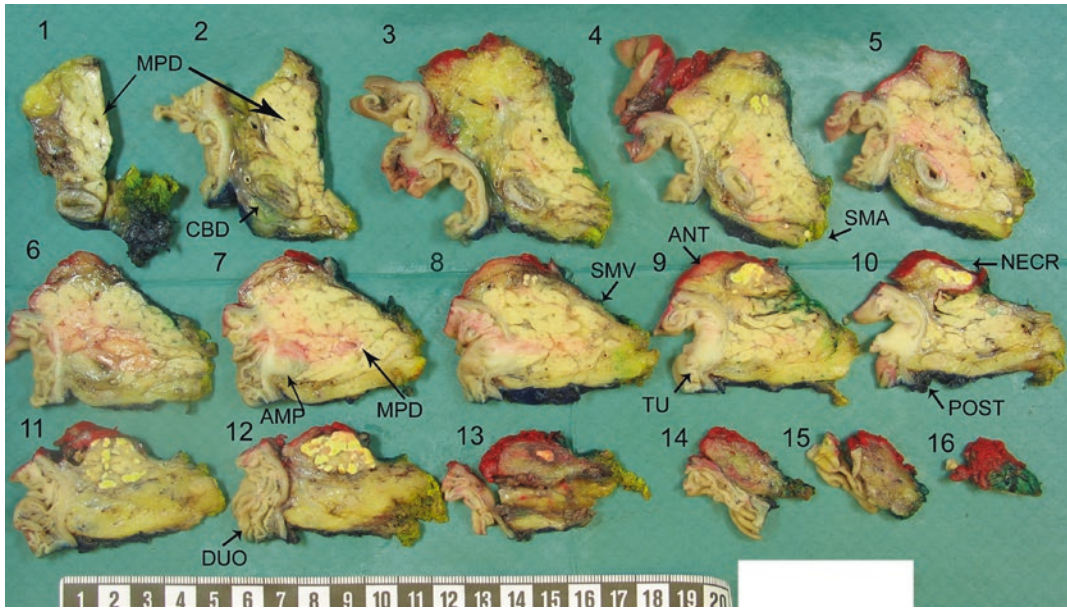

Fig. 5.7 Axial specimen slices of a pancreatoduodenectomy specimen are laid out in sequential order, from cranial (*top left*) to caudal (*bottom right*). Fourteen thin specimen slices provide detailed views on the local anatomy. *Abbreviations*: *AMP* ampulla, *ANT* anterior surface, *CBD* common bile duct, *DUO* duodenum, *MPD* main pancreatic duct, *NECR* necrosis, *POST* posterior surface, *SMA* superior mesenteric artery, *SMV* superior mesenteric vein, *TU* tumour (With permission of Springer, Pathology of the pancreas – a practical approach, [10], Fig. 3.10, p. 33)

5.5.2 Advantages of the Axial Slicing Technique

Compared to the bi- or multivalving and bread loaf slicing techniques, axial specimen slicing has the following advantages:

- *Technical ease*: slicing in the axial plane is easy to perform, especially because the duodenum is transected cross-sectionally (in contrast to the bread loaf slicing technique, according to which the duodenum is sliced longitudinally).
- *Universal applicability*: all pancreatoduodenectomy specimens can be dissected by axial slicing, irrespective of the pathology – neoplastic or nonneoplastic – they contain. This is important, as the correct diagnosis is often unknown preoperatively.
- *Standardized display*: as the plane of dissection (axial) is fixed, the local anatomy of the pancreas and adjacent structures is always displayed in the same fashion. This allows straightforward identification of pathological changes and recognition of anatomical variation, which is not uncommon in this area. In contrast, because the plane of sectioning of the bi- or multivalving technique is defined by probes in the common bile duct and pancreatic duct, and the position of these varies between individual patients, dissection varies between specimens. As a consequence, it is more difficult to compare findings between various cases. By using a single fixed plane – the axial plane – macroscopic findings in axial specimen slices are as easily and universally "readable" by pathologists from different centres as findings on CT imaging can be interpreted by radiologists worldwide.
- *Thin specimen sections*: as axial slicing is easy to perform, numerous thin specimen slices can be cut, which allow detailed views on local anatomy and pathological changes throughout the pancreatic head and adjacent structures.
- *Detailed display of the periampullary region*: thin axial specimen slices allow detailed examination of the minute structures of the major ampulla and papilla, the junction with the main pancreatic duct and common bile duct and the adjacent duodenum (see Sect. 5.6.1). Unlike the bi- or multivalving technique, which requires "releasing cuts" through the periampullary area [13], there is no need for additional dissection when using the axial slicing approach.
- *Comprehensive and accurate margin assessment*: in each axial specimen slice, all circumferential margins of the pancreatic head can be inspected. As such, the relationship of the tumour to the margins can be evaluated at multiple levels along the entire craniocaudal length of the pancreatic head. Multiple studies and a recent meta-analysis have shown that the detection of margin involvement is more accurate when using the axial slicing technique than any other dissection method [4, 14–16].
- *Easy tissue sampling*: because axial specimen slices are thin, tissue samples can be excised from the slices and directly transferred to the tissue cassettes without the need for further dissection.
- *Communication with clinical colleagues*: because the axial specimen slices display the local anatomy and pathological changes in the same way as they appear on CT imaging, findings are readily understandable by surgeons, oncologists and radiologists (Fig. 5.8).

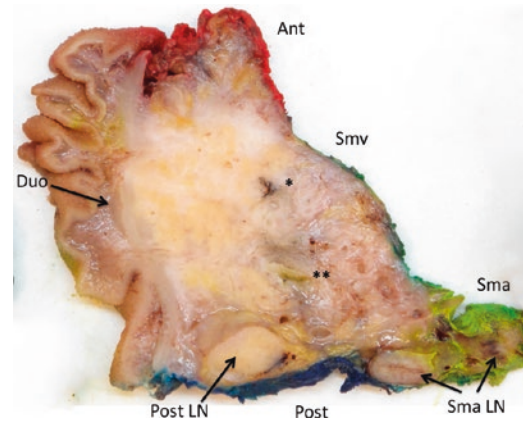

Fig. 5.8 Axial specimen slices of pancreatoduodenectomy specimens provide a view on the local anatomy that is similar to that seen on CT images. Note the main pancreatic duct (*) and distal common bile duct (**), which are partially involved by tumour. *Abbreviations*: *Ant* anterior surface, *Duo* duodenum, *Post* posterior surface, *Post LN* posterior pancreatoduodenal lymph node, *Sma* surface facing the superior mesenteric artery, *Sma LN* lymph nodes in the adipose tissue facing the superior mesenteric artery, *Smv* surface facing the superior mesenteric vein

5.5.3 Dissection of Distal and Total Pancreatectomy Specimens

Distal pancreatectomy specimens are dissected by serial slicing in the sagittal plane [5, 6, 8, 10, 11, 17]. Longitudinal opening of the main pancreatic duct is not recommended, because it may be technically difficult, it disrupts the specimen surface (and thus interferes with margin assessment) and does not result in a better display of lesions than by sagittal slicing. Total pancreatectomy specimens are best dissected by a combined axial and sagittal slicing technique. The point of change from axial to sagittal slicing may be moved towards the pancreatic body, depending on the site of a centrally located tumour and the involvement of resected segments of artery or vein.

5.5.4 Dissection of Extended Pancreatectomy Specimens

Dissection of these specimens may require deviation from the standard protocol, although in almost all instances, the pancreatic part of the extended resection specimen will be dissected as described in Sects. 5.5.1 and 5.5.3 (Fig. 5.9).

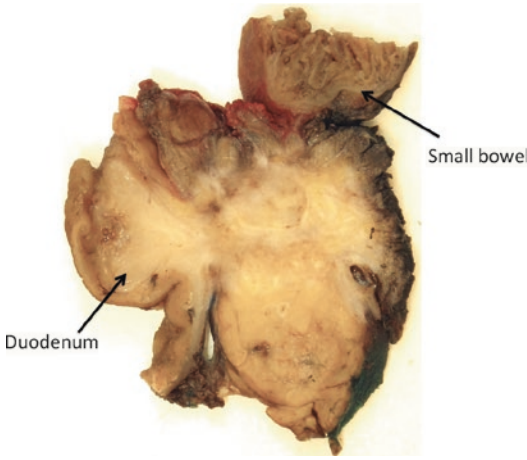

Fig. 5.9 Specimen resulting from an extended pancreatoduodenectomy with resection of a loop of small bowel that is adherent to the anterior surface of the pancreatic head. Note that the bowel wall proper is clear of tumour

5.6 Macroscopic Examination

The aim of the macroscopic examination of dissected specimens is to obtain an accurate record of the tumour: the appearance of the tumour, its size and extent, and its exact location and relationship to anatomical structures, specimen surfaces and margins. Furthermore, assessment of the relationship of the tumour to anatomical structures other than those of relevance for T-staging of pancreatic cancer [18, 19] is of particular interest to surgical and radiology colleagues regarding the preoperative assessment of resectability and patient selection. Equally important, the exact location of the tumour with respect to the bile duct, ampulla and duodenum is crucial for the identification of the cancer origin. Indeed, the distinction of pancreatic ductal adenocarcinoma from cancer of the common bile duct, ampulla or duodenum is primarily determined by the localization of the centre of the tumour mass, a finding that is appreciated macroscopically and confirmed microscopically [3]. The following sections provide guidance for the identification of such anatomical structures.

5.6.1 Identification of Anatomical Structures in Pancreatoduodenectomy Specimens

- The *intrapancreatic common bile* duct runs obliquely through the posterior aspect of the pancreatic head. It can be distinguished from the main pancreatic duct by its thicker wall (1–2 mm), the possible presence of green-stained bile and/or a stent in the lumen, the absence of communicating branch ducts and its more posterior position within the pancreatic head (Fig. 5.10).
- The *main pancreatic duct* lies medial to the common bile duct and has a thin, membranous, cream-coloured wall. Occasionally, communication with branch ducts may be visible macroscopically, if the latter are dilated (Fig. 5.10).
- The *ampulla of Vater* is an olive-shaped firm nodular structure that straddles the duodenal wall. The slightly elevated duodenal mucosa surrounding the draining ampullary channel is

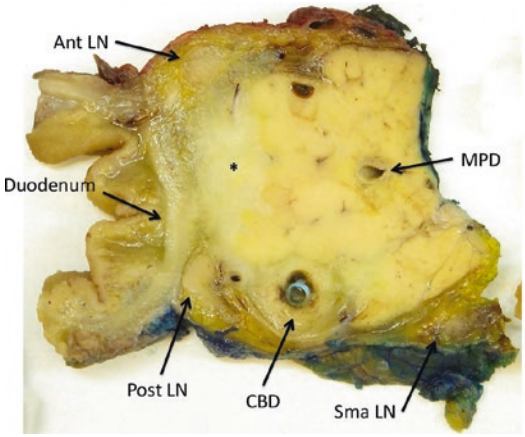

Fig. 5.10 Compared to the main pancreatic duct, the common bile duct has a thicker wall and lies more posterior in the pancreatic head. Note the presence of a plastic stent in the bile duct. *Abbreviations*: *Ant LN* anterior pancreatoduodenal lymph node, *CBD* common bile duct, *MPD* main pancreatic duct, *Post LN* posterior pancreatoduodenal lymph node, *Sma LN* lymph node in the adipose tissue facing the superior mesenteric artery

the *papilla of Vater*. The junction of the ampulla with the main pancreatic duct lies a few millimetres caudal to the junction with the common bile duct (Fig. 5.11).

- The *minor ampulla* is a similar, albeit much smaller nodular structure across the duodenal wall (Fig. 5.12). The overlying *minor papilla* is often no more than a 2–3 mm large elevation of the duodenal mucosa, which is typically located 10–20 mm proximal to the papilla of Vater. It drains the *Santorini duct*, which is very small (ca. 1 mm in diameter) and therefore not often seen (Fig. 5.12).
- The *gastroduodenal artery* is the larger of both arteries that are included in a standard pancreatoduodenectomy specimen. It runs through the anterior peripancreatic adipose tissue before dividing into pancreatoduodenal branches (Fig. 5.11, see also Fig. 5.14). On external examination, the artery may be visible as a very short stump, often with a surgi-

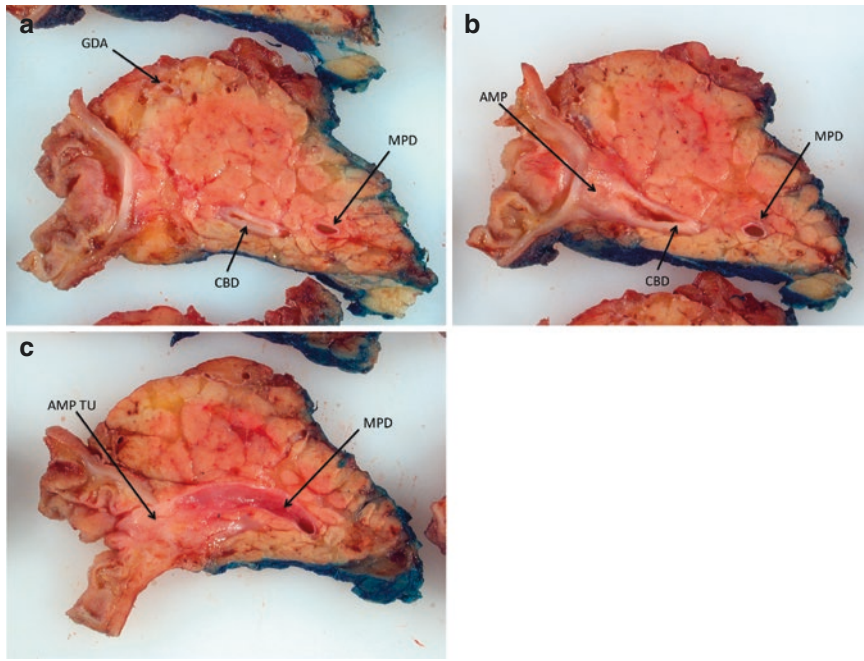

Fig. 5.11 The junction of the main pancreatic duct and common bile duct at the ampulla of Vater seen in three sequential (cranial to caudal) axial specimen slices (**a**–**c**). (**a**) Note the thicker wall of the common bile duct compared to the main pancreatic duct. (**b**) The distal common bile duct joins the ampulla, which is a slightly nodular structure. Note that the main pancreatic duct at this level has not yet joined the ampulla. (**c**) The main pancreatic duct joins the ampulla at a level that lies just caudal of the junction between the ampulla and common bile duct (as depicted in **b**). Note the dilatation of the main pancreatic duct due to a small ampullary tumour. *Abbreviations*: *AMP* ampulla of Vater, *AMP TU* ampullary tumour, *CBD* common bile duct, *GDA* gastroduodenal artery, *MPD* main pancreatic duct

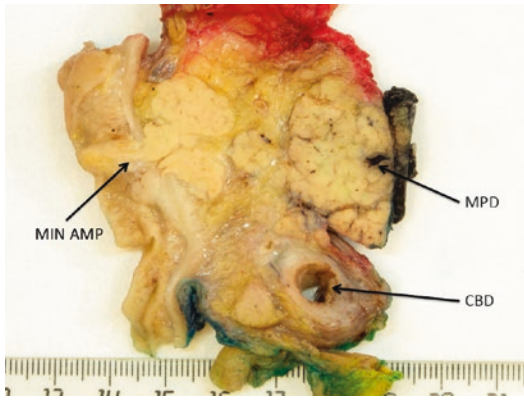

Fig. 5.12 The minor ampulla forms a small nodular structure across the duodenal wall. *Abbreviations*: *CBD* common bile duct, *MIN AMP* minor ampulla, *MPD* main pancreatic duct

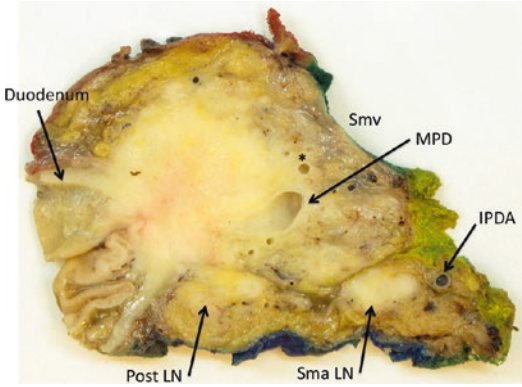

Fig. 5.13 The inferior pancreatoduodenal artery is located in the adipose tissue that faces the superior mesenteric artery at or below the level of the ampulla of Vater. *Abbreviations*: *IPDA* inferior pancreatoduodenal artery, *MPD* main pancreatic duct, *Post LN* posterior pancreatoduodenal lymph node, *Sma LN* lymph node in the adipose tissue facing the superior mesenteric artery, *Smv* surface facing the superior mesenteric artery

cal suture, at the superior aspect of the pancreatic head.

- The *inferior pancreatoduodenal artery* is the smaller of both arteries contained in a standard pancreatoduodenectomy specimen. It can been seen in the peripancreatic adipose tissue facing the SMA in axial specimen slices through the caudal half of the pancreatic head (Fig. 5.13). The artery forms often a small plexus with two or more vascular lumina.
- In case of an extended surgical procedure with resection of the *SMV or portal vein*, the venous segment will obviously be found adherent to the SMV groove (Fig. 5.14).
- In case of resection of the *hepatic artery*, the arterial segment will be found on the cranial aspect of the pancreatic head, close to the gastroduodenal artery (Fig. 5.15).

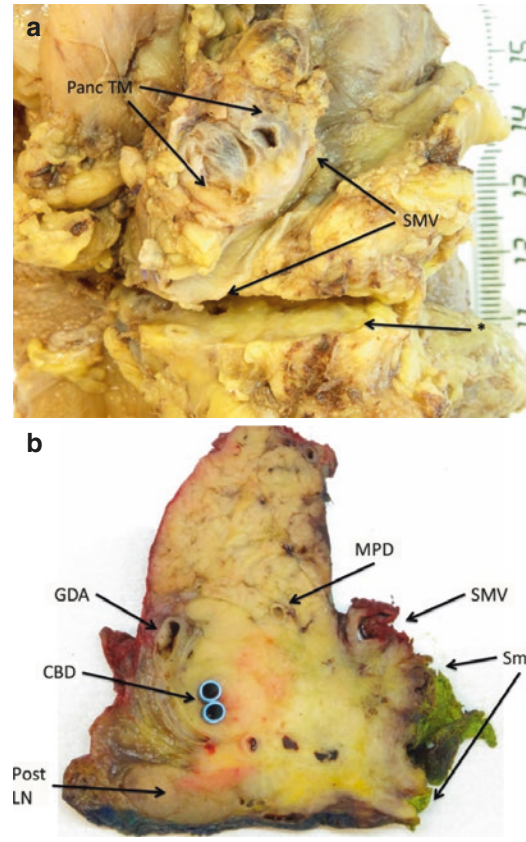

Fig. 5.14 Pancreatoduodenectomy specimen with resection of the superior mesenteric vein. (**a**) A 3 cm long segment of the superior mesenteric vein lies adjacent to the pancreatic transection margin. (**b**) An axial specimen slice shows a large tumour, which infiltrates the stented common bile duct, a posterior pancreatoduodenal lymph node and soft tissue at the surface facing the superior mesenteric artery. Note that the tumour grows close to the venous resection, gastroduodenal artery and main pancreatic duct. (**c, d**) A histological section taken from the resected vein (**c**, *boxed area* viewed in **d**) shows that the tumour (*small arrows*) infiltrates the adventitial layer of the venous wall and extends onto the specimen surface immediately adjacent to the adherent vein (**d**, *large arrow*). *Abbreviations*: *CBD* common bile duct, *GDA* gastroduodenal artery, *MPD* main pancreatic duct, *Panc TM* pancreatic transection margin, *Post LN* posterior pancreatoduodenal lymph node, *Sma* surface facing the superior mesenteric artery, *SMV* venous resection; * incision for biobanking

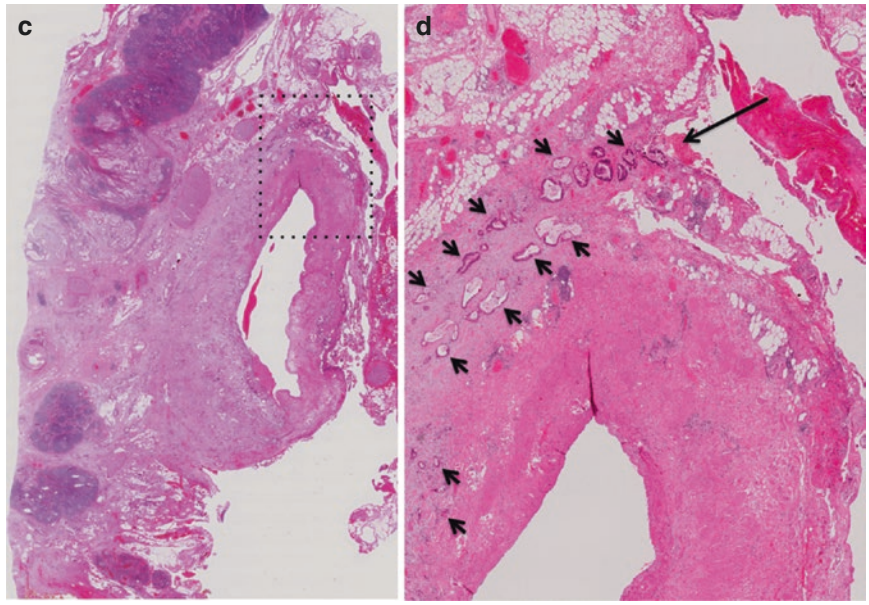

Fig. 5.14 (continued)

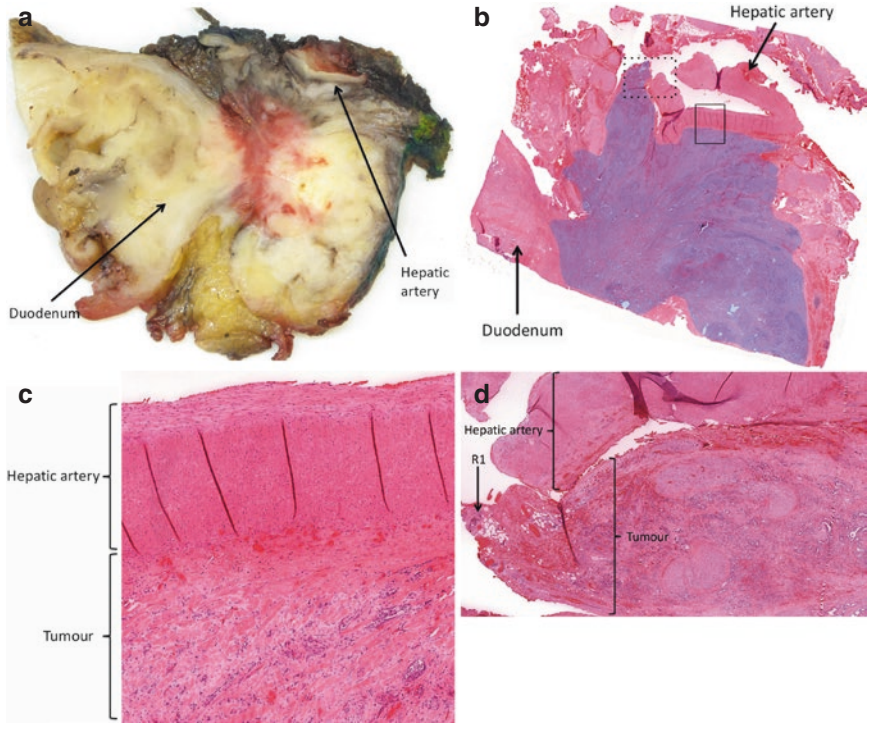

Fig. 5.15 Pancreatoduodenectomy specimen with resection of the hepatic artery. (**a**) An axial slice from the top of the pancreatic head shows a large tumour with infiltration of the duodenal wall and the soft tissue around the resected arterial segment. (**b**) The corresponding histological section shows extensive tumour infiltration (*blue shading*). The areas surrounded by full and dotted lines are shown at high magnification in (**c**, **d**), respectively. (**c**) Tumour infiltrates up to, but not into the arterial wall. (**d**) Tumour reaches the specimen surface immediately adjacent to the adherent arterial segment (R1, *arrow*)

5.6.2 Identification of Anatomical Structures in Distal Pancreatectomy Specimens

As outlined in Sect. 5.2.2, the splenic artery and vein run along the superior border of the pancreatic body and tail. Proximally, before reaching the coeliac trunk and SMV, respectively, both vessels take up a slightly more caudal position, midway the posterior pancreatic surface (Fig. 5.2).

5.6.3 Macroscopic Description

As a general rule, any pathological change should be recorded in terms of appearance, size, location and relationship to relevant anatomical structures and specimen margins. In addition, the dimensions of the various constituent structures of the surgical specimen should be recorded. Recording of macroscopic findings should be in accordance with (inter-)national guidelines and minimum data sets. The size of a tumour – or any other abnormality – should be recorded for three dimensions. Both dimensions in the axial plane can be easily measured in the axial specimen slices, while the craniocaudal dimension can be calculated by multiplying the slice thickness with the number of slices in which the lesion is present.

The anatomical structures described in Sects. 5.6.1 and 5.6.2, as well as the duodenum and peripancreatic adipose tissue, are important anatomical landmarks for the description of the localization and extent of a tumour. Description can and should be as detailed as that stated in radiology reports, such that preoperative imaging and pathology findings can be correlated carefully, and useful feedback regarding tumour resectability and patient selection can be provided. Furthermore, the commonly encountered but clinically irrelevant statement of "head of pancreas" as the localization of a tumour in a pancreatoduodenectomy specimen can be replaced by a clinically more meaningful detailed description of the three-dimensional position and extent of the tumour.

5.7 Photodocumentation

Photodocumentation of the macroscopic findings is highly recommended [8, 17, 20]. Photographs should be taken in close-up, such that the specimen slice or lesion fills the camera viewer (e.g. Fig. 5.10). Furthermore, an overview photograph of the specimen slices lined up in sequential order may also be helpful (Fig. 5.7).

Photodocumentation serves several purposes. First, it is of great help during microscopic examination, as close-up photographs of individual specimen slices allow accurate tissue orientation. In addition, it gives direct feedback to the pathologist regarding his or her interpretation of macroscopic changes, which in the long term is of significant educational value. Second, the photographs are very useful for case discussion with surgeons and radiologists, who can easily recognize the findings due to the similarity in display with CT imaging. Third, photodocumentation allows review of the macroscopic findings, which is an essential complement to microscopic slide review. Because key data, in particular the origin of the cancer in pancreatoduodenectomy specimens – the pancreas, ampulla, bile duct or duodenum – is first and foremost based on a detailed macroscopic examination [3], the possibility to review this part of the pathology reporting process is essential for the provision of second opinion on an individual case or for central review and systematic quality assessment of a case series.

5.8 Tissue Sampling

Tissue sampling plays a critical role, as it is at this point of the grossing procedure that the decision is taken as to which parts of the tumour will be available for microscopic examination. Tissue sampling of pancreatic tumours, in particular those in the pancreatic head, is challenging for two reasons. First, in this area of complex anatomy, multiple samples are required to examine and document the relationship of the tumour to

several important structures. The same requirement exists when sampling from extended pancreatic resection specimens. Second, pancreatic cancer, i.e. ductal adenocarcinoma, is typically poorly circumscribed, such that the outlines of the tumour are difficult or hardly identifiable by naked-eye inspection. The reason for this is first and foremost the highly dispersed growth pattern of pancreatic cancer, which is particularly pronounced in the periphery of the tumour [21, 22]. Indeed, invasive tumour cells and cell clusters are microscopically often found well beyond what macroscopically appeared to be the edge of the tumour. In addition, atrophy and fibrosis of pancreatic parenchyma adjacent to the invasive tumour edge further blur the distinction between tumour and nonneoplastic parenchyma. Hence, the general principle of targeted sampling, i.e. taking tumour tissue from areas with macroscopically visible tumour involvement, is not appropriate for pancreatic cancer, as it may lead to significant underestimation of the size and extent of the tumour and, consequently, underreporting of the T- and R-stage [13, 21, 23]. Not surprisingly, the rate of detection of microscopic margin involvement (R1) increases with the number of tissue blocks that are sampled from the tumour and adjacent specimen surfaces [14]. For the reporting of cancer specimens to be accurate, extensive tissue sampling is required, particularly from the tumour periphery, including areas without clear macroscopically visible tumour involvement. How extensive sampling should be, depends on the ambiguity of the gross findings [8].

5.8.1 Sampling Technique

Based on the above-described limited reliability of naked-eye assessment of the tumour outlines, it is important that samples from the tumour – or possible tumour-involved tissues – are taken en bloc with adjacent tissues and structures of interest (Fig. 5.16). The use of at least one whole-mount section is recommended, as it allows, for example, accurate measurement of the axial tumour dimensions [5, 17]. For the use of standard tissue cassettes, the following principles apply:

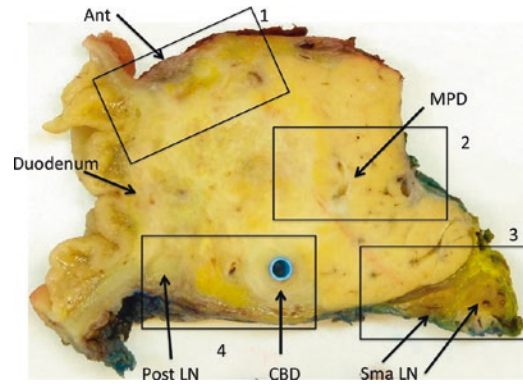

Fig. 5.16 Tissue samples should include at least two "landmarks" to allow unequivocal tissue orientation during microscopic examination. Sample *1*, duodenal wall and anterior surface inked red; sample *2*, main pancreatic duct and surface towards the superior mesenteric vein inked green; sample *3*, posterior surface and surface facing the superior mesenteric artery inked blue and yellow, respectively; sample *4*, duodenal wall, common bile duct and posterior surface inked blue. *Abbreviations*: *Ant* anterior surface, *CBD* common bile duct, *MPD* main pancreatic duct, *Post LN* posterior pancreatoduodenal lymph node, *Sma LN* lymph node in adipose tissue facing the superior mesenteric vein

- Tumour samples should be taken en bloc with adjacent anatomical structures (e.g. common bile duct, duodenal wall, circumferential margins). A tissue sample taken from the centre of a tumour, without inclusion of other anatomical structures, is of very limited informational value.
- Samples should include two "landmarks" to allow precise tissue orientation. Such landmarks can be, for example, the duodenal wall, ampulla, bile duct, main pancreatic duct or inked margins (Fig. 5.16).
- Lymph nodes should be sampled en bloc with the surrounding tissues and the overlying inked specimen surface. Dissection of individual lymph nodes from the peripancreatic adipose tissue, similar to the dissection of lymph nodes from colectomy specimens, is not recommended, as this disrupts the specimen surface and thus precludes accurate margin assessment. Removal of the peripancreatic fat layer accord-

ing to the so-called orange peel method [13] is not recommended either, as it disrupts the relation between the lymph nodes, the specimen surface and the underlying (tumour) tissue and thus precludes, for example, accurate measurement of the distance between the tumour and adjacent circumferential resection margin.
- Lymph nodes should be embedded in their entirety, unless metastasis is visible macroscopically [6, 20].
- Division of an axial specimen slice into four or five tissue samples is an easy way to ensure optimal orientation and reconstruction of findings.
- It is recommended to sample from the axial specimen slices in sequential order rather than to sample first the tumour, followed by, for example, the lymph nodes, ampulla, etc. Sampling in sequential slice order facilitates three-dimensional reconstruction of findings.

5.8.2 Sampling of Transection Margins

The transection margins of pancreatic resection specimens are sampled routinely, and this is best done prior to specimen dissection. For pancreatoduodenectomy specimens, these are the transection margins of the stomach or proximal duodenum, distal duodenum, pancreatic neck and common bile duct. For distal pancreatectomy specimens, this is the transection margin of pancreas. If the transection margin is closed with a staple line (Fig. 5.2), as is, for instance, the case in specimens resulting from a laparoscopic procedure, the staple line is removed, taking care to include as little as possible of tissue. Samples are taken en face. In case of suspicion of tumour involvement of the transection margin of the splenic vessels (Fig. 5.2), this margin can also be sampled for microscopic examination.

5.8.3 Sampling from Specimens with Venous or Arterial Resection

The resected blood vessel is sampled en bloc with the adjacent (often tumour-involved) tissue and margin (Figs. 5.14 and 5.15). This allows accurate microscopic assessment of the depth of tumour invasion into the vascular wall (i.e. invasion of the intima, media or adventitial layer) or, in case the vessel is clear of tumour, the minimum clearance between the invasive tumour front and the vessel wall. Because it is difficult to macroscopically distinguish true tumour infiltration of the vessel wall from fibrous adherence, the entire resected vessel should be embedded [6, 24].

5.8.4 Sampling from Extended Pancreatic Resection Specimens

The same principles for tissue sampling as described in Sect. 5.8.1 apply to extended resection specimens. Because the aim of tissue sampling is the demonstration of the relationship between the tumour and the additionally resected structures, it is important that tissue samples are taken en bloc from the tumour periphery onto the adherent structure, e.g. the bowel, stomach or adrenal gland. Regarding the resection margins, the circumferential surfaces that have been created by the extended resection, i.e. the surfaces of the soft tissue that connects the tumour with the resected structure(s), are usually the most critical. Sampling of the transection margins of the resected structures, i.e. a segment of the bowel, is usually irrelevant unless the resected structure is small and the tumour infiltrates close to the edges of the resected structure. Consequently, because venous or arterial resections are usually relatively small, examination of the resection margins of these structures is important. It is usually best done by complete embedding of the vessel en bloc with the adjacent pancreas and/or peripancreatic tissues, unless the vascular segment is of a considerable length and separate sampling of both transection margins of the vessel may be considered.

5.8.5 Routinely Sampled Tissues

A number of tissues are sampled routinely. The gallbladder and cystic duct should be dissected and sampled as per local standardized protocol. If

the stomach and duodenum appear macroscopically normal, the samples from the respective transection margins will usually suffice to assess both structures microscopically. One sample is usually taken from a macroscopically normal-looking spleen. One or more samples are required from background pancreatic parenchyma, depending on the pathology encountered.

5.8.6 Block Key

Because tissue samples that include anatomical landmarks, as outlined in Sect. 5.8.1, are easy to orientate, a description of the site of sampling other than the number of the axial or sagittal specimen slices from which the sample was taken is not necessary. Regarding other blocks, e.g. from the transection margins, gallbladder or spleen (see Sects. 5.8.2 and 5.8.5), it is recommended to take these in a standardized fashion at the start of the specimen dissection procedure to allow an optimal workflow. A step-by-step summary of specimen handling, dissection and sampling is provided in Sect. 5.12.

5.9 Assessment of the Margin Status

5.9.1 Macroscopic Examination

Over the past decade, assessment of the margin status in surgical resection specimens for pancreatic cancer, in particular in pancreatoduodenectomy specimens, has received increasing attention. While the evaluation of the transection margins is routine in all pancreatic cancer centres, practice varies considerable when it comes to the examination of the so-called circumferential margins. As outlined in Sects. 5.2.1.1 and 5.4, the circumferential margin of the pancreatic head includes four surfaces: the SMV groove, SMA margin, posterior margin and anterior surface. The latter is an anatomical surface rather than a true resection margin; however, as tumour involvement of this surface leads to an increased risk of cancer recurrence [12], the anterior surface needs to be included in the evaluation of microscopic residual disease. A further circumferential margin that needs consideration is the surface of the soft tissue sheath that surrounds the extrapancreatic common bile duct (Fig. 5.3). This surface may be involved by tumours that are either primarily seated in the extrapancreatic common bile duct or infiltrate this part of the bile duct by extension from a tumour mass located in the intrapancreatic common bile duct or cranial part of the pancreatic head. As the tissue sheath surrounding the bile duct is thin, even limited tumour extension outside the bile duct wall may result in tumour cells growing in close proximity of the specimen surface. Consequently, the rate of microscopic margin involvement (R1) of tumours affecting the extrapancreatic bile duct is significantly higher than that of tumours involving the distal end of the intrapancreatic bile duct, which is deeply buried inside the pancreatic head and thus separated from the specimen surfaces by a thicker layer of nonneoplastic tissue [25].

Because of the highly dispersed growth of pancreatic cancer and the resulting poor macroscopic delineation of the invasive tumour front, meticulous inspection and extensive tumour sampling are paramount to accurate reporting of the margin status. In practical terms, this means that axial specimen slices should be as thin as possible to increase the number of slices and thus improve the inspection of the margin. Furthermore, sampling from the tumour onto adjacent margins and surfaces should be extensive and include areas without macroscopically convincing tumour infiltration, because the R1-rate correlates with the number of tissue samples that have been examined [14]. The need for extensive tissue sampling to detect microscopic margin involvement is also supported by molecular studies [26].

The reported R1-rate varies considerably between studies, and this is most likely due to divergence in practice regarding specimen dissection and tissue sampling [3, 4, 11]. Indeed, some (inter-)national guidelines recommend an examination that is limited to systematic sampling of only the SMA margin, irrespective of the localization of the tumour and its possible proximity to other specimen surfaces [27]. Several

studies and a recent meta-analysis have demonstrated that specimen dissection by axial slicing results in a higher detection rate of microscopic margin involvement (as reflected by a higher R1-rate) than when using any other method [4, 14–16].

5.9.2 Margin Status of Extended Resection Specimens

Evaluation of the margin status is particularly challenging in specimens resulting from extended surgical resection, as these include margins in addition to those found in standard pancreatoduodenectomy or distal pancreatectomy specimens. Examination of these specimens requires an approach that is tailored to the individual case. If sampling of the circumferential margins is conducted according to "standard" procedure, possible tumour involvement of surfaces of the additionally resected structures will remain undetected. As outlined in Sect. 5.8.3, evaluation of the margins of resected blood vessels is best achieved by complete (en bloc) embedding of the entire vessel fragment. Particular attention should be paid to the pancreatic surface to which the vessel is adherent, e.g. the SMV groove in case of resection of a piece of SMV, as this surface is commonly found to be involved immediately adjacent to the resected vessel, also in cases in which the vessel wall proper is clear of tumour (Fig. 5.14).

5.9.3 Macroscopic Margin Involvement (R2)

According to the current UICC [18] and AJCC [19] staging systems, a distinction should be made between microscopic and macroscopic residual disease (R1 and R2, respectively). Size-based criteria that allow unequivocal categorization of residual disease as macroscopic or microscopic are currently lacking, and, in practice, this decision is usually left to the discretion of the operating surgeon. However, intraoperatively, it may not be obvious whether abnormal tissue at the specimen surface consists of tumour or fibrosis, and, consequently, the surgeon may not be able to commit to considering the resection as "R2". As a result, resection specimens with tumour involvement of a considerable area of the specimen surface – 10 × 10 mm or more – may nevertheless be reported as "R1", which eventually affects the statistical analysis of the prognostic impact of "microscopic" margin involvement (Fig. 5.17). To avoid a more or less arbitrary classification as R1 or R2, recording of the area of margin involvement is a more objective and accurate way to reflect the extent of residual tumour in the surgical bed. Measurement of the area of margin involvement is straightforward when using the axial slicing technique, as the axial dimension of the involved surface can be measured on the microscopic slides, while the craniocaudal extent can be assessed by multiplying the slice thickness with the number of slices in which the particular surface is involved [9].

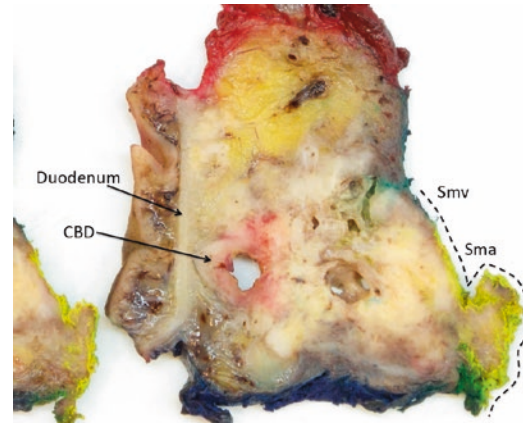

Fig. 5.17 Extensive margin involvement in a pancreatoduodenectomy specimen. A large centrally located tumour shows broad-front infiltration (*dotted line*) of the surfaces facing the superior mesenteric vein and artery, which are inked in green and yellow, respectively. *Abbreviations*: *CBD* common bile duct, *Sma* surface facing the superior mesenteric artery, *Smv* surface facing the superior mesenteric vein

5.9.4 Microscopic Examination

A further factor that contributes to the divergence in reporting of the margin status is the use of a non-uniform definition of microscopic margin involvement (R1). While some pathologists report margin involvement only if tumour cells are present at the margin (0 mm clearance), others will regard tumour growth within 1 mm to the margin as R1. The "1 mm rule" has been adopted from the margin assessment for rectal cancer [28], where through meticulous clinicopathological correlation, it was demonstrated that a clearance of less than 1 mm correlates with an increased risk for local tumour recurrence. Similar studies have not been undertaken for pancreatic cancer. However, in view of the fact that pancreatic cancer – unlike rectal cancer – grows in a highly dispersed fashion, the use of this R1 definition seems not appropriate. Indeed, a recent study has shown that the growth pattern of pancreatic ductal adenocarcinoma is significantly less compact than that of rectal cancer, at least in the periphery of the tumour [21]. In line with this, definitions of microscopic margin involvement based on a larger clearance – 1.5 mm, 2 mm or 3 mm – have been applied, and the results were found to be better predictive of patient outcome [29]. Although these considerations and observations indicate that 1 mm clearance may still lead to underestimation of microscopic margin involvement, an appropriate definition is currently not known. The issue of tumour clearance to the margin becomes even more acute in specimens from patients who underwent neoadjuvant treatment. Indeed, provided that the patient developed a certain response to treatment, the residual tumour cells or cell groups may be separate from each other by even larger distances. Hence, the prediction as to whether tumour cells were likely left behind in the surgical bed becomes even more difficult (Fig. 5.18). Therefore, recording of the exact minimum clearance of a tumour to the margin gives a more objective account than assignment to R0 or R1 based on criteria that seem inappropriate and have not been validated.

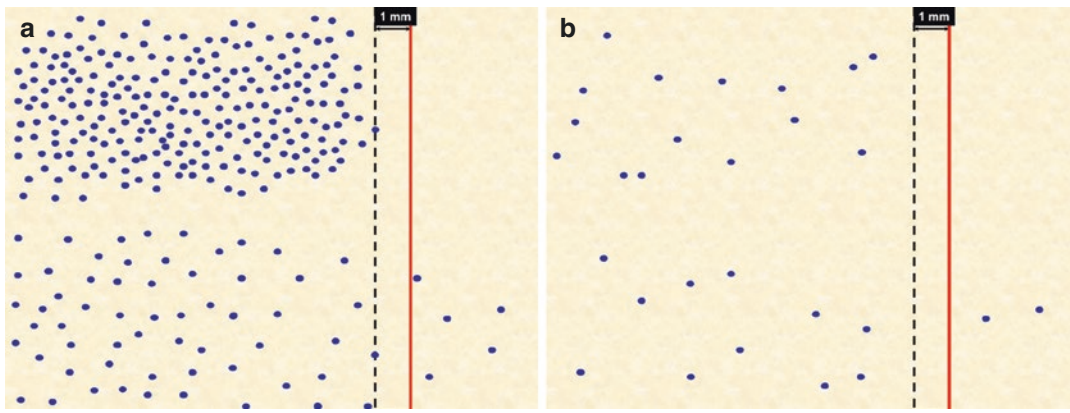

Fig. 5.18 Assessment of the resection margin following neoadjuvant treatment. (**a**) Prediction of the presence or absence of residual tumour at the resection margin is determined by the tumour growth pattern. In the tumour with a less compact growth pattern (*lower half*), a clearance of 1 mm does not guarantee the absence of residual disease. (**b**) As the growth pattern is altered by neoadjuvant treatment and tumour cells lie at greater distances from each other, the usual definition of R1 (<1 mm clearance) leads to underestimation of residual tumour (*blue dots*, tumour cells; *red line*, resection margin; *dotted line*, 1 mm from margin) (With permission of Springer, Pathology of the pancreas – a practical approach, [10], Fig. 9.72, p. 149)

5.10 Biobanking of Fresh Tissue

In most pancreatic centres, biobanking of fresh tumour and normal tissues is part of routine specimen handling. The use of the axial slicing technique for pancreatoduodenectomy specimens is also advantageous with respect to biobanking of fresh tumour tissue, because this method does not require the technically challenging probing or opening of the pancreatic and bile ducts. A smooth-surfaced incision through the (unfixed) pancreatic head in the axial plane will ensure good views on and easy access to the tumour, while ensuring that the standard dissection of the fixed resection specimen is not interfered with. Incision through key anatomical structures, e.g. a resected venous segment, should be avoided, if possible (Fig. 5.14a). For distal pancreatectomy specimens, incision of the fresh pancreas should be in the sagittal plane. The use of tissue corers of different sizes may facilitate tissue sampling, and the resulting punched-out shape may help with the microscopic identification of the site of biobanking and verification that the sample was indeed taken from the tumour.

To increase the yield of tumour tissue in the biobanked samples and at the same time reduce the number of "trial" incisions, it is important to identify the tumour site as accurately as possible. Palpation of the pancreas is important, because pancreatic cancers are usually characterized by a hard, "wooden" consistency. Externally visible indications of tumour infiltration may be bulging or retraction of the pancreatic surface, irregularity and/or narrowing of the SMV groove or irregularity of the duodenum or papillae. Resection of an additional structure, e.g. a piece of SMV, usually indicates nearby tumour infiltration. Dilatation of the common bile duct and/or pancreatic duct implies that the tumour is located in the pancreatic head at, or cranial to, the level of the ampulla of Vater. Information regarding the tumour site gleaned from preoperative imaging reports or discussed at the multidisciplinary team meetings is usually of great help in targeting tumour tissue sampling for biobanking.

5.11 Grossing of Specimens Following Neoadjuvant Treatment

The same procedure as outlined in the previous sections can be used for the grossing of pancreatic resection specimens following neoadjuvant treatment. The challenges with these specimens are multiple [30]. First, the local anatomy may be distorted by treatment-induced tumour regression and ensuing contraction, stricturing or deformation of the pancreas proper and adjacent structures, such as the common bile duct, duodenum or blood vessels. Second, surgery following neoadjuvant treatment often requires an extended resection, resulting in complex specimens that may include segments of, for example, the SMV and SMA, other blood vessels or neighbouring organs. Third, treatment-induced tumour regression is apparently random and results in haphazardly distributed residual tumour cell clusters or single tumour cells. Viable tumour is embedded in a prominent fibrous stroma and often intimately admixed with nonneoplastic tissues. As a result, residual tumour may be impossible to identify by naked-eye inspection, and the distinction between

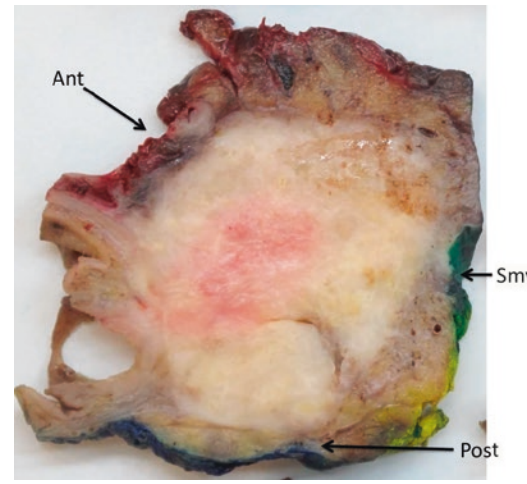

Fig. 5.19 Following neoadjuvant treatment, residual viable tumour and treatment-induced fibrosis may be indistinguishable. Note the extension of abnormal tissue close to the anterior (*Ant*) and posterior surfaces (*Post*) and the surface facing the superior mesenteric vein (*Smv*)

pancreatic cancer and the surrounding nonneoplastic tissues, which is already poorly delineated in primary resected specimens, usually becomes even more blurred following neoadjuvant treatment (Fig. 5.19). Finally, many of the patients who underwent neoadjuvant treatment will have a metal stent in the common bile duct to ensure biliary drainage during the months of preoperative therapy. The presence of a stent, in particular a metal stent, characteristically induces inflammatory changes and fibrosis within and around the bile duct, which may further enhance the difficulties with the macroscopic identification of viable tumour tissue. As a consequence, extensive sampling, often with (sub-)total embedding of the pancreas and additionally resected structures, is necessary to ensure an accurate record of viable tumour and to avoid underestimation of the size and extent of the residual tumour.

5.12 Summary of the Handling of Pancreatoduodenectomy Specimens

A brief step-by-step description of the handling of surgical pancreatoduodenectomy specimens is provided below:

Prior to fixation

- Open the stomach, duodenum and gallbladder longitudinally and rinse.
- For biobanking of fresh tumour tissue, identify the tumour site and incise the pancreatic head in the axial plane.

Fixation (in formalin for ca. *48 h)*
Following fixation

- Orientate the specimen and inspect externally.
- Record the dimensions of the pancreas, stomach, duodenum, gallbladder, extrapancreatic common bile duct and possibly other resected structures (e.g. vein).
- Record externally visible abnormalities.
- Carefully remove surgical sutures, clips or staples.
- Sample the transection margins of the pancreatic neck, extrapancreatic common bile duct and stomach/duodenum.
- Inspect and sample the gallbladder and cystic duct.
- Ink according to an agreed colour code:
  - The pancreatic surfaces: SMV groove, SMA, anterior and posterior
  - Important other structures, e.g. venous resection, if desired
- If a metal stent is present, remove it gently by cutting some of the wires of the metal mesh and extracting individual wires with small pliers.
- Slice in the axial plane (thickness: 3 mm) with violin bow strokes using a long knife.
- Place the slices in sequential order, their caudal surface facing up.
- Take photographs: an overview of the lined-up slices and close-up pictures of individual specimen slices.
- Describe the tumour and any other pathology.
- Take tissue samples following the sequential order of the specimen slices. Ensure to include "landmarks" (i.e. anatomical structures and inked specimen surfaces) to facilitate tissue orientation.
- Record in the block key the specimen slice number from which the samples are taken.
- Use at least one whole-mount block, best where the tumour is at its largest extension.
- For standard tissue cassettes, sample the tumour en bloc with anatomical structures (including a venous resection) and margins.
- Sample lymph nodes en bloc with the specimen surface or anatomical landmarks. Embed lymph nodes in their entirety, unless metastasis is macroscopically visible.

Conclusion

Specimen grossing is the first step in the examination procedure of pancreatic resection specimens and an important determinant of the quality of pathology reporting. Current divergent practice regarding specimen grossing leads to significant differences in the

reporting of key tumour features such as cancer origin, tumour size and extent, T-stage and margin status. Specimen dissection by axial slicing combined with extensive tissue sampling and inking of all circumferential margins ensures accurate reporting of these important data items, also for the often more challenging specimens following extended surgical resection and/or neoadjuvant treatment. Especially for the latter specimens, assessment of the margins requires meticulous specimen grossing. Photodocumentation is an integral part of the grossing procedure, as it is essential for case review, quality assessment and discussion with clinical colleagues.

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Tumor Markers

6

Ji Kon Ryu

6.1 Protein Markers

6.1.1 Carbohydrate Antigen 19-9 (CA 19-9)

The most widely used serum tumor marker is carbohydrate antigen 19-9 (CA 19-9).

The synthesis and expression of CA 19-9 depend on fucosyltransferase-2 and 3 activity. Approximately, 5–7% of general populations are unable to express CA 19-9 because they lack fucosyltransferase-3 activity (Lewis antigen negative). So, it is well reported that up to 15% of patients with an advanced stage have a normal CA 19-9 level. In addition, the levels are usually normal in the early stage and falsely elevated in patients with many kinds of benign conditions such as pancreatitis, cholangitis, and obstructive jaundice. Therefore, CA 19-9 has a roughly 80% sensitivity and 85% specificity for the diagnosis of pancreatic cancer [1]. Another important point is relatively low incidence of pancreatic cancer in general population (~10/100,000). Because the positive predictive value of CA 19-9 is extremely low, the screening is not cost-effective, and CA 19-9 is not recommended as a screening tool. In current practice, the roles of CA 19-9 are only restricted to detection of tumor recurrence after curative surgery [2] and prediction of prognosis after surgical resection or chemotherapy [3].

6.1.2 Carcinoembryonic Antigen (CEA)

Carcinoembryonic antigen (CEA) is another commonly used tumor marker for pancreatic cancer. CEA has a roughly 54% sensitivity and 79% specificity for the diagnosis of pancreatic cancer [4]. Therefore, the diagnostic accuracy of CEA is lower than that of CA 19-9. When CEA is used in conjunction with CA 19-9, the sensitivity and specificity can be changed to 86% and 72%, respectively [4]. So, CEA can be used in pancreatic cancer patients with normal CA 19-9 level as a prognostic marker in patients after surgical resection.

6.1.3 Others

Other reported tumor markers include CA 125 [5], CECAM-1 [6], MUC1 [7], and osteopontin [8], but the clinical utility of theses markers is undetermined and requires further validation studies. Recently, several novel markers are reported as potential candidate diagnostic biomarkers. They include intercellular adhesion molecule-1, macrophage inhibitory cytokine-1, osteoprotegerin, tissue inhibitor of metalloproteinase-1, and S100

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calcium-binding protein P (S100P). A meta-analysis reported that pooled sensitivity and specificity of S100P are 87% and 88%, respectively [9]. Further studies are necessary to define clinical significance of these novel candidate biomarkers.

6.2 DNA

6.2.1 Genetic Alterations

Commonly mutated genes in pancreatic cancers are known to be KRAS, P53, CDKN2, and SMAD4. The recent whole genome sequencing analysis of 100 patients with pancreatic cancer demonstrated that KRAS mutation was detected in almost all patients and the prevalence of other gene mutations was 74% for P53, 35% for CDKN2, and 31% for SMAD4 [10]. Although KRAS mutation seems to be an ideal tumor marker, a plasma assay lacks both sensitivity and specificity because of its insensitivity in the detection of early pancreatic cancer [11] and frequent detection in patients with chronic pancreatitis and smokers. Therefore, none of the DNA markers have demonstrated a promising outcome as a tumor marker in clinical practice. However, KRAS mutation analysis in samples of endoscopic ultrasound (EUS)-guided fine-needle aspirate (FNA) can be used as a good biomarker. A meta-analysis of eight prospective studies reported that sensitivity and specificity of KRAS mutation analysis in conjunction with cytology of EUS-guided FNA were 88.7% and 92% which are better than cytology alone [12]. Some studies investigated the feasibility of detecting DNA markers in stool and reported that KRAS mutation was detected in 67% of in patients with pancreatic cancer [13]. In the future, a very low level of circulating mutated DNA can be detected easily with high sensitivity due to the development of next-generation sequencing and innovative technologies, and a novel DNA marker will be developed.

6.2.2 Epigenetic Alterations

The aberrant methylation-mediated functional loss of tumor suppressor genes has been detected in all kinds of cancers including pancreatic cancer, and these changes are rarely detected in normal tissues. There are many cancer-related genes with aberrant methylation that play roles in pancreatic cancer carcinogenesis which include CDKN2A, MLH1, CDH1, SPARC, DUSP6, RELN, RASSF1A, CCND2, TFPI2, RUNX3, SOCS1, and TSLC1 [14].

Many of these aberrantly methylated genes are present frequently in pancreatic cancers and can be easily detected with methylation-specific PCR analysis which makes them attractive candidates for an early diagnosis of pancreatic cancer. This hypermethylation can be analyzed in pancreatic juice and EUS-FNA samples and be a promising biomarker for the diagnosis of pancreatic cancer [15]. There are several studies of hypermethylation analysis in blood samples [16]. All studies are based on the methylation status of a single or a few gene panels in small number of patients. No single gene has been reported to have good sensitivity and specificity, suggesting that a panel of several genes is necessary as a tumor marker for pancreatic cancer. Further researches are necessary in order to clinically apply these markers based on hypermethylation for pancreatic cancer.

6.3 MicroRNA

MicroRNAs (miRNAs) are small, single-stranded noncoding RNAs consisting of 18–22 nucleotides that control the post-transcriptional expression of many kinds of genes. The miRNAs have an important role in carcinogenesis by targeting the matched mRNA, and a single miRNA can control the expression of many genes. Because miRNA dysregulation is specific not only to tissue but also to cancer, the altered miRNA expression profile can be a good biomarker for cancer and an attractive therapeutic molecular target. Many studies have already demonstrated that miRNAs are highly deregulated in pancreatic cancer tissues. Some miRNAs are upregulated and others are downregulated. They are associated with pancreatic cancer cell proliferation, survival, chemoresistance, and metastasis [17]. Many recent studies focused on their diagnostic and prognostic biomarkers in pancreatic cancer.

Some studies have already demonstrated in 2008 that miRNAs released from cancer tissue were detected in blood even after freezing and suggested circulating miRNAs can be a promising biomarker for cancer detection [18]. In pancreatic cancer, several earlier studies focused on blood miRNA profiles to discriminate between patients with pancreatic cancer and normal controls. miR-21, miR-155, miR-196a, and miR-210 all of which have been known to be upregulated in pancreatic cancer tissue were suggested as a blood candidate biomarker [19]. The recent Danish study investigated miRNA expression profiles in blood of 409 patients with pancreatic cancer. This study identified two miRNA panels consisting of sets of four (miR-145, miR-150, miR-223, miR-636) and ten miRNAs (miR-26b, miR-34a, miR-122, miR-126, miR-145, miR-150, miR-223, miR-505, miR-636, miR-885.5p) that discriminate between patients with pancreatic cancer and normal controls [20].

The recent Japanese study also examined miRNA profiles in 571 blood samples including 100 with pancreatic cancer [21]. Eight miRNAs showed sensitivity for pancreatic cancer of 80.3%, specificity of 97.6%, and accuracy of 91.6% which were significantly better than CA 19-9.

Nowadays, microarray analyses and comprehensive sequencing have been performed to detect other blood-based miRNAs, and these analysis methods of several miRNA expression have achieved high detectability with good sensitivity and specificity. However, it may still take time to demonstrate their clinical role as diagnostic and therapeutic biomarkers and may require further studies for clinical applications.

6.4 Circulating Tumor Cells

Although circulating tumor cells (CTCs) have already been discovered in 1869, the roles of CTC detected in the blood of cancer patients are not yet entirely understood. Many clinical studies suggested that CTC can be applied for diagnostic and prognostic biomarker in cancer patients. CTCs have also been detected in the blood of patients with pancreatic cancer [22], and their presence was associated with poor survival [23]. CTCs can be also applied as a real-time liquid biopsy for new molecular targeted agents, enabling the detection of patients who will have a good response to certain drugs [24]. However, there remains many technical challenges to detect a few CTCs from the background of up to 10^8 normal blood cells. Therefore, extremely sensitive and specific analytical methods should be developed for the detection of a few CTCs, and further studies are warranted for clinical applications.

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Part II

Diagnostic Modalities

Imaging Diagnosis of Pancreatic Cancer: CT and MRI

7

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7.1 Imaging Modalities for Evaluation of Pancreatic Cancer

Pancreatic cancer is the fourth most common cause of cancer-related mortality worldwide and is the second most common gastrointestinal malignancy after colorectal cancer [1–4]. Despite the great advances in the early detection and treatment of other gastrointestinal malignancies, the 5-year survival rate of pancreatic cancer is less than 5% [5, 6]. Currently, only 15–20% of the diagnosed patients have a chance of successful resection at the time of presentation, and even in patients with resectable disease, the survival rate is only 23% [3]. Patients with complete (R0), incomplete (R1, residual microscopic), or margin-positive resection (R2, residual macroscopic) have progressively decreasing survival rates [4, 7, 8]. Therefore, accurate determination of disease extent in patients with pancreatic cancer at the time of presentation is crucial for appropriate selection of the best treatment option which can provide maximum survival benefit [4]. Imaging studies play a pivotal role in this initial decision-making process of patients with pancreatic cancer and, also, in surgical and therapeutic planning and assessment of the treatment response [9]. Until now, various imaging modalities, including ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), and endoscopic ultrasonography (EUS), have been used for evaluation of pancreatic cancer [10–15].

Among the various cross-sectional imaging modalities, US is frequently the first-line diagnostic tool for patients presenting with jaundice or abdominal pain, as it is a noninvasive and cost-effective modality, but, in cases of pancreatic body and tail cancers, tumor detection is quite difficult due to the presence of gas bubbles in the stomach and transverse colon, causing a posterior shadowing [16]. The sensitivity of US for detecting pancreatic cancer has been reported as anywhere between 50% and 90% [13, 17–20], and transabdominal US is not a reliable method for the confident diagnosis or exclusion of small pancreatic tumors [21]. Multidetector-row computed tomography (MDCT) has been widely accepted as the imaging technique of choice for diagnosing and staging pancreatic cancer [22, 23], although ultrasonography, endoscopic US, contrast-enhanced US, and MRI with MRCP provide complementary, sometimes even more detailed, information [24]. In particular, among the cross-sectional imaging modalities, MDCT has shown the best performance for the evaluation of vascular involvement, which is the most important factor for predicting the tumor

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resectability [25–31]. Recent version of National Comprehensive Cancer Network guidelines also recommends preferentially pancreatic protocol CT for evaluation of pancreatic cancer [32]. MRI with magnetic resonance cholangiopancreatography (MRCP) is commonly used as a problem-solving tool, particularly for characterization of CT-indeterminate liver lesions and when suspected pancreatic tumors are not visible on CT or when contrast-enhanced CT cannot be obtained due to several allergies to iodinated contrast material [32]. Given the greater soft tissue contrast of MRI compared with that of CT, there are several specific advantages of and situations in which MRI is superior to CT, i.e., small tumors, hypertrophied pancreatic head, isoattenuating pancreatic cancer, and focal fatty infiltration of the parenchyma [14]. In addition, PET or PET/CT scanning with fluorine-18-fluorodeoxyglucose (FDG) can also have a successful role as a secondary imaging modality under special circumstances when CT is not diagnostic or may be considered after pancreatic CT in high-risk patients such as borderline resectable disease, markedly elevated CA 19-9, large primary tumors, or large regional lymph nodes [11, 15, 32, 33]. Although wide anatomic coverage, which allows the depiction of all possible evidence of metastasis in the entire body, is one of the advantages of PET/CT [15], its inherent low spatial resolution and false-positive results, caused by normal physiologic FDG uptake, are well-known limitations [34, 35]. Although EUS can be favorably used after CT for early detection and staging of pancreatic cancer [36–38], it is not recommended as a routine staging tool [32]. When tissue diagnosis is necessary, EUS-guided fine-needle aspiration (FNA) can provide better diagnostic yield and safety than a CT-guided FNA and also potentially lower risk of peritoneal seeding. According to a recent meta-analysis, the pooled sensitivity and specificity of EUS-FNA were 86.8% and 95.8%, respectively, for diagnosing a solid pancreatic mass, during the time period between 1995 and 2008 [39]. In addition, recent development of contrast-enhanced EUS and EUS elastography are expected to improve diagnostic accuracy of EUS [40–44]. In general, the treatment of pancreatic cancer frequently requires multidisciplinary planning with aforementioned imaging modalities so as to optimize the management of patients, especially in the selection of patients to undergo surgery [45].

7.2 Standard CT and MRI Protocol for Pancreatic Cancer Evaluation

7.2.1 Computed Tomography

During the past few decades, CT scanners have developed tremendously resulting in the improved temporal and spatial resolution and hence their diagnostic capability. Furthermore, MDCT scanners provide ability to image during multiple phases of enhancement and excellent multiplanar imaging reconstructions. Indeed, MDCT allows better visualization of the pancreatic cancer in relation to the SMA, celiac axis, SMV, and portal vein as greater parenchymal, arterial, and portal venous enhancement is achieved with MDCT compared with single-detector CT [46]. Currently, the thin-slice (2–3 mm) intravenous contrast-enhanced CT scan using 64-slice or higher-slice multidetector CT (MDCT) is the radiological investigation of choice [12]. A pancreas-specific protocol for pancreatic cancer typically utilizes a thin-section, multiphase technique, with either two-phase or four-phase scans. Four-phase scans include precontrast images and early arterial phase (CT angiography phase, 17–25 s after the start of contrast injection), pancreatic phase (also known as the late arterial phase, 35–50 s after the start of contrast injection), and portal venous phase images (55–70 s after the start of contrast injection) [12, 16] (Fig. 7.1). Two-phase scans usually include pancreatic phase and portal venous phase images. Noncontrast images can be helpful in identifying pancreatic calcifications, ductoliths, and biliary stones. Early arterial phase is almost a CT angiography phase, with a weak pancreatic enhancement, and allows assessment of the arterial tree in relation to pancreatic cancer and, therefore,

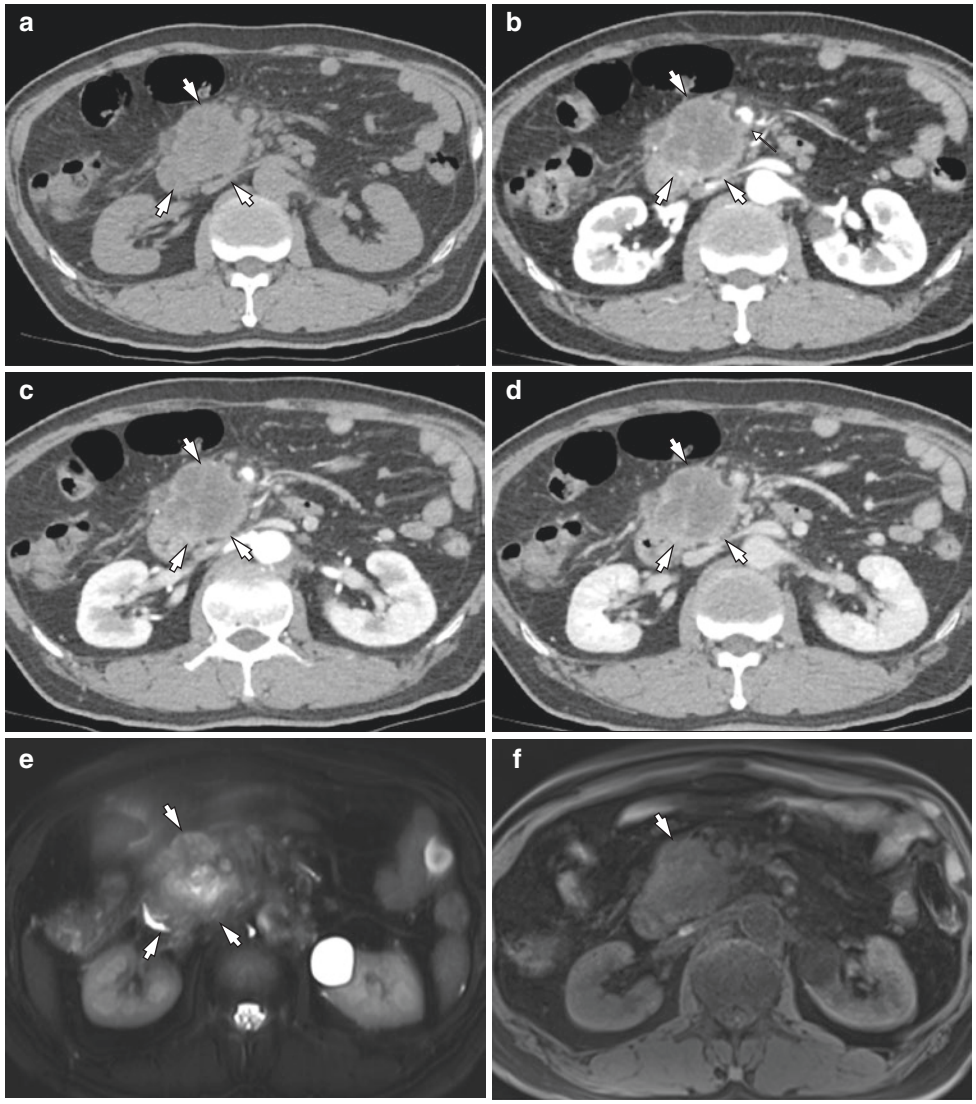

Fig. 7.1 A 69-year-old man with pancreatic head cancer. Pancreatic protocol MDCT and MRI examinations. (**a**–**d**) Pancreatic protocol MDCT examination composed of precontrast (**a**), early arterial (**b**), pancreatic (**c**), and portal venous phase (**d**) images. Note the pancreatic head tumor (*arrows*) shows central hypoenhancement with peripheral enhancement and also encases the superior mesenteric artery more than 180° (*thin arrow*). (**e**–**l**) Pancreatic protocol MRI examination. (**e**) Axial T2-weighted image shows the pancreatic head cancer (*arrows*) with heterogeneous hyperintensity due to central necrosis. (**f**) Axial fat-suppressed T1-weighted image shows a hypointense tumor (*arrow*) in the pancreatic head. (**g**) MR cholangiopancreatography shows strictures (*arrows*) of the main pancreatic duct and the common bile duct (double-duct sign +) with upstream ductal dilation. (**h**) Low b-value ($b = 0$) diffusion-weighted image shows the pancreatic head cancer (*arrows*) with heterogeneous hyperintensity due to central necrosis (*asterisk*) similar to T2-weighted image (**e**). (**i**) High *b*-value ($b = 1{,}000$) diffusion-weighted image demonstrates that the central portion of the pancreatic head cancer with central necrosis (*asterisk*) shows hypointensity, whereas the peripheral portion of the tumor with tumor cell infiltrations (*arrows*) shows hyperintensity due to restricted diffusion. (**j**) ADC map also demonstrates that the central portion of the tumor shows high ADC value which represent free diffusion, while the peripheral portion shows low ADC value representing restricted diffusion. Note a left renal cyst shows hyperintensity on low *b*-value (**h**), hypointensity on high b-value diffusion-weighted images (**i**), and hyperintensity on ADC map, representing free diffusion of the water. (**j**, **k**) Contrast-enhanced T1-weighted image obtained during pancreatic (**j**) and portal venous phases (**k**) shows a hypovascular tumor in the pancreatic head with peripheral enhancement and encasement of the superior mesenteric artery (*thin arrow*)

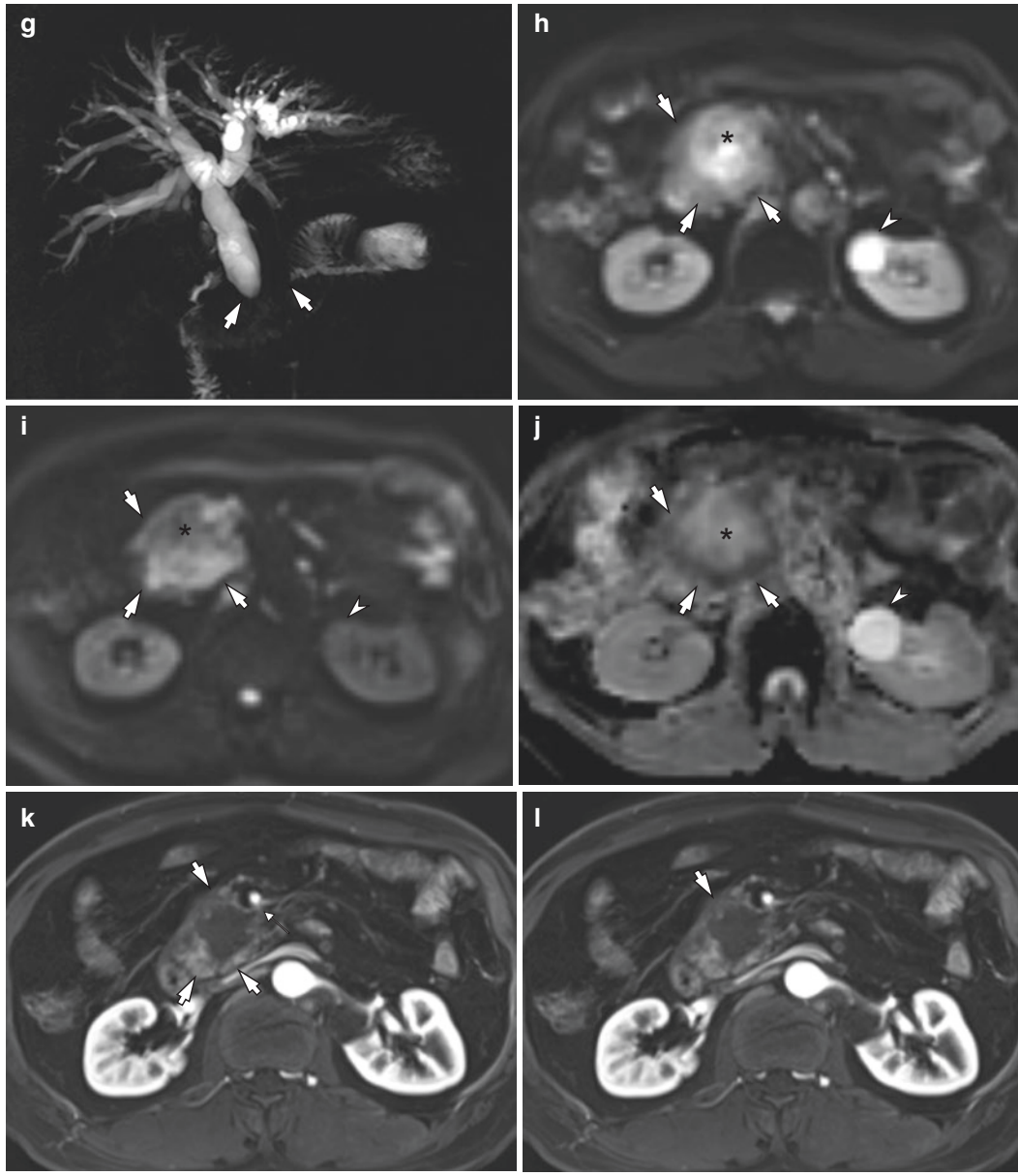

Fig. 7.1 (continued)

is useful in surgical planning [24]. Pancreatic phase images show peak pancreatic parenchymal enhancement and, therefore, provide the best lesion to pancreatic contrast and can be useful in identifying both hypervascular or hypovascular tumors and vascular involvement by pancreatic cancer (Fig. 7.1). The peripancreatic arteries are well opacified during the pancreatic phase, allowing for their concomitant evaluation. Portal phase images are helpful to assess the extent of the venous involvement as the portomesenteric venous system is well opacified and to identify possible liver metastases [23, 47–50]. After unenhanced scanning, patients received standard dose of iodine contrast media intravenously for 30 s using a power injector and at a rate of 3–5 ml/s. The bolus-tracking technique with a threshold of 100 HU is currently routinely used to adjust for variations in the cardiac circulation time [23]. For the clinical interpretation, the CT images were reconstructed with a slice thickness of

Table 7.1 Minimum technical specifications for pancreatic CT

Feature	Specification	Comment
Scanner type	Multidetector-row scanner	
Detector type	Minimum of 16 detector rows	Higher than 64 detector rows is preferable
Detector configuration	Preferably submillimeter (0.5~ <1 mm)	
Section thickness and interval	Minimum of 5 mm ST and RI	A slice thickness of 2.5–3.0 mm and a reconstruction interval of 1.5–2 mm is preferable
Oral contrast agent	Neural or low-Hounsfield unit oral agent	
Injector	Power injector, preferably dual chamber	Bolus tracking desirable
Contrast medium dose and injection rate	No less than 3 mL/s of contrast, 300 mg I/mL or a higher concentration, for an iodine dose of 550 mgI/kg of body weight	A saline flush desirable
Mandatory dynamic phases	1. Early arterial phase[a]	The split-bolus CT protocol can be used to reduced radiation dose[b]
	2. Pancreatic phase	
	3. Portal venous phase	
Reformatted images	Coronal and sagittal MPR	
	Curved MPR along the pancreatic duct	
	Maximum intensity projection for CT angiography	
	Minimum intensity projections are helpful for ductal structures	

ST reconstruction slice thickness, *RI* reconstruction interval, *MPR* multiplanar reformatted images
[a]Early arterial phase imaging can be added when patients with pancreatic cancer will undergo surgical resection
[b]Split-bolus CT protocol [53]

2.5–3.0 mm and a reconstruction interval of 1.5–2 mm for MDCT [51]. The minimum technical specifications for MDCT of the pancreas are summarized in Table 7.1. Nonetheless, multiphase CT exposes patient to a high radiation dose, and recently the split-bolus CT protocol has been proposed for staging of pancreatic cancer and for improving tumor conspicuity [52]. In brevity, split-bolus CT technique combines pancreatic phase and portal venous phase in a single scan: 70 s before CT, 100 mL of contrast material is injected for the portal venous phase followed approximately 35 s later by injection of 40 mL of contrast material to boost the pancreatic phase. It may provide optimal synchronous arterial and mesenteric venous opacification evaluating potential tumor resectability and reduce radiation dose [53].

Another recent development has been the use of a variety of types of reformations to enhance the conspicuity of tumor and its relationship to local structures [54]. For pancreatic cancer staging, the smallest available section thickness or detector configuration should be used to enable the production of high-fidelity reformatted and volumetric images from the nearly isotropic voxel acquisition [4, 49]. The most commonly used techniques are multiplanar reformations (MPR), curved multiplanar reformations (CMPR), and minimum intensity projections (MinIP) [49, 55] (Fig. 7.2). The use of CMPR reconstruction drawn along the common bile duct, pancreatic duct, and/or mesenteric vessels may help improve sensitivity for detection of pancreatic cancer and the speed of interpretation over axial images alone by demonstrating the relationship between tumors and the pancreatic duct or adjacent major structures [56]. MinIP images use the lowest density values along each ray and clearly show low-density structures such as pancreatic and bile ducts. The recommended MinIP slab thickness is 3 mm for the pancreatic duct [49, 50, 57]. Maximum intensity projections (MIP) are also often used to evaluate the relationship between tumors and adjacent, enhanced vessels.

Although MDCT shows excellent performance regarding its diagnosis and staging, the detection of small pancreatic cancers <2 cm in diameter, or of isoattenuating tumors, which account for

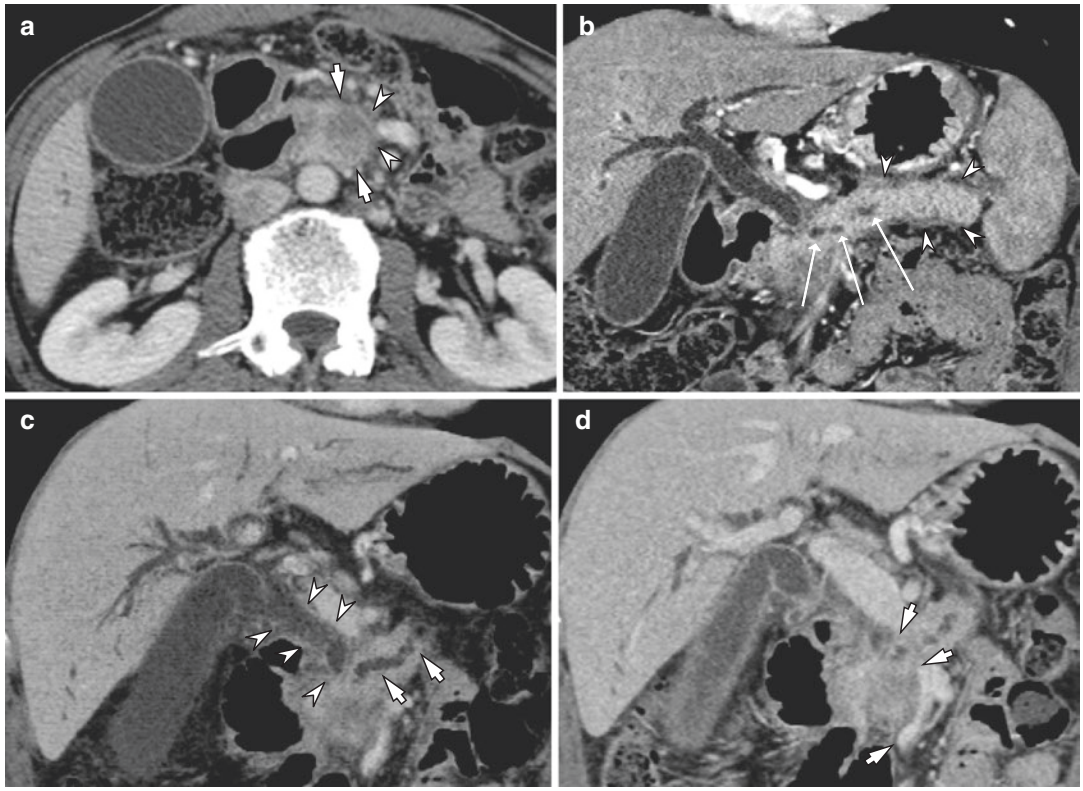

Fig. 7.2 Post-process of MDCT for pancreatic head cancer. (**a**) Approximately 2.5 cm, ill-defined hypovascular mass is seen in the pancreatic head (*arrow*), and the fat plane (*arrowheads*) between the mass and the superior mesenteric vein is not clearly depicted at CT. (**b**) Curved multiplanar reformation image along the pancreatic duct shows and demonstrates dilated upstream pancreatic duct (*open arrows*) and parenchymal swelling with peripancreatic fat infiltration (*arrowheads*) due to combined acute pancreatitis. (**c**) Oblique coronal minimum intensity projection image shows the dilated bile duct (*arrowheads*) and the pancreatic duct (*arrows*), which are suggestive of pancreatic head cancer invading intrapancreatic segment of the common bile duct. (**d**) On oblique coronal multiplanar reformation image, the main portal vein and proximal superior mesenteric vein show luminal narrowing (*arrows*) over 3.5 cm due to tumor involvement, and splenic vein is not opacified (not shown)

approximately 10% of all pancreatic adenocarcinomas, still remains challenging [58, 59]. For those cases, we can improve the contrast-to-noise ratio between pancreatic cancer and normal parenchyma using the dual-energy or low-tube-voltage techniques [60], as the X-ray absorption of iodine can be increased at low tube voltage (80 kVp) compared with a standard tube voltage (120 kVp) [60–64]. The downside of low-tube-voltage technique is increased image noise, but this could be reduced by iterative reconstruction (IR) algorithms [65]. Considering the effects of IR techniques on reducing image noise, these techniques could be used for high spatial resolution, pancreatic CT imaging which may provide high quality, 1–2 mm, thin-slice CT images. Optimizing the IR technique using a study protocol is necessary to balance imaging distortion and radiation reduction and to balance image quality and high spatial resolution along the z-axis.

7.2.2 Magnetic Resonance Imaging

MRI is frequently used as a problem-solving tool for the evaluation of pancreatic diseases, based on CT or sonographic findings. MRI has relatively high spatial and temporal resolution without exposure to ionizing radiation. Of recent advances in MRI including increased magnetic strength, improved coil technology, and advanced imaging sequences, the most significant is the increasing magnetic field strength resulting in increased signal-to-noise ratio, and commonly used scanners in

clinical practice are 1.5 T or 3.0 T [66]. In addition, with development of diffusion-weighted imaging (DWI) and rapid 3D T1-weighted gradient-echo (GRE) sequences, MR is able to offer improved ability to identify and stage pancreatic tumors. In addition, MR cholangiopancreatography (MRCP) can be used to visualize the pancreatic and biliary ductal system. According to a recent study, dynamic MRI with MRCP and a three-dimensional T1-weighted sequence showed superior tumor conspicuity and similar diagnostic performance compared with MDCT in evaluating the resectability of pancreatic cancer [67].

For comprehensive evaluation of the pancreatic parenchyma and the pancreaticobiliary ductal system, obtaining the following MR sequences is recommended [68]: T1-weighted in-phase and opposed-phase GRE; T2-weighted axial and coronal sequences, usually turbo spin echo (TSE) or single-shot fast spin echo (SSFSE); two-dimensional (2D) and three-dimensional (3D) MRCP; and fat-suppressed T1-weighted 3D gradient echo (GRE) before and after intravenous administration of gadolinium (Fig. 7.1). Diffusion-weighted imaging (DWI) is currently becoming an increasingly used, optional sequence for the detection and characterization of pancreatic lesions including cancer and inflammation [69]. T2-weighted images are useful for evaluating the pancreatic duct, fluid collections or necrosis in the pancreas or tumor, or cystic neoplasms such as intraductal papillary mucinous neoplasm (IPMN). T1-weighted dual-echo GRE sequence (3D two-point Dixon techniques) or multi-echo GRE sequence (three-point Dixon techniques) can estimate by assessing the signal loss on opposed-phase images compared with in-phase images, and recent three-point Dixon techniques may provide more precise estimation of pancreatic fat component by correcting for T2* decay by using the data from a third echo. On unenhanced fat-suppressed T1-weighted images, the pancreas is hyperintense relative to other abdominal organs. Focal pancreatic masses are best identified and evaluated using a combination of unenhanced and early gadolinium-enhanced T1-weighted sequences [66]. MRCP uses heavily T2-weighted sequences to evaluate the pancreatic duct and biliary tract and is regarded as being essential in evaluating for the presence of ductal communication with cystic lesions of the pancreas and ductal deformity caused by pancreatic cancer [66, 67, 70]. DWI can detect random water motion within cellular tissues and, therefore, may represent tissue cellularity and produces a representative apparent diffusion coefficient (ADC) value [71] (Fig. 7.1). Therefore, pancreatic cancers show increased signal on both low b-value and high b-value images and low ADC values due to restricted water motion, whereas cystic lesions show high signal intensity on low b-value images, lower signal intensity on high b-value images, and high ADC values because of the increased motion of water [66]. Therefore, DWI may allow better depiction of pancreatic neoplasms as well as detection of liver and lymph node metastases, which are not always apparent on other sequences [66, 72, 73] (Fig. 7.3).

At the author's institute, 2D thick-slab MRCP and 3D multislice MRCP sequences were used to evaluate the biliary and pancreatic ductal anatomy. 2D MRCP images provide a good information of gross anatomy, and 3D MRCP images can offer good demonstration of ductal anatomy as well as intraluminal abnormalities. However, image quality of 3D MRCP in patients with irregular breathing rhythm or in uncooperative patients could be subdiagnostic range [74]. Unenhanced T1-weighted images and dynamic images were obtained using fat-suppressed, 3D GRE sequences, i.e., LAVA [liver acquisition with volume acceleration] (GE Medical Systems) and VIBE [volume interpolation with breath-hold examination] (Siemens Medical Solutions) and mDIXON (Philips Medical Solutions) before and following the administration of gadolinium-based contrast agents at a dose of 0.1 mmol per kilogram of body weight and with an injection rate of 2 mL/s (injection duration approximately 5–8 s). The arterial phase images were obtained 5 s after the gadolinium-containing bolus was detected in the abdominal aorta. Acquisition of 3D GRE data for each phase was completed during a single breath hold at the end of expiration (mean time, 20 s; range, 18–21 s). Arterial, portal venous, and equilibrium phase images were obtained approximately 20–40 s, 45–65 s, and 3–5 min, respectively, after injection of the contrast agent. An additional, fat-suppressed 3D GRE sequence was performed 2 min after the contrast-agent injection (between the portal

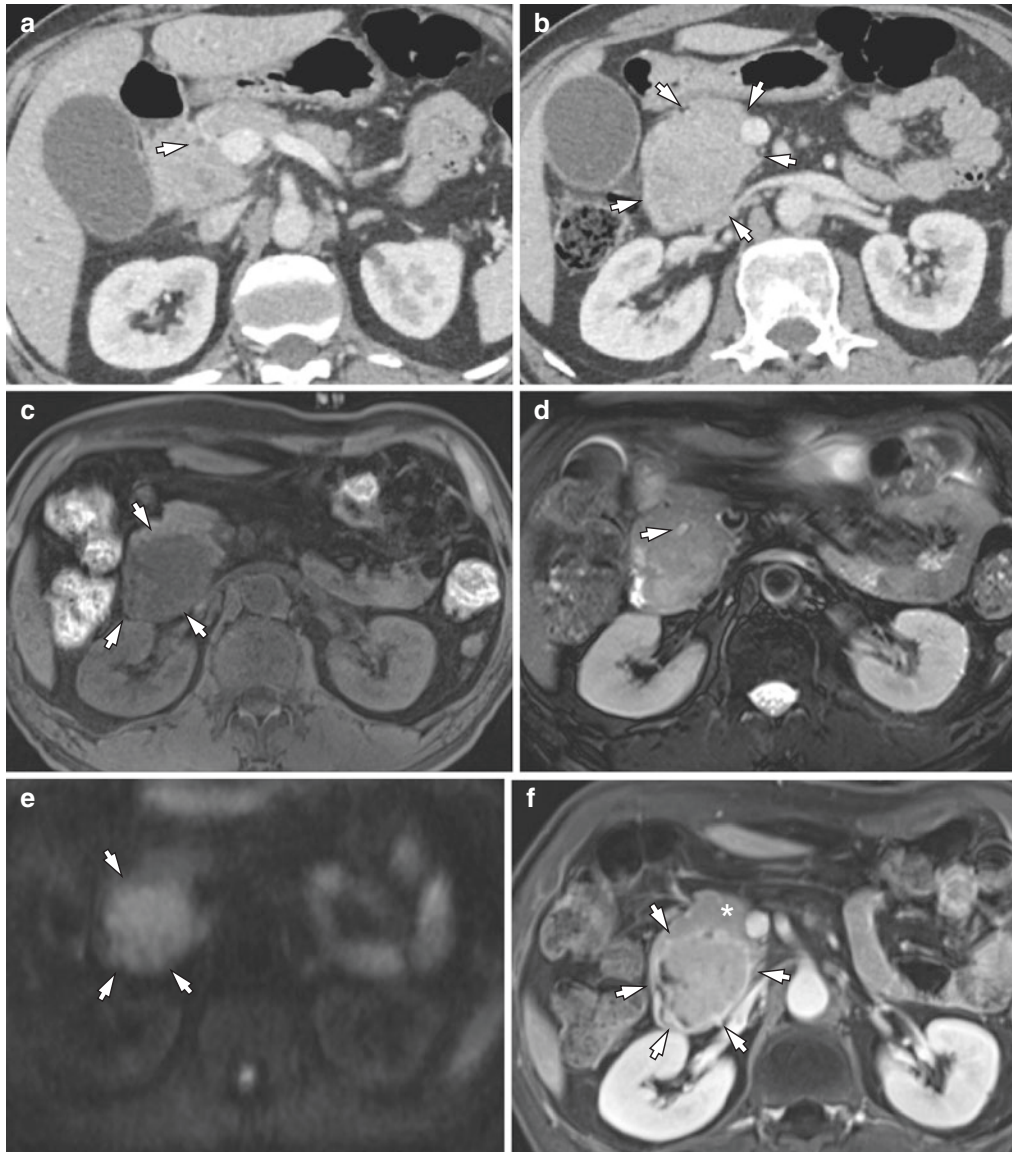

Fig. 7.3 CT and MRI of a 61-year-old man who presented with jaundice and weight loss. (**a**) Abrupt narrowing of intrapancreatic common bile duct (*arrow*) is shown, whereas pancreatic ductal dilatation is not seen on late arterial phase at MDCT. (**b**) Diffuse pancreatic head swelling is observed on portal venous phase (*arrows*) which may be a pancreatic cancer, but tumor contour is not clearly differentiated from the background parenchyma at CT. (**c**) Unenhanced T1-weighted image using a fat-suppressed 3D gradient-echo sequence shows a hypointense tumor (*arrows*) in the pancreatic head. Note the pancreatic parenchyma shows hypointensity on fat-suppressed T1-weighted image. (**d**) Axial T2-weighted image shows the distal common bile duct (*arrow*) which is displaced by a vaguely defined, slightly hyperintense solid tumor. (**e**) Diffusion-weighted image (b = 800) shows a hyperintense solid tumor (*arrows*) in the head of the pancreas which is more clearly distinguished from the background parenchyma than T2-weighted image. (**f**) Contrast-enhanced T1-weighted image during portal phase shows approximately 4.8 cm tumor (*white asterisk*) in the pancreatic head which is clearly distinguished from the background parenchyma by a peripheral enhancing rim. (**g**) MR image at a lower level shows that the tumor (*arrows*) abuts the main portal vein (*asterisk*)

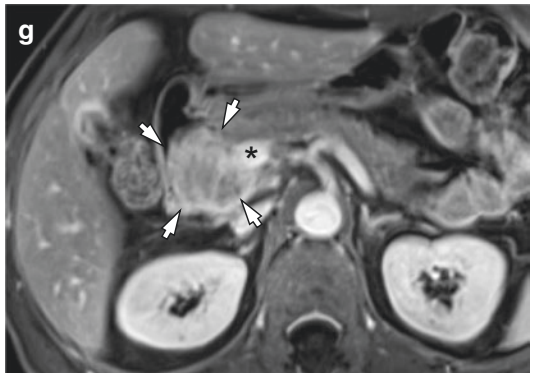

Fig. 7.3 (continued)

venous phase and the equilibrium phase) on the coronal plane and parallel to the portal vein bifurcation [75, 76]. Recently, gadoxetic acid-enhanced liver MR imaging and DWI are more widely accepted as one of the best imaging tools for detecting liver metastasis in patients with pancreatic cancer. The reported sensitivity of gadoxetic acid-enhanced liver MR is 85% for detecting liver metastasis in pancreatic cancer, which is significantly higher compared with that of CT which is 69% [77]. The minimum technical specifications for MRI of the pancreas are summarized in Table 7.2.

Table 7.2 Minimum technical specifications for pancreatic protocol MRI

Feature	Specification	Comment
Scanner type	1.5 T or 3.0 T main magnetic field	Low-field magnets not suitable
Coil type	Phased-array, multichannel torso coil	Unless patient-related factors preclude the use
Gradient type	Current-generation, high-speed gradients (providing sufficient coverage of upper abdomen)	
Slice thickness	5 mm or less for dynamic series	2–3 mm ST is preferable with 3D T1w-GRE sequence
	8 mm or less for other imaging	
Breath holding and matrix	Approximately 20 s of breath hold with a minimum matrix of 128–160×256	Breath-hold instructions are very important
Injector	Power injector, preferably dual chamber	Bolus tracking/MR fluoroscopy desirable
Contrast injection rate	1.5–2 mL/s of gadolinium chelate	Preferably resulting in the vendor-recommended total dose
Minimum sequences	T1-weighted, gradient echo (3D preferable)	DWI can provide high contrast of pancreatic tumors and is also valuable for detection of liver metastases
	T2-weighted, turbo spin echo (axial, coronal)	
	MRCP (both 2D and 3D preferable), DWI	
	Post-Gd, T1-weighted gradient echo	
Mandatory dynamic phases	1. Arterial	3D fat-suppressed GRE sequence
	2. Portal venous phase	
	3. Equilibrium phase	
Dynamic timing	Arterial: 20–40 s	
	Portal venous: 45–65 s	
	Equilibrium: 3–5 min after contrast injection	

ST slice thickness, *GRE* gradient echo, *MRCP* MR cholangiopancreatography, *DWI* diffusion-weighted imaging

7.3 Typical Imaging Features of Pancreatic Cancer

7.3.1 Morphologic Evaluation

On CT, pancreatic adenocarcinomas most often present as ill-defined, solid hypoattenuating masses compared to normal pancreatic parenchyma [78] (Figs. 7.1 and 7.4). However, approximately 5.4–10% of pancreatic adenocarcinomas are isoattenuating relative to the background pancreatic parenchyma [58, 79], especially in small tumors 2 cm or less [59], thus making diagnosis more difficult. In these situations, indirect (secondary) signs such as upstream pancreatic duct dilation or the double-duct sign caused by pancreatic and common bile duct obstruction are helpful for the diagnosis [59, 78]. In addition, other secondary signs of pancreatic cancer include focal pancreatic enlargement, extension of tumor beyond pancreas, and upstream pancreatic atrophy secondary to ductal obstruction [54]. As the tumor reaches into its advanced stage, it typically infiltrates the peripancreatic structures and involves adjacent vasculature such as celiac artery, superior mesenteric artery, portal vein or superior mesenteric vein, and in some cases adjacent organs. Approximately 88% and 100% of the isoattenuating adenocarcinomas <20 mm and >20 mm, respectively, are recognized only by the presence of secondary imaging findings highly suggestive of malignancy [80]. Pancreatic cancers can occasionally appear to be cystic or necrotic, and in rare cases they can contain calcium [81].

On MRI, pancreatic cancer typically shows the appearance of an ill-defined solid hypointense mass on fat-suppressed, T1-weighted imaging and on pancreatic parenchymal phase, dynamically enhanced, fat-suppressed, T1-weighted sequences and shows progressive delayed enhancement [54] (Figs. 7.1 and 7.3). Pancreatic cancers are best detected using unenhanced and early gadolinium-enhanced fat-suppressed T1-weighted images [66]. However, the relative signal intensity of the pancreatic cancer in comparison with pancreatic parenchyma on unenhanced fat-suppressed T1-weighted images can differ depending on the location of pancreatic tumor. If the mass is located within the pancreatic head, there can sometimes be loss of the normal high T1 signal of the pancreatic body and tail secondary to obstruction of the main pancreatic duct, leading to inflammation, fibrosis, and atrophy. In this situation, the early contrast-enhanced images may show a hypoenhancing mass with peripheral rim enhancement superimposed on a background of slightly greater enhancing pancreatic parenchyma [66]. If the pancreatic cancer is located within the pancreatic tail, it is usually well shown on the unenhanced fat-suppressed T1-weighted images. In addition, pancreatic cancers have a variable appearance on T2-weighted images. Pancreatic cancers frequently show increased signal on high b-value DWI and relatively low ADC values, because of fibrosis associated with the tumor [69, 73, 82] (Fig. 7.1). In addition, DWI is also valuable for detecting liver and lymph node metastases, as DWI can provide higher contrast than other imaging sequences. However, both benign and malignant lymph nodes can show restricted diffusion; overstaging for lymph node metastases should be avoided by knowing that not every lymph node seen on DWI is malignant [69]. Peritoneal metastases are usually best shown on the delayed postgadolinium images but can also be detected on DWI [83, 84].

7.3.2 Vascular Evaluation

Pancreatic cancer is a very aggressive malignant neoplasm with a high mortality rate, and adequate determination of the extent of the tumor on cross-sectional imaging studies at the time of staging is one of the most important steps in optimal patient management [4]. Pancreatic cancer staging is based on the determination of tumor size, location within the pancreas, local extent which may involve surrounding vessels, and the presence of metastatic disease. In the absence of distant metastasis, the presence of degree of contact between the tumor and the peripancreatic vessels is of paramount importance in determining surgical resectability. In addition, it is important to recognize variants of vascular anatomy

Table 7.3 Essential imaging features for evaluation of pancreatic cancer

Parameter	Findings	Comment
Morphologic features		
1. Main tumor		
Relative enhancement of tumor	Hypo-, iso-, or hyperenhancing	Preferably determine in pancreatic phase
Size of tumor	Measurable or nonmeasurable	Maximum axial dimension in centimeter
Location of tumor	Head/uncinate process or body/tail	SMV is a landmark to divide tumor location
2. Secondary findings		
Pancreatic duct	Narrowing or abrupt cutoff (±)	Measuring MPD diameter (> 2 mm)
	Upstream dilation (±)	
Bile duct	Narrowing or abrupt cutoff (±)	
	Upstream dilation (±)	
Proximal parenchymal atrophy	Present or absent	
Peripancreatic stranding	Present or absent	
Vascular evaluation		
1. Arterial evaluation		
Mandatory vessels to evaluate	SMA, celiac axis, CHA	Accessory RHA, replaced RHA, replaced CHA, others
	Arterial variant	
Degree of solid soft tissue contact	Present or absent or occlusion	Abutment: ≤ 180°
	If present, ≤ 180° or > 180°	Encasement: > 180°
Degree of increased hazy attenuation or stranding contact	Present or absent	
	If present, ≤ 180° or > 180°	
Focal vessel narrowing or contour irregularity	Present or absent	
2. Venous evaluation		
Mandatory vessels to evaluate	MPV, SMV	
Degree of solid soft tissue contact	Present or absent or occlusion	Abutment: ≤ 180° Encasement: > 180°
	If present, ≤ 180° or > 180°	
Degree of increased hazy attenuation or stranding contact	Present or absent	
	If present, ≤ 180° or > 180°	
Focal vessel narrowing or contour irregularity	Present or absent	Tethering or teardrop
Thrombus within vein	Present or absent	

MPD main pancreatic duct, *SMV* superior mesenteric vein, *SMA* superior mesenteric artery, *RHA* right hepatic artery, *CHA* common hepatic artery, *MPV* main portal vein

such as celiac and mesenteric arterial variants and variants of SMV-PV in the preoperative planning of extended pancreatic resection [22] (Table 7.3).

According to the National Comprehensive Cancer Network (NCCN) guideline, less than or equal to 180° tumor contact of the vessel circumferential is described as "abutment" (Fig. 7.4) and more than 180° tumor contact of the vessel circumference is referred to as "encasement" (Fig. 7.4). The utility of these terms includes the ability to differentiate clearly resectable tumor from "borderline resectable tumor," from clearly unresectable tumor [9, 85]. According to the previous study by Lu et al. [29], more than 180° of tumor-vessel contact is highly specific (a sensitivity of 84% and specificity of 98%) for vascular invasion by the tumor and for tumor unresectability if the involved vessels are either celiac artery or superior mesenteric artery. In addition, another

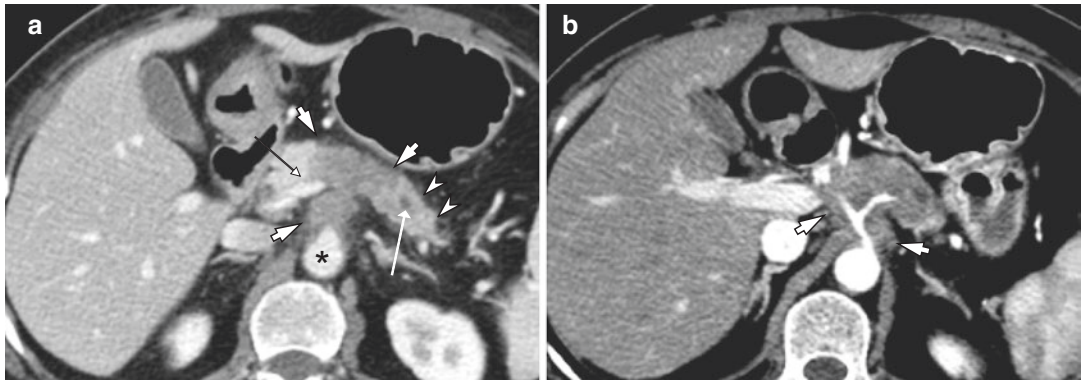

Fig. 7.4 A 58-year-old woman with cancer of the pancreatic body. (**a**) At MDCT, Approximately 4.1 cm hypovascular soft tissue mass is seen in the pancreatic body and tail (*arrows*) which extends to the aorta (*asterisk*) and main portal vein (*small arrow*). Upstream pancreatic duct is dilated (*open arrow*) and the parenchyma is atrophied (*arrowheads*). (**b**) Soft tissue density tumor encases the celiac trunk and the proximal common hepatic artery (*arrows*) on arterial phase, which often hampers curative resection of the pancreatic body cancer

sign of vascular invasion by pancreatic cancers is irregularity of the vessel contour (including "teardrop" deformity) or changes in caliber, and when irregularity of the vessel contour is seen, regardless of the degree of contact between tumor and vessel, vascular invasion should be considered [86, 87]. The irregularity of vessel contour by vascular invasion occurred more often than that of the artery, because the wall of the vein is much thinner and weaker than the wall of the artery [88]. On the contrary, as all of the artery is thicker and more flexible than the vein wall, invaded arteries may show regular wall and may appear stretched on MDCT or MR images because of the presence of focal tissue fibrosis [22]. It is of important note that the positive predictive value of CT for determining nonresectability based on vascular involvement is very high (89–100%), but it is lower for predicting resectability (45–79%) [4, 9, 29, 67, 86, 87, 89]. This is because the diagnostic criteria for vascular invasion have been developed for being more specific than sensitive to minimize the number of patients inappropriately denied surgery and potential cure [27]. Occasionally, perivascular haziness can be caused by pancreatitis secondary to ductal obstruction by the tumor or recent procedures such as endoscopic retrograde cholangiopancreatography or biliary drainage for biliary decompression or biopsy; it should be taken into account to differentiate it from perivascular tumoral invasion.

7.3.3 Extrapancreatic Evaluation

The presence of extrapancreatic tumor extension, either local or distant, needs to be cautiously evaluated as it can affect the surgical decision-making. If focal hepatic lesions are present that demonstrate suspicious features concerning for metastasis (poorly defined margins, rim enhancement) or are indeterminate if the lesion is too small to characterize by means of CT, then further imaging such as MRI or tissue sampling to arrive at a final diagnosis may be warranted [4]. With development of DWI and hepatobiliary contrast agent, several studies demonstrated that MRI performed significantly better than MDCT in the detection of liver metastases in patients with pancreatic tumors [77, 90].

With regard to lymph node staging, the presence and location of suspicious lymph nodes (defined as short axis > 1 cm, abnormal round morphology, heterogeneity, or central necrosis) should be noted [4]. This is especially true for enlarged lymph nodes which are outside the immediate local drainage pathways based on tumor location (i.e., aortocaval or paraaortic lymph nodes), as these can alter staging from local node involvement to metastatic disease. However, unfortunately, both CT and MRI are not accurate at lymph node staging in patients with pancreatic cancer [91].

7.4 Performance of CT and MR for Diagnosis, Staging, and Resectability of Pancreatic Cancer

The most commonly used staging system is that from the American Joint Committee on Cancer (AJCC) [92]. This system assesses the status of the primary tumor (T), lymph nodes (N), and metastases (M). In clinical practice, as pancreatic cancers are advanced at a time of initial detection, only 4–8% of pancreatic cancers are T1 or T2 [79, 93, 94]; the real question at T staging in clinical practice would be differentiation of T4 from T3, which is a matter of tumor involvement of the celiac axis or superior mesenteric artery. With the advent of vascular resection and reconstructions, there has been a shift in staging to emphasize arterial involvement [9, 95]. Recently published pancreatic adenocarcinoma oncology guidelines by the NCCN describe grouping patients based on radiographic criteria into those with clearly resectable disease, borderline resectable disease, or clearly unresectable disease [32] (Figs. 7.5, 7.6, and 7.7). Clearly resectable disease corresponds to AJCC stages I and II (Fig. 7.5), while clearly unresectable disease represents AJCC stages III and IV (Fig. 7.7). According to the NCCN guideline, borderline resectable patients have no distant metastases, short segmental venous involvement with suitable vessel above and below the point of involvement allowing for safe and complete resection and vein reconstruction, SMA and CA abutment (≤180° of the circumference of involvement), and CHA involvement without extension to CA or HA bifurcation [32] (Fig. 7.6). As of now, there are various definitions of "borderline resectable" pancreatic cancers which have been proposed by different organizations, and consensus is not yet reached. Furthermore, although imaging evaluation plays a central and primary role in staging of

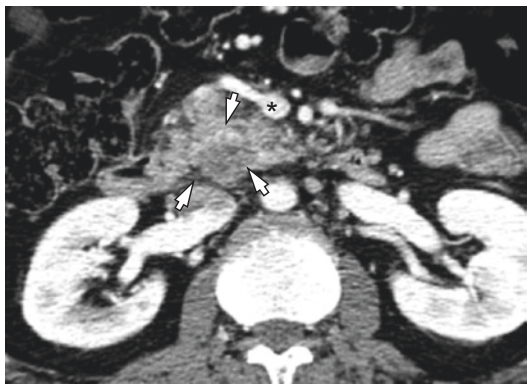

Fig. 7.5 MDCT of a 55-year-old man with clearly resectable pancreatic cancer. Approximately 3 cm hypovascular mass is in the pancreatic head, which is confined to pancreatic parenchyma (*arrows*). Major vessels including the superior mesenteric artery and superior mesenteric vein show clear fat plane with the mass

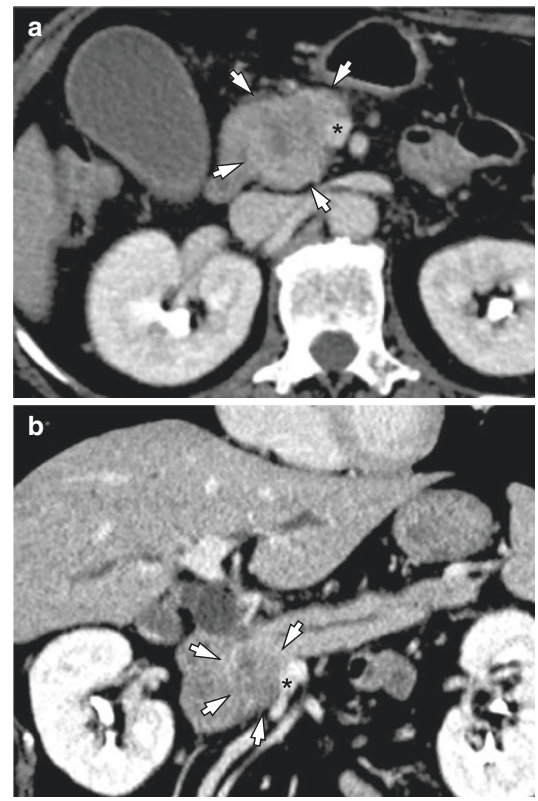

Fig. 7.6 A 65-year-old woman with borderline resectable pancreatic cancer. (**a**) Approximately 3 cm hypovascular mass (*arrows*) is seen in the pancreatic head, and it abuts SMV (*asterisk*) in 150° in axial plane. (**b**) On MPR image, the mass attaches to the proximal SMV (*arrows*) over 2 cm, but there was no gross tumor thrombus in SMV lumen

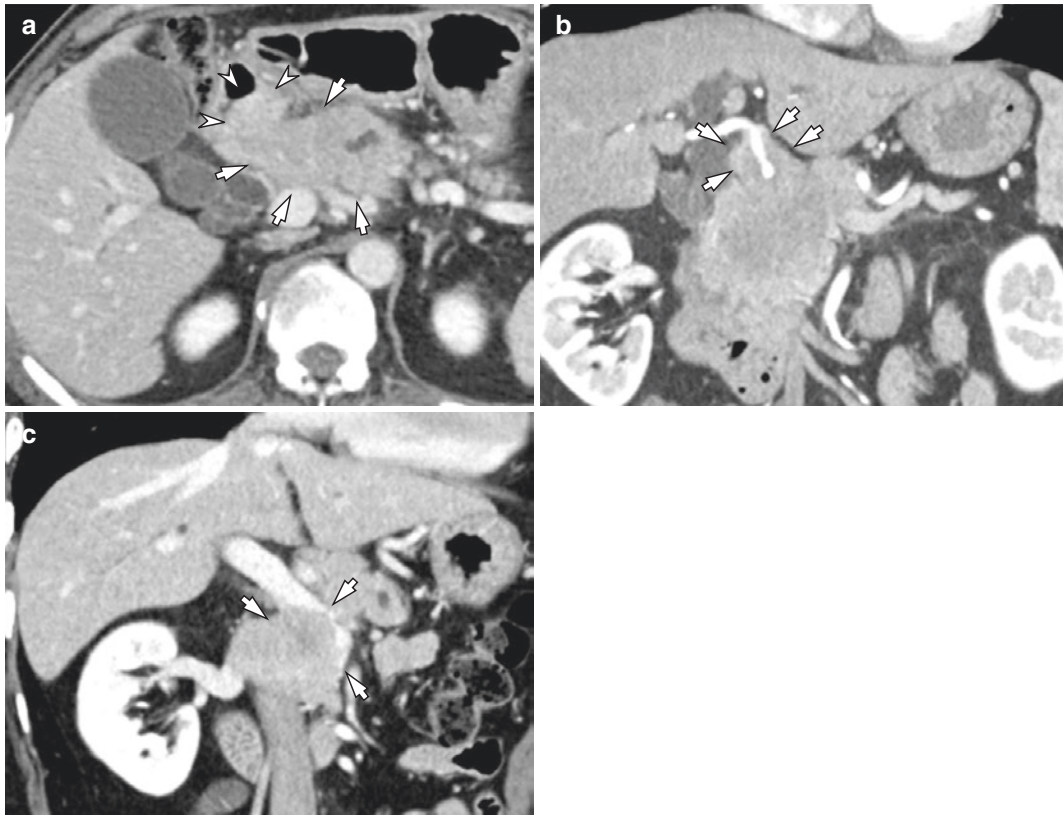

Fig. 7.7 A 60-year-old man with unresectable pancreatic cancer. (**a**) Approximately 7 cm enhancing soft tissue mass (*arrows*) is in the pancreatic head, and it invades the gastric antrum (*arrowheads*). Coronal reformatted CT images (**b**, **c**) display diffuse soft tissue infiltration along the proper hepatic artery (**b**, *arrows*) and also segmental gross invasion of the main portal vein and superior mesenteric vein (**c**, *arrows*)

pancreatic cancer and, therefore, in initial therapeutic decision-making process, in clinical practice, there are limitations in the current freestyle reporting of these imaging studies including variability of descriptive terminology [4].

Therefore, previous studies including clinical trials on borderline resectable pancreatic cancers were heterogeneous in terms of the populations studied, the metrics used to characterize therapeutic response, and the indications used to select patients for surgery [96]. A generally accepted definition of borderline resectable pancreatic cancer is needed, and standardized imaging reporting template must be adopted in all future studies of borderline resectable pancreatic cancer. A recent consensus statement of the Society of Abdominal Radiology and the American Pancreatic Association proposed adoption of the standardized imaging reporting template in order to improve the decision-making process for the management of patients with pancreatic cancer by providing a complete, pertinent, and accurate reporting of disease staging [4]. According to a recent study [97], structured reporting of pancreatic multiphasic CT provided superior evaluation of pancreatic cancer and facilitated surgical planning. Surgeons were more confident regarding decisions about tumor resectability when they reviewed structured reports before review of multiphasic CT images.

With the continuing, substantial improvements in CT technology, the capacity of MDCT for the detection, diagnosis, and local staging of pancre-

atic cancer has increased. MDCT is very effective for detecting and staging adenocarcinoma, with a sensitivity of up to 90% for the detection and an accuracy of 80–90% for the staging [21]. In addition, MDCT has shown excellent performance for evaluating vascular involvement thanks to its high spatial resolution and good delineation of perivascular fat plane in many studies [25–31, 98]. Determination of the extent of vascular involvement is usually made by identifying the extent to which the tumor involves the cross-sectional circumference of a vessel, as described above [29]. Recently, distinct advances in MR technology have caused great improvement in pancreatic cancer imaging. Several recent reports have been published describing the comparable diagnostic performance of MDCT and MR in diagnosis and local staging of pancreatic cancer [67, 89, 99–102]. According to a recent study by Park et al., dynamic 3D GRE MRI with MRCP shows superior tumor conspicuity and similar diagnostic performance compared with MDCT in evaluating the resectability of pancreatic cancer [67]. However, as MDCT is less expensive and is also more widely available than MRI, MDCT is still the modality of choice for the diagnosis as well as the local staging of patients with pancreatic cancer [32].

Concerning determination of vascular invasion by pancreatic cancer, a serious diagnostic dilemma occurs following neoadjuvant chemotherapy and radiation therapy, as the vascular contact by the pancreatic cancer may be replaced by perivascular haziness or fat stranding (Fig. 7.8). In fact, as those perivascular haziness developed after neoadjuvant treatments can be caused by either posttreatment fibrosis or viable tumor, neoadjuvant therapy significantly decreases the accuracy of CT scan in determining resectability R0 of pancreatic carcinoma and results in overestimation of vascular invasion [83, 103]. Therefore, given that overestimation of vascular invasion may significantly reduce CT scan specificity for resectability after preoperative treatment [103–105], increased hazy attenuation or stranding contact with the major peripancreatic vessels in patients with prior radiation therapy or combined chemoradiation therapy needs to be considered in conjunction with the treatment response of the main tumor and changes of tumor markers such as CA 19-9. In addition, baseline studies are useful for identifying the extent of the tumor before radiation therapy, and if patients show stable, minimal stranding without significant soft tissue thickening adjacent to vessels, they should not be prevented from undergoing surgery [106]. In addition, a recent study demonstrated that partial regression of tumor-vessel contact indicates suitability for surgical exploration, irrespective of the degree of decrease in tumor size or the degree of residual vascular involvement [107]. As of now, however, there are no clear diagnostic criteria to differentiate perivascular invasion from tumor progression from posttreatment fibrosis after neoadjuvant treatments. Further study is necessary to find optimal diagnostic criteria for determining vascular invasion in patients with received preoperative neoadjuvant treatments for pancreatic cancer.

7.5 New Imaging Technique for Evaluation of Pancreatic Cancer: Hybrid PET/MR

Integrated PET and MR (PET/MR) scanners have recently been available for use in humans. As MR has the inherent strength of superior soft tissue contrast resolution, multiplanar imaging acquisition, and functional imaging capability such as that seen in DCE-MR, DWI, MR spectroscopy, or elastography, PET/MR may exhibit superior diagnostic performance compared with that of PET/CT [108, 109]. In our medical institution, PET/MR imaging is now being used for evaluation of staging in patients with locally advanced pancreatic cancers and also for evaluation of tumor response in patients with pancreatic cancer undergoing neoadjuvant chemoradiotherapy before and after treatment (Fig. 7.8). It is expected that various imaging biomarkers from integrated PET-MRI may help predict clinical stage and PFS in patients with pancreatic or periampullary cancer [110].

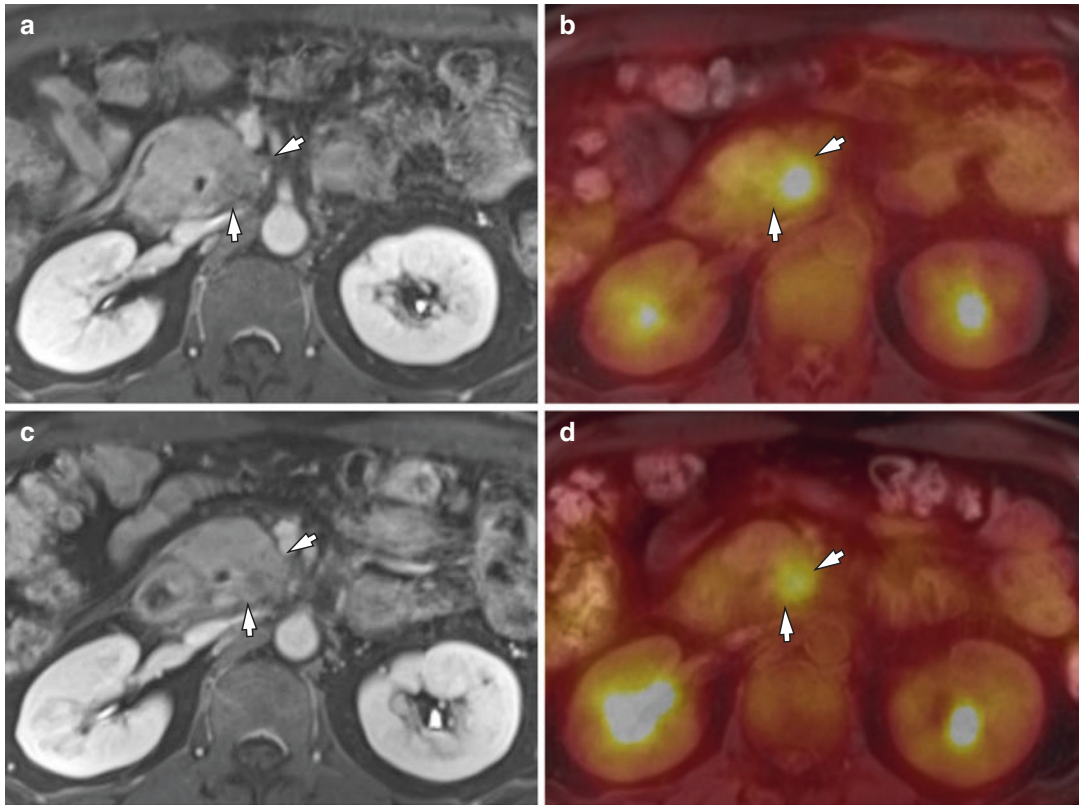

Fig. 7.8 A 55-year-old man who underwent concurrent chemoradiation therapy (CCRTx) for histologically confirmed pancreatic adenocarcinoma. At pre-CCRTx PET-MRI, approximately 3.2 cm hypovascular mass (*arrows*) is seen in the pancreatic head which encases the first jejunal branch of the superior mesenteric vein (**a**), and the mass shows increased maximum standardized uptake value (5.6) on fusion image (**b**). After CCRTx, PET-MRI showed equivocal change of tumor size from 3.2 to 2.6 cm (**c**, *arrows*) and slightly decreased maximum standardized uptake value of 3.2 (**d**, *arrows*)

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Endoscopic Diagnosis

8

Takao Itoi and Atsushi Sofuni

8.1 Introduction

Pancreatic cancer is thought to be one of poor prognostic diseases in the world. Recent progress of computed tomography (CT) and magnetic resonance imaging (MRI) has been marked and popular all over the world. However, most of pancreatic cancers show advanced stage when they are detected by CT/MRI. Thus, early detection and accurate staging of pancreatic cancer are crucial for optimal therapy.

Endoscopic diagnoses using an endoscopic ultrasonography (EUS) and endoscopic retrograde cholangiopancreatography (ERCP) have been conducted for the diagnosis of pancreatic cancers although it is more invasive modalities compared with CT/MRI. The most valuable advantage as a diagnostic modality is to not only observe the primary lesion but also obtain the pathological sampling at the close position through the gastrointestinal tract and pancreatic or bile duct [1]. Nowadays, pretreatment evidence by cytology or histology is mandatory to determine the therapeutic strategy, namely, malignant or nonmalignant masses and adenocarcinoma or other histology like neuroendocrine tumors before administration of anticancer drugs. Herein, we describe the current status of endoscopic diagnosis of the pancreatic cancer.

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8.1.1 EUS

8.1.1.1 EUS Imaging

Fundamental Image (B-Mode Image)

EUS was introduced to clinical practice more than 30 years ago [2]. Nowadays, EUS has become popular for the diagnosis of pancreatic cancer because it provides high-resolution imaging and allows the precise delineation of the entire pancreas through the gastrointestinal tract without intervening bowel gas. EUS appears more useful to detect small pancreatic cancer because of its high-resolution ability at the close position to the pancreas. It has a higher sensitivity in detecting small pancreatic cancers compared with CT (98% vs 86%, respectively, $p = 0.012$) [3]. In particular, for tumors less than 30 mm in diameter, EUS has a 93% sensitivity compared with the 53% sensitivity of CT and the 67% sensitivity of MRI [4] (Fig. 8.1). EUS has higher sensitivity compared with CT for local tumor staging (67% vs 41%, $p < 0.001$) although there is no difference in terms of node staging and potential tumor resectability [3]. Large vessel invasions like celiac artery, portal vein, splenic artery/vein, and superior mesenteric artery/vein are the most important factor to evaluate the resectability and strategy of operation. EUS has an accuracy of 90% for evaluation of portal and splenic vein invasion [5, 6], though it has low accuracy regarding superior mesenteric artery and vein

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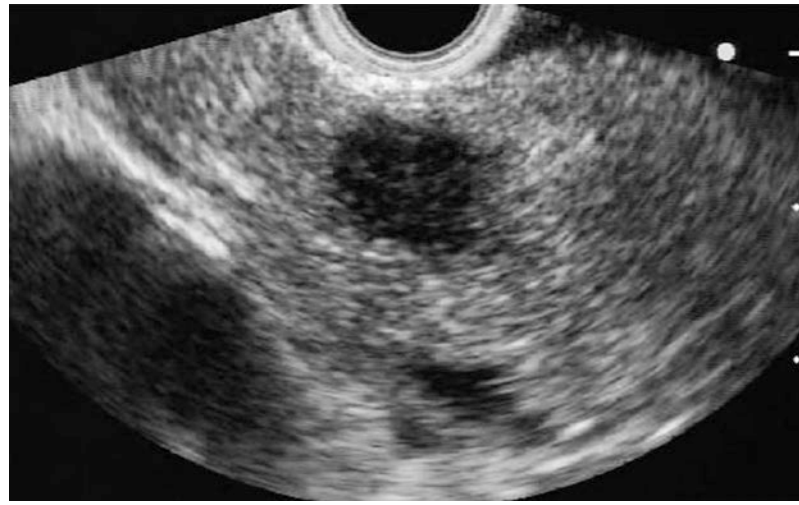

Fig. 8.1 EUS of small pancreatic cancer. EUS shows small hypoechoic area in the head of pancreas

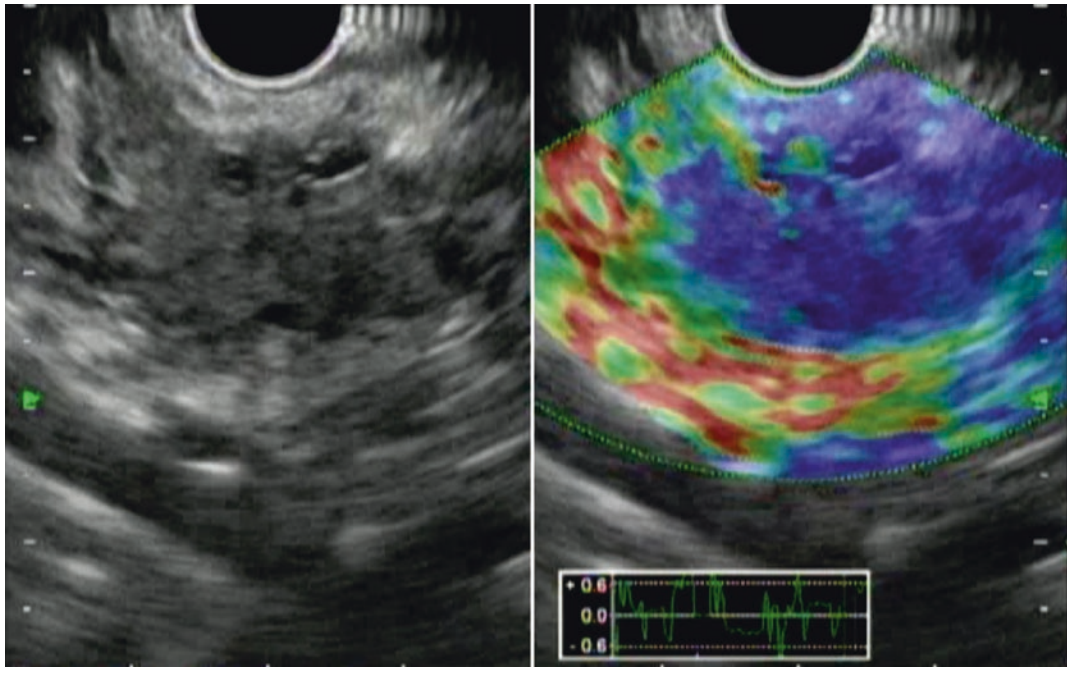

Fig. 8.2 EUS elastography. EUS elastography demonstrates *blue* area according to pancreatic cancer (*left*, fundamental image; *right*, elastography)

invasions [7, 8] because the tip probe of echoendoscope is far from the target area. Nowadays, two types of EUS, namely, radial type and curved linear type (convex) EUS, are commercially available. Interestingly, one prospective comparative study shows that there is no difference between radial EUS and convex EUS for delineation of the pancreas [9].

Elastography

Elastography is an imaging modality that can assess the hardness of different tissues and their deformation under compression [10]. In general, pancreatic ductal cancer is well known as the hard tumor including rich fibrosis in the tumor. Pancreatic cancer in the EUS elastography shows predominantly blue, suggesting hard tissue (Fig. 8.2). Recently,

the usefulness of elastography by means of has been reported for the diagnosis of pancreatic lesions [10, 11]. However, EUS elastography was not objective at early stage because of the use of elasticity distribution alone. Lately, elasticity semi-quantification, using the strain ratio (SR) of tissue elasticity, is used for objective evaluation [10]. Clinical utility of EUS elastography has been shown by meta-analyses to have a high sensitivity of 95–97% but a low specificity of 67–76% for diagnosing pancreatic cancer [12, 13]. Thus, the improvements in specificity like "measurement of subjective elasticity" appear to be mandatory to become diagnostic standard.

Contrast-Enhanced EUS (CE-EUS)

Although fundamental EUS allows the detection of even small pancreatic cancer, it has disadvantage in terms of evaluation of vascularity of the lesions compared with contrast-enhanced CT and MRI. In particular, since pancreatic adenocarcinoma shows hypovascularity, fundamental EUS with color Doppler is not useful unlike for pancreatic neuroendocrine tumor which is hypervascularity tumor. Recently, contrast-enhanced EUS (CE-EUS) using an intravenous contrast agent which characterizes the vascularity of pancreatic masses has been developed [14]. Mostly, pancreatic cancer shows hypovascular pattern in CE-EUS (Fig. 8.3). Furthermore, it aids in not only tumor characteristics but also tumor staging, leading to the guidance of therapeutic procedures. A recent meta-analysis of CE-EUS showed a sensitivity of 94% and a specificity of 89% for diagnosing pancreatic cancer and concluded that it is a promising, reliable modality for the differential diagnosis of pancreatic adenocarcinoma [15]. However, the vascularity pattern of CE-EUS, as well as EUS elastography, is not standardized. Then, one prospective study revealed the usefulness of the quantitative contrast-enhanced harmonic EUS using the use of time-intensity curve (TIC) analysis in an artificial neural network (ANN) classification model [16]. For the ANN, sensitivity was 94.64%, specificity 94.44%, PPV 97.24%, and NPV 89.47% in patients with 112 cases of pancreatic carcinoma and 55 cases of chronic pancreatitis [16].

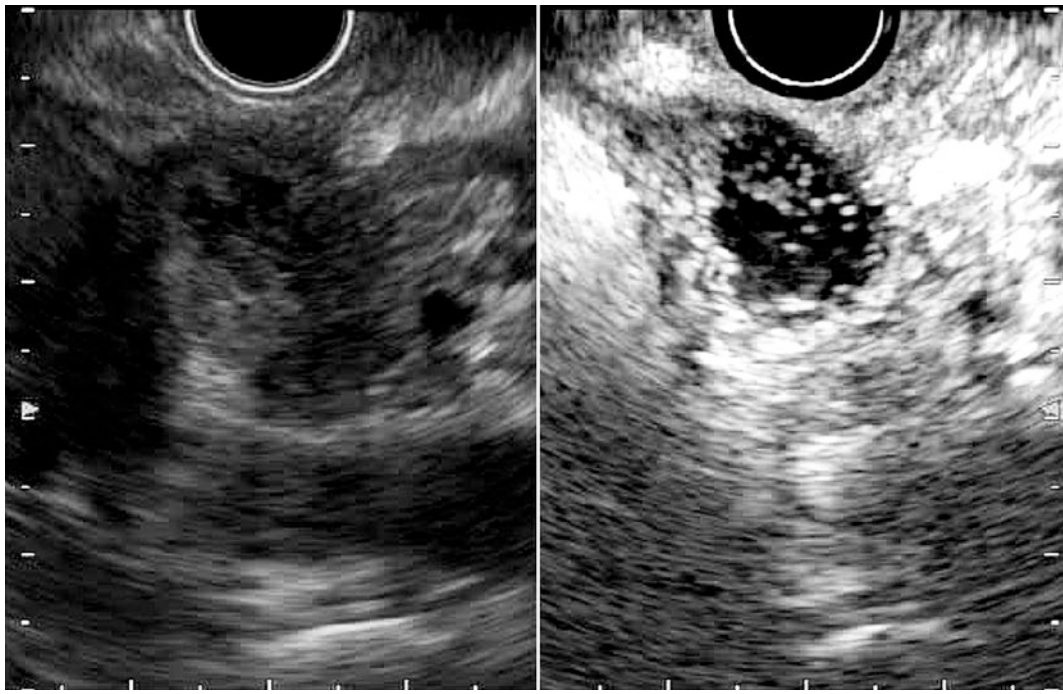

Fig. 8.3 Contrast-enhanced EUS (CE-EUS). CE-EUS demonstrates hypovascular area suggesting pancreatic cancer (*left*, fundamental image; *right*, CE-EUS)

Highly diagnostic performance may allow to be replaced with conventional contrast-enhanced CT/MRI in selected patients who have allergy to iodine, renal dysfunction, and metal in the body. Furthermore, in case of difficult EUS-guided fine-needle aspiration (EUS-FNA) like the presence of inevitable large intervening blood vessel in the puncture line, the diagnosis only by CE-EUS seems safe and valuable to avoid unnecessary complication.

8.1.1.2 EUS-FNA

EUS-FNA, which emerged for diagnosis of pancreatic lesion in 1992 [17], has a high diagnostic ability for pancreatic cancer because it allows not only precise images but also sampling for pathological diagnosis (Fig. 8.4). The diagnostic accuracy of EUS-FNA is 85–90% in high-volume centers in the world [18–22]. Recent meta-analyses of EUS-FNA demonstrated its high sensitivity of 86.8–91% and specificity of 94–99.3% for diagnosing pancreatic masses [23–25]. Thus, nowadays, despite the presence of resectability, pathological sampling by EUS-FNA is standard diagnostic strategy when pancreatic masses are detected by imaging modalities like CT and MRI. However, EUS-FNA has several points of weakness. Standard EUS-FNA technique, e.g., selection of needle, sampling technique (funning technique, etc.), and the presence of on-site pathologist (rapid on-site evaluation, ROSE), is not established yet. Furthermore, it is likely that the outcome of EUS-FNA depends on the endosonographers' skill. Although transabdominal ultrasound (US) also depends on operator's skill, interestingly sequential comparative study in the same institution showed that EUS-FNA can obtain significantly adequate specimens compared with US-FNA (100% vs 91.3%, $p = 0.019$), and diagnostic accuracy by EUS-FNA cytology was significantly superior to that of US-FNA (94.6% vs 78.6%, $p = 0.0079$), though there was no significance on the serious adverse events rate between EUS-FNA and US-FNA (1.3% vs 4.3%) [26]. Theoretically, small pancreatic mass may preclude adequate pathological sampling. In fact, one study in high-volume center revealed that size of mass affected diagnostic yield of EUS-FNA in patients with pancreatic masses (accuracy: <1 cm, 47.4%; 1–2 cm, 78.9%; 2–3 cm, 86.9%; 3–4 cm, 92.6%) [27].

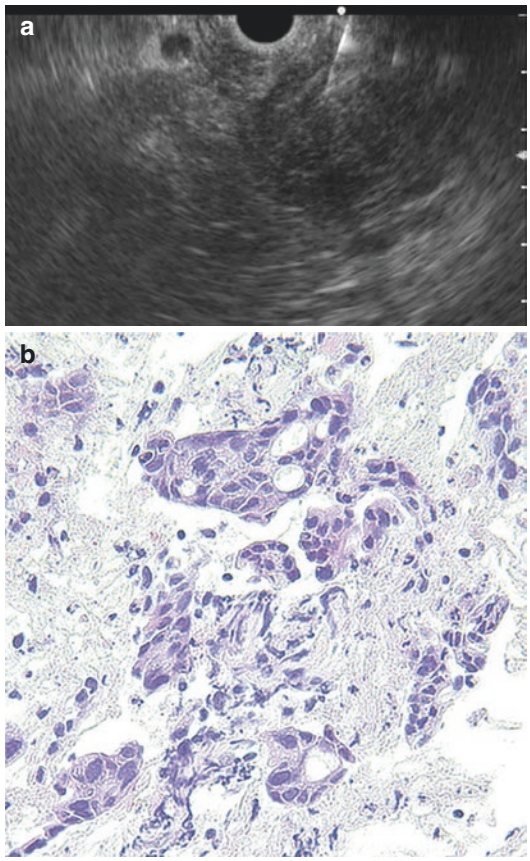

Fig. 8.4 EUS-FNA of pancreatic head cancer. (**a**) A 22-gage fine needle is advanced into the pancreatic head mass. (**b**) Histology (H&E staining)

Multiple gene abnormalities influence the progress of pancreatic cancer. Until now, several investigators suggested that sample analyses obtained by EUS-FNA are useful not only for diagnosis of pancreatic cancer [28, 29] but also selection of therapeutic strategy even in advanced pancreatic cancer [30]. Thus, the progress of genetic technology may allow tailor-made medicine in patients with pancreatic cancer.

8.1.2 Endoscopic Retrograde Cholangiopancreatography (ERCP)

First endoscopic retrograde pancreatography (ERP) was reported by Mucune et al. in 1968 [31]. Since then, ERCP has been used for diagnosis

and therapy of pancreatic cancer. Theoretically, pancreatic ductal carcinoma seems to be originated from main or branch pancreatic duct. Thus, it shows morphologic change of pancreatic duct like disruption, stricture, and dilation (Fig. 8.5). ERP enables not only possibility of the presence of pancreatic cancer but also obtaining pathological sampling in the pancreatic duct. If cancer has invasion to the bile duct, resulting obstructive jaundice, ERC shows bile duct stricture and shift of bile duct to the pancreatic side. In general, since biliary stent is placed across the biliary stricture following diagnostic ERCP, sampling by brush cytology and transpapillary biopsy is usually performed before stent placement. However, the most worrisome problem with ERCP is the development of procedure-related complications particularly post-ERCP pancreatitis, though it may not be so many in case of head of pancreatic cancer because of few intact pancreatic duct. Thus, with MRCP development, the use of simple ERCP has considerably decreased only as a diagnostic tool unless therapeutic ERCP like biliary stenting is needed.

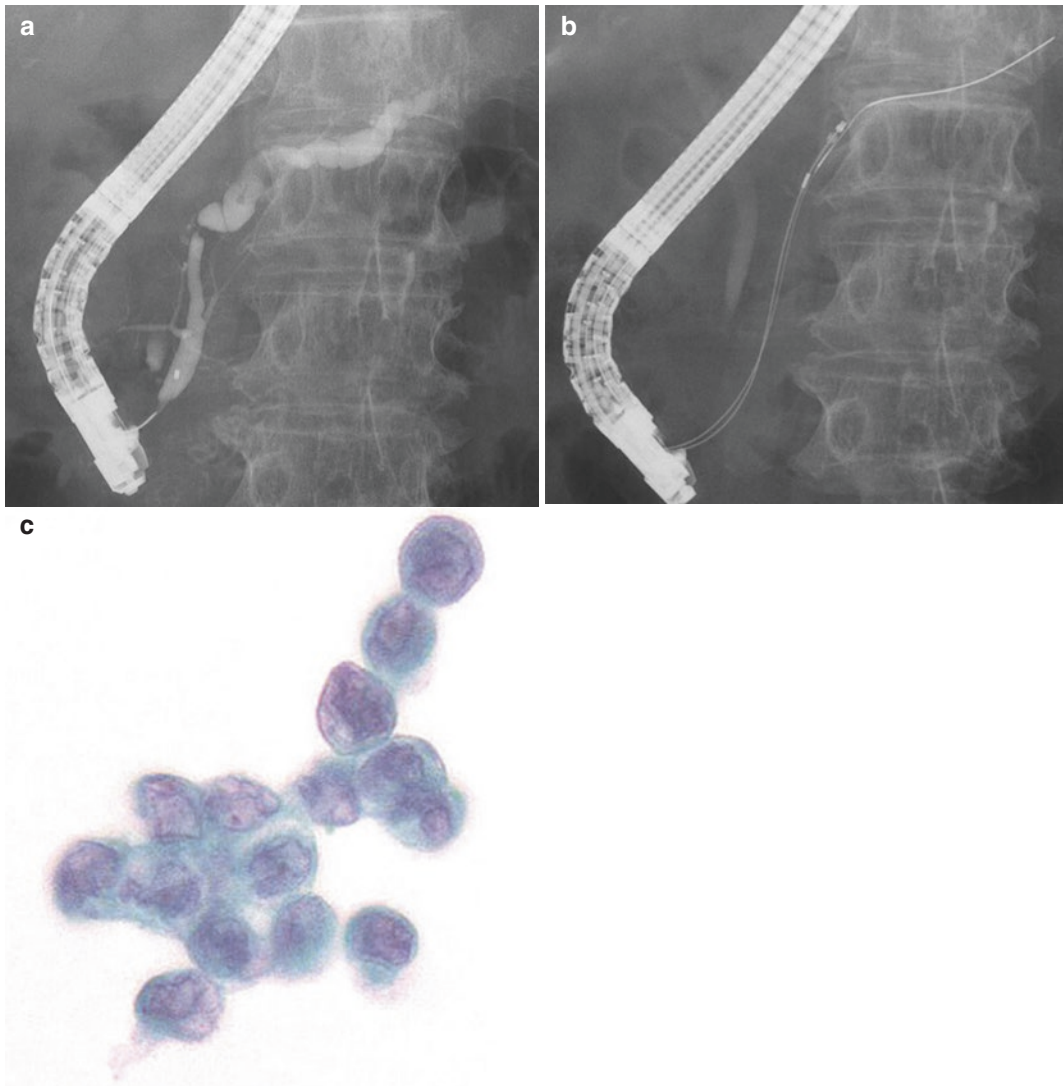

Fig. 8.5 Endoscopic retrograde pancreatography (ERP). (**a**) ERP showed main pancreatic duct stricture. (**b**) Brushing cytology was conducted. (**c**) Cytological specimen showed malignant cells

Recently, one worrisome paper described that cytodiagnosis of pancreatic juice may be useful in the diagnosis of pancreatic carcinoma in situ [32]. However, such kind of invasive diagnostic ERCP should be performed based on the benefit and harm for the patients. Nevertheless, ERCP may have small potential as a diagnostic modality in combination with EUS. Another interesting study showed that the ERCP and EUS combination was associated with a high diagnostic value for detecting pancreatic neoplasms compared with ERCP or EUS alone for pancreatic solid lesions [33].

Intraductal ultrasonography (IDUS) had been performed more than one decade ago for diagnosis of pancreatobiliary strictures. However, catheter mostly cannot pass the stricture and provide additional information compared with conventional EUS.

There are few data on the cholangiopancreatoscopy in patients with pancreatic cancer. In general, diameter of peroral cholangiopancreatoscopy is approximately 3 mm, and it is inadequate for the pancreatic duct. On the other hand, several endoscopists have performed cholangioscopy for diagnosis of indeterminate biliary strictures. They revealed that apart from cholangiocarcinoma which is originated from bile duct, cholangioscopy has few indication in patients with pancreatic cancer because the sensitivity is extremely low (8%) due to extrinsic stricture [34, 35].

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PET and Other Functional Imaging

9

Keon Wook Kang

9.1 Positron Emission Tomography

Positron emission tomography (PET) is a nuclear medicine imaging which detects gamma rays from the body. After targeting molecules labeled by positron-emitting radionuclides are injected into patients, they are distributed throughout the body and accumulated to specific organs or tissues. PET scan is a molecular imaging which reveals molecular phenomena of the body. Various radiopharmaceuticals have been developed for diagnostic PET imaging.

Positron-emitting radionuclides ^{18}F-labeled fludeoxyglucose (FDG) are the most commonly used radiopharmaceuticals in clinics. FDG is a glucose analog and actively transported into cells via glucose transporters. FDG PET localizes organs and tissues which consume glucose higher than surrounding organs or tissues. In fasting status, FDG accumulates in the normal brain and malignant tumors which express glucose transporter 1 (GLUT1). GLUT1 is insulin independent and actively transports glucose or FDG into cells in the brain or tumors even though insulin level is low due to fasting.

Whole body FDG PET/CT imaging is now widely used for oncologic diagnostic studies, including staging, detecting recurrence, restaging, treatment monitoring, and estimating prognosis. Whole body imaging is practical for M staging by detecting or ruling out unexpected distant metastasis. The concentration of FDG uptakes varies among types or grades of tumors. Generally high-grade malignant tumors which have poor prognosis uptake FDG in high concentration.

PET has an advantage of quantifying accumulation of radiopharmaceuticals. The standardized uptake value (SUV) is the most frequently used semiquantitative measured value. In case of FDG PET, SUV is calculated as a concentration of FDG in the tissues divided by injected dose per body weight. SUV is a useful measure for the evaluation of therapy response. SUV can be expressed in various ways. SUVmax is a value representing one maximum value in the region of interest (ROI). SUVmean is an average value in ROI. In clinical practice, SUVmax is most commonly used because it is not only simple to measure but also independent from the bias of drawing ROI.

PET can detect trace amount of radiopharmaceuticals. However, spatial resolution of clinical PET scanners is around 5 mm which is poorer than CT or MRI. Thus, hybrid imaging system PET/CT is favored. PET/CT produces tomographic PET imaging overlaid on CT imaging which is acquired simultaneously. PET highlights functional status and CT provides anatomical information. Imaging speed and diagnostic accuracy increase by

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combining two imaging modalities. Nowadays, PET/MRI is also developed and commercially available.

Radiation dose of a single PET study is less than 10 mSv which is comparable with a single enhanced CT examination. In the case of recent sensitive PET/CT scanners, dose of a single whole body PET/CT examination is less than 10 mSv when low-dose CT is applied. PET/MRI has an advantage in the point of view of radiation safety, because patients receive no radiation from MRI studies.

9.1.1 Pancreatic Adenocarcinoma

FDG PET or PET/CT has limited role in the initial diagnosis of pancreatic cancer, but studies showed its benefits in initial staging and prognosis evaluation. PET/CT lacks the necessary sensitivity and specificity for detection of small lesions less than 5 mm of pancreatic cancer. FDG also accumulates in inflammatory tissue of pancreatitis.

According to a meta-analysis of 19 studies of FDG PET in patients with suspected pancreatic cancer, diagnostic performance of FDG PET was sensitivity 90%, specificity 76%, positive predictive value (PPV) 90%, negative predictive value (NPV) 76%, and accuracy 86% [11]. Pooled estimates from nine studies for FDG PET/CT were sensitivity 90%, specificity 76%, PPV 89%, NPV 78%, and accuracy 86%. Diagnostic performance between PET and PET/CT was almost identical. While sensitivity of PET or PET/CT was high, specificity of them was relatively low. In most studies, the most prevalent disease among controls was chronic pancreatitis. From nine studies differentiating between pancreatic cancer and chronic pancreatitis, the pooled sensitivity and specificity for FDG PET were 90% and 84%, respectively. Although some pancreatitis may resemble pancreatic cancer, FDG does not accumulate in most chronic pancreatitis. In a previous study, 87% (67/77) of chronic pancreatitis had minor or no FDG uptakes [14]. In some false positive cases, FDG was accumulated in inflammatory cyst or obstructed duct. FDG PET detected pancreatic cancer in five out of six patients with chronic pancreatitis. FDG PET is able to detect pancreatic cancer in the context of long-standing chronic pancreatitis.

Staging and predicting prognosis is more important because unnecessary surgical exploration may be avoided. FDG PET was superior to CT in diagnosing distant disease, while CT was better than FDG PET in local staging due to the poor spatial resolution of PET. The reported sensitivities of FDG PET in nodal staging have varied between 46% and 71% [15]. They were especially poor when peripancreatic and para-aortic lymph nodes close to the primary tumor were evaluated.

PET has an advantage to identify distant metastases (Fig. 9.1). According to the previous reports, the sensitivity of FDG PET for detecting hepatic metastases is about 70%. However, small lesions less than 1 cm could not be detected. The sensitivity for lesions less than 1 cm was 43%, while that of greater than 1 cm was 97%. Gd-EOB-DTPA-enhanced MRI can detect small hepatic metastasis accurately with a sensitivity of 90% and a specificity of 100%. FDG PET/MRI marginally improved in sensitivity of detecting lesions greater than 1 cm from 93% to 98%.

In a retrospective study with 14 patients with metastasis, the sensitivity of detecting metastatic disease for PET/CT, standard CT, and the combination of the two were 61%, 57%, and 87%, respectively [4]. In seven patients occult metastatic disease was found on PET/CT scan alone. Two patients had metastasis in a supraclavicular lymph node. Two patients had occult liver metastases. Two patients had a peritoneal implant and one had a periesophageal lymph node. These seven patients (11%) with invasive cancer had a change in their management.

According to National Comprehensive Cancer Network (NCCN) guideline 2016, PET/CT can be considered as an adjunct to a formal pancreatic CT protocol in high-risk patients including borderline resectable disease, markedly elevated CA 19-9, large primary tumors, large regional lymph nodes, and patients who are very symptomatic [8].

There are limited data on the use of FDG PET to assess early tumor response after

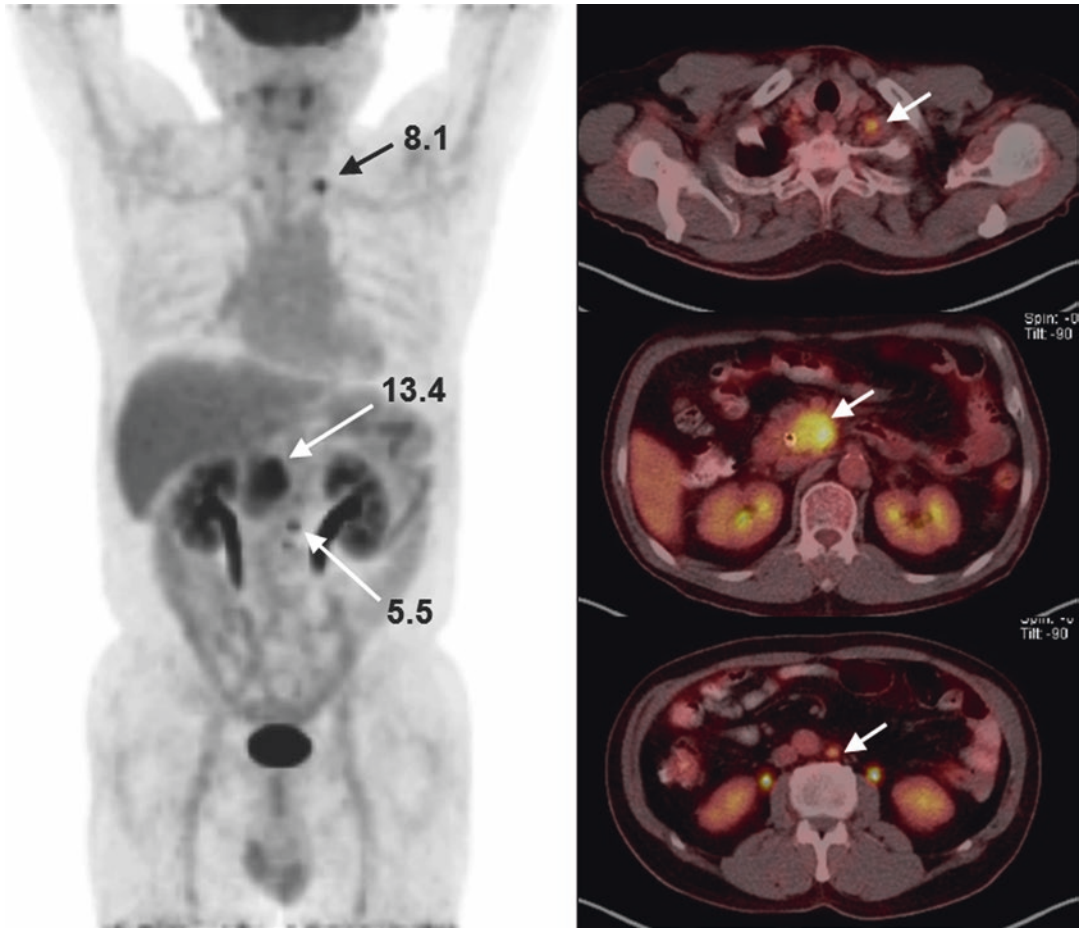

Fig. 9.1 FDG PET/CT imaging of a patient with pancreatic adenocarcinoma. Primary tumor is located at uncinate process of the pancreas. Whole body projection image and PET/CT tomography reveal metastasis at para-aortic and supraclavicular lymph nodes (*arrows*). Metastasis in supraclavicular lymph nodes was not detected by other conventional imaging modalities. The numbers along the *arrows* represent SUVmax of each lesion

treatment in pancreatic cancer. In a study with small number of patients, FDG PET scans helped monitoring clinical outcome of complete surgical resection as early as one cycle after neoadjuvant treatment in patients with locally advanced pancreatic cancer. Among patients who were PET responders (≥50% decrease in SUVmax), 100% (2/2) had complete surgical resection. Only 6% (1/16) had surgical resection in the PET nonresponders (<50% decrease) [1]. Further studies with larger population of patients are needed to confirm the role of FDG PET in identifying patients who could undergo complete surgical resection after the neoadjuvant treatment.

There are several studies that FDG PET can predict prognosis of patients with pancreatic cancer. Generally speaking, the higher the FDG uptake, the poorer the survival outcome. In a retrospective study analyzing 118 patients with pancreatic cancer who had performed FDG PET before receiving palliative chemotherapy, patients with high metabolism showed shorter survival than patients with low metabolism (SUVmax <4.5, 11.1 months; HR 1 vs SUVmax ≥ 4.5, 7.8 months; $p = 0.004$) [2].

Since SUVmax represents only one value of single pixel in ROI, it is vulnerable to noise. Thus, values representing tumor burden in whole body were developed. Metabolic tumor volume (MTV)

is a sum of each tumor volume above certain FDG uptakes. Generally, all voxels with an SUV of 2.5 or greater within the isocontour line were counted for the calculation of MTV. Total lesion glycolysis (TLG) reflects FDG activities from all tumors in the body. TLG is calculated as MTV multiplied by the SUVmean. In a retrospective study, 51 patients with resectable pancreatic cancer underwent FDG PET/CT and curative operation [5]. SUVmax, MTV, and TLG were compared as prognostic factors. Multivariate analysis revealed that MTV and TLG were independent prognostic factors for recurrence-free survival (RFS) and overall survival (OS). SUVmax was an independent prognostic factor for OS, but not for RFS.

9.1.2 Intraductal Papillary Mucinous Neoplasms

Intraductal papillary mucinous neoplasms (IPMN) are cystic tumors of the pancreas. IPNMs are important because if they are left untreated some of them may progress to invasive cancer. However, up to 85% of patients treated surgically according to the international consensus guidelines (ICG) subsequently reveal no malignancy. Thus, it could be said that the resection of these IPMNs was unnecessary. In a report analyzing 162 patients with IPMN, the sensitivity of the ICG in detecting malignancy was 93.2%, but their specificity was only 22.2%. Therefore, more accurate diagnostic methods differentiating between benign and malignant IPMNs are needed.

The sensitivity and specificity of multi-detector CT were 32–53% and 77–95%, respectively [6]. Those of magnetic resonance cholangiopancreatography were 37–59% and 71–91%. Those of endoscopic ultrasound-guided aspiration were 55–60% and 74–93%. In a study analyzing 69 histologically confirmed patients, the sensitivity and specificity of FDG PET were 83.3% and 100%, respectively [9]. The cutoff value was set as SUVmax of 2.5 or more. FDG PET is more accurate than any other procedures in differentiating benign and malignant lesions in patients already diagnosed as IPMN (Fig. 9.2). On the other hand, ICG is useful for predicting the incidence of malignant transformation and the consequent need for resection in low-risk patients with a long life expectancy.

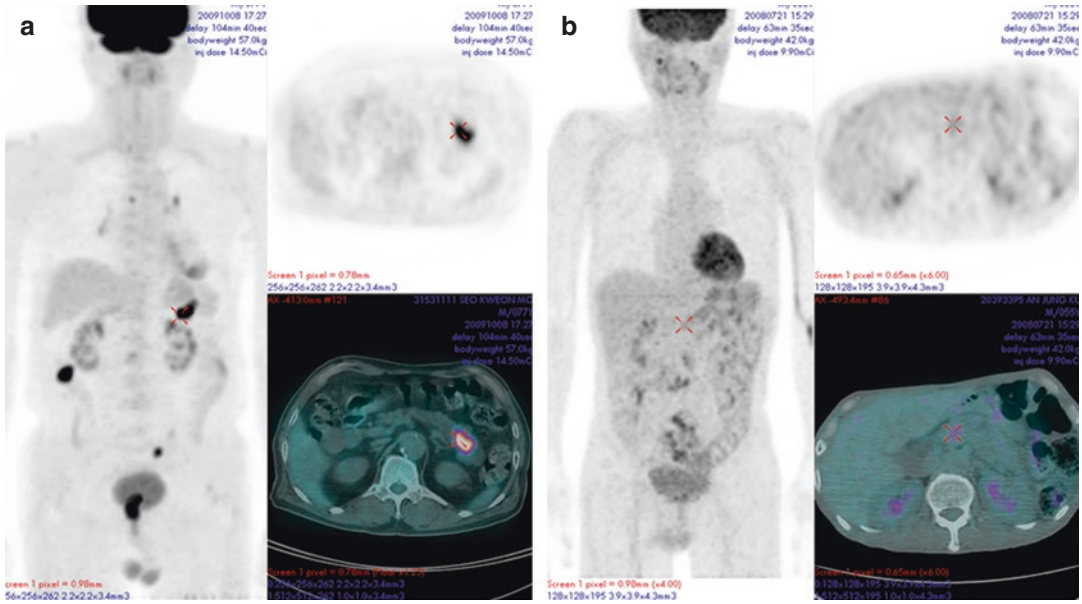

Fig. 9.2 FDG PET/CT images in patients with intraductal papillary mucinous neoplasm. While a malignant lesion (**a**) shows high FDG uptake in the tumor, a benign lesion (**b**) cannot be distinguished from background of the normal pancreas

9.1.3 Neuroendocrine Tumor

Neuroendocrine tumor (NET) is a heterogeneous group of malignant tumors that originate from the neuroendocrine system. For diagnosis of NETs, conventional radiological imaging methods such as CT, MRI, and ultrasonography (US) have been used. However, these anatomical imaging methods have a limitation in diagnostic value when the lesions are small and located at unexpected sites. By the use of these conventional imaging, endocrine pancreatic tumors can be localized in approximately 50% of the cases. Patients with metastatic NET had improved survival after the removal of the primary tumor, even in the presence of liver metastasis. Locating the primary tumor is important to the surgeon. Thus, functional nuclear imaging covering the whole body has been applied to diagnose NETs.

The most ubiquitous inhibitory receptor of neuroendocrine cells is the somatostatin receptor (SSTR). Whether they are functioning or not, NET can retain SSTR to a variable degree despite malignant change. An 8-amino acid peptide, octreotide (Sandostatin®) is used to inhibit NET as a therapeutics. ^{111}In-DTPA-octreotide scan (OctreoScan®) has been used in the diagnosis of NET. Gamma camera produces planar images as well as tomographic images. Nowadays, hybrid system combining single-photon emission computed tomography (SPECT) and CT is commercially available. However, PET/CT has a better sensitivity and resolution than SPECT/CT (Fig. 9.3).

Recently, ^{68}Ga-labeled somatostatin analogs have been developed for PET imaging of NETs. They are ^{68}Ga-labeled DOTA-Tyr^3 octreotide (DOTA-TOC), DOTA-Tyr^3, Thr^8 octreotide (DOTA-TATE), and DOTA-1-Nal^3-octreotide (DOTA-NOC). Although they have different affinities to subtype of SSTR, their clinical performance is almost the same. Since SSTR-targeted imaging reflects SSTR status of tumor, not all tumors are visualized. In a study using

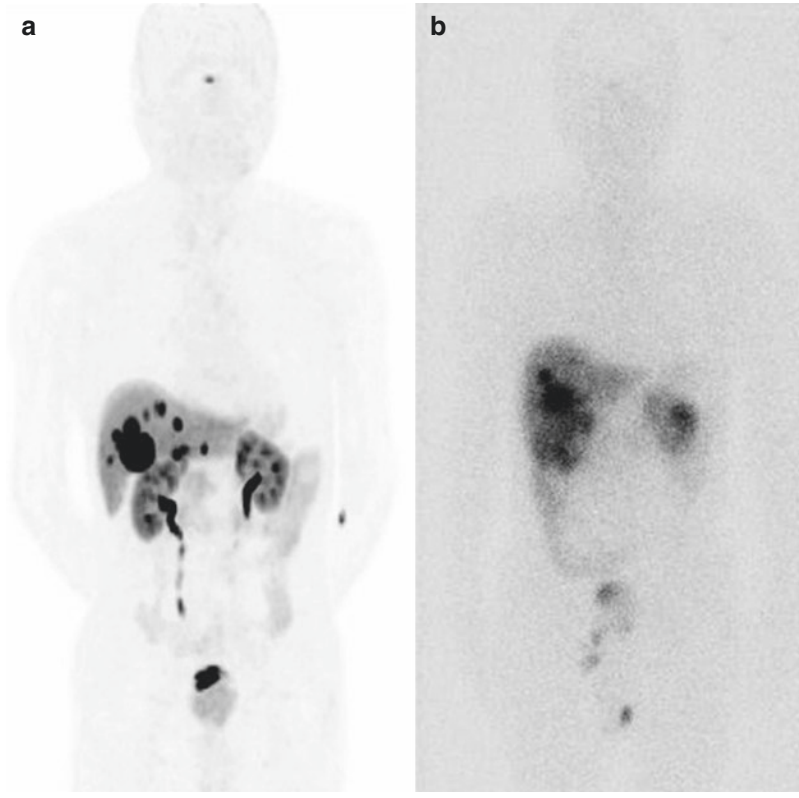

Fig. 9.3 ^{68}Ga-DOTA-TOC PET/CT (**a**) and ^{111}In-DTPA-octreotide scan (OctreoScan) (**b**) in a patient with metastatic neuroendocrine tumor in the liver. PET/CT shows better resolution than planar scan. Thus, small lesions can only be delineated in PET/CT

^{68}Ga-DOTA-NOC PET/CT, uptake in the pancreas was only seen in 76 of the 103 scans (74%). In another study enrolling 109 patients with known or suspected gastroenteropancreatic NET, ^{68}Ga-DOTA-NOC PET/CT showed a sensitivity of 78.3% and specificity of 92.5% for primary tumor and 97.4% and 100% for metastatic disease [7]. ^{68}Ga-DOTA-NOC PET/CT showed higher accuracy for both primary (83.4% vs 74.3%) and metastatic (98.2% vs 87.2%) lesions when comparing with conventional imaging including contrasted enhanced CT and MRI.

In a study of head-to-head comparison with 13 patients with NET, ^{68}Ga-DOTA-TOC PET/CT detected 16 additional lesions (6 in the liver, 9 in the pancreas, and 1 in the spleen) which were not detected by ^{111}In-DTPA-octreotide scan and SPECT/CT. PET/CT exhibited a significantly higher sensitivity than SPECT/CT (100% vs 54%, $p < 0.001$) [10].

Grade 1 and 2 NETs have a more favorable outcome than Grade 3. Poorly differentiated NETs have a low density of somatostatin receptors but are metabolically active. Thus, FDG PET accumulates in these tumors and is useful to evaluate them. On the other hand, well-differentiated NETs exhibit low glycolytic metabolic activity and demonstrate minimal FDG uptake. Therefore, staging by FDG PET is limited. In a retrospective study of gastrointestinal and pancreatic NETs, OctreoScan was more sensitive than FDG PET for the detection of well-differentiated and Grade 1 NETs, whereas FDG PET demonstrated significantly superior sensitivity for poorly differentiated and Grade 3 NETs [12]. Among patients with WHO Grade 1 NETs ($n = 94$), the sensitivity of OctreoScan was 79%, compared with a sensitivity of 52% for FDG PET ($p = 0.16$). For patients with WHO Grade 2 NETs ($n = 42$), OctreoScan and FDG PET performed similarly, with sensitivities of 83% and 86%, respectively. Among patients with WHO Grade 3 NETs ($n = 17$), the sensitivity of OctreoScan was 57%, significantly less than the sensitivity of 100% by FDG PET ($p = 0.02$). FDG PET may have a better role in patients with neuroendocrine tumor which is not visualized by SSTR-targeted imaging.

9.1.4 Metastatic Tumor in Pancreas

FDG also accumulates in pancreatic metastasis from other primary tumors. Three patterns of accumulation have been described: a solitary mass, multiple pancreatic lesions, and diffuse infiltration. The most common pattern was a solitary lesion with high FDG uptake. It resembles the more common pancreatic adenocarcinoma. FDG PET/CT has an advantage in detecting unsuspected pancreatic metastases over contrast-enhanced CT in small intrapancreatic isodense nodules.

9.2 Other Functional Imaging

Traditionally, gamma camera is widely used for functional imaging in nuclear medicine such as liver scan, hepatobiliary scan, etc. In 1970s, ^{75}Se-selenomethionine scan was used for detecting pancreatic mass. Since it accumulates in normal pancreas, tumor was visualized as a space-occupying defect. Nowadays, this scan giving anatomical information is replaced by US, CT, or MRI.

^{111}In-DTPA-octreotide scan (OctreoScan) targeting SSTRs has been used for the last two decades for the diagnosis of NETs. Reported data on the sensitivity of OctreoScan in patients with gastrinomas vary from 60% to 90%. The discrepancy in results is probably due to short acquisition time, planar imaging (not performing SPECT studies), or low doses of radiopharmaceutical. Integrated SPECT/CT provides tomographic radionuclide images overlaid on CT images which is used for localization and attenuation correction. In a study enrolling 18 patients with endocrine pancreatic tumors, SPECT/CT had an incremental value over planar scan [13]. Superior lesion localization helped to detect additional sites of tumors and physiological uptakes.

If we substitute diagnostic radionuclide with therapeutic nuclide, molecular targeting imaging can be easily translated into molecular targeted therapy. Peptide receptor radionuclide therapy (PRRT) with radiolabeled somatostatin analogs is one of the examples. β-rays from ^{177}Lu-DOTA-TATE and ^{90}Y-DOTA-TOC can kill cells in neuroendocrine tumors. There is evidence from large studies

that PRRT achieved 25–30% tumor response rates in patients with metastatic neuroendocrine tumors [3]. Radioactive lutetium ^{177}Lu emits both γ- and β-ray at the same time. Thus, after ^{177}Lu-DOTATATE therapy, whole body scan or SPECT/CT allows restaging or monitoring of therapy.

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Part III

Treatment Guideline

10 Staging and Determination of Resectability of Pancreatic Cancer

Motoki Miyazawa, Seiko Hirono, and Hiroki Yamaue

10.1 Introduction

In major specialized centers, 5-year survival rates are approaching 30–50% in selected patients [1]. However, more than 80% of patients present with unresectable tumors due to either local extension or distant metastases [2]. For the majority of patients presenting with advanced disease, patient prognosis is therefore extremely poor. Early diagnosis and staging thus are indispensable for the improvement of outcomes in patients with pancreatic cancer. Preoperative staging of pancreatic cancer helps to determine the therapeutic strategy for pancreatic cancer. It is the most important to decide whether surgical resection is appropriate or not. TMN staging system placed emphasis on both resectability and prognostic classification. With accurate staging, inappropriate therapy, such as non-curative surgical resection, can be avoided, and palliative therapy can be provided to patients with far advanced disease. This chapter reviews TMN staging system and discusses the resectability of pancreatic cancer.

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10.2 TNM Staging of Patients with Pancreatic Cancer

The Union for International Cancer Control/American Joint Committee on Cancer (UICC/AJCC) TNM staging system is used for the standard staging of pancreatic cancer (Table 10.1) [3, 4]. The TNM staging of pancreatic cancer includes tumor size and extent, lymph node status, and evidence of distant metastases. The T (primary tumor) staging of pancreatic cancer is classified as T1–T4 based on the size and extent of the primary tumor. T1 lesions consist of an intrapancreatic tumor measuring 2 cm or less in greatest diameter. T2 lesions consist of an intrapancreatic tumor measuring more than 2 cm in greatest diameter. Primary tumors that have extended beyond the pancreas such as the duodenum, stomach, bile duct, and peripancreatic fat are classified as T3 lesions. T3 lesions don't involve the celiac axis or the superior mesenteric artery, but it doesn't matter whether tumors extend to the superior mesenteric/portal vein or not. T4 lesions have involved the celiac axis or the superior mesenteric artery.

The N (regional lymph nodes) staging is classified as N0 or N1 based on the presence or absence of regional lymph node metastasis. The M (distant metastasis) staging is classified as M0 or M1 based on the presence or absence of distant metastasis such as liver, peritoneum, lung, and bone metastases.

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Table 10.1 Staging of pancreatic exocrine cancer

TNM classification (UICC/AJCC 7th edition)			
Primary tumor (T)			
TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
Tis	Carcinoma in situ (including lesions classified as PanIn III)		
T1	Tumor limited to the pancreas, 2 cm or less in greatest dimension		
T2	Tumor limited to the pancreas, more than 2 cm in greatest dimension		
T3	Tumor extends beyond the pancreas but without involvement of celiac axis or the superior mesenteric artery		
T4	Tumor involves celiac axis or the superior mesenteric artery		
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)			
M0	No distant metastasis		
M1	Distant metastasis		
Staging			
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

Tumors localized to the pancreas are classified in stage I (T1-2, N0, M0). Tumors extending to adjacent organs or involving regional lymph node metastases without distant metastases or invasion into celiac axis or superior mesenteric vein are classified in stage II (T3, N0, M0 or T1-3, N1, M0). Locally advanced Tumors involves celiac axis or superior mesenteric vein without distant metastases are classified in stage III (T4, any N, M0). Tumors with distant metastases at the time of diagnosis are classified in stage IV (any T, any N, M1).

The combination of T, N, and M into stage groupings accurately reflects the differences in prognosis among patients with resectable, locally advanced, and distant metastatic disease. Matthew H. G. Katz et al. previously reported the 6th edition of the AJCC TMN staging system applied to 2981 patients with pancreatic adenocarcinoma evaluated at MD Anderson Cancer Center between August 1996 and August 2006 [5]. In this report, median survival of patients who initially presented with resectable (stage I/II), locally advanced (stage III), and metastatic disease (stage IV) was 15 months, 11 months, and 6 months, respectively. Bilimoria, K. Y. et al. also reported that by using the National Cancer Database (1992–1998), 121,713 patients were identified with pancreatic adenocarcinoma. All patients were restaged by AJCC 6th edition guidelines. Stage-specific overall survival was estimated by using the Kaplan-Meier method and compared with log-rank tests. Concordance indices were calculated to evaluate the discriminatory power of the staging system. Cox modeling was used to determine the relative impact of T, N, and M classification on survival. For all patients, there was 5-year survival discrimination by stage ($P < 0.0001$). For patients who underwent pancreatectomy, stage predicted 5-year survival: stage IA, 31.4%; IB, 27.2%; IIA, 15.7%; IIB, 7.7%; III, 6.8%; and IV, 2.8% ($P < 0.0001$) (Table 10.2). The concordance index for the staging system was 0.631 for all patients, 0.613 for those who underwent pancreatectomy, and 0.596 for patients who did not undergo resection. In patients who underwent pancreatectomy, tumor size, nodal status, and distant metastases were independent predictors of survival ($P < 0.0001$) [6].

Table 10.2 Five-year overall survival for resected pancreatic adenocarcinoma from the National Cancer Database (1992–1998, at a time when adjuvant therapy was not typically administered)

Stage	Number of patients	%	5-year survival (%)	Median survival (months)
IA	1886	8.8	31.4	24.1
IB	2364	11.0	27.2	20.6
IIA	3846	17.9	15.7	15.4
IIB	7828	36.4	7.7	12.7
III	2850	13.2	6.8	10.6
IV	2738	12.7	2.8	4.5
Total	21,512			12.6

Prognostic factors in stage I and stage II are tumor size and lymph node status. Pathologically measured tumor size in greatest dimension was significant independent prognostic factor in previous reports about the patients with resected pancreatic ductal adenocarcinoma after pancreaticoduodenectomy [7–12] (Table 10.3). In most of these reports, the cutoff size was between 2 cm and 3 cm with significant differences in prognosis. Although the survival of patients with small pancreatic cancers was more favorable, 41% of tumors up to 2 cm in diameter had lymph node metastases [9]. Therefore, T1 tumors are not necessarily early-stage disease.

Pathologically metastasis to regional lymph nodes was also significant independent prognostic factor in previous reports about the patients with resected pancreatic ductal adenocarcinoma after pancreatic resection (Table 10.4) [7–15]. Considering its prognostic significance, TNM staging system classifies node-positive tumors as stage IIb.

Table 10.3 Correlation between tumor size and survival

Institution (country)	Diameter of tumor	Number of patients (%)	5-year survival (%)	Median survival (months)	*P*
University of Naples (Italy)	>3	34 (51)	9	11	0.006
	<3	33 (49)	33	18	
Jagiellonian University (Poland)	>2	NR (94)	NR	26	0.04
	≤2	NR (6)	NR	46	
Nuremberg (Germany)	>2	80 (78)	5	13	0.001
	≤2	22 (22)	19	25	
Harvard School of Public Health (USA)	>2	239 (77)	NR	15	0.002
	≤2	70 (23)	NR	38	
Kansai Medical University (Japan)	≥3	57 (63)	7	8	0.006
	<3	33 (37)	26	22	
Johns Hopkins University (USA)	≥3	NR	4	15	<0.0001
	<3	NR	23	21	

Table 10.4 Correlation between lymph node status and survival

Institution (country)	Lymph node status	Number of patients (%)	5-year survival (%)	Median survival (months)	*P*
University of Maryland Medical Center (USA)	Positive	261 (81)	NR	NR	0.001
	Negative	127 (69)	NR	NR	
Jagiellonian University (Poland)	Positive	86 (63)	4	15	0.01
	Negative	50 (37)	42	38	
Nuremberg (Germany)	Positive	74 (73)	5	13	0.008
	Negative	28(27)	27	25	
Harvard School of Public Health (USA)	Positive	193 (49)	NR	16	0.05
	Negative	203 (51)	NR	20	
Kansai Medical University (Japan)	Positive	42 (48)	9	9	0.02
	Negative	46(52)	17	20	
Johns Hopkins University (USA)	Positive	919(78)	16	17	0.0001
	Negative	256 (22)	27	23	
University of Naples (Italy)	Positive	51 (68)	8	13	<0.001
	Negative	24 (32)	42	33	
University of Amsterdam (Netherlands)	Positive	109 (68)	NR	NR	0.02
	Negative	51 (32)	NR	NR	
MD Anderson Cancer Center (USA)	Positive	186 (52)	NR	22	0.002
	Negative	174(48)	NR	32	

In addition, number of positive nodes, total nodes examined, and lymph node ratio are three lymph node parameters related to survival after resection of pancreatic ductal adenocarcinoma. Increasing number of positive nodes was correlated with shorter overall survival for patients with lymph node-positive pancreatic ductal adenocarcinoma [16], and increasing total nodes examined was correlated with longer overall survival for patients with lymph node-negative pancreatic ductal adenocarcinoma [17–19]. Lymph node ratio, the ratio of the number of positive nodes to the total nodes examined, was reported to be correlated with overall survival for resected pancreatic ductal adenocarcinoma [16, 20, 21]. These results suggest that lymph node ratio may be incorporated into staging system for pancreatic ductal adenocarcinoma in the future.

10.3 Resectability of Pancreatic Ductal Adenocarcinoma

The goal of the NCCN/AJCC staging system is to identify patients who are eligible for resection with curative intent. Tumors classified in stage I are small and localized within pancreas, therefore, are routinely resectable. Tumors classified in stage II are extent to adjacent organs or involving regional lymph nodes, without distant metastases or invasion to the celiac trunk or superior mesenteric artery, and are usually resectable. On the other hand, tumors classified in stage IV are unresectable due to distant metastases, because patients with stage IV pancreatic ductal adenocarcinoma have systemic disease spread with micrometastases which are impossible to be detected by multidetector-row CT. There is no room for disputing the unresectability of stage IV pancreatic ductal adenocarcinoma; however, the resectability of stage III is controversial. Tumors classified in stage III involving the celiac trunk and/or superior mesenteric artery are usually contraindication for surgical resection. According to the previous report [5], resection of tumors involving the celiac axis or superior mesenteric artery is unlikely to be completed because these vessels are surrounded by a perineural plexus through which tumor cells may extent to the celiac ganglion and the retroperitoneum. Even if a portion of the celiac axis or superior mesenteric artery is resected with reconstruction, R0 resection is very difficult due to perineural tumor invasion. In addition, most of patients with such locally advanced disease also have synchronous systemic metastases, even if not detected on imaging studies [22, 23].

However, involvement of a limited area of the visceral arteries is so-called a borderline resectable situation. The stage III category includes a wide range of tumor-vessel involvement – from minimal tumor abutment of the superior mesenteric artery to complete 360-degree encasement of the superior mesenteric artery. Tumors that demonstrate arterial abutment (tumor-vessel involvement of 180° or less) may be considered for surgery as part of a multimodality approach to the disease that includes neoadjuvant chemotherapy or chemoradiotherapy [24]. According to NCCN Guidelines Version 2 2015 for pancreatic adenocarcinoma [25], patients with borderline resectable pancreatic cancer include those whose tumors exhibit abutment or encasement of a short segment of the hepatic artery, without evidence of tumor extension to the celiac artery that is possible to perform R0 resection with interposition grafting or primary end-to-end anastomosis. These limited tumor involvements of the common or proper hepatic arteries may derive from pancreatic neck origin and extent along the gastroduodenal artery.

The resectability of tumor abutment or encasement of the SMV or portal vein remains controversial, and, therefore, the presence or absence of venous involvement was not specifically described in the T staging. The T3 category includes all forms of non-arterial tumor extension beyond the pancreas, including extension to the superior mesenteric vein and portal vein. From several institutions, it was reported that venous resection and reconstruction is safe with the same morbidity or mortality as standard pancreaticoduodenectomy [13, 26]. Moreover, there was no difference in survival between the patients who were performed with vascular resection and those who underwent standard pancreaticoduodenectomy [27, 28].

Venous resection is, therefore, no longer a contraindication to pancreaticoduodenectomy at many centers. Nonetheless, pancreaticoduodenectomy with the resection of superior mesenteric vein or portal vein remains controversial because of the complexity of the surgical procedure combined with the aggressive oncologic behavior of pancreatic cancer, which results in modest postoperative survival even if curative surgery were performed [29, 30].

The best treatment for patients with locally advanced stage III disease is still unresolved; primary treatment for such patients typically incorporates systemic chemotherapy or chemoradiotherapy. That is to say, patients with stage III disease are often enrolled in clinical trials using chemoradiation for the purpose of local control. One study of 257 patients with stage III pancreatic cancer (all T4 lesions based upon infiltration of the celiac axis or superior mesenteric artery) found that 30% could undergo a successful R0 resection after chemoradiation or chemotherapy alone [31]. Therefore, revisions to the TNM staging system are anticipated.

Conclusion

TNM staging system is important to classify patients with pancreatic adenocarcinoma into prognostic subgroups and perform appropriate therapies for each stage patient. However, the resectability of pancreatic adenocarcinoma is changing as the improvement in surgical techniques and chemotherapeutic options. Further clinical trials are required to establish evidence-based multimodality approach for borderline resectable pancreatic adenocarcinoma.

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11 Current Issues of Borderline Resectable Pancreatic Ductal Adenocarcinoma

Jason W. Denbo and Jason B. Fleming

11.1 Identification of the Borderline Resectable Patient

11.1.1 Biology of PDAC and Surgical Therapy

The initial clinical evaluation of pancreatic ductal adenocarcinoma (PDAC) occurs very late in the course of the disease, [1] as evidenced by the fact that only 10–20% of patients are eligible for surgical resection [2–5]. Possibility of a potentially curative surgical resection often pushes the surgeon and the patient toward immediate surgical resection, which could actually prevent the long-term goal of survival. These facts are especially evident in patients with borderline resectable PDAC where the risks of surgery are high and the chances of cure slim. For this reason the surgeon must take a thoughtful approach as just one part of a multidisciplinary effort designed to achieve long-term patient survival.

Pancreatic surgery is becoming safer, especially at high-volume centers where the postoperative mortality following pancreaticoduodenectomy has decreased from 30% to 1% [6]. In spite of these advances, patients with PDAC have not reaped the benefit of improved long-term survival when surgery is used as initial therapy [3, 6–8]. One perceived reason is that patients often do not receive additional therapy after surgery, although there are multiple trials demonstrating a survival benefit with adjuvant therapy after surgical resection [7, 9–11]. Up to 47% of patients treated with upfront surgical resection fail to receive any adjuvant therapy [12], usually due to delayed postoperative recovery or early disease recurrence [13, 14]. These pitfalls of surgery as primary therapy are amplified in borderline resectable (BR) patients for which careful staging, meticulous patient evaluation, and preoperative therapy are necessary to identify the subset of patients most likely to benefit from the aggressi Anbazhagan, Kuppusamy ve surgical procedures necessary for complete surgical resection.

11.1.2 Initial Evaluation

All PDAC patients evaluated by a pancreatic surgeon could possibly require a high-risk but potentially curative, surgical procedure. A new diagnosis of PDAC is often made in patients with multiple underlying medical conditions of variable significance with respect to the risks of pancreatectomy. This high-stake clinical scenario mandates that the surgeon employs an organized approach to ensure a thorough and efficient initial evaluation. The anatomic relationship of the tumor and critical vessels as determined by a

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pancreas protocol CT scan and this data is of crucial significance, but other nonanatomic factors must also be evaluated, such as suspicion for extrapancreatic disease, comorbidities, and functional status. Using this approach, the whole patient and not just tumors are classified as potentially resectable or borderline candidates for surgical resection of the primary tumor.

11.1.3 MDACC Borderline Patient Types

Our center has developed a systemic approach in which all patients with localized PDAC receive a physical exam, review of laboratory studies, and radiographic imaging as part of a comprehensive evaluation in a surgical clinic. These data are then collated using a system denoted by the acronym "ABC" in which "A" refers to tumor "anatomic" considerations for surgery, "B" to cancer "biology" or stage, and "C" to patient "condition" or performance status and fitness for surgery (Fig. 11.1). In the course of treatment planning and communication across our multidisciplinary care team, patients are classified as clinically resectable (CR) borderline resectable (BR) using the common nomenclature BR-A, BR-B, or BR-C [15, 16]. BR-A patients have no major comorbidities, have no clinical findings that are suspicious for extrapancreatic disease, and meet anatomic imaging criteria for a borderline resectable tumor, as outlined below. BR-B patients have no major comorbidities or anatomic imaging criteria for a borderline resectable tumor and have clinical findings suspicious for extrapancreatic disease: (1) indeterminate liver lesions; (2) serum carbohydrate antigen (CA) 19-9 ≥1,000 U/ml, in setting a normal bilirubin; or (3) biopsy-proven involvement of regional lymph nodes. BR-C patients are advanced in age (≥80 years old) or possess severe comorbidities

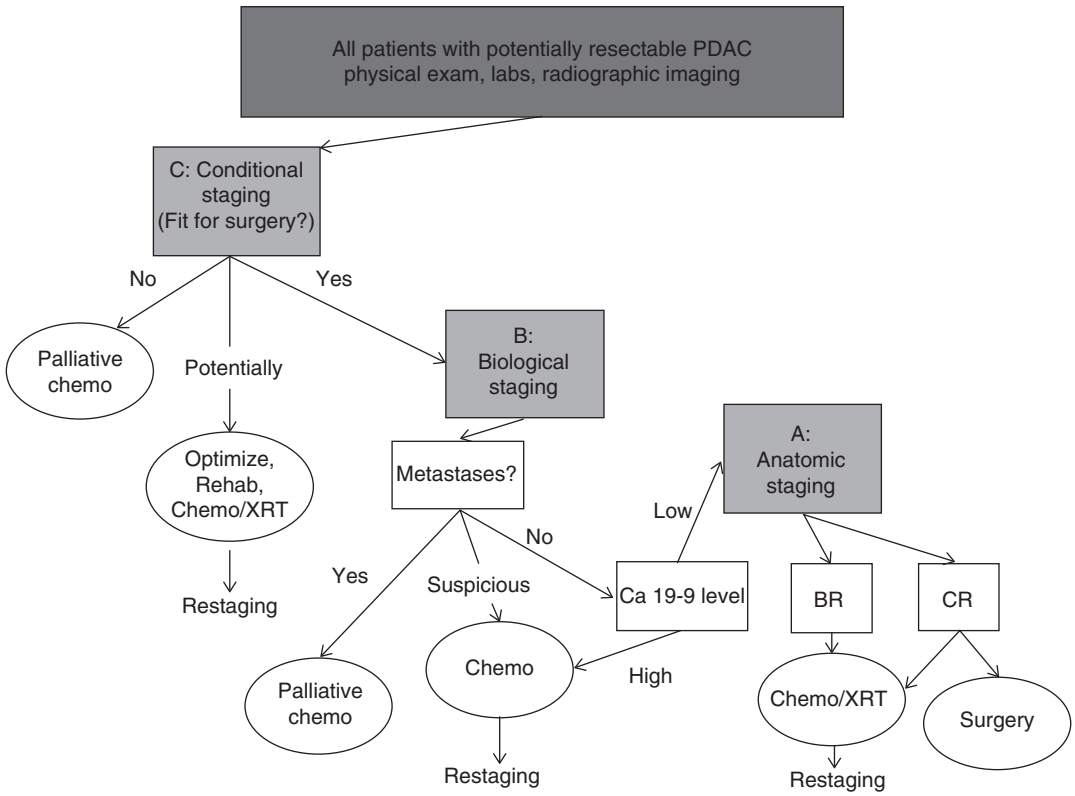

Fig. 11.1 Schema for initial evaluation and categorization of patients with pancreatic adenocarcinoma

requiring extensive evaluation or optimization or depressed performance status (ECOG ≥2). They may or may not have clinical findings suspicious for extrapancreatic disease.

11.1.4 Stratification Using MDACC Borderline Patient Types

In practice, the fitness of each patient for pancreatic surgery is evaluated first (Fig. 11.1). A patient who is too frail for surgery secondary to uncorrectable comorbidities does not need to undergo extensive evaluation for surgical resection or consideration for preoperative therapy since surgical resection will not be the end result. These patients can therefore be efficiently triaged for palliative therapy or supportive care. If the patient is not currently fit for surgery but has a potentially reversible condition, then medical optimization or pre-habilitation during preoperative therapy is the goal. These patients are referred to as BR-C and are generally older (median age 75 years) with a higher ECOG status (44% ECOG 2) usually secondary to cardiopulmonary disease (63%). If the patient is fit for surgery, biological staging is the next. Evidence of distant metastases on radiographic imaging is a contraindication to resection, but in many cases there are suspicious radiographic findings, but not diagnostic for distant metastatic disease. These patients are termed BR-B and receive chemotherapy followed by restaging. Similarly, patients with a high CA-19-9 (≥1,000) even with negative imaging are considered BR-B and receive chemotherapy followed by restaging. Finally, local anatomic factors related to the primary tumor are considered in patients who are without metastases and are fit for surgery. This necessitates careful review of radiographic image using standard anatomic criteria designed to categorize tumors as resectable, borderline, or locally advanced. Patients who are fit for surgery with no evidence or suspicion of metastases and borderline tumors are considered BR-A and usually receive chemotherapy plus or minus chemoradiation and restaging prior to proceeding with surgical resection.

11.1.5 Clinical Application of MDACC Borderline Patient Types

Clinical application of this approach to initial evaluation identifies that at least 50% of our patients have borderline clinical features. When treated preoperatively, only 37% of BR-C patients can be expected to undergo resection, while the others fail to reach surgical resection due to poor performance status (31%) or interval identification of metastatic disease (26%). BR-C patients who receive resection experienced a median survival of 38.6 months versus 13.3 months ($p = 0.02$) for those not receiving surgery. Roughly 46% of BR-B patients receive surgical resection of preoperative therapy, and an equal portion (46%) is found to have distant metastases precluding surgery. The loss of performance status is uncommon (4.9%) in BR-B patients. Resection conferred a 33-month median survival versus 11.8 months in those patients unable to proceed to resection ($p < 0.001$). Of note, local progression was rarely observed during preoperative therapy in either BR-B or BR-C patients (2.6%) [15, 17]. Management of patients with BR type A is considered below.

Key Point

- Pretreatment evaluation of patients can aid in accurate communication and treatment planning for patients with borderline resectable pancreatic cancer; many patients may have technically resectable tumors but may not be adequate candidates for surgery.

11.2 Defining Borderline Resectable PDAC Tumors

11.2.1 Imaging Using Contrast-Enhanced CT

All patients with apparent localized disease are evaluated with a contrast-enhanced computed tomography (CT) scan, which provides essential information about presence of regional or distant metastases and the site and local extent of the

primary tumor. This allows the surgeon to determine whether the patient has a resectable tumor and the likelihood of a margin negative resection. Multi-detector row CT is the most widely used staging modality for pancreas cancer and a workhorse for new patient evaluation. When performed and interpreted correctly, it provides valuable staging for both distant and regional metastases as well as local extrapancreatic extension of the primary tumor to adjacent critical vascular structures [18]. The National Comprehensive Cancer Network (NCCN) recommends that all patients with suspicion for PDAC have a dedicated pancreas protocol CT scan as part of the initial evaluation (Version 2.2015). At MD Anderson Cancer Center (MDACC), a pancreas protocol CT scan uses water as a negative oral contrast agent and starts with pre-contrast imaging from the dome of the liver extending caudally to include the entire liver reconstructed to 2.5 mm slice thickness. Next, 125 ml of iodinated contrast is administered intravenously at a rate of 3–5 ml/s. The pancreas phase/arterial phase uses bolus tracking, and images are obtained 10 s after a Hounsfield unit value of 100 is reached in the aorta at the level at the celiac axis from the dome of the liver to the iliac crests. Images for the portal venous phase are obtained at a 20 s delay from the pancreas phase. Hepatic metastases are usually best visualized on the portal venous phase. Delayed images are obtained 15 s after the portal venous phase. The images are reconstructed to 2.5 mm slice thickness for imaging review and at 0.625 mm or 1.25 mm slice thickness to create coronal and sagittal reformatted images [19].

11.2.2 CT Identification of Pertinent Vascular Anatomy

The primary pancreatic tumor is best seen on the pancreas phase of the CT scan and is usually a hypodense mass, because the surrounding normal pancreatic parenchyma enhances. The pancreas phase/arterial phase illuminates the branches of the celiac axis and superior mesenteric artery (SMA), enabling one to identify important arterial anatomy variants and discern whether the tumor has any arterial involvement. As many as 40–45% of patients have variants of "normal" hepatic arterial anatomy, which are of vital importance to appreciate on preoperative imaging as these variants can impact operative planning [20]. A replaced or accessory right hepatic artery is present in up to 15% of patients and most commonly arises from the SMA and courses posterior to the pancreas and posterolateral to the bile duct. An additional 2.5% of patients have a replaced common hepatic artery (CHA) that arises from the SMA and follows a similar path to a replaced or accessory right hepatic artery. The superior mesenteric vein (SMV) and portal vein (PV) are best evaluated on the portal venous phase. The initial staging CT scan has 94% sensitivity and 84% specificity of determining vascular involvement, and the surgeon should carefully note the tumor-vein interface, vein contour, and/or deformity; there are multiple classification schemes that predict venous involvement based on imaging characteristics, and these should be employed for operative planning [21–24]. Additionally, the surgeon should identify the location and relationship of the gastroepiploic vein, colic veins, inferior mesenteric vein (IMV), and jejunal/ileal branches of the superior mesenteric vein as these have variable courses, and the drainage pattern directly impacts surgical options for reconstruction of the superior mesenteric-portal vein (SMV-PV) confluence, which can be expected in over 40% of cases. Terminology that describes vascular involvement has become standardized and is reviewed in detail below. If the vascular involvement is $\leq 180°$, the circumference of the vessel is termed abutment. If the vascular involvement is $>180°$, the circumference of the vessel is termed encasement. The importance of properly staging patients and determining potential vascular involvement is a cornerstone of treatment planning and cannot be overstated [25].

11.2.3 Imaging Definitions of Resectability

As patient assessment, imaging, and multidisciplinary treatment techniques for patients with localized PDAC were refined in the late 1990s, it became evident that this patient group included a spectrum of primary tumor types from removable to unresectable. To allow common classification, the multidisciplinary team at MDACC developed imaging criteria that are still in use that define clinically resectable (CR) tumors by the following: (1) absence of extrapancreatic disease; (2) clear tissue plan between the tumor, the celiac axis, hepatic artery, and SMA; and (3) a patent SMV-PV confluence, abutment, or encasement is allowed as long as the vessel is patent [4, 16, 26]. Locally advanced (LA) tumors are defined by the following: (1) encasement of the celiac axis, (2) encasement of the hepatic artery with no options for vascular reconstruction, (3) encasement of the SMA >180°, and (4) occlusion of the SMV-PV confluence with no options for vascular reconstruction [4, 16, 26]. Patients who were classified as CR based on these imaging criteria were likely candidates for a R0 resection, while patients with LA tumors were unlikely to respond to chemotherapy and/or chemoradiation to a degree that would allow surgical resection; however, improved response to systemic therapy increasingly allowed patients with advanced tumors to undergo resection.

Currently, NCCN defines resectable PDAC as a tumor with no contact of celiac axis, SMA, or CHA and no contact with the SMV-PV or ≤180° contact without vein contour irregularity (Version 2.2015). LA PDAC of the head/uncinate process is a tumor that contacts the SMA >180°, the celiac axis >180°, the first jejunal SMA branch, and the most proximal draining jejunal vein or has unreconstructible SMV-PV involvement or occlusion. Tumors of the body/tail are LA when there is contact of >180° with SMA or celiac axis, contact with the aorta, or unreconstructible SMV-PV involvement or occlusion (Version 2.2015).

11.2.4 Imaging Criteria for Borderline Resectable Tumors

In 2001, Mehta et al. described a group of "marginally" resectable patients who were treated with chemoradiation preoperatively in order to downstage the tumor and increase the likelihood of a margin negative resection [27]. "Marginally" resectable was defined as a tumor in which the perivascular fat plane was absent over 180° of the SMA, SMV, or PV and persisted for a length >1 cm [27]. The NCCN adopted the term "borderline resectable" in 2006 to describe patients with localized tumors who blurred the lines between CR and LA tumors. These patients were felt to be at higher risk of a margin-positive resection, if upfront surgery was employed; thus, the NCCN suggested the use of preoperative therapy.

Over the last several years, several groups developed specific radiographic features to define BR-PDAC. At MDACC, the imaging criteria used to define a BR tumor are (1) abutment of the celiac axis, (2) abutment of the hepatic artery or short-segment encasement, (3) abutment of the SMA ≤180°, and (4) short-segment occlusion of the SMV-PV confluence amendable to resection and reconstruction [4, 16, 26]. The AHPBA, SSO, and SSAT societies define BR-PDAC as tumors with no abutment or encasement of the celiac axis, short-segment abutment or encasement of the CHA amenable to reconstruction, abutment <180° of the SMA, or abutment with or without impingement or narrowing of the SMV-PV or encasement with or without occlusion with suitable vein proximal and distal to allow resection and reconstruction [28, 29]. The difference between the MDACC and AHPBA/SSO/SSAT definitions hinges around the extent of SMV-PV involvement that differentiates BR from resectable tumors (Fig. 11.2). The NCCN definition for BR-PDAC has changed multiple times over the years but currently includes tumors of the head/uncinate process that contact the

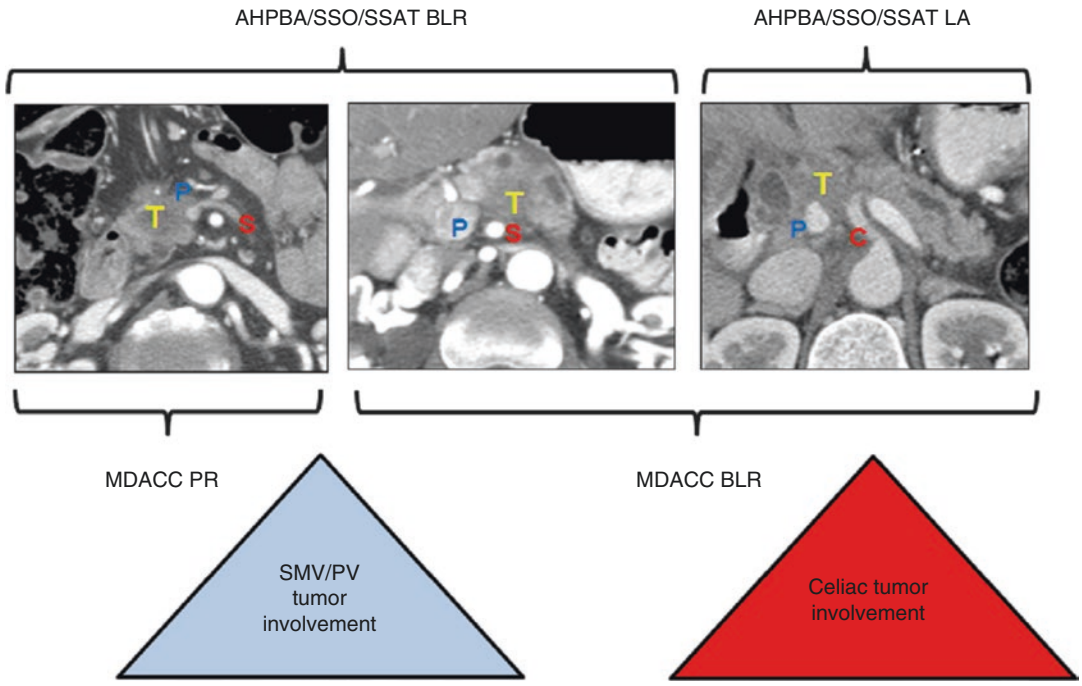

Fig. 11.2 This schematic uses representative CT scan images to display the overlap between definitions of borderline resectability between MDACC and AHPBA/SSO/SSAT criteria. MDACC criteria allow SMV-PV involvement (P) of the tumor (T) within the potentially resectable group but allow tumor abutment of the celiac trunk (C) within the borderline group

Table 11.1 Definitions of BR-PDAC

	MDACC	AHPBA/SSO/SSAT	NCCN
CA	Abutment	No abutment or encasement	Contact ≤180°
CHA	Abutment of short-segment encasement	Short-segment abutment or encasement amenable to reconstruction	Contact without extension to celiac axis or hepatic artery bifurcation amenable to resection and reconstruction
SMA	Abutment <180°	Abutment <180°	Contact ≤180°
SMV-PV	Short-segment occlusion amenable to resection and reconstruction	Abutment >180° or occlusion amenable to resection and reconstruction	Contact of >180°, contact of ≤180° with irregularity of vein or thrombosis amenable to resection and reconstruction

CHA without extension to the celiac axis or the hepatic artery bifurcation, contact ≤180° of the SMA, contact >180° of the SMV or PV, contact ≤180° with a contour irregularity or thrombosis of the SMV-PV with suitable vessel proximal and distal that will allow venous resection and reconstruction, or contact with IVC. Tumors of the body/tail are classified as BR when there is contact of ≤180° with the celiac axis or contact of >180° with the celiac axis without involvement of the aorta and an intact and uninvolved gastroduodenal artery (Version 2.2015) (Table 11.1).

A current multi-institutional treatment trial investigating preoperative FOLFIRINOX and chemoradiation defines borderline resectable PDAC as radiographically localized tumors with

one or more of the following: (1) an interface between the tumor and SMV-PV ≥180°, (2) short-segment occlusion of the SMV-PV with normal vein above and below that is amendable to resection and reconstruction, (3) short-segment interface between the tumor and hepatic artery with normal artery proximal and distal that is amendable to resection and reconstruction, and (4) interface between the celiac axis or the SMA <180° [30].

11.2.5 Common Themes of Imaging Criteria

Although no consensus definition for BR has been reached, common themes can be appreciated. All BR criteria include statements regarding the ability or inability of the surgeon to reconstruct the SMV-PV or the hepatic artery involved with tumor. This implies that anatomic resectability is heavily dependent upon the judgment and experience of the surgeon. The importance of this expertise cannot be overemphasized. Conversely, another common theme of borderline criteria is the exclusion of tumors involving >180° of the superior mesenteric artery: a practice largely derived from the concept that tumor involvement of the nerves and periadventitial tissue reflects an aggressive tumor biology that likely cannot be overcome through surgical technique alone.

Key Point

- Imaging using contrast-enhanced computerized tomography is necessary to stage the patient and evaluate extrapancreatic extent of the primary tumor.

11.3 Management

11.3.1 Multimodality Preoperative Therapy

Despite differences in definitions of BR-PDAC, there is agreement that these patients are at a higher risk for margin-positive resection and that preoperative therapy is prudent. Since initially described by Evans and Rich in 1995 [31], the potential benefits of preoperative therapy have been itemized and include (1) early treatment of micrometastatic disease, (2) higher proportion of patients receive multimodal therapy, (3) select patients with localized disease and more favorable tumor biology, who are most likely to benefit from surgical resection, (4) increase the likelihood of a R0 resection, and (5) smaller radiation fields with well-oxygenated tissue. At MDACC, all patients with BR-PDAC receive chemotherapy, chemoradiation, or both prior to surgical resection. Chemotherapy regimens have continued to evolve over the years; currently, most patients receive either gemcitabine with nab-paclitaxel or FOLFIRINOX. External beam radiation therapy is utilized and consists of 50.5 Gy delivered in 28 fractions or 30 Gy in 10 fractions with a concomitant radiosensitizing dose of 5-fluorouracil, gemcitabine, or capecitabine. The most common treatment sequence for BR-PDAC is 2–4 months of chemotherapy, followed by chemoradiation, and a 6-week treatment break prior to surgical resection. Patients are typically restaged every 2 months. Patients only undergo surgical resection if the operating surgeon and multidisciplinary treatment group reach consensus that pancreatectomy will safely achieve an R0 resection and provide a reasonable chance for cure.

11.3.2 Restaging During Preoperative Therapy

Restaging should include a pancreas protocol CT scan and measurement of CA 19-9. Katz et al. evaluated the radiographic response, using RECIST criteria, of 129 patients with BR-PDAC after completion of preoperative therapy (Fig. 11.3). The preoperative therapy consisted of gemcitabine-based chemotherapy followed by chemoradiation (30 Gy or 50.4 Gy) or chemoradiation alone. One hundred twenty-two patients completed therapy and were restaged, 84 (69%) had stable disease, 15 (12%) had a partial

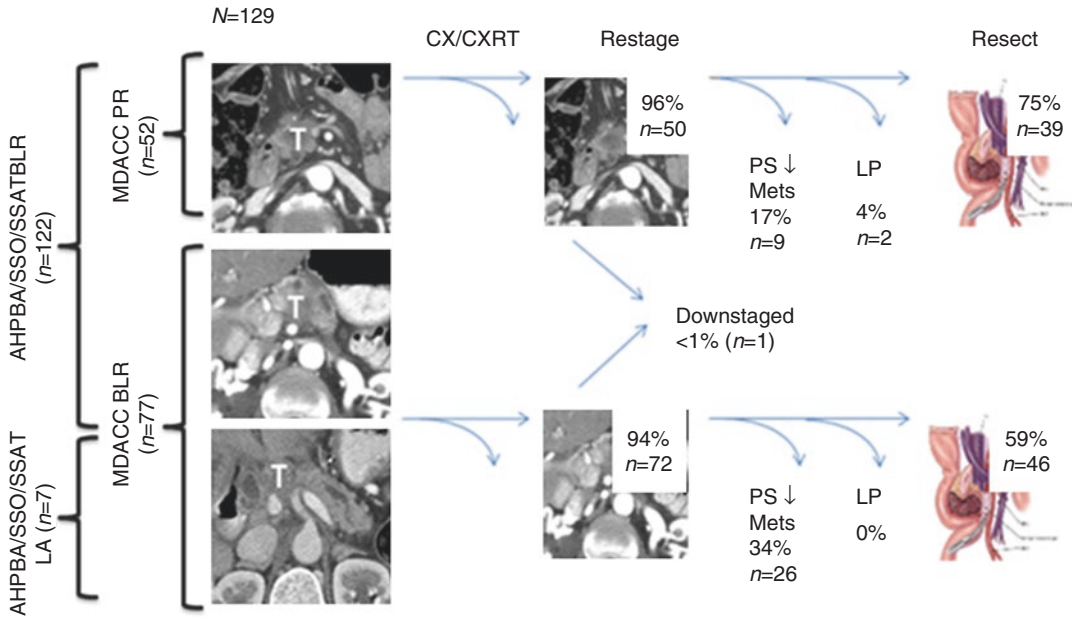

Fig. 11.3 Outcomes after preoperative therapy of 129 patients with borderline tumor criteria classified by AHPBA/SSO/SSAT and MDACC criteria. Regardless of criteria, local downstaging or progression is uncommon

response, 23 (19%) had progressive disease (development of metastases, $n = 21$; primary tumor growth, $n = 2$), and no patient had a complete response. All patients were classified by the MDACC and AHPBA/SSO/SSAT definitions, and only one patient was downstaged, while approximately 80% remained at the same stage and 20% were upstaged [32]. Donahue et al. reported a series of patients with BR and LA pancreatobiliary malignancies who were treated with preoperative chemotherapy and were restaged with CT/MRI imaging, which only had a 71% sensitivity and 58% specificity for vascular involvement after completion of preoperative therapy [33]. Ferrone et al. reported a series of patients with BR and LA PDAC treated with preoperative FOLFIRINOX with or without radiation therapy, and 30% were deemed to be resectable on posttreatment imaging. Most patients were still classified as LA (48%) and BR (22%), as there were no clear fat planes around the critical vascular structures. Nonetheless, an R0 resection was achieved in 92% of the patients [34]. Current cross-sectional imaging does not differentiate viable tumor from fibrosis. Tzeng et al. compared pretreatment and posttreatment CA19-9 levels in patients with BR-PDAC [35]. All patients had a pretreatment CA19-9 ≥40 U/ml and a total bilirubin ≤2 mg/dl. A decline in CA19-9 was seen in 116 (82%) patients and 47 (33%) had normalization of CA19-9. Posttreatment CA19-9 was a predictor of failure to undergo pancreatectomy. Normalization of CA19-9 was associated with improved median overall survival in resected (38 versus 26 months, $p < 0.02$) and unresected patients (15 versus 11 months, $p = 0.02$) [35]. After completion of preoperative chemotherapy/chemoradiation, patients without evidence of radiographic disease progression and a decrease in CA19-9 should undergo attempted surgical resection, if medically fit for an operation.

11.3.3 Preoperative Therapy Based Upon MDACC Borderline Patient Type

The application of these management approaches is described in recent report in which 160 patients with BR-PDAC (BR-A 84, BR-B 44, BR-C 32) were followed prospectively (Fig. 11.4). One

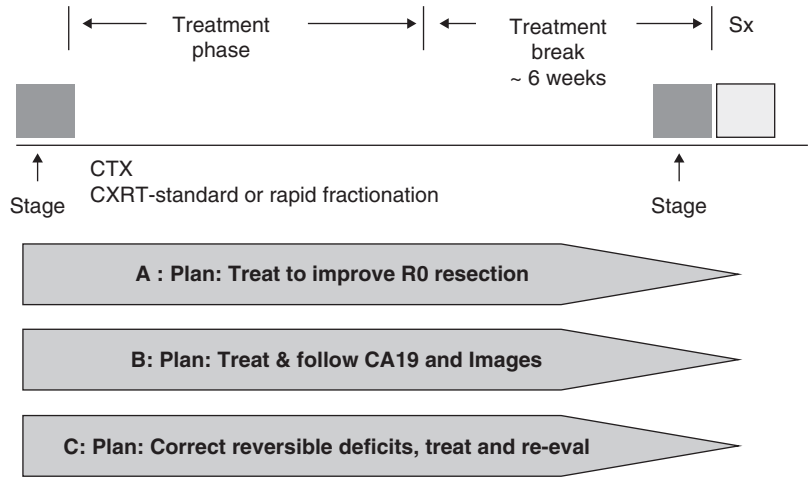

Fig. 11.4 This schematic demonstrates the overall strategies of preoperative therapy when employed for patients based upon MDACC borderline patient type

hundred twenty-five (78%) patients completed induction therapy and a restaging evaluation. Forty-three patients were determined to not be surgical candidates: poor performance status ($n = 10$), distant disease progression ($n = 16$), and unresectable local-regional disease ($n = 17$). Seventy-nine patients were taken to the operating room, 13 were found to have radiographically occult distant metastases, 4 had locally advanced disease, and the other 63 underwent a grossly complete resection of the primary tumor −53% of the patients who underwent restaging. Majority underwent a pancreaticoduodenectomy (86%), 27% required a SMV-PV resection, and an additional 3% required a hepatic artery resection. An R0 resection was achieved in 94% of the patients, and four patients had microscopically positive margins (2, SMA; 1, pancreatic duct; 1,bile duct). Twenty-six (39%) patients had nodal metastases. A partial or complete pathologic response (<50% remaining viable tumor cells) was seen in 56% of patients, and four (6%) had a complete pathologic response. Considering the entire cohort of 160 patients, 41% of patients underwent resection; the resection rate for BR-A, BR-B, and BR-C was 38%, 50%, and 38%, respectively. The median overall survival for the entire cohort was 18 months with a 5-year survival of 18%. For the 66 patients who completed all therapy, the median survival was 40 months with a 5-year survival of 36% [16]. Together, these prospective data provide support for planned and ongoing single and multi-institutional prospective studies evaluating this multidisciplinary approach for patients with BR-PDAC.

Key Point

- Preoperative therapy allows selection of borderline resectable patients who are fit for surgery and have locally dominant PDAC.

Conclusion

Patients with BR-PDAC represent a heterogeneous group of patients at high risk of regional and distant recurrence after therapy. The first step is to evaluate, accurately identify, and stage, so that an optimal treatment plan can be developed. Future improvements in systemic therapy will open the door for more patients to receive potentially curative resection.

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Guidelines for the Management of Pancreatic Cystic Neoplasms

12

Masao Tanaka

12.1 Introduction

Recent awareness and widespread increasing usage of cross-sectional imaging studies are resulting in increased detection of incidental pancreatic cystic neoplasms (PCNs).

Pancreatic cysts were detected in 10% of 123 patients who underwent magnetic resonance cholangiopancreatography (MRCP) for nonpancreatic diseases [1]. Likewise, abdominal magnetic resonance imaging (MRI) and multi-detector computed tomography (MDCT) examinations were associated with a 2.4–20% incidence of PCNs [2–5]. A population-based study showed IPMN identified in one per 1,009 persons 60 years and older [6]. All these figures indicate that PCNs are far more frequent than previously thought.

Most of these incidentally detected PCNs are asymptomatic, and the vast majority of them are branch duct intraductal papillary mucinous neoplasms (BD-IPMNs) (Fig. 12.1). Mucinous cystic neoplasm (MCN) may be the second most frequent PCN (Fig. 12.2). Other sorts of PCNs, including serous cystic neoplasm (SCN), solid pseudopapil-

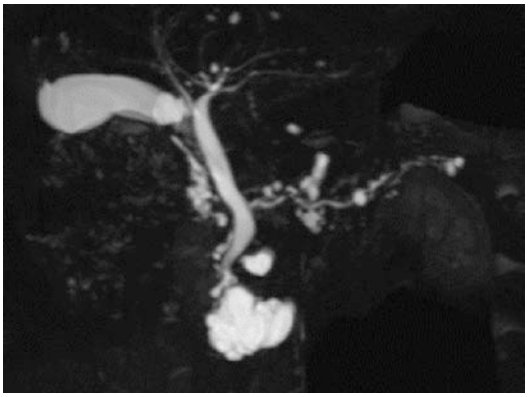

Fig. 12.1 Magnetic resonance cholangiopancreatogram showing multiple branch duct intraductal papillary mucinous neoplasms (BD-IPMNs)

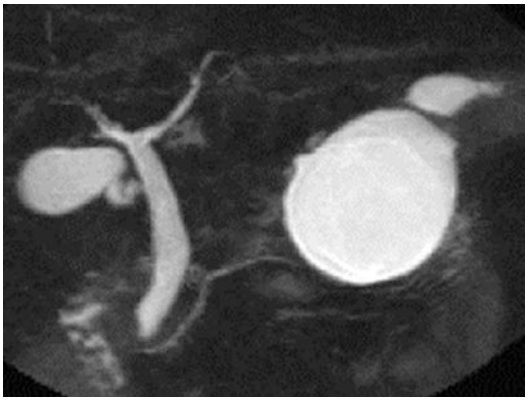

Fig. 12.2 Magnetic resonance cholangiopancreatogram demonstrating a mucinous cystic neoplasm (MCN)

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lary neoplasm (SPN), and cystically degenerated solid neoplasms such as neuroendocrine neoplasm and ductal adenocarcinoma, are rather rare and are beyond the scope of this chapter.

12.2 Guidelines for the Management of PCNs

To date, at least eight guidelines or statements for the management of PCNs, or more specifically IPMN and MCN, have been published in the English literature. Since no significant data exist from prospective studies yet, all the guidelines and statements are based on a critical review of available data and consensus of experts.

12.2.1 American Society for Gastrointestinal Endoscopy (ASGE) Guideline

To the best of our knowledge, the guideline on the role of endoscopy in the management of cystic lesions of the pancreas published by the ASGE in 2005 might be the first [7]. This ASGE guideline described the roles of endoscopic ultrasonography (EUS) with/without EUS-guided fine needle aspiration (FNA) with cyst content cytology, chemistry, and tumor marker analysis for differentiation of mucinous from non-mucinous PCNs and for diagnosis of malignancy. The CEA cutoff level of 192 ng/ml provided a sensitivity of 75% and a specificity of 84% for differentiating mucinous tumors from other cystic lesions. CEA is invariably below 5 ng/ml in SCNs, while the level was usually, but not always (<5 ng/ml in 7%), high in mucinous cysts. Malignancy within a PCN could be identified by cytology with 83–100% specificity, although sensitivity greatly varied from 25% to 88%. Among a variety of roles of endoscopic retrograde cholangiopancreatography (ERCP), duodenoscopy might disclose the highly specific finding of patulous orifice of the papilla filled with mucin in IPMN patients. The rest of the guideline dealt with EUS morphology, cytology, chemistries, and tumor markers of the cyst content obtained by EUS-FNA, other kinds of PCNs, and the roles of endoscopy in the management of pancreatic fluid collection.

12.2.2 American College of Gastroenterology Guideline

In 2007, American College of Gastroenterology proposed a guideline for the diagnosis and treatment of PCNs with their suggestions on 13 common clinical problems [8]. This guideline dealt with a variety of PCNs and nonneoplastic pancreatic cysts. Regarding IPMN, it described that the risk of malignancy increases with older age, the presence of symptoms, involvement of the main pancreatic duct (MPD), dilation of the MPD over 10 mm, the presence of mural nodules, and size over 3 cm for BD-IPMN. It also referred to cytological analysis, determination of tumor marker concentrations, and molecular diagnostic evaluations from samples obtained by EUS-FNA. It mentioned identification of papillary projections associated with malignant transformation and determination of the longitudinal extent of IPMN by pancreatoscopy as well. The risk of malignancy of MCN was claimed to be less than that associated with MD-IPMN and suggested by greater size (>2 cm), cyst wall irregularity and thickening, intracystic solid regions, an adjacent solid mass, and perhaps calcification of the cyst wall. It also referred to EUS-FNA but the sensitivity of cytology was suboptimal (<50%). Resection was recommended for patients with MCN considered to be at acceptable risk for perioperative complications as was the recommendation in MD-IPMN.

12.2.3 Korean Guideline

A Korean group reported their guideline focusing on the treatment of BD-IPMN in 2008 [9]. Granting that many factors must be considered when choosing between the surgical and observation options, such as operative risk based on general condition, estimated remaining life span, the risk of malignant transformation, and the extent of surgery, they claimed that the cutoff of the cyst size of BD-IPMN for malignancy prediction should be lowered to 2 cm based on their observation of a sharp increase in malignancy potential from 2 cm, regardless of the presence of mural nodules. They stated that observation could only be recommended for BD-IPMN ≤2 cm without

mural nodule. They also observed 9 "combined" pancreatic cancers (6.5%) among 31 previous or concurrent malignancies in 29 (21.0%) of 138 patients with BD-IPMN.

12.2.4 American College of Radiology White Paper

The American College of Radiology issued a white paper regarding the management of incidental CT findings including PCNs in 2010 [10].

The Incidental Findings Committee recommended the following for managing incidental pancreatic cysts:

1. Surgery should be considered for patients with cysts ≥3 cm.
   (a) If the lesion is an SCN, surgery is deferred until the cyst is ≥4 cm.
   (b) SPN should be resected.
   (c) Patient factors ultimately determine the appropriateness of surgical treatment.
2. Patients with simple (not containing any solid elements) cysts ≤3 cm can be followed.
   (a) Attempts should be made to characterize all cysts ≥2 cm at the time of detection. Magnetic resonance imaging is the imaging procedure of choice.
   (b) Cyst aspiration is strongly advised before any surgery is undertaken in a patient with a cyst of this size.
   (c) Cysts ≤2 cm can be followed less frequently than those between 2 and 3 cm.
   (d) Avoid characterizing cysts ≤1.5–2 cm unless absolutely characteristic.
3. The presence of symptoms is a critical factor in deciding appropriate therapy.
   (a) The frequency of malignancy in small cysts is significantly higher in symptomatic patients.

12.2.5 European Consensus Statements

Consensus statements on the PCNs were reported from the European study group on cystic tumors of the pancreas in 2013 [11]. A total of 26 questions concerning the diagnosis, treatment, and follow-up of IPMN, MCN, SCN, and SPN but no other PCNs were presented along with recommendations with grade classification where appropriate. As readily expected, there were no grade A recommendations. Resection should be considered in all symptomatic lesions, MCN, MD-IPMN, and SPN as well as in BD-IPMN with mural nodules and dilation of the MPD>6 mm considered as the most important risks for malignancy.

The statements were unique in four points. First, they admitted resection of cystic lesions without any risk factors in high-volume centers due to a cumulative risk of cancer in patients with long life expectancy or with an increased risk for cancer development. Also, a large SCN (>6 cm) and location in the head of the pancreas were considered independent risk factors for aggressive behavior that might justify surgical resection. Second, the attitude toward EUS-FNA for BD-IPMN was modest. They stated that EUS-FNA with cyst fluid analysis might be used, but there was no evidence to suggest this as a routine diagnostic method. Third, they recognized that there was no safe lower limit in size of BD-IPMN that could completely exclude malignancy. Fourth, they mentioned the limit of surveillance for BD-IPMN. If no changes occur during the first year of a 6-monthly follow-up, a yearly follow-up is then recommended for the following 5 years, and even if the patient remains asymptomatic and the IPMN unchanged, surveillance should be continued as long as the patient is fit for surgery. In other words, surveillance should be stopped when the patient has become unfit for surgery.

12.2.6 Italian Consensus Guidelines

Italian experts also issued their consensus guidelines for the diagnosis and follow-up of PCNs in 2014 [12]. With the characteristics of the Italian Healthcare System taken into consideration; this consensus was reached for each statement according to the Delphi procedure. Both the level of evidence and the grade of recommendation were reported according to the Oxford criteria. This consensus is unique in that they stressed at the beginning that no additional examinations are

required when the patient is found to be unfit for any treatment and remains asymptomatic. Based on this assumption, they reported recommendations regarding the most appropriate use and timing of various imaging techniques, the role of circulating and cyst fluid markers, and the pathologic evaluation for the diagnosis and surveillance of IPMN, MCN, SCN, and SPN.

Of note is a comment that a significantly higher incidence of complications for EUS-FNA of PCNs than for solid lesions (14% vs. 0.5%, $P < 0.001$) has been reported, including hemorrhage, pancreatic fistula, acute pancreatitis, pancreatic abscess, and infection. Nonetheless, there is a statement that a cytological examination is useful in the differential diagnosis between benign and malignant PCNs (evidence level 2a, recommendation grade B, agreement 100%), although the adequacy and accuracy strongly depend on the overall institutional experience.

12.2.7 American Gastroenterology Association Guidelines

Most recently, two groups of the American Gastroenterology Association (AGA) performed an extensive literature review [13] and issued their guidelines on the management of asymptomatic PCNs employing the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework [14]. Just as expected, since all the evidences are graded as of *very low quality*, all the recommendations are *conditional* except for the recommendation of surgical expertise, i.e., if surgery is considered for a PCN, patients should be referred to a center with demonstrated expertise in pancreatic surgery (*strong recommendation*, *very low quality* evidence).

12.2.8 International Consensus Guidelines

The International Association of Pancreatology (IAP) issued consensus guidelines for the management of IPMN and MCN in 2006 [15], and these guidelines were updated in 2012 [16]. Sendai consensus for prediction of malignancy and the clinical management of IPMN proposed in the initial IAP guidelines was widely employed. MD-IPMN with dilation of the MPD >10 mm was a surgical indication as frequently malignant. The criteria for resection of BD-IPMN comprised of clinical symptoms (pain, pancreatitis), positive cytology, the presence of mural nodules, MPD dilation >6 mm, and cyst size >3 cm ("Sendai criteria"). Although the cyst size >3 cm was not proposed as an absolute indication for resection in the Sendai consensus, many patients were recommended surgery employing this criterion. However, the rate of malignancy in surgical specimens of this group of patients was only 13–23% [17, 18].

Then, the international consensus guidelines revised in 2012 (Fukuoka consensus) proposed two-layer criteria for prediction of malignancy in IPMN, i.e., "high-risk stigmata" to recommend immediate resection for fit patients and "worrisome features" to warrant complete examinations by EUS (Fig. 12.3) [16]. Fukuoka consensus is accepted well with higher sensitivity to diagnose main duct (MD)-IPMN and to predict malignancy in IPMN [19–21], while the adequacy of the cyst size moved from the "high-risk stigmata" to "worrisome features" is still controversial [21–24]. One meta-analysis reported that the cyst size >3 cm was associated most strongly with malignant IPMN [24], while another meta-analysis declaimed that the presence of mural nodules should be regarded most highly suspicious of malignancy [21].

In this regard, there exist many reports of invasive carcinoma found in BD-IPMNs ≤3 cm without mural nodules ("flat" BD-IPMN) [23, 25]. This is contradictory to the white paper issued by the American College of Radiology that recommends avoidance of characterizing asymptomatic small cysts <2 cm. The relationship between the risk of malignancy and cyst size should be evaluated without the influence of mural nodules or MPD dilation.

Sadakari et al. [17] reported the frequency of malignancy of 3.6% in BD-IPMNs ≥30 mm with-

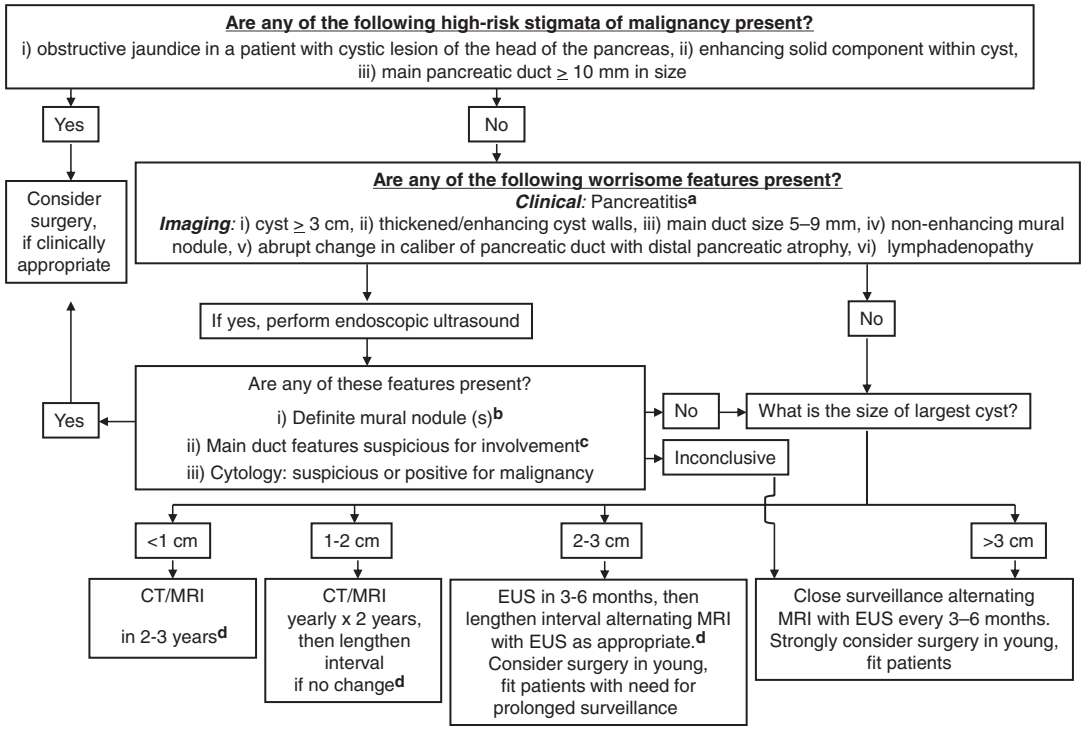

Fig. 12.3 Management algorithm with two-layer criteria for stratifying risk factors to predict malignant changes of branch duct intraductal papillary mucinous neoplasm (BD-IPMN) (Cited and reproduced with permission from Pancreatology 2012;12:183–197 with minor correction). (**a**) Pancreatitis may be an indication for surgery for relief of symptoms. (**b**) Differential diagnosis includes mucin which can move with change in patient position, may be dislodged on cyst lavage, and does not have Doppler flow. Features of true tumor nodule include lack of mobility, the presence of Doppler flow, and FNA of nodule showing tumor tissue. (**c**) The presence of any one of thickened walls, intraductal mucin, or mural nodules is suggestive of main duct involvement. In their absence, main duct involvement is inconclusive. (**d**) Studies from Japan suggest that on follow-up of subjects with suspected BD-IPMN, there is increased incidence of pancreatic ductal adenocarcinoma distinct from malignant transformation of the monitored BD-IPMN(s). However, it is unclear if imaging surveillance can detect ductal adenocarcinoma in its early phase and, if so, at what interval surveillance imaging should be performed

out mural nodules or MPD dilation (<5 mm), while it was 26.3% when the MPD diameter was ≥5 mm or more. Fritz et al. [22] reported that 17 of 69 patients (24.6%) with BD-IPMNs <3 cm showed malignancy (invasive carcinoma or HGD), but EUS was not performed in all the patients. Wong et al. [23] reported 105 patients with BD-IPMN without Sendai criteria on EUS. Twenty-four (34%) of 70 cysts ≤3 cm were invasive cancer, including 1 of 7 cysts <1 cm (14%), 2 of 19 cysts 1–2 cm (11%), and 21of 44 cysts 2–3 cm (48%). On the other hand, 15 of 35 cysts (43%) >3 cm were invasive cancer. Sixteen cysts ≤3 cm (23%) had HGD, including 3 of 7 cysts <1 cm (43%), 3 of 19 cysts 1–2 cm (16%), and 10 of 44 cysts 2–3 cm (23%). Shimizu et al. [26] also reported that 9.4% of 160 patients with malignant IPMN (noninvasive 100, invasive 60) had no mural nodules on EUS. Furthermore, Koshita et al. [27] reported that 9 (43%) of 21 patients with invasive IPMN had no mural nodules on EUS.

Although the reliability of EUS examination is quite observer dependent, we have to realize that the absence of mural nodules does not absolutely guarantee the safety of IPMN. The patient's age, location of the cyst, medical conditions, and operative risks must also be considered. Younger ages of the patient should be taken into account as well in view of the cumulative risk of cancer development during his/her lifetime [28].

12.3 Lengthening of Surveillance Interval

Adequate methodologies and intervals of surveillance of BD-IPMN to check the malignant changes and/or the development of concomitant but distinct PDAC remain to be determined. Fukuoka consensus recommended yearly follow-up for cysts <10 mm, 6–12 monthly follow-up for cysts 10–20 mm, and 3–6 monthly follow-up for cysts >20 mm [16]. Fukuoka consensus advocated lengthening of the surveillance interval after 2 years of no change on images, whereas it suggested not to lengthen the intervals >6 months in view of the relatively high incidence of concomitant PDAC mentioned above. A French group claimed the adequacy of lengthening of the surveillance intervals in view of a low incidence of the malignant change in IPMN, yet they recommended biannual imaging studies [29]. Tamura et al. [30] showed that even a 6-month interval might be insufficient for the timely diagnosis of a concomitant PDAC in a patient with IPMN.

12.4 When to Stop Surveillance

Whether we can stop surveillance of patients with BD-IPMNs or not, and, if yes, when to stop remain debatable. It is surely useless to continue surveillance of those who cannot be candidates for surgery. However, the chronological age per se, 85 years old, for example, should not be taken as the limit for surveillance, because the medical condition of each patient is different.

The American College of Radiology recommended stopping the surveillance after 2 years when a small cyst shows no change [10]. Fukuoka consensus stated that there were no good long-term data to indicate whether surveillance can be safely spaced to every 2 years or even discontinued after long-term stability [16]. Recently, the AGA guidelines have recommended quitting surveillance when a cyst does not show a significant change in 5 years, if high-risk features are completely negated and the patient does not have a strong family history of PDAC [14]. They state that the small risk of malignant progression in stable cysts is likely outweighed by the costs of surveillance.

However, these recommendations to stop surveillance of BD-IPMNs are now questioned as there are no long-term data to support this concept, and moreover, there are so many reports of retrospective studies addressing the long-lasting risk of development of concomitant pancreatic cancer in patients with IPMNs and a history of IPMNs [30–60]. Khannoussi et al. [46] found two PDACs concomitant with IPMN both after 84-month follow-up and concluded that imaging surveillance was still necessary beyond 5 years. Likewise, Lafemina et al. [49] also noted that 5 of the 18 patients with invasive carcinoma found in 97 patients with BD-IPMN resected developed PDAC in a region distinct from monitored IPMN (5.2%) and stressed the importance of consideration of risk not only to the index cyst but also to the entire gland in surveillance strategy of IPMN. The significance of indefinite surveillance was repeatedly noted as early as in the 2000s as well [61, 62]. He et al. [50] also emphasized that patients who have undergone resection for noninvasive IPMN require indefinite close surveillance because of the risks of developing a new IPMN, of requiring surgery, and of developing cancer (0%, 7%, and 38% at 1, 5, and 10 years, respectively). More recently, Miyasaka et al. [58] also stated that the incidences of both malignant IPMN and concomitant cancer rise further even after 5 years.

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13 Guideline for the Management of Pancreatic Neuroendocrine Tumor

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13.1 Introduction

Pancreatic neuroendocrine neoplasms (PNENs) are divided in functional tumors, which cause syndromes deriving from the secretion of active hormones, and nonfunctional tumors, which commonly secrete hormones, not causing specific symptoms. A number of factors influence treatment and prognosis, which are discussed in this chapter.

13.2 Management of Functioning Pancreatic Neuroendocrine Neoplasms (F-PNENs)

13.2.1 Surgery for Gastrinoma

Gastrinomas are neuroendocrine neoplasms generally localized in the duodenum and pancreas that secrete gastrin hormone, causing Zollinger-Ellison syndrome (ZES), and are characterized by gastric acid hypersecretion and severe acid-related peptic disease and diarrhea [1].

Approximately 80% of gastrinomas are sporadic, while 20–30% are associated with multiple endocrine neoplasia type 1 (MEN1) [2].

Gastrinomas are the most frequent malignant, functional pancreatic neuroendocrine neoplasms (F-PNENs), but only around 25% of them are localized in the pancreas. In fact the majority of them is found in the "gastrinoma triangle" that comprises the head of the pancreas and the duodenal sweep.

Medical therapy is the mainstay in patients with ZES in order to control acid hypersecretion and to prevent peptic complications. Proton pump inhibitors (PPIs) are the current standard of care, and after their introduction, total gastrectomy for control of symptoms has become extremely rare [3].

There is general consensus that complete resection of the primary neoplasm and the involved lymph nodes should be offered to all patients with sporadic ZES and potentially resectable disease arising from the pancreas and/or the duodenum with no metastatic disease and who are fit for surgery [4].

Surgery decreases the rate of development of LM, which is the most important prognostic factor for long-term survival and to increase disease-related survival [5].

In both sporadic gastrinoma and MEN1-associated gastrinoma, duodenal lesions are frequently small, have positive lymph nodes in

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40–60% of cases, and are often not seen on preoperative imaging including endoscopic ultrasound (EUS) [6].

Experienced surgeons are usually able to identify over 90% of sporadic gastrinomas with the combination of preoperative imaging techniques, while intraoperative transduodenal illumination and duodenotomy are essential in detecting very small gastrinomas within the duodenum wall [7].

For sporadic left-sided pancreatic gastrinoma, central or distal pancreatectomy (with or without splenectomy) can be proposed [8].

However, the type and extent of surgery to be offered remain a controversial issue for gastrinomas due to the morbidity associated with pancreatic surgery. Several groups have suggested that gastrinomas should be enucleated or removed by a formal pancreatic resection with lymphadenectomy. The most common operation for duodenal gastrinomas includes duodenotomy, enucleation of any head or uncinate tumors, and peripancreatic lymph node dissection with or without distal pancreatectomy. However, it was noted that more conservative approaches rather than formal resections are associated with higher recurrence rates [9]. Other groups favor more aggressive approaches such as pancreaticoduodenectomy (PD) as the first-line procedure both in sporadic and MEN1-associated gastrinoma [10].

Regional lymphadenectomy is recommended in sporadic gastrinomas, independently of the primary location, because lymph node involvement is almost the rule in this type of neoplasms [11]. A blind resection in non-radiologically seen lesions should not be recommended and must be carefully evaluated by a multidisciplinary setting. A recent study demonstrated that all sporadic gastrinomas may benefit from radical surgery regardless of a preoperative radiological proof of localization. In this study the disease-free rate after curative resection was higher among patients with no radiological proof compared with those with radiologically seen gastrinomas [12].

Gastrinomas in MEN1 occur frequently in the duodenum. Traditionally, MEN1-associated gastrinomas were considered virtually impossible to cure with surgery, which was aimed at symptom control and prolonging survival. More recent studies demonstrated that patients treated conservatively with medical therapy for ZES have a risk of developing liver metastases of 23–29% compared with the 3–5% in patients treated with surgical resection [13]. One study demonstrated that gastrinomas larger than 3 cm in size had a ten times higher risk of developing liver metastases than smaller tumors [14]. As the risk of LM is strictly related to the size of primary lesion, Bartsch et al. suggest to offer surgical resection if the biochemical diagnosis is unequivocal and in the presence of lesions >1 cm [15]. The most appropriate surgical treatment in MEN1-associated gastrinoma is still debated. The North American Neuroendocrine Tumor Society (NANETS) consensus guidelines highlight that PD is rarely indicated for gastrinomas in MEN1 [16].

Instead, some groups regard PD as the most effective procedure. Lopez et al. achieved significantly higher long-term cure rate of ZES in a group of patients undergoing PD (92%) than in a group receiving atypical resections (33%), although the disease-specific 10-year survival was not statistically different (PD group 100%, non-PD group 89%). Notably, the two groups had similar incidence of postoperative diabetes mellitus and pancreatic fistula rate [10]. Even total pancreaticoduodenectomy has been advocated as an adequate procedure in selected patients [17].

13.2.2 Surgery for Insulinoma

Insulinomas are the most common F-PNENs and cause a syndrome characterized by severe hypoglycemia due to unregulated insulin secretion.

The vast majority of insulinomas are benign, unifocal lesions, arising within the pancreatic gland. Around 5% of the insulinomas are diagnosed in the setting of a MEN1 syndrome [4].

Being intra-pancreatic, they can be detected by EUS which has greater sensitivity and specificity for lesions located inside the pancreas than those outside of it. EUS can also elucidate whether the tumor can be enucleated or requires a formal resection, by measuring the distance

from the main pancreatic duct (MPD). Surgical treatment in most of the cases is curative, with 100% rates in some series [18]. Due to the unifocality and benign nature, a laparoscopic approach is feasible in most cases and has shown equivalent outcomes for cure and shorter hospital stay [19]. If the tumor is farer than 3 mm from the MPD, enucleations are commonly performed, after exploration of the whole pancreas including intraoperative ultrasound (IOUS). Tumors of larger size or close to the MPD should be treated with a standard resection. In case of unclear preoperative tumor location, a surgical exploration is recommended, and frozen section analysis and insulin sampling may be required intraoperatively [20]. Lymphadenectomy is not routinely required due to the most likely benign nature of insulinomas. The use of ablative techniques for insulinomas is controversial. Although firm evidences are still lacking, endoscopic or percutaneous ablative technique may be a valid option in patients who are unfit for surgery [18]. In those rare malignant cases, in recurrent or metastatic disease, a radical surgery aimed at treating locoregional or metastatic deposits has been performed and may be indicated. Peripancreatic lymph node dissection should be performed and resection of the primary tumor and accessible metastases is advocated. Tumor debulking is useful for reducing hypoglycemic symptoms and improving long-term survival [21]. Insulinomas occur in almost 20% of patient with MEN1 syndrome. They tend to have a more aggressive behavior comparing to sporadic cases. They are usually multiple and associated with an earlier age at onset. Since insulinomas in MEN1 are at higher risk for being malignant and multifocal, formal pancreatic resections have been advocated [22]. In MEN1-affected patients with insulinoma, other PNENs are often present. Preoperative localization to determine which PNENs are the insulinomas is mandatory. Instead, other small NF-PNENs may be left behind in order to minimize the amount of parenchyma excised. In these patients, preoperative intra-arterial calcium injections with hepatic venous insulin sampling as well as intraoperative insulin sampling may be required [23].

13.2.3 Surgery for Rare Functioning Neuroendocrine Neoplasms (RF-NENs)

Rare functioning neuroendocrine neoplasms (RF-NENs) can occur in the pancreas or in other locations [VIPomas, somatostatinomas, GRHomas, ACTHomas, PNENs causing carcinoid syndrome or hypercalcemia (PTHrp-omas)]. Each RF-NEN is associated with a particular syndrome that results from the excessive hormonal secretion [24]. Indications for surgery are based on symptom control, tumor morphology and extent, malignancy, and possible presence of metastases.

In patients who are fit for surgery, curative treatment should always be sought, especially if metastatic disease is only localized to the liver and is potentially resectable [25]. The type of surgery depends on the location of the primary – PDs, distal pancreatectomy, or other partial resections. A proper lymphadenectomy is required as RF-NENs are often of malignant nature [8].

In general laparoscopic surgery is not recommended because of the need for lymphadenectomy and careful inspection for invasion/metastases [4]. Cytoreductive surgery should be considered if most of the tumor load is thought to be resectable which may help to reduce the amount of hormones released and potentially extend survival, although this is not proven [26].

13.3 Management of NF-PNENs

13.3.1 Localized NF-PNENs

13.3.1.1 NF-PNETs

Most of PNET are incidentally discovered during imaging follow-up performed for other reasons, also due to the widespread use of high-resolution images [27]. The incidence of PNENs ≤2 cm increased by 710.4% (annual percentage change 12.8%) over the last 22 years [28]. As a consequence many of these tumors have small dimension and most of patients are totally asymptomatic. The incidental diagnosis represents a favorable

predictor of overall survival for patients with PNENs. Crippa et al. published a series of 355 patients of which 124 (35%) incidentally diagnosed, and they showed that the 5-year progression-free survival (PFS) was 83% and 32% for incidental and symptomatic NF-PNENs, respectively [27]. Cheema et al. recently demonstrated that progression-free survival rates are significantly higher in patients with incidentally detected lesions [29]. The presence of symptoms occurs usually in patients with larger lesions or in the presence of advanced disease. Patients often present late in their course with symptoms of mass effect or with symptoms related to metastases including abdominal pain, weight loss, and jaundice [30, 31]. The small dimension of the tumor, in association with the incidental finding, is associated with a negligible risk of recurrence after radical surgery [32, 33]. Bettini et al. showed that only 6% of NF-PNENs ≤2 cm have an aggressive behavior after radical surgery when incidentally discovered [32]. The choice to treat these lesions with surgery or conservatively should be balanced with the risks and benefits of the surgery itself. Pancreatic resections are associated with a high risk of morbidity and mortality rate remains around 2% also in high-volume centers [34]. Recently, Ateema et al. published a comparison between resections for PNENs and resections for other lesions in terms of postoperative pancreatic fistula (POPF) rate. They showed that grade B and C POPF [35] have higher incidence after resection for PNENs compared with resection for other lesions (22.7% vs 17.2), and if compared only with PDAC, this difference is highly significant (22.7% vs 9%) [36]. In this setting, considering the less aggressive behavior of asymptomatic NF-PNENs ≤2 cm, conservative management has been proposed for these tumors. Recently, several experiences have demonstrated the safety of an active surveillance for small, asymptomatic PNETs [37, 38]. No disease progression among observed NF-PNEN ≤2 cm was reported in any of the published series, and surgery during follow-up was indicated for 4–20% of patients [37]. However surgery is still the treatment of choice for small NF-PNETs in selected cases. Main reasons for surgery are a rapid tumor size increasing, a dilatation of the MPD, a suspicious lymph node metastases, the presence of a Ki67 >2%, and an excessive anxiety experienced by the patient during follow-up. In these cases, surgery should be tailored on the patients' characteristics and on the localization of the tumors. Conservative, parenchyma-preserving procedures should be avoided in the presence of suspicious signs for malignancy (i.e., lymph node involvement at imaging or dilatation of the MPD). In the remaining cases, middle pancreatectomy is indicated for small tumors of the pancreatic body, whereas an enucleation should be considered only if the main pancreatic duct can be preserved. The main advantage for atypical resections is the possibility to reduce as much as possible the risk of endocrine and/or exocrine insufficiency compared to standard resections although they are associated with a high rate of pancreatic fistulas [39, 40].

In both enucleation and middle pancreatectomy, a lymphadenectomy is not routinely performed, but a nodal sampling should be always recommended for final histological assessment. Atypical resection should be considered only for small lesions with benign or uncertain behavior. Surgical resections can be performed either open or laparoscopically. Both laparoscopic enucleation and distal pancreatectomy are safe and feasible in patients with PNETs [41].

Lesions larger than 2 cm show different behavior: they are associated with a higher risk of malignancy and a poorer disease-free survival. The risk of nodal metastases is also higher and is up to 50% in case of lesions >4 cm [32]. In most series, NF-PNETs >2 cm are usually diagnosed at an advanced stage with 60–85% presenting with synchronous liver metastases [42, 43]. Considering the risk of malignancy all these lesions should be treated with a standard resection and adequate lymphadenectomy. In case of lesions localized in the head of the pancreas, PD is the treatment of choice, whereas in lesions of the body and tail of the pancreas, left pancreatectomy (LP) and splenectomy are indicated.

13.3.1.2 Neuroendocrine Carcinomas (NECs)

Neuroendocrine carcinomas (NECs) are defined as lesions with a mitotic count of >20 mitoses per 10 high-power fields and/or a Ki67 index of >20% (WHO 2010 G3) [44]. Pancreatic NECs are rare (only 2–3% of all PNENs) and are associated with a poor prognosis [45]. Most of patients with NECs are diagnosed at advanced stage with a high rate of nodal metastasis, higher than 90% in some series [46]. Median survival ranges from 11 to 21 months [47]. Curative (R0/R1) resection of pancreatic NEC is associated with improved survival, and in localized and resectable disease, surgical exploration for potentially curative resection should be considered. Resection of primary pancreatic neuroendocrine neoplasms in the presence of not resectable hepatic metastases is still controversial, but considering their poor outcomes, palliative resection of the primary pancreatic NEC in the setting of not resectable liver metastases cannot be recommended [48, 49].

13.3.1.3 MEN1-Associated NF-PNETs

MEN1 is characterized by the combined occurrence of primary hyperparathyroidism, duodenopancreatic neuroendocrine neoplasms, and tumors of the anterior pituitary gland. These tumors include nonfunctioning PNETs (NF-PNETs) (30–80%), gastrinomas (50%), and insulinomas (20%). The presence of malignant NF-PNEN represents one of the leading causes of disease-specific death in these patients [50]. Nowadays, the recommendation for surgical resection has been based on tumor size, because of a higher rate of metastases in patients with larger tumors [51]. Tumor size is significantly correlated with the presence of metastases and tumor size >30 mm is associated with a reduction in survival time. Patients with tumors between 11 and 30 mm have a risk of death slightly, but not significantly, higher than patients with tumors <10 mm [15]. Surgery represents the treatment of choice for NF-PNENs >2 cm associated with MEN1 [52]. Many controversies remain in the management of tumors ≤2 cm. No survival benefit is demonstrated for patients with NF-PNENs ≤2 cm who receive surgery compared with patients who had conservative management [53] [54]. PNENs in the context of MEN1 are often multifocal. In this setting, careful microdissection of the pancreas demonstrates multiple, small microadenomas. While only a minority of the microadenomas acquire the potential to grow unrestrictedly, larger lesions may be genetically unstable, develop secondary mutations, and will grow into clinically relevant lesions. Prophylactic surgery aims to remove these lesions before malignancy develops. However, while recent data show that early diagnosis and surgery improve survival [55], others suggest a more conservative approach, as their data indicate that only tumors >2 cm are associated with an increased risk of malignancy [56]. Pancreatic surgery is graved by a high rate of morbidity as well as a high rate of mortality particularly in non-referral centers. In these patients, the texture of the pancreatic remnant is usually soft. As a consequence there is an increased risk of failure for the pancreatic anastomoses or suturing of the resection margins. Thus, pancreatic surgery in patients with MEN1 syndrome is challenging and associated with high risk of postoperative complications.

13.3.2 Metastatic Disease

13.3.2.1 Surgery for Liver Metastases

Liver metastases (LM) develop commonly (up to 95% in some case series) in the natural history of NENs [57]. Hepatic involvement differs between primaries. Gastric, appendiceal, and rectal tumors rarely cause metastases, while pancreatic and small bowel have 28–78% and 67–91% incidence rates, respectively [58]. LM represent a strong prognostic factor, along with histologic differentiation and proliferative activity. Among patients with LM, the origin of the primary tumor influences prognosis. PNENs have the worst prognosis within all metastatic NENs, with 5-year survival rates of 40–60% [59]. Patients with gastrinoma and no metastatic disease have 95% survival at 20 years, while only a 10-year survival of

15% is reported when diffuse metastatic liver disease is present [60]. Most of the published series on the management of metastatic NENs are heterogeneously made from different primaries including gastro-entero-pancreatic and pulmonary NENs. Although most of these tumors share similar characteristics, long-term outcomes can change considerably among different forms. A recent study focused selectively on PNENs with LM and showed improved overall and progression-free survival in patients who underwent radical surgery comparing to those who underwent palliative surgery and those who had nonoperative treatments [61].

The decision to offer liver surgery is based on a multifactorial assessment taking into account tumor grading (only G1-G2 should undergo liver surgery; G3 cancers have overtly high recurrence rates and disseminated disease), the presence of extrahepatic disease, volume of liver remnant, and the presence of symptoms [62]. This latter is often developed with the onset of hepatic metastases, as the result of tumor-secreted hormones reaching the systemic circulation. Only 20–30% of patients with metastatic disease are suitable for radical intent at presentation [63]. Debulking surgery (R2) in incompletely resectable metastatic disease is not universally accepted, but particularly in symptomatic patients, it may improve the quality of life when medical treatment failed [62]. For surgery with curative intent, ENETS have proposed the following criteria: (i) resectable G1-G2 liver disease with acceptable morbidity and less than 5% mortality, (ii) absence of right heart insufficiency, (iii) absence of unresectable lymph node and extra-abdominal metastases, and (iv) absence of diffuse or unresectable peritoneal carcinomatosis [58]. The type of surgical resection depends on patient and liver conditions (i.e., performance status, number and location of hepatic deposits, complexity of the resection, and predicted future liver remnant). NEN LMs have been classified morphologically as type I (single metastasis), type II (isolated metastatic bulk accompanied by smaller deposits), or type III (disseminated metastatic spread) [64]. For otherwise unresectable disease, two-step approaches have been proposed including portal vein embolization and two-stage hepatectomies including associating liver partition to portal vein ligation (ALPPS) [65, 66]. The overall survival after hepatic resection is 46–86% at 5 years and 35–79% at 10 years [58]. In comparison, patients who do not receive resection of liver metastases show a survival rate of only 30–36% [61, 67]. Selection biases due to better performance status or less advanced disease are likely to have influenced such differences in favor of the outcomes associated with surgery. Nevertheless, resection shows low mortality rate (0–5%) and acceptable morbidity (30%). Interestingly, resections with microscopically invaded margins (R1) do not seem to affect the overall survival [68]. Analysis of histopathology specimens revealed that often the disease burden in the liver is underestimated, with almost half the number of LM from neuroendocrine tumors undetectable on preoperative imaging [69]. These results suggest that NEN LM are frequently more extensive than identified, even intraoperatively, and that a real curative R0/R1 resection is difficult to achieve. As a consequence, a high rate of recurrence is reported, after a median time of 16–20 months and the majority of patients experience recurrence at 5 years. Robust studies comparing nonsurgical against surgical treatments are lacking and those available are subject to relevant selection biases [70]. In the last 20 years, nonsurgical novel techniques have become available and gained popularity mainly as complementary treatment options. The lack of randomized data makes the comparison with a surgical approach in terms of survival benefit and symptomatic relief difficult.

13.3.2.2 Surgery of the Primary Tumor

In Locally Advanced PNENs

An aggressive surgical approach for PNENs in selected patients showed a survival benefit in the presence of nearby organ invasion or the invasion

of vascular structures for G1-G2 neoplasms. In a recent retrospective analysis, for patients undergoing en bloc resections of adjacent organs, the 5-year DFS was 42% and did not differ from patients undergoing pancreatic resection alone [71]. Conversely, the results with NEC G3 were similar to those of pancreatic adenocarcinoma, and R0 resections did not lead to improved survival rates compared to R1 and R2 resections. However, any type of resection had better outcomes than exploration only [72]. Selected cases seem to benefit from alleviation of symptoms from debulking surgery, mainly as part of multimodal treatment.

In Metastatic Disease

At the time of presentation, 80% of patients have unresectable LMs. For most other malignancies, there is little rationale to resect the primary site when widespread, unresectable metastases are present. However, because a prolonged life expectancy is associated with slowly growing PNETs, resection of the primary tumor may be beneficial if the primary site is causing symptoms and to avoid local complications such as intestinal occlusion, mesenteric retraction, and hemorrhage [61]. Also, resection of the primary tumor allows focusing the treatment on liver metastases including liver transplantation.

Synchronous or staged resections are performed if the primary and liver metastases are both amenable to potentially curative resection. Recurrence rates are reported as high as 89%, mainly to the liver, and 5-year symptom-free survival and overall survival of 60% and 69%, respectively [73]. In patients with unresectable LMs, an advantage in terms of survival after primary pancreatic tumors resection is not clearly demonstrated. Improved results in resected patients may be due to a bias toward a more aggressive surgical approach in patients with a better performance status or less advanced disease [49]. In addition, surgery of the primary tumor is only recommended for G1 and G2 tumors. In case of surgery for NF-PNENs, the choice of a pancreatic resection needs careful evaluation due to the risks of morbidity and mortality associated with major resections (i.e., PD and total pancreatectomy) [52].

13.3.2.3 Liver Transplantation

In NEN LM in which resection is not possible, total hepatectomy and liver transplantation (LT) have been performed for symptom control, potential for cure, and removal of tumor burden. High tumor grade, non-portal tumor drainage, and extrahepatic metastases (with the exception of resectable peri-hilar lymph node metastases) represent accepted contraindications. Sparse reports of few cases with the initial experiences were the only available literature in the field for years. Recently, multicenter databases have been collected, and single centers have implemented policies and guidelines for LT for metastatic NEN. The two largest retrospective multicenter studies so far have shown that in the absence of poor prognostic factors, LT is associated with satisfactory outcomes and can be performed alone or in combination with the resection of the primary tumor: (i) a European study reports a large retrospective cohort from 35 centers in 11 European countries of 213 patients who underwent LT for NEN LMs from 1982 to 2009. At a mean follow-up of 56 months, 17% of patients died from early or late complications of LT, and the 5-year overall survival rate was 52% with a disease-specific survival rate of 30% [74]; (ii) a study from the USA included 85 patients who underwent LT from 1988 to 2012 at 28 centers. One-, 3-, and 5-year patient survival rates were 83%, 60%, and 52%, respectively; 20 of 40 deaths were due to recurrent disease. Synchronous major primary tumor resections (i.e., pancreaticoduodenectomy, small bowel resection with distal pancreatectomy, multivisceral transplant) appeared to contribute to worse outcomes [75]. Single-center policies have been proposed and received nonuniform acceptance. Moving from their former experience with hepatocellular cancer, the Milan group manage to show improved outcomes of LT for NEN LMs by prospectively applying strict inclusion criteria: (i) well-differentiated

NENs (Ki67 <5%), (ii) portosystemic tumor drainage, (iii) patient age <55 years, (iv) stable disease for at least 6 months, (v) pretransplant R0 primary tumor resection, (vi) hepatic tumor involvement <50% of total liver volume, and (vii) absence of extrahepatic disease [76]. Because of the low biological aggressiveness and slow growth, LT is an accepted treatment for NEN LMs. However experience is still scarce because only 0.3% and 0.2% of transplants are performed for such indication (European Liver Transplant Registry and United Network for Organ Sharing database, respectively) [77]. In the last 15 years, short-term outcomes have improved because of better selection of transplantation candidates, refinement of surgical techniques, and the introduction of novel immunosuppressive regimens. In single-center series, the 5-year overall survival rate ranged from 33% to 90%, and disease-free survival rates from 11% to 77% at 5 years [78, 79]. Timing of transplantation (e.g., whether stable disease needs to be observed for a certain amount of time) and selection criteria, including the development of patient-specific biomarkers for the identification of those who gain a long-term benefit from the procedure, still remain under debate.

13.3.2.4 Nonsurgical Interventions in NF-PNENs

In patients with LM who are ineligible for complete surgical resection, locoregional and ablative modalities have been used either as a primary treatment modality for neuroendocrine liver metastases or as an adjunct to surgical resection [26]. The choice of the type of procedure depends on the local expertise, extension, and location of liver involvement. Both functioning and nonfunctioning tumors have been treated with these approaches [80]. Locoregional treatments such as transcatheter arterial embolization (TAE) or chemoembolization (TACE) and selective internal radiotherapy (SIRT) have been used for the palliation of unresectable LM. In a comparative study TACE showed equivalent initial response rates for symptoms control, though TACE was associated with more durable and improved cost-effectiveness compared to SIRT [81]. When extrahepatic is higher than intrahepatic tumor burden, systemic medical therapies or peptide receptor radionuclide therapy (PRRT) is used preferentially compared to locoregional approaches.

As the zone of ablation is limited, ablative techniques are applied only to smaller lesions (typically ≤3 cm). Radiofrequency ablation (RFA) is the most widespread technology, while microwave ablation (MWA) has become available more recently but is thought to be more efficacious because a shorter time is needed for each ablation and higher intratumor temperatures can be reached [82]. Combining resection and RFA may provide the opportunity to achieve complete tumor removal [83]. Symptomatic relief has been obtained in up to 95% of patients also accompanied by a significant decrease in biochemical markers [80]. Ablation seems to play its main role in the therapeutic management of small neuroendocrine LM. As most of the patients present with grade 2 and 3 LMs, ablation mainly represents a complement to surgical resection, allowing more limited resections when otherwise more extensive hepatectomies could compromise residual liver function [26].

Ablation is particularly useful also when surgical options are limited in cases of intrahepatic disease recurrence after previous hepatectomies.

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Part IV

Surgical Treatment

The History and Evolution of Pancreaticoduodenectomy

14

James F. Griffin and Christopher L. Wolfgang

14.1 Introduction

Pancreaticoduodenectomy (PD) is the procedure of choice for periampullary cancers, which include four separate malignancies occurring in the region of the ampulla of Vater: pancreatic ductal adenocarcinoma (PDAC), ampullary cancer, distal cholangiocarcinoma, and duodenal adenocarcinoma. The evolution of PD began as a series of isolated, independent resection attempts in the late 19th and early 20th centuries, but the procedure failed to gain momentum because of its great technical difficulty and dismal outcomes. Allen O. Whipple and colleagues were the first to adopt a systematic approach to radical pancreaticoduodenal resections and by 1935, they had demonstrated the technical feasibility of the procedure. However, the highly morbid operation was nearly abandoned altogether after postoperative outcomes failed to improve in the decades following Whipple's initial success. Fortunately, a trend in centralization and standardization of care beginning in the 1980s fueled a decrease in perioperative mortality rates that now stands at 1-2% at high volume centers.

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14.2 The Modern Surgical Era

Prior to the mid-nineteenth century, surgical expertise and scope was limited by two primary barriers. First, there were no effective means of anesthesia. Procedures had to be quick and relatively straightforward in order for patients to tolerate them. The other barrier was the extraordinarily high rate of surgical site infections. Infectious complications generated mortality rates exceeding 50% for patients undergoing amputations and abdominal procedures were almost uniformly fatal [1–3]. Together, these factors limited the majority of surgical procedures to amputations, lancing of boils, and resection of small subcutaneous lesions. Major surgeries were rare and generally reserved as the last resort for life-threatening conditions.

Change began in 1842 with the introduction of ether anesthesia by a rural Georgia surgeon named Crawford W. Long [4]. Although Dr. Long's use of ether anesthesia was well known in the surgical circles of the Southern United States, he did not initially publish his findings. Instead, the technique was made famous independently by William T. G. Morton's widely publicized demonstration at Massachusetts General Hospital in 1846 [5, 6]. The arrival of ether anesthesia eliminated the issue of human suffering and set the stage for longer, more complex procedures.

Infectious complications were more difficult to address because their causes were not well understood. Germ theory had not yet been widely

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accepted and surgeons rarely cleaned their instruments or hands between patients. Joseph Lister believed that infection resulted from wound contamination by airborne microorganisms and introduced the concept of surgical antisepsis in 1867 [7, 8]. This technique relied upon the application of carbolic acid to the wound during surgery and afterwards in wound dressings to kill any contaminating microorganisms. By the early twentieth century, Listerian antisepsis had evolved into early modern aseptic technique, which was responsible for a dramatic decrease in postoperative mortality. In one report from 1895, the introduction of antisepsis and eventually asepsis at the University Hospital in Munich led to a reduction amputation-associated mortality from greater than 60% to just 2% [2].

14.3 The First Pancreatic Resections

The earliest pancreatic resections involved the tail of the pancreas since it was more easily accessible and amenable to resection without the need for complicated reconstructions. Friedrich Trendelenburg (1824–1924), professor of surgery at the University of Bonn, is credited with the first distal pancreatectomy in 1882 for a massive spindle cell carcinoma in the tail of the pancreas [9]. The procedure lasted and hour and a half and was complicated by an injury to the spleen requiring splenectomy. The patient suffered a complicated postoperative course and died shortly after discharge, but details regarding the exact cause of death are unclear.

Resections in the head of the pancreas were approached with more caution due to its intimate association with the confluence of the biliary, pancreatic, and gastrointestinal systems and its proximity to major vascular structures. The Italian surgeons Giuseppe Ruggi and Domenico Biondi made the first attempts at pancreatic head resection in 1889 and 1894, respectively. Ruggi enucleated a large pancreatic head mass that did not involve the ductal system or require a reconstructive procedure. Biondi's procedure was more extensive and essentially constituted a duodenum-sparing pancreatic head resection for a fibroadenoma. This was the first procedure to involve transection of the pancreatic duct and was followed by reapproximation of the pancreatic remnant to the duodenum.

14.4 Early Attempts at Pancreaticoduodenectomy

The first PD was performed in 1898 by Alessandro Codivilla (1861–1912), an Italian surgeon best known for his contributions to the field of orthopedic surgery [10]. Prior to his appointment as a professor of orthopedic surgery, Codivilla was a skilled abdominal surgeon with considerable expertise in gastric procedures. His patient was a 46-year-old gentleman who presented with several days of abdominal distension and vomiting. Upon exploration, the patient was found to have a large pancreatic tumor involving the duodenum and stomach and was not amenable to a limited resection. Instead, Codivilla performed an ambitious *en bloc* resection of the pancreatic head, proximal duodenum, distal stomach, and distal common bile duct. His reconstruction consisted of a Roux-en-Y gastrojejunostomy with cholecystojejunostomy over Murphy buttons. He is presumed to have ligated and oversewn the pancreatic remnant, but this is not explicitly stated in his operative report. Unfortunately, the patient developed complications consistent with a pancreatic fistula and died in the early postoperative period [10, 11].

William Stewart Halsted (1852–1922) performed the first successful ampullary resection at the Johns Hopkins Hospital just 5 days after Codivilla's PD [12]. He accessed the ampulla through a transduodenal incision and resected the tumor with generous margins that included segments of the pancreatic and common bile ducts. Using silk sutures, he restored biliopancreatic outflow by reimplanting the ducts into the primary duodenal closure. The procedure was a technical success, but the patient ultimately died the following year after her cancer recurred.

The first successful PD was performed for ampullary cancer in 1909 by the German surgeon Walther Kausch (1867–1928). He divided the procedure into two stages, the first of which was designed to relieve the patient's severe jaundice through a loop cholecystojejunostomy and Braun anastomosis. In the second stage, he resected most of the duodenum en bloc with a small portion of the pancreatic head, followed by gastrojejunostomy (GJ) and end-to-end pancreaticojejunostomy (PJ). Despite Kausch's success, he never performed another PD and only a few more attempts are documented in the literature over the next two decades. Among these was the first successful one-stage PD by Georg Hirschel of Heidelberg in 1912, which was notable for the use of rubber tubing to reconstruct the biliary tract. Another was the Italian surgeon Ottorino Tenani's successful two-stage PD in 1918, which was the first to utilize blood transfusion and pancreatic enzyme supplementation.

14.5 The Whipple Era

Allen O. Whipple (1881–1963) is the father of pancreatic surgery in North America and namesake of pancreaticoduodenectomy. Although he was not the first surgeon to attempt PD, the Whipple procedure is aptly named because he was the first to systematically optimize it enough for clinical relevance, the first to recognize the importance of a truly radical resection, and the first to mobilize the surgical community at large into concerted action.

Whipple was surgeon-in-chief and Valentine Mott Professor of Surgery at Columbia Presbyterian Medical Center in New York when he began tackling the problem of periampullary cancer. He believed that the transduodenal approach in use at the time carried too much surgical risk without offering a sufficient oncologic benefit; patients either died from surgical complications or survived to see their disease rapidly recur [13]. However, Whipple was inspired by recent advances in pancreatic surgery including Roscoe Graham's enucleation of an insulinoma in 1929 [14] and Evarts Graham's subtotal pancreatectomy for hypoglycemia in 1934 [15]. These successes chipped away at the *noli me tangere* perception of the pancreas by demonstrating "that a large part of the pancreas [could] be safely excised" [13, 16]. In 1934, following a failed transduodenal resection attempt, Whipple began devoting his research efforts to developing a safer and more oncologically sound resection technique. Prior to Whipple, such procedures were rarely performed due to prohibitively high mortality rates. However, he persevered through setbacks and methodically improved his technique through a process of trial and error. From his writings, Whipple clearly understood the gravity of his undertaking and frequently referenced Kehr's belief that "many failures would be necessary before the radical operation would prove successful" [16, 17].

14.5.1 Whipple's Two-Stage Pancreaticoduodenectomy

In 1935, Whipple presented his landmark manuscript *Treatment of Carcinoma of the Ampulla of Vater* to the American Surgical Association [13]. In it, he described a two-stage technique for the radical resection of periampullary cancers that he developed over the course of management for three successive patients. The first was a 60-year-old woman with 10 weeks of painless progressive jaundice from an obstructing periampullary cancer. Like Kausch, Whipple favored a staged approach to address the biliary obstruction and its associated risks prior to definitive tumor resection. The first stage consisted of choledochoduodenostomy and cholecystostomy, followed by transduodenal *en bloc* resection of the ampullary region and a portion of the pancreatic head 7 weeks later. For reconstruction, Whipple used chromic catgut sutures to anastomose the pancreatic stump to the duodenal resection window. Although Halsted had already successfully performed a similar anastomosis using silk sutures [12], Whipple and his contemporaries preferred catgut because they considered the duodenum a

contaminated field. Unfortunately, Whipple failed to account for the presence of activated pancreatic "ferments," which rapidly digested the absorbable sutures. The pancreatic anastomosis subsequently dehisced and the patient died of diffuse peritonitis within 30 hours of the procedure.

Whipple initially opted for transduodenal excision because of the prevailing belief that the duodenum and exocrine pancreatic function were necessary for life. However, based on his experience with his first patient, he decided that transduodenal excision did not allow for wide enough margins and was "at best . . . an inadequate attempt at cancer surgery" [16]. Furthermore, he decided that the pancreatic anastomosis should be avoided since re-establishing pancreatic outflow led directly to activation of pancreatic secretions (through interaction with intraluminal contents) and inherently endangered such an anastomosis. Undeterred, Whipple envisioned a more radical resection based on animal studies demonstrating survival following total duodenectomy [18–20] and pancreatic duct [21–23]. For his second attempt in a 53-year-old man with periampullary cancer, he excised *en bloc* a full segment of duodenum with the ampulla and head of the pancreas followed by end-to-end duodenoduodenostomy and pancreatic stump exclusion. He made use of other lessons from his earlier experience as well by replacing catgut sutures with more durable fine silk and revising the biliary bypass to a cholecystgastrostomy to minimize interference with the definitive resection to follow. Unfortunately, the patient developed an anastomotic stricture and required a gastrojejunostomy to bypass his duodenoduodenostomy. Despite recovering well from this, he ultimately died 8 months after the original procedure due to cholangitis. Subsequent autopsy revealed that he had developed critical stenosis of his cholecystgastrostomy, but notably showed no evidence of recurrent disease.

The second patient was further evidence for Whipple that the duodenum was nonessential to life. For the third patient, a 49-year-old man with periampullary cancer, Whipple performed the first recorded total duodenectomy in man *en bloc* with a wedge-shaped portion of the pancreatic head. Gastrointestinal continuity was maintained through a gastrojejunostomy constructed preemptively during the first stage, and the pancreatic stump was again excluded. This procedure was considered a success overall, and the patient lived another 25 months before succumbing to metastatic disease.

Whipple made just one more significant modification to his two-stage procedure by revising the biliary bypass to a Roux-en-Y cholecystojejunostomy to address the issue of recurrent cholangitis. His report to the American Surgical Association reignited interest in the surgical management of periampullary cancers and soon an entire community of pioneering surgeons had emerged. In 1937, Alexander Brunschwig extended the indications for PD by performing the first successful radical resection of a pancreatic cancer [24].

14.5.2 Whipple's One-Stage Pancreaticoduodenectomy

Transition to a one-stage radical resection occurred quite by chance on March 6, 1940. While operating on 53-year-old woman with presumed gastric cancer, Whipple transected the midportion of the stomach and was "astonished and chagrined" to find that the tumor was actually located in the head of the pancreas [17]. Since the patient was not jaundiced, he proceeded with conversion to an improvised PD by extending the usual *en bloc* resection to include the distal stomach along with the duodenum and head of the pancreas. For the reconstruction, he performed an antecolic loop gastrojejunostomy and introduced the choledochojejunostomy instead of using the gallbladder for the biliary anastomosis [25, 26]. Pathology revealed a nonfunctioning islet cell carcinoma, and the patient lived an additional 9 years before dying of metastatic disease. Shortly thereafter, successful one-stage pancreaticoduodenectomies were independently performed by Verne Hunt [27] in Los Angeles and Ridgway Trimble [28] in Baltimore as well.

Whipple's one-stage procedure was serendipitously timed because vitamin K had just become clinically available within the past year [25]. Vitamin K's ability to correct the coagulopathy

associated with prolonged biliary obstruction eliminated much of the surgical risk driving the need for a staged procedure. Thereafter, Whipple recommended the one-stage technique as the procedure of choice because it avoided the increased risk associated with two operations.

Although Whipple initially condemned attempts at pancreatic anastomoses, he continued to struggle with complications from pancreatic fistulae despite his method of pancreatic exclusion. In 1941, Hunt [27] reported a successful pancreaticojejunostomy during a radical two-stage PD and was soon joined by several other surgeons in adopting the pancreatic anastomosis [29, 30]. By 1942, Whipple had also incorporated pancreaticojejunostomy into his technique, which at the time consisted of the following:

> At least two days of vitamin K and bile salts therapy; 2) the distal half of the stomach, the entire duodenum, the terminal portion of the common duct and the head of the pancreas were removed en masse; 3) a vertical limb of the jejunum, starting at the duodenojejunal junction, was brought up through a rent in the mesocolon, behind the colon, with the following anastomoses in sequence: a) a choledochojejunostomy, end-to-end; b) an anastomosis between the pancreatic duct and the wall of the jejunal opening the size of the pancreatic duct, followed by the tacking of the stump of the resected pancreas to the wall of the jejunum; c) an end-to-side gastrojejunostomy. A sum drain in the bed of the duodenum was used. Silk technic was employed throughout [17]

14.6 Evolution After Whipple

Whipple's one-stage procedure remained the gold standard for resection over the next several decades. Although many variations were reported over the years, already at least 68 by 1956 [31], these generally consisted of minor changes to one or more of the anastomoses with preservation of the overall structure and principles pioneered by Whipple.

In 1978, Traverso and Longmire reintroduced the pylorus-preserving pancreaticoduodenectomy (PPPD) as a method of reducing the incidence of postgastrectomy syndrome and marginal ulceration [32]. PPPD was first described in 1944 by Kenneth Watson and advocated reconstruction via end-to-end duodenojejunostomy similar to Whipple's original two-stage procedure [33]. Traverso and Longmire's PPPD employed an end-to-side duodenojejunostomy and gained popularity because of its simplified procedure and faster operative times. Proponents of PPPD believed that it reduced gastrectomy-related complications by preserving the pyloric sphincter complex, while detractors argued that the intact sphincter increased delayed gastric emptying and the more limited resection risked leaving behind microscopic disease [34, 35]. Although studies comparing PPPD to classical PD have been inconsistent and often contradictory, a recent systematic review and meta-analysis of randomized, controlled trials found that PPPD is associated with decreased blood loss and reduced operative times, but the two procedures are otherwise equivalent in terms of mortality, morbidity, and survival [36].

Whipple performed a total of 37 PDs with a cumulative mortality rate of approximately 33% over the course of his career [37]. Unfortunately, the next 30 years failed to see much improvement over Whipple's outcomes with reported mortality rates ranging from 20% to 40%, morbidity between 40% and 60%, and 5-year survival rates of less than 5% for PDAC [38, 39]. During the 1960s, some surgeons questioned whether PD, which was already performed infrequently, should be abandoned altogether in favor of palliative bypass procedures, which some studies had demonstrated to have better quality of life and longer survival [40, 41].

The tide finally began to turn in the 1980s when several institutions began reporting mortality rates of <5% [42–45]. This was not due to any major changes in surgical technique but was the result of a move toward centralization of care at high-volume centers. This trend emerged from the early successes of a few talented surgeons who, like Whipple, made concerted efforts to continue improving outcomes. Their initial successes generated increasing referrals, which fueled more progress by encouraging surgical specialization and attracting additional talented

surgeons to the field. Larger caseloads allowed surgeons to acquire more experience and greater technical proficiency with PD, which in turn led to faster operative times with fewer complications [46, 47]. In addition to improving surgeon experience, higher volumes had a larger, system-wide effect of creating demand for specialized resources and expertise from other disciplines. As this demand was met, centers of excellence emerged with multidisciplinary teams to assist in all phases of management and critical pathways that ensured delivery of high-quality, standardized care to all patients [48].

The team of surgeons led by Dr. John L. Cameron at Johns Hopkins Hospital was among those leading the effort to centralize care. Between 1970 and 2006, a total of 1423 consecutive PDs were performed for PDAC, and 80% were performed by just three surgeons (John L. Cameron, Keith D. Lillemoe, and Charles J. Yeo) [46]. This period saw the yearly case volume rise from approximately two to more than 120 cases per year with an inverse decline in mortality from 30% to 1%. A study conducted between 1985 and 1995 demonstrated that Johns Hopkins increased its share of Maryland PDs from 21% to 59% of the total statewide volume and the first to achieve statewide regionalization of pancreatic surgery at a single institution. As a result, mortality decreased from 3.2% (1984–1987) to 1% (1992–1995), while the relative risk at low-volume outside institutions increased from 4.4% to 12.6% [48].

14.7 Pancreaticoduodenectomy in the Modern Era

14.7.1 Expanding Indications

Traditional indications for PD were previously limited to "resectable" periampullary cancers, which are early stage malignancies presenting straightforward resections and the best possible chance for cure. Unfortunately, in the case of PDAC, these account for only 15–20% of patients and a median survival of <20 months [49]. The combination of poor long-term outcomes, limited surgical candidacy, and improvements in perioperative mortality has led to the expansion of surgical indications for PD to a broader range of patients. One such example is the targeting of malignant precursors such as noninvasive intraductal papillary mucinous neoplasms (IPMN) as a means of prophylactic intervention to prevent progression to cancer altogether [50]. Resections are also being performed with increasing frequency for locally advanced borderline resectable (BLR) disease [51, 52]. These patients present with limited involvement of nearby major vascular structures and no evidence of metastatic spread. Long-term survival may still be achieved in a subset of BLR patients when combined with neoadjuvant therapy, which helps to select patients' good tumor biology for subsequent resection and improves rates of margin negativity. However, these often present more challenging procedures that may require vascular resection and reconstruction to attain an R0 resection. Fortunately, recent studies have shown that these can be performed safely by experienced surgeons at high-volume centers with no additional morbidity or mortality [53, 54].

14.7.2 Minimally Invasive Techniques

The most notable recent innovation in the performance of PD is its adaptation for minimally invasive (MIS) techniques. Laparoscopic (LPD) and robotic (RPD) procedures have both been described and are now gaining widespread acceptance and support.

The first LPD was performed in 1994 by Gagner and Pomp [55] for chronic pancreatitis, but the technique was slow to gain traction due to its high degree of technical difficulty, significant learning curve, and generally longer operative times [56, 57]. Over time, studies showed that experienced surgeons at high-volume centers could perform LPD with morbidity or mortality rates similar to the open procedure. Furthermore, there was no evidence to substantiate early fears of increased postoperative hemorrhage, delayed

gastric emptying, or pancreatic fistulae [58–60]. However, LPD did demonstrate advantages in the form of decreased surgical site infections, fewer blood transfusions, and decreased length of stay [58, 59, 61, 62].

Compared to LPD, RPD has the advantages of 3-D visualization, ergonomic design, and additional degrees of freedom that more closely recapitulate the open procedure. Although the technique is still in its infancy, early results have shown morbidity and mortality rates similar to open and laparoscopic approaches [63–65]. However, these results are the product of small series performed at high-volume centers.

Minimally invasive approaches to PD have demonstrated safety and efficacy comparable to the open procedure with the potential for quicker recovery times and fewer wound-related complications when performed in select patients by experienced surgeons. These improvements could have a significant impact on long-term survival for some patients since wound-related complications and prolonged recovery times are major factors delaying or altogether preventing the delivery of adjuvant therapy.

Conclusion

Although PD dates back more than a century, its acceptance as the standard resection for periampullary cancers is a relatively recent event in its tumultuous history. This is because development of the technique for PD far outpaced development of the infrastructure necessary to support it. The groundbreaking efforts of Whipple and his contemporaries led to 10 years of explosive progress followed by over three decades of stagnation with high mortality rates. When perioperative mortality suddenly began to decline in the 1980s, it was not due to improvements in technique, since this had remained largely unchanged. Instead, the major precipitating factor was the concentration of care at high-volume centers of excellence, where specialized surgeons fostered the development of multidisciplinary infrastructures to assist in the care and management of their growing patient numbers.

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Major Vascular Resection in Pancreatic Carcinoma

15

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15.1 Introduction

Pancreatic cancer (PDAC) is one of the leading causes of cancer-related death worldwide. Despite the effort to develop and implement new therapeutic strategies the incidence and mortality of PDAC are rising [1] (The Cancer Statistics Review (2009–2013) online). The major problem to improve individual survival rates is the delayed diagnosis of PDAC. Consequently, the majority of patients have to be excluded from surgical resection due to an already distant spread or locally advancement of the disease. Hence, only 10–20% of PDAC patients are primarily eligible for potential curative surgical approach aiming at a complete oncologic resection of the carcinoma with negative margins (R0). Despite controversies in definition of true R0 resection in PDAC and lessons learned in histological workup of the specimen, tumor-free resection margins still remain the goal of radical operation in PDAC with a reported prolonged survival of 5-year survival rates of up to 25% in selected series [2–7].

In 1985, 5-year survival rates of only 3% for PDAC patients treated with surgery have been reported, and operative mortality rates for pancreaticoduodenectomy were >10% [8]. Due to better patient selection, centralization of such complex surgeries in high-volume centers, an improved perioperative management, and more specialized surgeons, morbidity and mortality rates have greatly improved [9, 10]. Since pancreaticoduodenectomy is being performed more safely, surgeons gradually expanded the indications for surgical resection. Although surgery is clearly contraindicated in situations such as peritoneal carcinomatosis and liver metastases, the encasement of major vessels is no longer considered a mandatory contraindication. Pancreaticoduodenectomy with venous resection of the portal vein (PV) and superior mesenteric vein (SMV) is performed routinely and has been implemented in national guidelines [11, 12]. In selected patients, arterial resection for the common hepatic artery (HA), superior mesenteric artery (SMA), and celiac trunk (CT) is recommended if R0 resection can be achieved [13]. Although a combination of both venous and arterial vascular resection is technically possible, sufficient data proving the benefit are still missing.

Due to the anatomical location of the pancreas, tumor growth rapidly affects major abdominal vessels. *Since only R0 resections offer the possibility of a curative approach in patients with PDAC, the evidence of major vascular resections in PDAC are evaluated and potential techniques for vascular resections in pancreaticoduodenectomies are being discussed.*

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15.2 Diagnosis

Preoperative staging is essential to distinguish between PDACs that are eligible for surgery and cases where the tumor is unresectable or distant metastases are present.

Computer tomography (CT) scan, PET/CT, and endoscopic ultrasound (EU)-guided fine needle biopsy have been proven as feasible techniques for staging PDACs [14]. To test vascular involvement, a high-resolution CT with a specialized pancreatic protocol should be performed [15]. However, in approximately one third of the cases, CT scan can't identify vascular involvement [16]. Hence, accurate assessment of the vascular status remains difficult, and exploration is mandatory before putting the patient of palliative treatment in unclear cases [14, 17].

15.2.1 Evaluation of Resectability

A reasonable number of PDAC diagnosed by CT scan are considered to be borderline resectable pancreatic cancers. Different classification systems for borderline resectable PDAC have been proposed in the past [18, 19]. The lack of uniformity led to difficulties in finding the optimal therapeutic strategy in these patients [20]. In 2014, the International Study Group for Pancreatic Surgery (ISGPS) published a consensus statement to standardize the definition of borderline resectability with the guidelines of the National Comprehensive Cancer Network (NCCN) and defined the term of extended resections [15, 21]. Resectable tumors demonstrate no involvement of the vessels or only venous contact of less than 180° without any irregularity of the venous wall. Borderline resectability was defined as distortion/narrowing/occlusion of the mesentericoportal veins with the possibility to safely resect and replace the vein. In addition, encasement of less than 180° of the SMA or attachment at the HA without extension to the celiac axis was also considered borderline resectable. The tumor should be considered unresectable if the encasement of the SMA is greater than 180° or an invasion or encasement of the aorta is present. The tumor should be classified unresectable as well if an occlusion of the portal vein or a complex infiltration of the SMV without chance of reconstruction is diagnosed (see Table 15.1).

Table 15.1 Criteria defining resectability status

Resectability status	Arterial	Venous
Resectable	No arterial tumor contact	No tumor contact with the superior mesenteric vein (SMV) or portal vein (PV) or ≤180° contact without vein contour irregularity
Borderline resectable	Solid tumor contact with HA without extension to celiac axis or hepatic artery bifurcation allowing for safe and complete resection and reconstruction Solid tumor contact with the SMA of ≤180° Solid tumor contact with the CT of ≤180°	Solid tumor contact with the SMV or PV of >180° and contact of ≤180° with contour irregularity of the vein or thrombosis of the vein but with suitable vessel proximal and distal to the site of involvement allowing for safe and complete resection and vein reconstruction Solid tumor contact with the inferior vena cava
Unresectable	Distant metastasis (including non-regional lymph node metastasis) Solid tumor contact with SMA >180° Solid tumor contact with the CT >180° Solid tumor contact with the first jejunal SMA branch Solid tumor contact with the CA and aortic involvement	Unreconstructible SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus) Contact with most proximal draining jejunal branch into SMV Unreconstructible SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus)

Modified from NCCN Guidelines Version 1.2016
HA common hepatic artery, *SMA* superior mesenteric artery, *CT* celiac trunk, *SMV* superior mesenteric vein, *PV* portal vein

15.3 Neoadjuvant Therapy

Patients with borderline resectable PDAC can be considered as potential candidates to receive neoadjuvant radio-/chemotherapy [15]. However, the treatment scheme (gemcitabine vs. 5-FU-based protocols + radiation) is still being discussed conversely. New studies demonstrate that neoadjuvant treatment should be done with the combination of FOLFIRINOX and radiation since this combination showed promising short-term outcomes allowing more potential R0 resection [22, 23]. Tumor response like downsizing and development of fibrosis is reevaluated after 4–6 weeks.

To determine the correct approach in each patient, it is of great importance to preoperatively distinguish between an arterial and a venous involvement of the PDAC. In the case of a venous involvement, no neoadjuvant treatment is recommended, and surgical resection should be planned accordingly if technical options for resection are possible. Though, higher rates of intraoperative and postoperative morbidity must be accepted [15, 21, 24, 25].

If a borderline resectable arterial encasement has been diagnosed preoperatively and true arterial infiltration is present during surgical exploration, a case-specific decision has to be made since no clear recommendations are available. In principle, a palliative treatment should be considered prior to any other approach. In some cases, neoadjuvant therapy and consecutive re-exploration or even immediate vascular resection in clinical trial settings can be evaluated [15].

If arterial involvement has been diagnosed preoperatively, neoadjuvant radio-/chemotherapy should be considered. Although rates of downstaging after neoadjuvant therapy have been reported to be low in most of the patients, R0 resections were possible due to an improvement of resectability [26–30]. However, the major problem after neoadjuvant therapy is proper restaging, since differentiation between vital tumor and fibrotic tissue continues to be difficult even with advanced imaging techniques like PET-CT [29, 31]. Hence, surgical exploration and immediate histopathological examination remains the only valid option in patients with regression or stable disease to get certain evidence of the nature of the remaining tissue and in consequence for the necessity and the extent of further resection.

If preoperative restaging demonstrates a progression of the disease, palliative treatment should be initiated.

15.4 Arterial Resections

Although already proposed by Appleby in 1953, resection of the celiac trunk or the superior mesenteric artery is still a rare condition in pancreaticoduodenectomies and should only be performed in high-volume centers by experienced surgeons [15, 32]. Emphasizing the latter statement, it could be demonstrated that patients being operated on in high-volume centers had more tumor-free resection margins [33]. Since perineural invasion is common in PDAC, the level of dissection should be at the adventitia; otherwise, the periarterial nerve plexus is not resected, which then leads to a significant decrease in survival [34, 35]. The approach of extended vascular resection is also supported by the study of Rehders et al. who confirmed that there is no correlation between vascular spread and the incidence of the spread of tumor cells. So arterial involvement does not predict a more aggressive tumor biology, but reflects the poor localization of the disease [36].

15.4.1 Superior Mesenteric Artery (SMA)

The area most infiltrated by the tumor is the margin toward the SMA [37]. Because of this, the "artery-first" procedure was developed. In general, before mobilizing the pancreatic head, the SMA is identified and dissected alongside its anatomical location. Then the neck of the pancreas and the stomach is separated. For this approach, several techniques have been proposed so far. Some start with a left-sided and others with a right-sided arterial resection and some with a supracolic approach [38–42]. Difficulties with the technique can occur in obese patients

and with large tumors. In most cases, the SMA is reconstructed with a saphenous vein graft; however, transposition of the splenic artery is also an option. In addition, the "artery-first" approach has not only been proposed in conventional pancreaticoduodenectomies but also in field of minimal invasive surgery [43].

The "artery-first" technique allows identifying true involvement of the SMA before committing an irreversible step during surgery. It also provides a good balance between achieving tumor-free resection margins and preserving the nerve plexus around the SMA, which is important to avoid postoperative diarrhea. Except for the latter reasons, the approach also provides an early vascular control of the SMA and the SMV.

One of the common hepatic artery variations is the replacement of the right hepatic artery, which directly arises from the SMA (Michels III) and is located behind the pancreatic head. In addition, the common HA can also be completely replaced by a vessel, which directly originates from the SMA (Michels IX) [44–46]. These conditions should be known preoperatively. The "artery-first" approach allows early identification and handling of vascular anomalies [47].

15.4.2 Celiac Trunk and Common Hepatic Artery

Distal splenopancreatectomy with resection of the celiac trunk (CT) or the common hepatic artery (HA) is performed more frequently in borderline resectable PDACs. Several modifications of the original Appleby's procedure have been published [48, 49]. The CT or HA is resected in approximately 20% of all arterial resections performed for advanced PDACs [50]. The challenge of resecting the CT or HA is to simultaneously sustain perfusion of the liver, which should be taken over by the collateral flow through the pancreaticoduodenal arcade and the gastroduodenal artery. When performing Appleby's procedure, a constant monitoring of the vascularization of the liver is mandatory. This can be achieved by assessment of the color and tension of the liver supported by intraoperative Doppler ultrasound. The arterial flow should be greater than 22 cm/s in order to prevent liver ischemia, postoperative liver failure, and infection, which could lead to biliary complications [51, 52]. The celiac trunk can be resected down to its origin from the aorta. In case of insufficient perfusion by the collaterals or necessity of total pancreaticoduodenectomy due to oncologic reasons, reconstruction is possible as long as the proper HA can be preserved. Reconstruction can either be done by primary tension-free end-to-end anastomosis or by using a venous, arterial, or synthetic graft [48]. The right gastric and gastroepiploic arteries should be conserved to secure adequate perfusion of the stomach.

15.4.3 Outcome

Few studies with a small numbers of patients included have evaluated the outcome after arterial resection [13, 37, 50, 53]. In general, the analyzed data is heterogeneous, and most of the conducted studies were non-randomized and retrospective. So reliable data on this topic are still missing. The meta-analysis of Mollberg et al. demonstrated that arterial resection is associated with increased perioperative morbidity and mortality as well as with a reduced 1-year survival as compared to the patients with venous vascular resection. Though, patients with advanced PDAC and arterial resection showed a better survival as compared to patients with advanced PDAC without any surgical intervention [13, 53]. Another study supports the results of the latter meta-analysis in regard to more tumor-free margins and better patient survival after arterial resection [37]. In summary, arterial resection should only be performed in high-volume centers by experienced surgeons and only in selected patients. Thereby, similar survival rates between vascular resected and nonvascular resected patients of up to a median of 18 months can be achieved [54, 52].

15.5 Venous Resections

15.5.1 Superior Mesenteric Vein and Portal Vein

Resection of the superior mesenteric and portal vein has gained concurrent acceptance to achieve tumor-free margins in centers for pancreatic surgery over the last decades. If suspicion of venous involvement has been raised in preoperative imaging, the subsequent vessel should be treated as truly involved during surgery to avoid experimental dissection and potential opening of the tumor. The localization of the tumor plays an important role in further management. If tumor involvement is close to the confluence of the splenic and mesenteric vein, resection and consecutive reconstruction can be performed more easily since the lumen is large enough to create a reliable anastomosis. The farther distal the tumor is located from the confluence the more limited the technical options in resection and reconstruction of the SMV are [15].

Depending on the relation of the tumor to the vein, varying techniques in venous resections have been performed. If only minimal contact to the vessel is present, a partial venous excision with direct closure (venorraphy) or closure by a patch is suitable.

In general, if local resection of the SMV is not possible, the mesenteric root should be mobilized completely by dissecting the retroperitoneal adhesions of the right hemicolon [55]. This provides great maneuverability of the SMV and consecutively improves alignment for anastomosis.

Segmental resection with primary venovenous anastomosis or segmental resection with interposed venous graft is necessary if tangential resection of the vein is not possible [56, 57]. The clamp time of the SMV and PV should be kept to a minimum to reduce edema of the bowel. The vascular graft can either be autologous (e.g., saphenous vein) or synthetic (e.g., goretex). Implanting a synthetic graft saves operation time, since no additional venous harvesting is needed, but bears the risk of every synthetic material in regard to infection and anastomotic leakage. Especially in the setting of an increased risk for developing pancreatic fistulas, graft infection can become chronic and eventually lead to hemorrhage. Though, in a series of 110 patients, no differences in morbidity and mortality between different types of portal vein reconstruction techniques were observed [58]. Since more evidenced-based data of venous reconstructions are needed, the ISGPS proposed a classification of venous resections to standardize nomenclature for improved recommendations in the future (see Table 15.2) [15].

Table 15.2 Proposed ISGPS classification of venous resections

Type	Classification
I	Partial venous excision with direct closure (venorraphy) by suture closure
II	Partial venous excision using a patch
III	Segmental resection with primary venovenous anastomosis
IV	Segmental resection with interposed venous conduit and at least two anastomoses

15.5.2 Outcome

In two systematic reviews, no differences in morbidity and mortality have been observed for patients undergoing pancreaticoduodenectomy with and without venous resection [25, 59]. The latter studies demonstrated 3-year survival rates of 16–19.4% and 5-year survival rates of 7–12.3%, which are better than palliative treatment alone. The most important factors for survival were depth and the length of venous involvement and tumor-free resection margins. Patients with less than 3 cm of tumor involvement yielded a better survival than patients with more than 3 cm of tumor attachment. In addition, true involvement of the intima seems to be a factor of poor prognosis even in R0 resections [60–62]. After pancreaticoduodenectomy with venous resection, patients should receive adjuvant chemotherapy to further improve survival rates [63].

Venous resection during surgery for pancreatic cancer has become a standard procedure in recent years and has been included in several guidelines for pancreatic surgery. It should be performed on a routine basis by experienced surgeons if complete resection of the tumor can be achieved.

Conclusion

Tumor infiltration either venous or arterial is no contraindication for resection in PDAC anymore. Extensive preoperative workup with regard to vascular anatomy and surgical tolerance is mandatory. Correct staging after neoadjuvant therapy remains challenging, but is essential for patient selection to further improve long-term outcomes. Especially arterial resections should only be performed in selected patients in high-volume centers. Further prospective randomized trials are needed to elucidate the benefits of arterial resections.

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16 Retroperitoneal Nerve Plexus Dissection During Pancreatoduodenectomy

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16.1 Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the most lethal cancer of the human digestive system and is the fourth leading cause of cancer-related death worldwide. Approximately 10–20% of PDAC patients can undergo potentially curative surgery after diagnosis, which results in a long-term 5-year survival rate of 20–25%, meaning only 2–5% of all PDAC patients survive for 5 years [1–3]. Although the treatment strategies for PDAC have changed in recent years, particularly with the development of antineoplastic agents such as gemcitabine [4], surgery with curative intent remains the only therapeutic option that has the potential for a cure [5–8]. The poor prognosis after surgery has been attributed to early lymph node involvement and distant metastasis as well as to a strong tendency of the cancer cells to spread along the peripancreatic neural plexuses and to infiltrate into the retropancreatic tissue.

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16.2 Anatomy Around the Pancreatic Head

The posterior side of the pancreatic head is covered by the fusion fascia of Treitz, which is histologically composed of a loose connective tissue membrane (Fig. 16.1). Pancreatic head cancer generally infiltrates to the left side along the fusion fascia of Treitz and is less likely to infiltrate directly into the inferior vena cava and the aorta [9].

The concept of the nerve plexus around the pancreatic head was first reported by Yoshioka in 1958 [10]. The Japan Pancreas Society incorporated this concept and a corresponding diagram in the third version of the *General Rules for the Study of Pancreatic Cancer* in 1986 [11]. In this

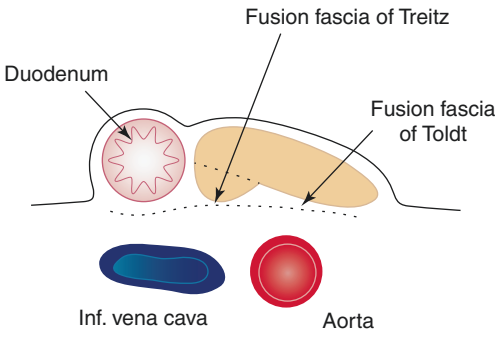

Fig. 16.1 The fusion fascia of the pancreatic head is called the "fusion fascia of Treitz" and that of the pancreatic body and tail is the "fusion fascia of Toldt." *Inf* inferior (From reference Kimura [9])

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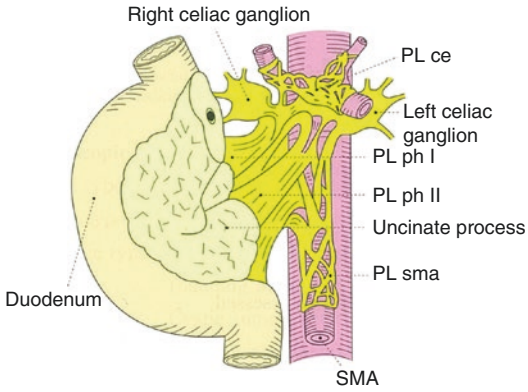

Fig. 16.2 The extrapancreatic nerve plexuses were categorized into seven groups according to the *General Rules for the Study of Pancreatic Cancer*. *PL ph I* pancreatic head plexus I, *PL ph II* pancreatic head plexus II, *PL sma* superior mesenteric arterial plexus, *PL cha* common hepatic artery plexus, *PL hdl* plexus within the hepatoduodenal ligament, *PL sp*. splenic plexus, *PL ce* celiac plexus (From reference Japan Pancreas Society [11])

classification, the extrapancreatic nerve plexuses were categorized into seven groups: pancreatic head plexus I (PL ph I), pancreatic head plexus II (PL ph II), superior mesenteric arterial plexus (PL sma), common hepatic artery plexus (PL cha), plexus within the hepatoduodenal ligament (PL hdl), splenic plexus (PL sp), and celiac plexus (PL ce) (Fig. 16.2). After extrapancreatic nerve plexus invasion, particularly PL ph I and PL sma invasion, was found to have a correlation with patient prognosis and lymph node involvement along the superior mesenteric artery (SMA), it was adopted as a staging factor in the fifth edition of the *General Rules for the Study of Pancreatic Cancer*. However, the plexuses seemed to be exaggerated in this diagram because no dense nerve fibers had been shown in the previous anatomical report (Fig. 16.3) [12].

In 2007, Gockel et al. introduced the concept of the "mesopancreas" (Fig. 16.4) [13]. The mesopancreas is a retropancreatic structure extending from the back of the pancreatic head to the SMA, including the lymphatic system, vessels, and nerves, which corresponds to PL ph I and PL ph II according to the *General Rules for the Study of Pancreatic Cancer* [14]. Gockel and colleagues were the first to anatomically or surgically classify this structure. They advocated a complete resection of the

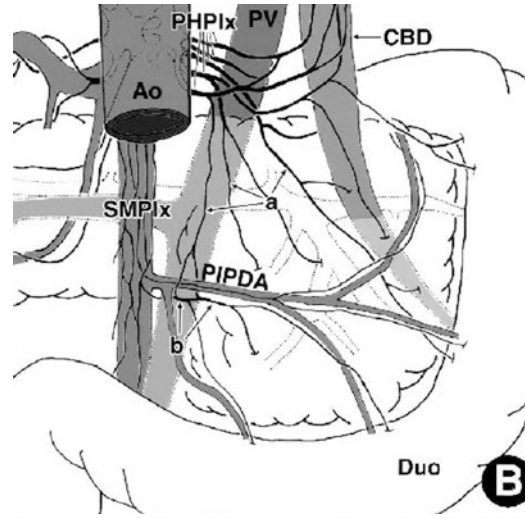

Fig. 16.3 Schema indicating the branches that originate from the posterior hepatic plexus (PHPlx) and superior mesenteric plexus (SMPlx) and spread on the deep surface of the head. (*a*) Twigs (twiglike nerves) independently running from the PHPlx to the pancreatic head. (*b*) Twigs originating from the SMPlx innervating the uncinated process. *Ao* aorta, *CBD* common bile duct, *Duo* duodenum, *PIPDA* posterior inferior pancreaticoduodenal artery, *PV* portal vein (From reference Yi et al. [12])

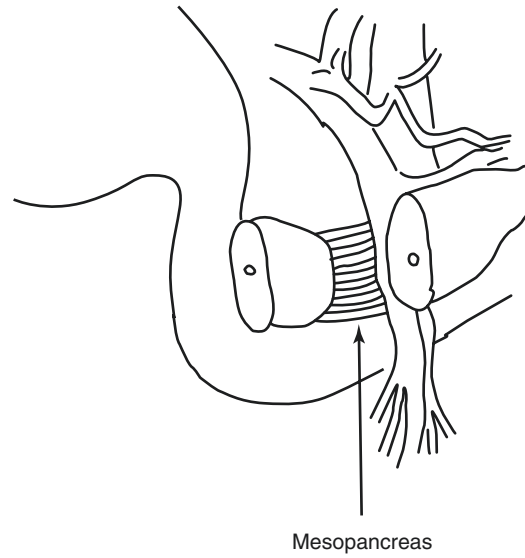

Fig. 16.4 The mesopancreas strains itself dorsally of the mesenteric vessels as a whitish-firm, fatty tissue-like layer (From reference Gockel et al. [13])

mesopancreas to achieve curability of a pancreatic head tumor with direct or indirect invasion of the major vessels or regional lymph node metastasis.

16.3 Nerve Plexus Invasion by Pancreatic Cancer

The pancreas is richly innervated by nerve fibers of the autonomic nervous system, and extrapancreatic nerve plexus invasion is known to be one of the most significant prognostic factors in patients with PDAC. Given the poor prognosis of patients with extrapancreatic nerve plexus invasion, preoperative diagnosis including multidetector computed tomography (MDCT) is crucial for staging and for treatment decision such as neoadjuvant therapy. Mochizuki et al. categorized four CT patterns of extrapancreatic nerve plexus invasion as follows (Fig. 16.5): (a) fine reticular and linear pattern (fine lines (less than 2 mm in diameter) and fine reticula (reticulation composed of fine reticular lines with abundant intermingled fat density)), (b) coarse reticular pattern (coarse reticula (reticulation also composed of reticular lines with less intermingled fat density)), (c) mass and strand pattern (over 2-mm diameter mass or strand-shaped soft tissue density connecting to the PDAC), and (d) nodular pattern (over 2-mm diameter isolated nodules) [15]. A point-by-point correlation between the MDCT findings and pathological specimens at the same section revealed that the (b) coarse reticular pattern and (c) mass and strand pattern reflected extrapancreatic nerve plexus invasion.

16.4 Pancreatic Cancer Surgery

Several randomized controlled trials and meta-analyses have concluded that prophylactic extended radical lymph node dissection does not contribute to improved survival after surgery [16–22]. Recently, Jang et al. compared standard pancreatoduodenectomy including dissection of proximal lymph nodes with extended pancreatoduodenectomy with extensive dissection of lymph nodes and the right half of the nerve plexus around the superior mesenteric artery (SMA). Their study revealed no significant differences in overall survival [22].

On the other hand, outcomes related to the resection margin have been controversial. Several authors have reported that a positive resection margin is a poor prognostic indicator, whereas other studies have failed to demonstrate a difference [23–29]. In 2012, Konstantinidis et al. proposed a "true" R0 resection (no evidence of malignancy in any of the resection

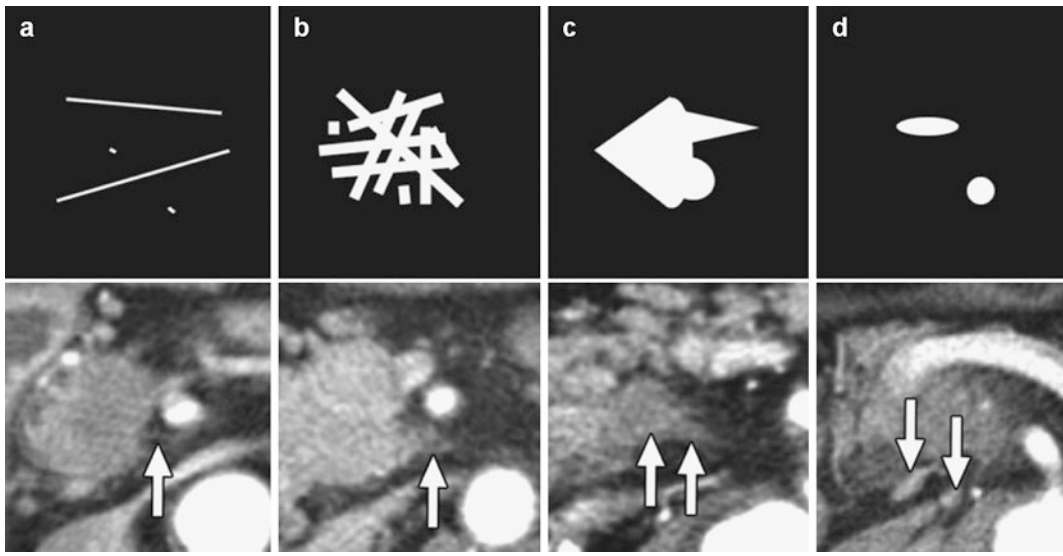

Fig. 16.5 Summaries of the four CT patterns. *Top*: schemas. *Bottom*: contrast-enhanced CT images corresponding to the respective schemas. (**a**) Fine reticular and linear pattern (*arrow*). (**b**) Coarse reticular pattern (*arrow*). (**c**) Mass and strand pattern (*arrows*). (**d**) Nodular pattern (*arrows*) (From reference Mochizuki et al. [15])

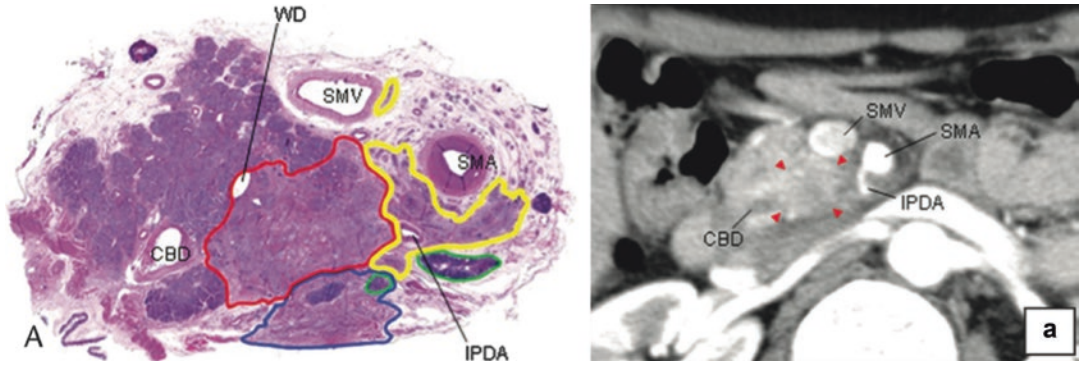

Fig. 16.6 (**a**) Photograph of the resected specimen with PL ph II invasion. (**a**) CT scan image corresponding to A. The carcinoma spread from the left side of lower uncinate process along the inferior pancreaticoduodenal artery, continued behind the SMA, and finally extended to the left side of the SMA. *Red*, *yellow*, *green*, and *blue* enclosures on the photograph indicate the area of the primary tumor, extrapancreatic nerve plexus invasion, lymph node metastasis, and retropancreatic tissue invasion, respectively. *Red arrowheads* on the CT scan image indicate the primary tumor. *CBD* indicates the common bile duct, *WD* Wirsung duct, *IPDA* inferior pancreaticoduodenal artery (From reference Makino et al. [35])

margin) and showed that patients with R0 resections had a favorable survival compared with those with R1 resections (23 vs. 14 months; $P < 0.001$). However, survival after resections of 1-mm margin or less (R0-close) was similar to that of R1 resections; both groups had a significantly shorter median survival than patients with a margin of greater than 1 mm (R0-wide) (16 vs. 14 vs. 35 months in the R0-close, R1, and R0-wide groups, respectively; $P < 0.001$) [30]. They concluded that R0 resections have an improved survival compared with R1 resections but that this survival benefit is lost when the tumor is within 1 mm of the resection margin. It remains unclear whether small differences in the procedures contribute to patient survival after surgery because PDAC is extremely malignant; however, the procedure should be completed if the invasiveness of the procedure is acceptable to the patient.

To date, whether the complete resection of the mesopancreas is involved in disease recurrence and patient survival after surgery for pancreatic head cancer remains unclear. However, the mesopancreas was reported to be the most frequent site of R1 resections [31]; therefore, total excision of the mesopancreas and complete circumferential lymphadenectomy have recently been considered to be key points in curative surgery, as described by several authors [31–34].

Nerve plexus invasion frequently spreads toward the dorsal side of the PL sma (Fig. 16.6) [35]. PDAC abutting the SMA not exceeding 180 degrees of the circumference of the vessel wall is defined as "borderline resectable" disease; however, up-front surgery for this condition is highly controversial. We compared between patients who underwent up-front surgery and patients who underwent neoadjuvant chemoradiotherapy (NACRT) followed by surgery [36]. The rate of curative resection was statistically similar. The results of the propensity score weighted logistic regressions indicated that the incidences of pathological lymph node metastasis and a pathological positive resection margin were significantly lower in the NACRT group (odds ratio, 0.006; $P < 0.001$ and odds ratio, 0.007; $P < 0.001$, respectively). Among the propensity score-matched patients, the estimated 1- and 2-year survival rates in the NACRT group were significantly longer than those in the up-front surgery group. Therefore, we concluded that NACRT, rather than up-front surgery, provided short-term clinical benefits and better survival in patients with PDAC in contact with the major arteries (Fig. 16.7) [36].

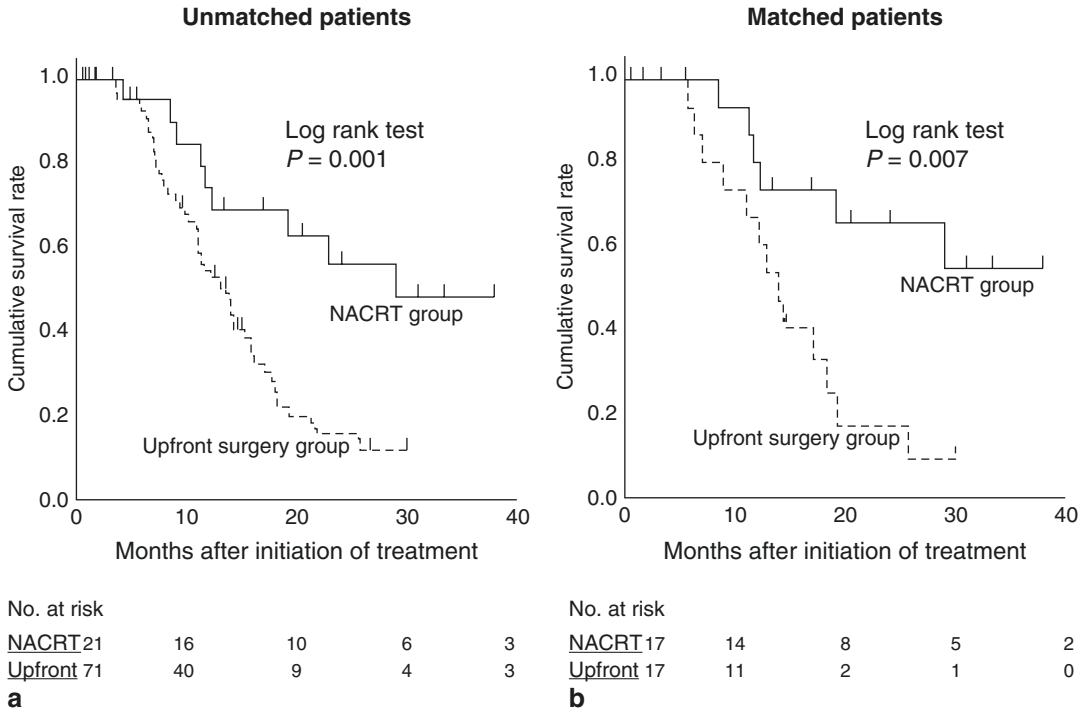

Fig. 16.7 (**a**) Kaplan–Meier curves for disease-specific survival after the initiation of treatment for unmatched patients who underwent up-front surgery ($N = 71$) or neoadjuvant chemoradiotherapy (NACRT) ($N = 21$; $P = 0.001$). The median survival times in the up-front surgery and NACRT groups were 13.1 and 29.1 months, respectively. (**b**) Kaplan–Meier survival curves for the propensity score-matched upfront surgery ($N = 17$) and NACRT ($N = 17$) groups ($P = 0.007$). In the upfront surgery group, the median survival time was 13.9 months, and the estimated 1- and 2-year survival rates were 66.7% and 16.0%, respectively. In the NACRT group, the median survival time could not be calculated because the survival curve did not reach the 50% line before the end of the study, and the estimated 1- and 2-year survival rates were 80.0% and 65.2%, respectively (From reference Fujii et al. [36])

16.5 Complete Resection of the Mesopancreas (Including the Retroperitoneal Nerve Plexus) Using the Mesenteric Approach

1. The first step of the mesenteric approach [37] is to incise the transverse mesocolon between the superior border of the Treitz ligament and the inferior border of the third portion of the duodenum (Fig. 16.8). All connective tissues around the SMA and superior mesenteric vein (SMV) are dissected toward the lower border of the pancreatic head region to expose the SMA and SMV (Fig. 16.9). The middle colic artery is ligated and divided at the root (Fig. 16.10).

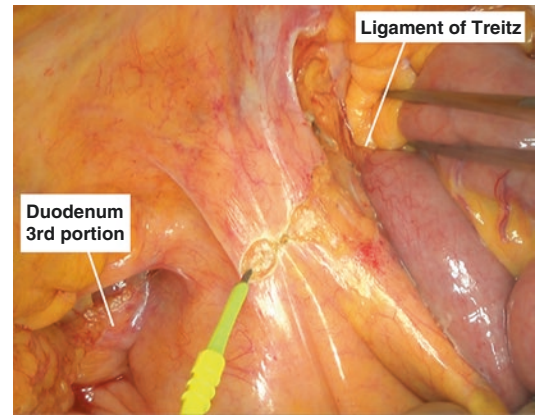

Fig. 16.8 Incision in the transverse mesocolon between the superior border of the Treitz ligament and the inferior border of the third portion of the duodenum

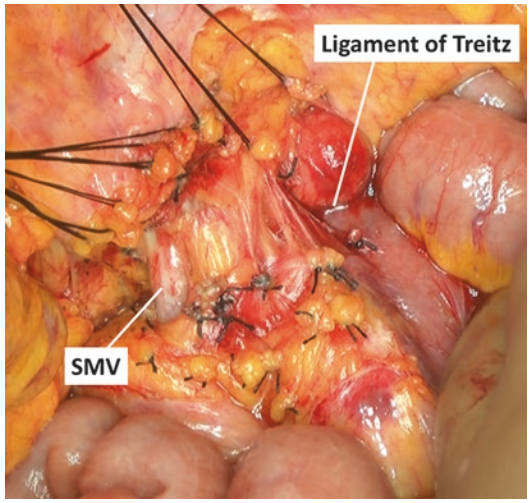

Fig. 16.9 All connective tissues around the SMA and SMV are dissected toward the lower border of the pancreatic head region

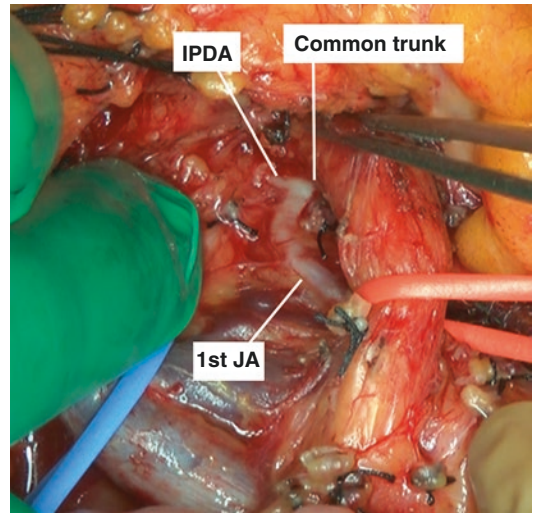

Fig. 16.11 The IPDA and the 1st jejunal artery are exposed

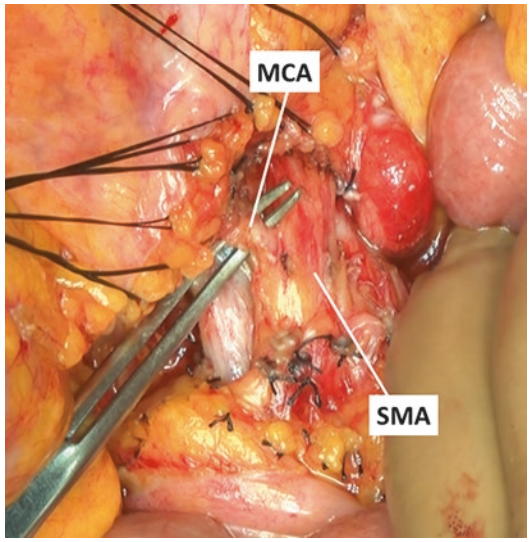

Fig. 16.10 The middle colic artery is ligated and divided at the root

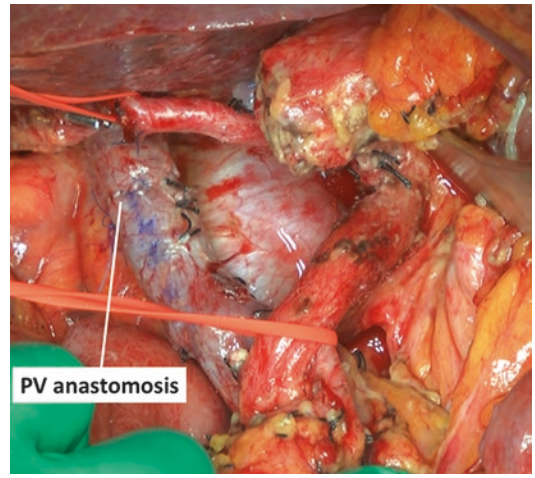

Fig. 16.12 Total mesopancreas excision is completed

2. The IPDA, 1st jejunal artery, and a common trunk of these two arteries are divided (Fig. 16.11).
3. Total mesopancreas excision is completed (Fig. 16.12).

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Mesenteric Approach for Pancreaticoduodenectomy

17

Seiko Hirono and Hiroki Yamaue

17.1 Introduction

Despite advanced radiographic images, operative techniques, operative managements, and chemo(radiation) therapies, the survival for pancreatic cancer patients is still dismal. Curative treatment for pancreatic cancer is only surgical resection with negative surgical margins (R0) and adjuvant therapy. R0 rates are lower in the advanced pancreatic cancer with involvement of the major arteries, including the superior mesenteric artery (SMA), common hepatic artery, or celiac artery than in resectable pancreatic cancer without vascular invasion [1–5]. Pancreatic head cancer often invades to the superior mesenteric vein (SMV) as well as SMA; therefore, the dissected margins around the SMV and/or SMA are favorable possible cancer-positive sites [6–9].

Since "artery-first approach" during pancreaticoduodenectomy was reported in 2010 [10], the term has become widespread. The concept of "artery-first approach" is that pancreaticoduodenectomy starts from the dissection of the surrounding tissues around the SMA [6, 10]. The aims of "artery-first approach" are (1) early determination of the resectability for pancreatic cancer, (2) complete dissection of the connected tissues around the SMA, and (3) control of blood flow into the pancreatic head [6, 10–12]. Several different "artery-first approach" techniques have been reported [10, 11, 13–21]. This chapter introduces "mesenteric approach" [11], which is one of the "artery-first approach" techniques during pancreaticoduodenectomy.

17.2 Surgical Resection for Pancreatic Head Cancer

Only curative treatment for pancreatic cancer is surgical resection and adjuvant therapy.

However, the recurrence rates have been still high, and the 5-year survival rate after surgical resection has been still low in pancreatic cancer patients. National Comprehensive Cancer Network (NCCN) guideline has defined the resectability of pancreatic cancer, and the criteria become widespread [2]. The NCCN criteria defining the resectability of pancreatic cancer without distant metastasis are based on the involvement extents of major arteries (superior mesenteric artery, common hepatic artery, or celiac artery), and of the portal vein (PV) and/or superior mesenteric vein (SMV), and categorized pancreatic cancers as resectable, borderline resectable, or unresectable pancreatic cancer [2]. The therapeutic strategy for pancreatic cancer is determined according to the resectability, which means surgery first,

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neoadjuvant therapy followed by surgery, or chemo(radiation) therapy. Therefore, the determination of the resectability is the most important step for pancreatic cancer patients [2].

High-resolution dynamic computed tomography (CT) predicts the resectability with a high accuracy in pancreatic cancer [22–24]. However, the diagnosis whether true cancer invasion or inflammation mimicking cancer invasion to the major arteries or PV/SMV is difficult, especially after neoadjuvant therapy [25]. Therefore, the resectability is diagnosed finally at the operation, and one aim of "artery-first approach" is early determination of the resectability before committing an irreversible step in operation.

Curative surgical resection (R0) is essential to prolong the survival for pancreatic cancer patients. Favorable positive surgical margins are the connective tissues around the major arteries or PV/SMV [6–9]. As operative techniques and postoperative management are advanced, the PV/SMV resection and reconstruction have been reported as a safe and feasible procedure [26–28]. Therefore, if cancer invasion to the PV/SMV is suspected pre- or intraoperatively, PV/SMV resection is usually performed during pancreatectomy to obtain the negative surgical margins. However, resection and reconstruction of the major arteries during pancreatectomy for R0 resection are controversial, because the procedure might cause high mobility and mortality rates and there have been not enough evidences that resection of the major arteries improves the survival for advanced pancreatic cancer patients [29, 30].

In pancreatic head cancer, the connective tissues around the SMA are the most frequent positive surgical margin spot. The surrounding tissues around the SMA included lymphatic, nervous, and vascular structures toward the third and fourth portions of the duodenum and proximal jejunum as well as pancreatic head. Not enough dissection of this area may cause local recurrence around the SMA after surgery and poor survival for pancreatic head cancer. Other aim of "artery-first approach" is complete dissection of the connective tissues around the SMA to obtain the negative surgical margins for pancreatic head cancer. Complete dissection behind the SMA and SMV is a difficult step during pancreaticoduodenectomy, and several "artery-first approach" techniques, which are feasible for the dissection around the SMA, have been reported [10, 11, 13–21]. In this chapter, "mesenteric approach" is introduced as one technique of "artery-first approach" during pancreaticoduodenectomy [11].

17.3 Optimal Dissection Area Around the Superior Mesenteric Artery and Superior Mesenteric Vein for Pancreatic Head Cancer

One of the favorable R1 or R2 spots for pancreatic head cancer is dissected margins around the SMA [6–9]. Retropancreatic structures extending the SMA included vascularized and nerve-rich lamina, including the first and second nerve plexuses around the pancreatic head (plPh-I and plPh-II) to the SMA and right celiac ganglion, named by the Japanese General Rules for the Study of Pancreatic Cancer [31], and inferior pancreaticoduodenal artery (IPDA), which often forms the common trunk with the jejunal artery, jejunal veins, and lymph nodes. These connected tissues around the SMA and SMV are usually called "mesopancreas" [7, 11, 12, 31–35] or "mesopancreatoduodenum" [9]. Complete excision of these tissues is considered to be necessary to obtain negative surgical margins for pancreatic head cancer.

"Artery-first approach" is the term coined by Weitz and coworkers [10], as the procedure allowing an earlier dissection of the connective tissues around the SMA and SMV during pancreaticoduodenectomy. The aims of "artery-first approach" are (1) early judgment of the resectability in advanced pancreatic head cancer, by clearance margins around the SMA, (2) gaining R0 resection rates, and (3) reduction of intraoperative blood loss by avoiding venous congestion in the pancreatic head specimen [6, 10–12]. The term "artery-first approach" during pancreaticoduodenectomy has become widespread since then, and several techniques of "artery-first approach" have been reviewed in 2012 [6].

17.4 Advantages of "Artery-First Approach" for Pancreatic Head Cancer

17.4.1 Early Determination of Resectability for Pancreatic Cancer

As radiographic imaging using three-dimensional CT advances, the diagnosis of the resectability in pancreatic head cancer is more accurate recently [22–24]. However, preoperative determination of cancer involvement extent of the tissues around the SMA is sometimes difficult, especially in advanced pancreatic head cancer after neoadjuvant therapy [25]. Therefore, the decision of resectability should be made early in operation by dissection of surrounding tissues around the SMA first, and "artery-first approach" arises from this concept [10].

17.4.2 Gaining Negative Surgical Margins Around the SMA

"Artery-first approach" allows complete dissection of the tissues behind the SMA and SMV early in operation, where dissection of this region is a difficult step during pancreaticoduodenectomy [9–12]. If the dissection of this region is not enough, the rate of positive margin may increase, which causes increase of local recurrence and shorten the survival for pancreatic head cancer patients. Some retrospective studies reported that the R0 rates were higher and local recurrence rates were lower in "artery-first approach" pancreaticoduodenectomy than in standard pancreaticoduodenectomy [9, 12].

17.4.3 Reducing Intraoperative Blood Loss

"Artery-first approach" allows control of early blood inflow into the pancreatic head by early ligating the IPDA in operation, which may lead to reduction of intraoperative blood loss and transfusion rates [9, 12].

17.5 Mesenteric Approach

Nakao et al. first reported "mesenteric approach" during pancreaticoduodenectomy for pancreatic head cancer in 1993 [11]. They suggested non-touch isolation technique, the concept of which is that the pancreatic head is not manipulated (Kocher's maneuver) prior to ligating and dividing the arteries supplying the pancreatic head [11]. Therefore, this approach starts from the dissection of lymph node, arteries, veins, and nerve plexus around the SMA at the mesentery cranially toward the mesenteric root. "Infracolic approach" named by Weitz et al. [10] and "total mesopancreatoduodenum excision" named by Kawabata et al. [9] are similar techniques to "mesenteric approach," although "infracolic approach" starts from the identification of the origin of the SMA by Kocher's maneuver.

This approach has some advantages of "artery-first approach," and it is useful especially for the pancreatic head cancer involving the mesocolon and/or SMV as well as the SMA because of gaining the well-opened view by dissection of the connective tissues around the SMA [6, 9–12]. However, the technique may be difficult in some patients, such as obese patients or patients with a high origin of the SMA [6, 10].

17.6 The Surgical Procedure of Mesenteric Approach During Pancreaticoduodenectomy

The mesenterium is incised from the Treitz ligament to the inferior duodenal flexure after lifting the transverse colon cranially and bringing the upper jejunum caudally to identify the SMA and SMV. The middle colic artery is exposed arising from the anterior side of the SMA easily, and this artery is usually divided if pancreatic cancer invasion is severe (Fig. 17.1). The dissection of connective tissues around the SMA starts from the left side of the SMA, and the origins of IPDA and the first jejunal artery are identified at the left posterior side of the SMA (Fig.17.2). IPDA

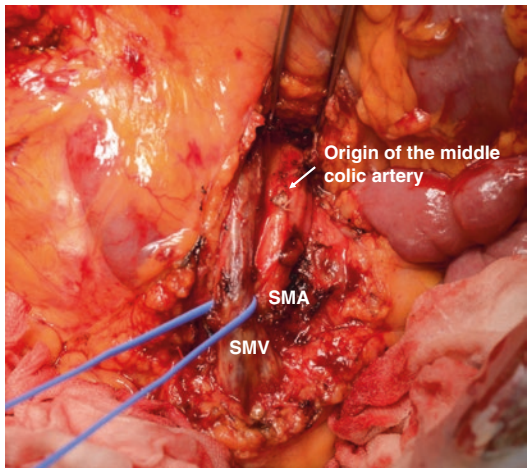

Fig. 17.1 The superior mesenteric artery (*SMA*) and superior mesenteric vein (*SMV*) are identified at the infracolic mesentery. The middle colic artery is usually divided if cancer invasion is severe

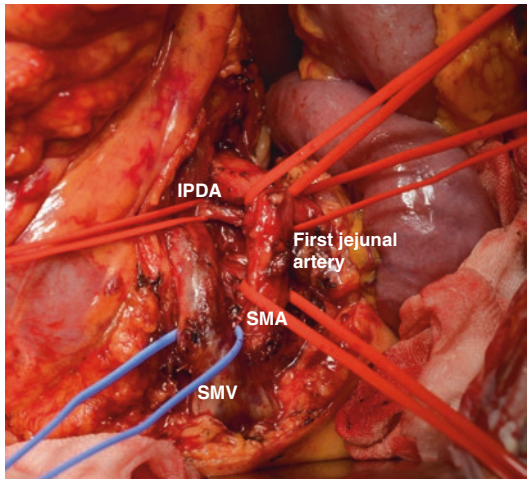

Fig. 17.2 The origins of the inferior pancreaticoduodenal artery (*IPDA*) and the first jejunal artery are identified by dissection of the connective tissues around the SMA from the *left side*

forms usually the common trunk with the fist jejunal artery; however, IPDA is sometimes found to branch from the SMA separately. It is important to check the location of the IPDA and the first jejunal artery by the preoperative CT imaging to proceed with this dissection successfully. After the origin of the common trunk of the IPDA and the first jejunal artery is ligated and divided, by pulling the tape of the SMA to the left

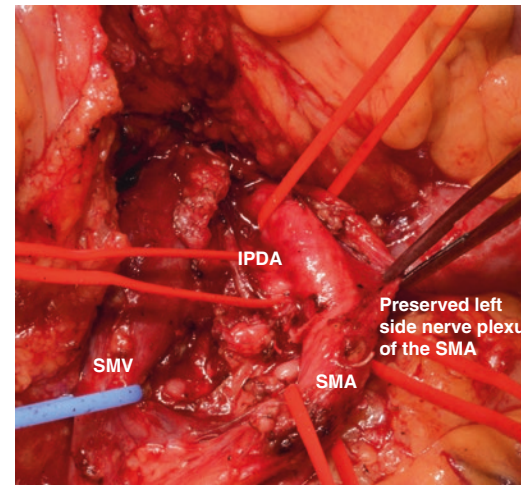

Fig. 17.3 The left side of nerve plexus of the SMA is preserved to prevent postoperative severe diarrhea

side, the connective tissue around the SMA containing neurovascular bundle that includes the plPh-I and plPh-II and lymph nodes was dissected up to the origin of the SMA in a longitudinal direction.

The appropriate dissection of the nerve plexus of the SMA, which means circumferential dissection, semicircle dissection, or no dissection, is controversial. The nerve plexus dissection of the SMA could cause postoperative severe diarrhea and may delay the start of the adjuvant therapy [36, 37]. Furthermore, it is reported that the semicircle dissection of the nerve plexus of the SMA could not improve the survival for the patients with resectable pancreatic cancer [36]. Therefore, the nerve plexus of the SMA may not be necessary for pancreatic cancer without invasion to the nerve plexus around the SMA. However, borderline resectable pancreatic cancer sometimes needs semicircle or circumferential dissection of the SMA to obtain the negative margins (R0). If the nerve dissection is necessary, the nerve plexus of the SMA is also dissected outside of the SMA adventitial during dissection of the connective tissues around the SMA (Fig. 17.3).

The connective tissues around the SMV also are dissected, and the inferior pancreaticoduodenal vein, first jejunal vein, Henle's gastrocolic trunk, and middle colic vein (if necessary)

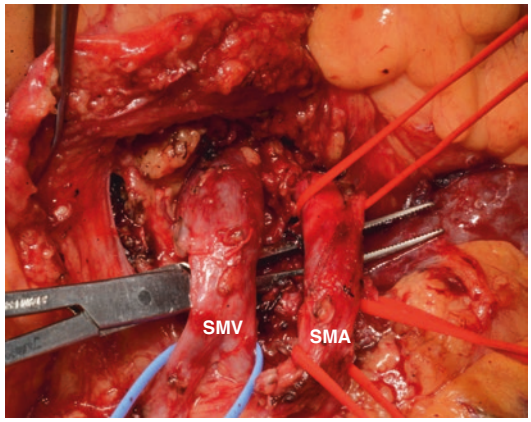

Fig. 17.4 Mesenteric approach is finished at the time of completion of dissection around the SMA and SMV

are ligated and divided. Mesenteric approach is finished at the time of completion of dissection around the SMA and SMV (Fig. 17.4).

Conclusion

"Mesenteric approach" is a feasible "artery-first approach" technique during pancreaticoduodenectomy. Recent some retrospective reports described the superiority of "artery-first approach" to standard pancreaticoduodenectomy. However, further prospective studies are necessary to confirm the superiority of "mesenteric approach" pancreaticoduodenectomy.

Disclosure of Financial Interests and Potential Conflicts of Interest We have no financial interests and potential conflicts of interest.

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Artery-First Approach for Pancreatic Cancer

18

Sanjay Pandanaboyana and John A. Windsor

18.1 Background

Pancreatic resection for cancer continues to evolve. Invasion of portal-superior mesenteric vein is no longer considered a contraindication for pancreatoduodenectomy (PD), and resection of the vein is often used to achieve a negative resection margin [1–3]. In contrast, involvement of superior mesenteric artery is still considered a contraindication for PD, and resection of SMA is not routinely offered [4].

The need to determine whether the SMA is involved at an early stage during PD or distal pancreatectomy and before any irreversible steps are undertaken, i.e. transection of the neck of the pancreas, has led to the development of artery-first approach. This approach is founded on the principle that the status of the SMA and common hepatic artery (CHA) in regard to tumour encasement and/or invasion has become the primary determinant of resectability. High-resolution computerized tomography (CT) is performed routinely prior to PD and has a 95% accuracy in determining resectability [5]. Despite this accuracy, trial dissection remains the gold standard to determine true resectability, and this is particularly the case in patients after neoadjuvant chemotherapy for 'borderline resectable' disease [6]. In this setting, the accuracy of CT staging is greatly reduced, with a positive predictive value of 25% [7] because it is not possible to distinguish tumour invasion from peritumoural inflammation and the effects of neoadjuvant therapy. Thus, the historical criteria for determining resectability by cross-sectional imaging are no longer applicable, and this means that an AFA to trial dissection is particularly important in determining resectability at an early stage of pancreatic resection.

18.1.1 Technical Descriptions of Artery-First Approaches to Cancer of Pancreatic Head

There are six different techniques of the AFA in the literature. These are summarized briefly here (Fig. 18.1).

18.1.1.1 Posterior Approach

The first technical description of AFA was described in 2003 by Pessaux et al. [8], and this was for a posterior approach to the SMA. The posterior approach is the most commonly performed technique, and there have been several

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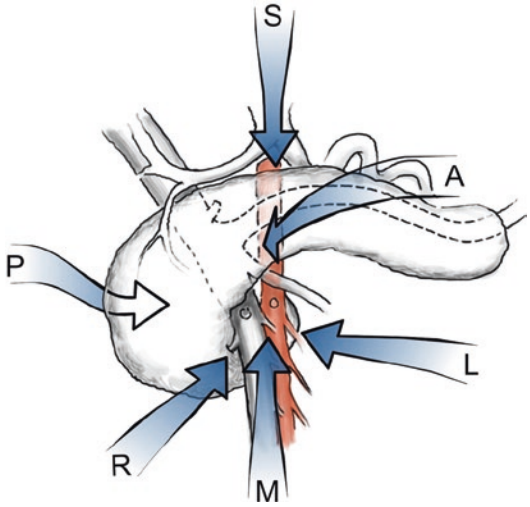

Fig. 18.1 Demonstrating the six approaches to the SMA. *S* superior approach, *P* posterior approach, *R* right/medial uncinate approach, *M* mesenteric approach, *L* left posterior approach, *A* anterior approach

modifications [9–11]. Following an initial exploratory laparotomy, an extended kocherization of the duodenum is performed exposing the inferior vena cava, left renal vein and abdominal aorta. This is assisted by full mobilization of the right colon and hepatic flexure to the left of midline. The pulsations of the SMA are identified in front the left renal vein, and the perivascular connective tissue is incised to expose the adventitia of the SMA. The dissection on the adventitia of the SMA is continued in a caudal direction posterior to the pancreatic head to where it crosses the third part of the duodenum further dividing the attachments between the SMA and uncinate process to expose the border of the PV–SMV. The origins of the superior pancreaticoduodenal and inferior pancreaticoduodenal (IPDA) arteries are divided as they enter the pancreatic head and uncinate process, respectively. Care must be taken to identify a replaced right hepatic artery that usually arises 1–2 cm from the origin of the SMA. By now, all of the connective tissue attachments between the PV and the SMA have also been divided, and a negative SMA margin confirmed, with frozen section if necessary.

18.1.1.2 Medial or Uncinate Approach

In 2010, Hackert and co-workers [12] described a medial or 'uncinate-first' approach to the SMA. Following an initial extended kocherization, a Cattell–Braasch manoeuvre is performed, which involves dissection along the right-sided white line of Toldt and then across the small bowel mesenteric root, which allows the colon and small bowel to be retracted well to the left, facilitating exposure of the SMV as it passes over the third part of the duodenum. The pancreas is dissected free from the SMV, often requiring the division of two or three venous tributaries. The duodenojejunal (DJ) flexure is then mobilized, and the proximal jejunum transected and transposed to the right abdomen by passing it behind the superior mesenteric vessels. Further exposure of the SMA and SMV is facilitated by division of proximal jejunum although this is not always necessary. The Cattell–Braasch manoeuvre facilitates retraction of the right colon and small bowel to the left, which lifts and rotates the SMV up and to the left, and with retraction of the third and fourth parts of the duodenum to the right, the SMA is rotated into view under the SMV. It is then possible to dissect down on the medial aspect of the SMA in a cephalad direction under the neck of the pancreas. The IPDA and RRHA are encountered and divided on the way, similar to the posterior approach.

A modified medial uncinate approach is described by Shukla and colleagues [13] in 2007 which entails division of the ligament of Treitz and translocation of the proximal jejunum with its intact mesentery into the supracolic compartment, by passing it to the right under the superior mesenteric vessels. This is said to facilitate alignment of the uncinate process with the jejunal mesentery, enabling easier dissection of the SMV and SMA.

18.1.1.3 Inferior Infracolic Approach (Mesenteric Approach)

In 2010, Weitz and co-workers [14] coined the term 'artery-first approach' and described the inferior approach to the SMA from the infracolic

compartment, at the base of the transverse mesocolon. Mobilization of the DJ flexure is performed initially, and the peritoneum is divided over the palpable SMA. The SMA is exposed, with the SMV to the right. The middle colic artery is identified arising from the SMA and coursing anteriorly within the transverse mesocolon. The IPDA is identified on the right aspect of the SMA as it enters the uncinate process under the SMV. The IPDA is divided, and dissection continues up and along the anterior and right medial aspect of the SMA to its origin, under the neck of the pancreas and splenic vein. This approach exposes the SMA in the infracolic compartment at the root of the mesentery.

18.1.1.4 Left Posterior Approach

Kurosaki and colleagues in 2011 [15] described the left posterior approach to the superior mesenteric vascular pedicle. Following division of ligament of Treitz, the proximal jejunum is pulled to the left exposing the first and second jejunal arteries which are divided at their origin from the SMA. Further traction on the proximal jejunum produces a counterclockwise rotation to the SMA that allows identification and division of the IPDA, arising from the posterior surface of the SMA in addition to enabling clearance of the posterior and right aspects of the SMA. With the SMA freed and retracted to the right, and with the proximal jejunum still retracted to the left, the SMV appears under the SMA, and the first jejunal branch of the SMV is divided. The SMV is then skeletonized up to its confluence with the splenic vein. This frees the superior mesenteric pedicle from the uncinate process and the mesentery of the proximal jejunum. The jejunum is then divided and the duodenum transposed to the right, allowing exposure and division of the remaining connective tissue where it attaches to the superior mesenteric pedicle.

18.1.1.5 Inferior Supracolic Approach (Anterior Approach)

Hirota and co-workers [16] described the inferior supracolic approach in 2011. An initial division of the gastric antrum is described; however, it is possible to expose the pancreatic neck by cephalad retraction of the stomach after division of the gastrocolic ligament without division of the gastric antrum. The next step in this technique is to divide the pancreatic neck to expose the SMV–PV junction, but it is worth doing as much dissection as possible by elevating the inferior edge of the pancreas to determine resectability before division of the pancreas. The authors then describe the 'hanging manoeuvre', which involves passing a tape along the right surface of the aorta to the origin of the SMA and coeliac trunk, and then passing it between the CHA and the superior margin of the pancreatic neck, after first dissecting this area. Traction on this tape exposes the peripancreatic retroperitoneal margin with the neural plexi and lymphatics and facilitates their division. The next step is a 'reversed kocherization' with en bloc mobilization of the duodenum and pancreatic head, in a medial to right lateral direction, in a plane deep to Gerota's fascia and anterior to the left renal vein and inferior vena cava. The disadvantage of the technique as originally described is the (irreversible) transection of the stomach and pancreatic neck at an early stage to achieve adequate exposure of the SMA, but this is not always necessary.

Inoue and colleagues [17] more recently described the supracolic anterior approach to the superior mesenteric artery with an aim to undertaking systematic mesopancreas dissection to achieve adequate clearance of perineural and lymphatic tissue and negative margins along the SMA. After an initial extended kocherization, the right side of the SMA root is identified in front of the LRV. The gastrocolic ligament and greater omentum are then dissected until the pancreas head is well exposed. The duodenum is dissected to the left, exposing the superior mesenteric vein (SMV) from the right side. The SMV is dissected and taped, and Henle's gastrocolic trunk and inferior pancreaticoduodenal vein are sacrificed. By retracting the SMV leftward, the first jejunal vein is identified. This also enables visual inspection and palpation of the SMA. The mesopancreas division is initiated from the caudal end anteriorly to the immediate right of the JV, which would be

preserved throughout dissection. The mesopancreas is divided layer to layer exposing the IPDA. In cases where the uncinate process extends to the left of the SMA, the first jejunal vein is divided at its origin from the SMV to gain more access. If there is SMV involvement by the tumour, the dissection plane around the SMA is just outside of the adventitia usually from 11 to 5 o'clock, peeling off the nerve plexus around the SMA like a plate. In cases where there is a common trunk of IPDA and first jejunal artery, the common trunk is divided at its root. After separation of the SMA from the pancreatic head, the dissection is carried caudally until it reaches the left renal vein completing the SMA artery-first dissection.

18.1.1.6 Superior Approach

In this approach, the hepatoduodenal ligament is dissected first to expose the CHA and the gastroduodenal artery by dissecting from right to left to remove the anterior lymph nodes en bloc or separately. The dissection is then carried down the coeliac trunk, inside the perineural and lymphatic tissue, on to the aorta and origin of the SMA, aided by caudal retraction of the pancreas.

18.1.2 Technical Description of Artery-First Approaches to Cancer of Pancreatic Body

More recently, an AFA has been described for borderline resectable pancreatic cancer of the body of the pancreas during the radical antegrade modular pancreatectomy (RAMP) [18, 19]. This facilitates the identification and dissection of the SMA behind the body of the pancreas. Following an initial exploratory laparotomy, the ligament of Treitz is divided to expose the left side of the DJ flexure, and further dissection is carried out to expose the anterior surface of the aorta, IVC and left renal vein together with the origin of the SMA from the aorta. This enables adequate clearance of posterior surgical margin. The dissection is then directed to the supracolic compartment with division of the gastrocolic ligament thereby exposing the inferior border of the pancreas. The middle colic artery in the transverse mesocolon is traced caudally to help identify the SMA. The SMA is then fully exposed from the origin of the middle colic artery to the origin of the SMA. If there is tumour infiltration of the MCA and transverse mesocolon, resection of these should be undertaken, and in the majority of cases, the marginal artery of Drummond is sufficient. Following confirmation of clear SMA margins, the PV–SMV trunk is freed from the posterior aspect of the pancreas. This will enable passage of a dissecting forceps from the inferior border of the pancreas, anterior to the SMA towards the inferior border of the coeliac trunk. This technique termed as the pancreas hanging manoeuvre enables or allows elevation of the pancreas away from the SMA to obtain a wide view of the anterior surface of the SMA. A standard radical antegrade modular pancreatosplenectomy (RAMPS) procedure is then undertaken to complete the pancreatosplenectomy (Ref).

Indications, advantages and disadvantages of the AFAs are summarized in Table 18.1.

18.1.3 Impact of AFA on Outcomes

The current published data regarding the impact of AFA on perioperative outcomes is conflicting. Blood loss is said to be reduced because all AFAs allow identification and ligation of IPDA at an earlier stage of the dissection. Three studies comparing standard PD to AFA PD have shown reduced blood loss with an AFA [17, 20, 21], while others did not show any difference [15, 23]. The perioperative morbidity, mortality and hospital stay were comparable with both approaches [15, 17, 20, 21, 23]. Similarly, published data showed the lymph node yield was similar for both approaches. However, more recent data from Leeds (unpublished data) has shown higher median lymph node yield in the SMA-first group 28 (range 13–50) vs 21 (range 5–50).

More recent data on survival after AFA is more encouraging with data suggesting improved survival [15, 16]; however, the studies were non-randomized and retrospective in design, and long-term data is not available. The left posterior approach [15] was associated with fewer

Table 18.1 Summary of indications, advantages and disadvantages of various 'artery-first approaches'

Approach	References	Indication(s)	Advantages and disadvantages
Posterior	Pessaux et al. (2006) [13]	Postero-medial tumour in the head/neck, especially involving the PV/SMV Periampullary tumour extending from the body to the head	Advantages Early identification of SMA involvement Identification of replaced RHA Enables adequate retropancreatic lymphadenectomy Early identification of SMV involvement and facilitates en bloc resection Disadvantages Difficult in cases of PD with peripancreatic inflammation and adhesions around the head of the pancreas
Medial uncinate	Hackert et al. (2010) [19] Shukla et al. (2007) [23]	Malignant tumours of the uncinate process	Advantages Early identification of SMA involvement at the uncinate Early ligation of IPDA arteries minimizing bleeding Useful approach in peripancreatic inflammation with difficulty tunnelling above the portal vein Useful approach for total pancreatectomy as mobilization can be achieved without transecting the gland Disadvantages Late identification of replaced RHA
Inferior infracolic (mesenteric approach)	Weitz et al. (2010) [20]	Locally advanced tumours with questionable infiltration of SMA at its origin from the aorta Malignant tumours of uncinate and ventral pancreas	Advantages Early identification of replaced right hepatic artery Allows better exposure and dissection of the region posterior to the SMA Early ligation of IPDA thereby minimizing bleeding Disadvantages Difficult in morbidly obese patients Difficult exposure in cases with high origin of the SMA
Left posterior approach	Kurosaki et al. (2011) [21]	Tumours along the uncinate and ventral pancreas	Advantages Facilitates skeletonization of SMA in the retroperitoneum without kocherization of the duodenum Early ligation of IPDA Disadvantages Extensive dissection of SMA requiring antidiarrhoeals
Inferior supracolic (anterior approach)	Hirato et al. (2010) [22]	Tumours along the inferior border of the pancreas	Advantages Facilitates better retroperitoneal dissection especially with locally advanced tumours with neoadjuvant treatment A 'no-touch technique' with en bloc kocherization theoretically prevents tumour cell dissemination Disadvantages Early division of the stomach and neck of the pancreas
Superior		Malignant tumours of the superior border of pancreas	Advantages Early identification of CHA, celiac and SMA involvement Disadvantages Difficult exposure in cases with low origin of the SMA

recurrences (10% vs 37%; $p = 0.006$) and improved survival compared to the standard PD [1- and 3-year survival rates 90% and 53% (AFA) vs 80% and 16% (standard PD); $p = 0.004$]. Similarly, the inferior supracolic approach (anterior approach) [16] has been shown to achieve an R0 rate of 82% for pancreatic adenocarcinoma and 91% for biliary adenocarcinoma, with a combined overall 2-year survival rate for these subgroups of 75%. Similarly unpublished data from Leeds Pancreatic Unit has shown a trend towards improved disease-free survival (median 13 vs 19 months) and overall survival (median 19 vs 30 months) in the AFA group; however, this was not statistically significant ($p = 0.19$ and $p = 0.18$).

There are no published data comparing survival from standard and AFA RAMPS. The R0 rate after AFA RAMPS has been published as 82% and 100% [18, 19]. There was also a higher lymph node yield 26 (range 9–80) compared with published data after standard RAMPS [24]. At the median follow-up after surgery of 12.4 months (range 3.5–16.4 months), the overall survival rate was 100% at 1 year. The 1-year disease-free survival rate was 91%. No long-term data is currently available.

18.2 Discussion

The driving force for the AFA was the need for early identification of SMA involvement before the point of no return and to facilitate the accurate dissection of the SMA (posteromedial) margin of the pancreas to give the best chance of a negative resection margin. The SMA margin is the most commonly involved margin during an R1 resection [25] especially in patients undergoing PD with vein resection. The ubiquitous finding of perineural invasion in pancreatic ductal adenocarcinoma helps explain the high risk of a positive margin, as periarterial neural plexus surround the origin of the SMA. The existing evidence suggests that the AFA improves the negative margin rate during distal pancreatectomy, but the effect on overall survival is difficult to determine because of the effect of neoadjuvant therapy. It therefore remains an open question as to whether the AFAs alone can improve the margin status after PD. Another important advantage of the AFA is that the surgeon is more likely to identify SMA involvement at an earlier stage of the trial dissection, before the point of no return, and can stop the operation and elect for neoadjuvant therapy to increase the chance of a margin-negative resection. Recent studies have shown impressive outcomes after neoadjuvant chemotherapy with FOLFIRINOX-based regimens, including an impressive 64% R0 resection rate in borderline resectable [25]. It is particularly with these patients that AFA has an important and defined role, as it is often difficult to differentiate tumour from inflammation and fibrosis. Another situation in which the AFA is helpful is in those who will require resection of the PV–SMV. Here, the early dissection of the SMA leaves only the tumour to the vein, and this often facilitates the vein resection, reducing the venous clamp time and probably reduces blood loss. The AFA is also useful for the early identification and dissection of an anomalous RHA, especially when it requires preservation as the sole supply to the right liver. The most recent publications indicate an emerging role for AFA in the RAMP procedure for borderline resectable pancreatic body and neck tumours. Data suggests a superior negative margin rate, but evidence for long-term survival benefit is lacking. In conclusion, there is insufficient evidence for the routine use of AFA for PD, especially in relation to oncological benefits. Nevertheless, the various AFAs provide the surgeon with range of options based on the location and size of the tumour to undertake trial dissection to determine SMA involvement before the point of no return both for tumours in the head and body of the pancreas.

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Mesopancreas Excision for Pancreatic Cancer

19

Yosuke Inoue and Akio Saiura

19.1 Background

Regarding the optimal extirpation technique for gastrointestinal cancers, many surgical oncologists have historically advocated en bloc resection of the cancer and cancer-bearing regions including lymph nodes (LNs) and organ parenchyma in the region of the stomach [1–3], colon [4], rectum [5], and liver [6]. Although the oncological benefit of this method has been proven in only a limited number of reports [3, 7], the principle has gained popularity among surgeons worldwide. Particularly for colonic cancers, en bloc resection of the cancer-bearing intestine and mesocolon with high ligation of the supplying arteries of corresponding regions is termed central vascular ligation (CVL) [4]. To date, however, CVL during pancreaticoduodenectomy (PD) has rarely been discussed, where margin-negative resection often depends on adequate dissection around the superior mesenteric artery (SMA).

Concurrently with introduction of the artery-first approach, the concept of "mesopancreas" was suggested as one of the important oncological concepts during PD [8]. The mesopancreas represents a retropancreatic structure extending to and behind the SMA, including well-vascularized and nerve-rich lamina, which corresponds to the first and second nerve plexus of the pancreas head (plPh-I and plPh-II) according to the Japanese General Rules for the Study of Pancreatic Cancer [9]. In this chapter, we describe a procedure for mesopancreas excision or SMA dissection that uses the SMA hanging technique following the supracolic anterior artery-first approach to facilitate CVL. This technique is based on the anatomical features around the SMA and ligament of Treitz, and its performance is feasible without special devices or expertise.

19.2 Concept of Central Vascular Ligation in Pancreaticoduodenectomy (PD-CVL)

Figure 19.1a shows the conceptual schema of vascular anatomy of the digestive system, wherein the anatomical intestinal rotation was released and each organ was arranged in a single plane [10]. The pancreas head is connected to the SMA system, celiac ganglion, and celiac axis system. In this chapter, "the mesopancreas" is defined as the neurovascular bundle that includes the plPh-I, plPh-II, inferior pancreaticoduodenal arteries (IPDAs), jejunal arteries (JAs), jejunal veins (JVs), and LNs. When we perform CVL, the supplying arteries of pancreas head, i.e., IPDAs and gastroduodenal artery, should be ligated at their

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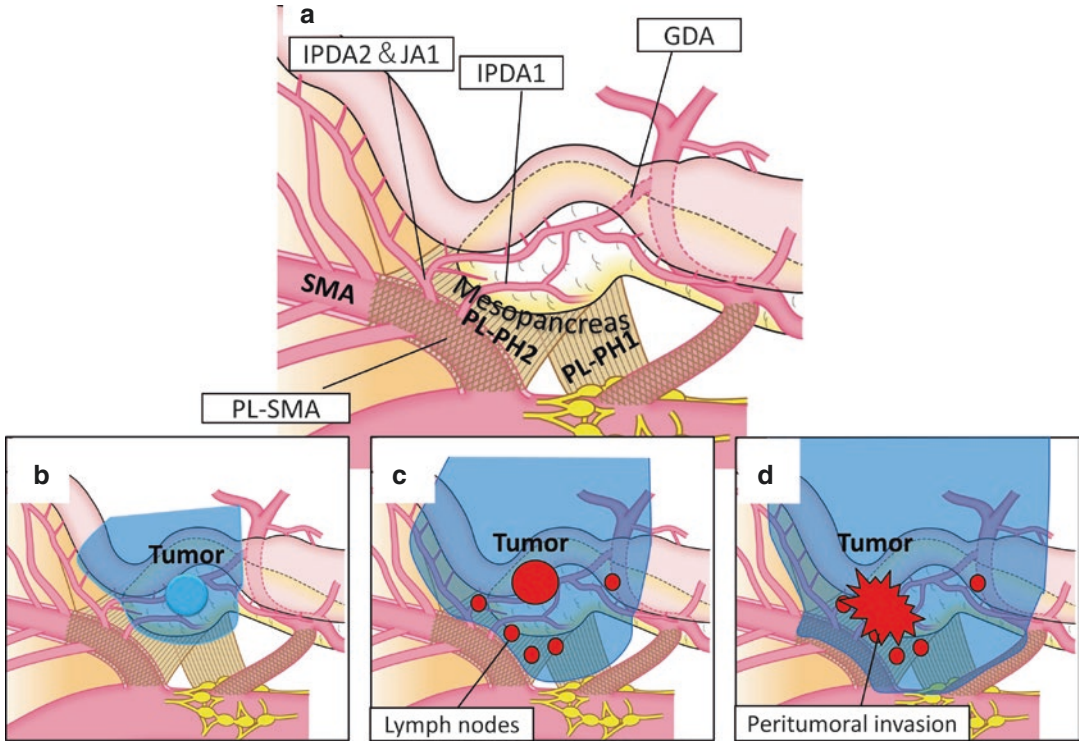

Fig. 19.1 Conceptual schema of central vascular ligation during pancreaticoduodenectomy (quoted from reference [10] with modification). (**a**) Magnified view of systems around the pancreas head with the components arranged in a single plane. The mesopancreas includes the plPh-1, plPh-2, arteries, and veins. (**b**) Level 1 dissection, which aims to resect the pancreas head alone without systematic lymph nodes (LNs) dissection. (**c**) Level 2 dissection, which aims to dissect the pancreas head and the mesopancreas en bloc. (**d**) Level 3 dissection, which aims to dissect the pancreas head, the mesopancreas, and the hemi-circumferential nerve plexus around the SMA and if needed the celiac axis

root (Fig. 19.1a). Because IPDA often has a common trunk with the 1st or 2nd JA, CVL would cover up to the watershed of the corresponding jejunal artery. In our theory described previously as systematic mesopancreas dissection [11], level 1 dissection aims to resect the pancreas head without LNs dissection in artery-first fashion as depicted in Fig. 19.1b. Level 2 dissection includes complete mesopancreas excision and systematic dissection of regional LNs around the SMA (Fig. 19.1c). Level 3 dissection is extended dissection involving hemi-circumferential resection of nerve plexus of the SMA (plSMA), facilitating to maximize the resection margin toward the SMA (Fig. 19.1d). In this chapter, we describe the detail of level 2 and 3 dissection around the SMA for pancreatic cancers using CVL by supracolic anterior artery-first approach.

19.3 PD-CVL Surgical Technique

19.3.1 Abdominal Exploration and Preparation for PD-CVL

After an upper abdominal midline incision, the peritoneal cavity is explored to confirm the tumor stage and operability. After a wide Kocher maneuver, the para-aortic LNs are explored and resected if necessary. The duodenum is dissected to the left, exposing the superior mesenteric vein (SMV) from the right side. The gastrocolic ligament and greater omentum is then dissected until the pancreas head is well exposed. The superior right colic vein is ligated routinely, followed by further dissection along the same plane to expose the middle colic artery, which is exposed to its root to identify the SMA and to dissect the LNs

above the SMA. The SMV is then taped at the level of the transverse portion of the duodenum.

19.3.2 Right Dorsal Dissection of the SMA Using Supracolic Anterior Artery-First Approach

In level 2 dissection usually without SMV co-resection, branches such as Henle's gastrocolic trunk or the first JV are divided to free the SMV from the pancreas head. A diamond-shaped window is then created by retracting the SMV rightward, the transverse mesocolon caudally, the SMA leftward, and the pancreas neck cranially (Fig. 19.2a). If the middle colic vein obstructs this window, it can be ligated and divided. In this field, the right and dorsal aspects of the SMA are dissected using the supracolic anterior approach while preserving the circumferential plSMA (Fig. 19.2b).

In level 3 dissection, wherein the cancer has invaded the mesopancreas and SMV, the connective tissue around the SMV is not detached from the SMV. The middle colic vein is routinely ligated and divided. The hemi-circumferential plSMA in the corresponding direction is resected to gain an optimal margin from the area of cancer infiltration (Fig. 19.3a, b).

In both level 2 and 3 dissection, the JV running behind the SMA should be adequately separated from the SMA, i.e., up to 1 cm left to the SMA (Figs. 19.2b and 19.3b). The root of the IPDA or the common trunk of the IPDA and first JA is exposed, ligated, and cut at this stage. We then convert the procedure to left-sided dissection of the SMA.

19.3.3 Finger-Guided Connection of the Dissection Space of Both Sides of the SMA

At this stage, we can easily identify the root of the second JA to be preserved (Fig. 19.4a). The surgeon inserts the left fingers behind the SMA

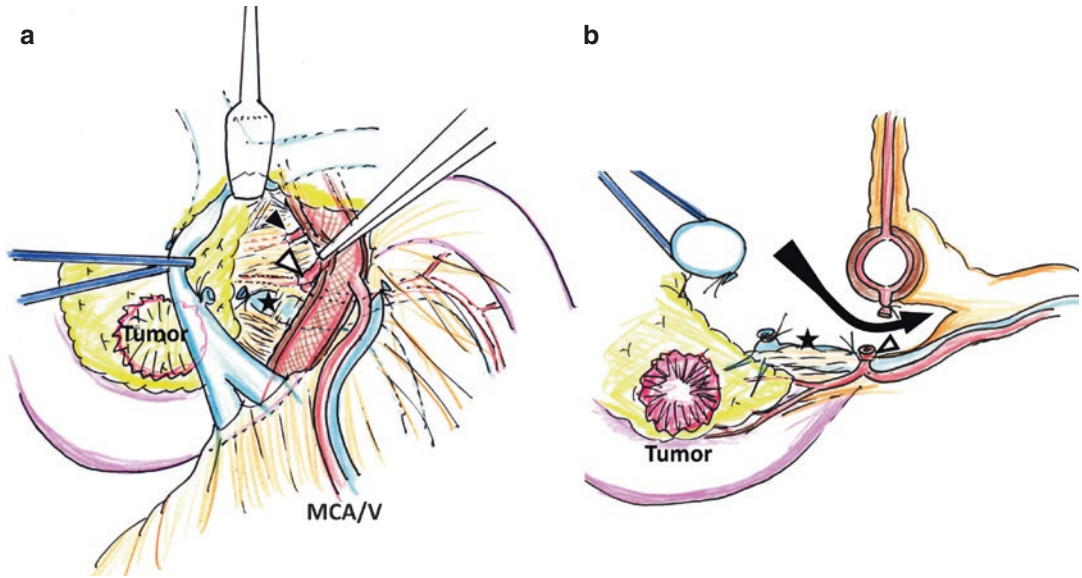

Fig. 19.2 Level 2 supracolic anterior dissection. (**a**) Frontal view. By retracting the pancreas neck using thin retractor and rotating the SMA at pinpoint, the mesopancreas was detached from plSMA. The IPDA 1 (*black arrow*) and the common trunk of IPDA 2 and JA 1 (*blank arrow*) were exposed. The JV (*star*) was ligated and exposed on the surface of the mesopancreas. (**b**) Transverse view. The plSMA was entirely preserved. The dissection reaches to the left side of the SMA (*black arrow*). The common trunk of IPDA 2 and JA was ligated by the central vascular ligation

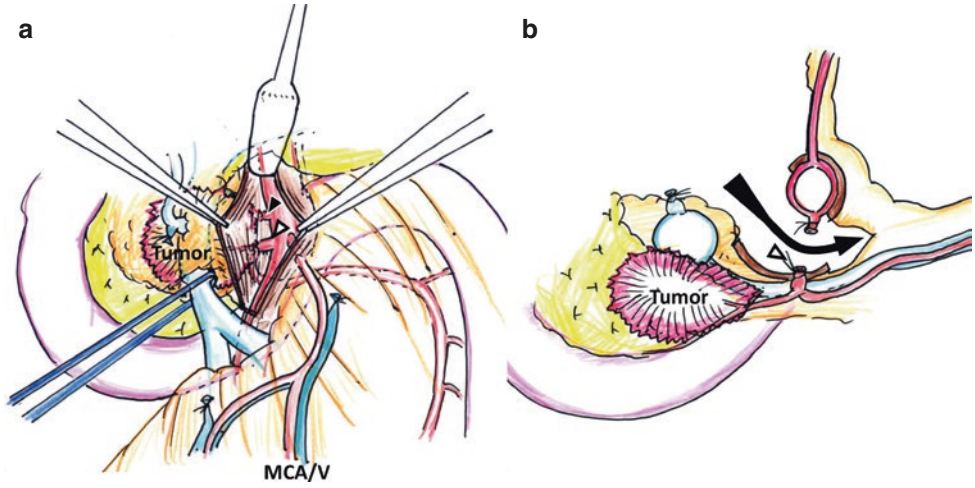

Fig. 19.3 Level 3 supracolic anterior dissection. (**a**) Frontal view, showing the plSMA dissected from the SMA adventitia hemi-circumferentially under pancreas neck retraction and pinpoint rotation of the SMA. The dissection along the SMA depended on the tumor invasion. The IPDA 1 (*black arrow*) and the common trunk of IPDA 2 and JA 1 (*blank arrow*) were exposed. (**b**) Transverse view. The plSMA was entirely preserved. The dissection reaches to the left side of the SMA (*black arrow*). The common trunk of IPDA 2 and JA was ligated by the central vascular ligation

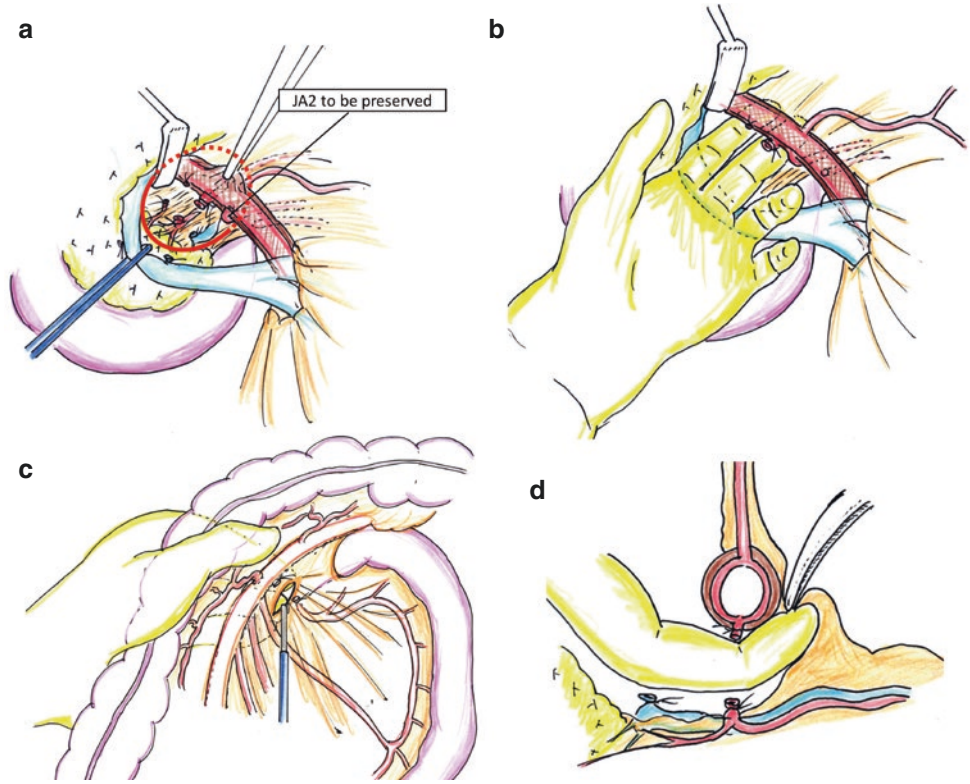

Fig. 19.4 Finger-guided connection of dissection space of the both sides of the SMA. (**a**) After LV-2 supracolic anterior dissection, the mesopancreas was dissected from the SMA, preserving PL-SMA. The dissection space reached to the left side of the SMA (*red circle*). The second jejunal artery (JA2) is preserved in this dissection. (**b**) The surgeon's finger is inserted into the dissection pocket. (**c**, **d**) By the finger guidance, the mesentery is opened by an electric cautery, and the dissection space was opened atraumatically using Kelly clamp, and the SMA was taped

from the right side at a point just proximal to the second JA (Fig. 19.4b). Under the guidance of the surgeon's fingers, the serosa of the mesentery is opened, connecting the right and left dissection spaces (Fig. 19.4c, d). A tape for hanging is placed through this hole, encircling the dorsal aspect of the SMA.

19.3.4 Left-Sided Dissection of the SMA

The transverse colon is then reflected cranially, and the left side of the SMA is dissected so that the previous opening is enlarged toward the root of the SMA, preserving the plSMA (Fig. 19.5a). This procedure can be performed bloodlessly because the root of the first JA has already been ligated and cut, and the JV has been separated from the SMA during the previous supracolic anterior approach. The mesentery of the first JA territory is divided from the remnant, and the corresponding jejunum is cut. The dissection of the left side then progresses, and the ligament of Treitz is identified as a membranous muscular layer that narrows cranially [12, 13]. The ligament is dissected from the SMA, then ligated and cut at the level of the SMA root. The left side of the SMA is thus fully dissected while preserving the plSMA (Fig. 19.5b).

19.3.5 Completion of PD-CVL

After the stump of the jejunum is reflected rightward, the SMV is retracted to the left, and the upper portion of the mesopancreas is dissected (Fig. 19.6a). Once the right-sided dissection reaches the root of the SMA, en bloc dissection around the SMA is completed (Fig. 19.6b). Division of the pancreas neck, common bile duct, stomach, or duodenum is then performed, and PD resection is competed.

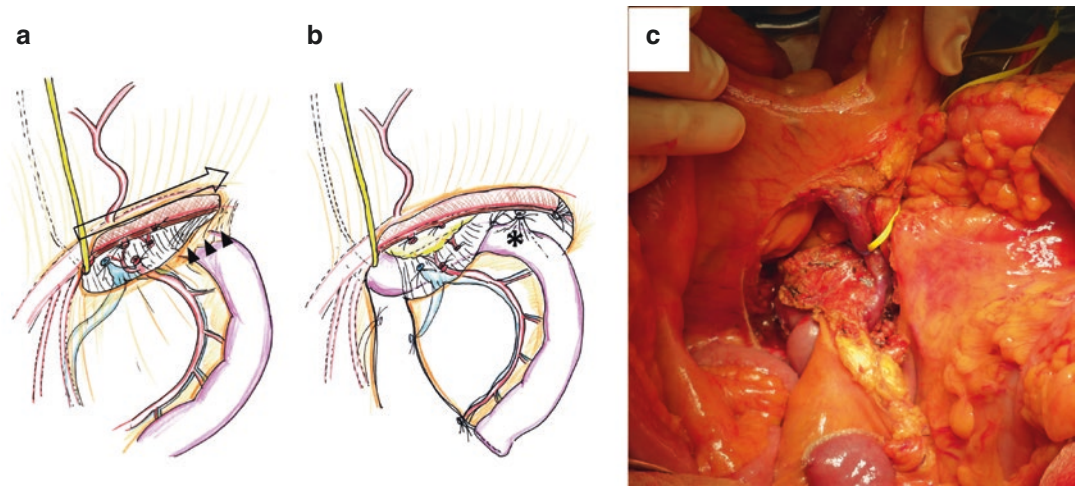

Fig. 19.5 The left-sided dissection around the SMA. (**a**) Initial part. The dissection begins from the point at which the tape is applied and progresses toward the root of the SMA, preserving the nerve plexus of the superior mesenteric artery. The tape represents the starting point of the longitudinal dissection of the SMA (*blank arrow*). Left-sided superior mesenteric artery dissection is then promoted further, identifying the ligament of Treitz as a membranous muscular layer (*black arrows*). (**b**) Final part. The ligament is detached from the superior mesenteric artery, ligated, and cut beyond the left renal vein (*asterisk*). At this stage, complete dissection of the left side of the superior mesenteric artery is achieved with preservation of this side of the nerve plexus of the superior mesenteric artery. (**c**) The intraoperative view after the left-sided dissection of the SMA. The pancreas head and the mesopancreas were detached from the SMA and the SMV

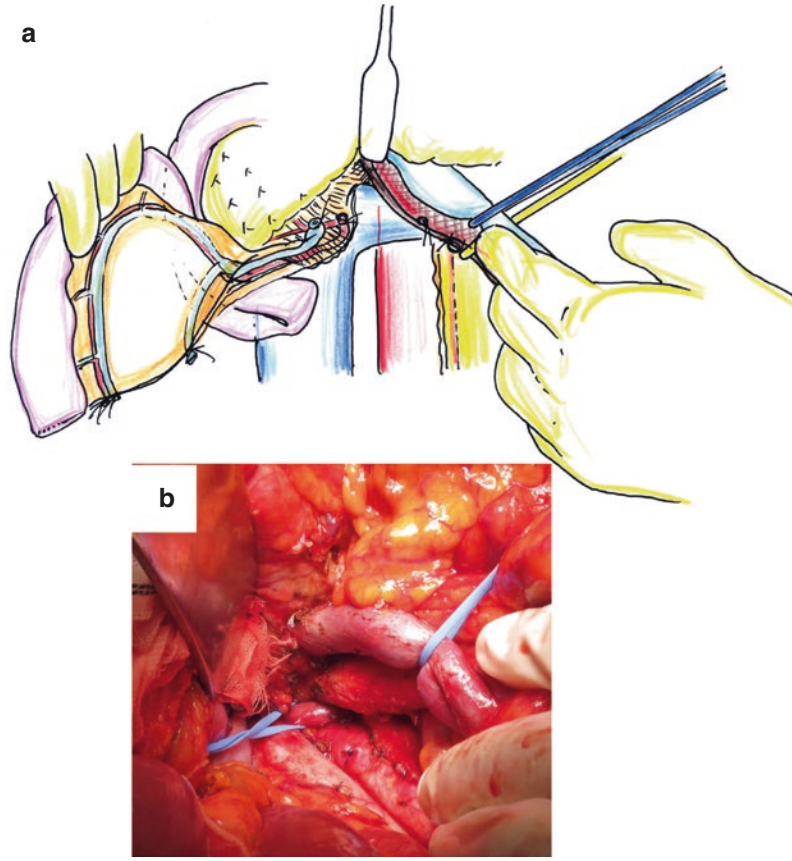

Fig. 19.6 The final stage of the central vascular ligation of the pancreas and the SMA. (**a**) The proximal jejunal stump is reflected to the right, whereas the superior mesenteric vein is reflected to the left, and the right dorsal aspect of the SMA is well exposed. (**b**) The intraoperative view of completion of LV-2 dissection around the SMA using central vascular ligation. The mesopancreas is entirely detached from the SMA

19.4 Indication

PD-CVL is indicated for periampullary malignancy requiring LNs dissection and is subclassified according to the extent of dissection: Level 2 dissection should be used for malignancies that need total resection for the mesopancreas. By dividing IPDA and 1st JA at their roots, corresponding LNs and mesojejunum can be resected systematically. Dissection along the SMA is determined according to the site of IPDA branch. The disease suitable for level 2 dissection includes ampullary, distal bile duct, and duodenal cancers or pancreatic cancers with limited invasion. In level 3 dissection, the right half circle of plSMA is resected en bloc with tumor to obtain maximal margin length from potentially invasive tumor, and it should be used for pancreatic ductal cancer or advanced bile duct cancer. Dissection along SMA should be determined based on the extent of tumor invasion. Corresponding mesojejunum is also resected.

19.5 Comment

In this chapter, we described a comprehensive technique for mesopancreas excision during pancreaticoduodenectomy using CVL by a supracolic anterior artery-first approach. Several technical modifications in PD applying so-called artery-first principle have been proposed previously [14–21]. However, few reports have documented the whole outline of the SMA up to its root and the circumference of the SMA. We [22] recently described a technique termed "pancreaticoduodenectomy with systematic mesopancreas dissection (SMD-PD)" with en bloc mesopancreas resection including staged dissection around the

SMA using a supracolic anterior artery-first approach. The technique described here is the extension of the concept of SMD-PD, and this allows precise and bloodless SMA dissection as we reported previously [10, 11, 23].

The advantage of level 2 dissection is multifold; first, early ligation of the supplying artery reduces the bleeding during SMA dissection, which is often bloody otherwise. Secondly, complete removal of LNs corresponding to IPDA and JA secures the oncologic clearance. For example, in ampullary cancers, LN metastasis into the proximal jejunal region via mesopancreas is reportedly substantial, and complete dissection of this area has been advocated [24, 25]. Actually, we sometimes encounter LN metastasis in the mesojejunum in patients with ampullary, duodenal, and pancreatic cancers. Likewise, distal bile duct cancer has been reported to be potentially more aggressive compared to ampullary cancers, indicating that the level 2 dissection should be applied. Lastly, PD-CVL using supracolic anterior approach enables straightforward dissection along the SMA without distorting the in situ anatomy, helping the surgeon to grasp the dissection margin clearly. This approach resembles the concept of total mesorectal excision [5], and like rectal cancer, standardization of systematic mesopancreas excision and LN dissection may improve the clearance of cancer spread via the lymphatic pathway.

The primary goal of level 3 dissection is to obtain negative cancer margin around the SMA. This area, called the medial margin of pancreas head resection, is the most common site for R1 resection in pancreatic head cancers [26, 27]. To maximize the chance of negative medial margin, extension over the dissection plane of level 2 dissection is reasonable. As circumferential resection of plSMA will cause severe diarrhea, we leave the left side of plSMA intact. In cases where the tumor has invaded the mesocolon, the SMV and SMA was taped infracolicly followed by coring out of the mesocolon, which extends this technique to a so-called mesenteric approach [28].

In borderline resectable pancreatic head cancer, two important issues are gaining the resection margin, especially to the SMA, and preserving the plSMA at least to the hemi-circle to avoid uncontrollable postoperative diarrhea. These two themes were paradoxical to each other, and anterior approach would be optimal to achieve them in good balance. Other approaches such as the posterior approach [18–20, 29–31] or left posterior approach [15, 21, 32, 33] in which the SMA was dissected from the proximal to distal end were well established and seem useful for en bloc mesopancreatectomy or reducing blood loss. In these methods, however, extended mobilization and retraction of viscera is necessary to gain a safe surgical field. In such a situation, the SMA might become twisted and lifted substantially during dissection, and this may lead to disorientation compared to preoperative image inspection. Furthermore, preservation of at least a half circle of the plSMA seems difficult in such a situation, especially with the left posterior approach. In our anterior supracolic approach, the pancreas head and SMA are in the same respective positions as found in situ, and deformation or rotation is minimal, making it easier to compare the macroscopic finding with preoperative images and to dissect the plSMA linearly from the SMA. As previously reported, the root of the IPDA came from the right dorsal aspect in 86% of patients, and tumor abutment of invasive cancer occurred from exclusively the right side of the artery in patients with SMA abutment [11]. These results supported our principle, and in the case in which the IPDA root was originated from the left aspect of the SMA and no plSMA dissection was required (as for patients undergoing level 2 CVL), the left posterior approach would be a good choice.

The PD-CVL described in this chapter is based on three anatomical features of the SMA. The first is the absence of obstacles to the surgical viewing field in the supracolic anterior approach. The diamond-shaped surgical field created by appropriate mobilization of the SMV allows good exposure of the right dorsal aspect of the SMA. At this stage, the dissection level can be adjusted by preserving or resecting the plSMA (corresponding to level 2 or 3, respectively) or judging the extent of resectability in cases involving cancer invasion of the SMA. In previous reports, the most common site for R1 resection

was around the SMA [26, 27, 34, 35]. Therefore, it is reasonable to access this part first to judge the resectability with respect to the SMA margin. The second anatomical feature of the SMA on which PD-CVL is based is the branching pattern of the IPDAs, JAs, and JVs. Preoperative inspection of the root of the IPDA, JA, JV, and MCA (as a landmark) by high-quality CT scan is essential to achieve accurate and safe primary dissection. The JVs run behind the SMA in most cases, and primary dissection between the JV and SMA facilitates bloodless dissection of the left side [10, 11, 36]. In the left posterior approach, the dissection is initiated without ligation of the thick jejunal branches from the SMA or the SMV; therefore, bleeding from JA or JV might be problematic. Finally, the third anatomical aspect is identification of the ligament of Treitz, as the membranous muscular tissue forming the duodenojejunal junction [12, 13, 37]. Detaching the ligament of Treitz from the SMA exposes the left aspect of the SMA covered by the plSMA. This technique is useful to avoid too extensive dissection of plSMA. As in patients with resectable pancreatic head tumors, the left-sided plSMA is almost always uninvolved and should be preserved to avoid severe postoperative diarrhea.

In conclusion, we have described the details of a new technique of complete mesopancreas excision and dissection around the SMA. This technique allows safe dissection around the SMA without the need for any specific devices and maximal chance of oncological clearance. This procedure should be a standard PD for all periampullary malignancies.

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20 Concepts in Isolated Pancreatectomy for Pancreatic Cancer Using the Nakao Mesenteric Approach and Catheter Bypass of the Portal Vein

Akimasa Nakao

20.1 Introduction

Performing pancreatoduodenectomy (PD) for pancreatic head cancer under non-touch isolation techniques can be difficult, as is colectomy for colon cancer, because of the complex vessel anatomy of the pancreatic head region (Fig. 20.1). In 1981, we developed an antithrombogenic bypass catheter for the portal vein to prevent portal congestion by bypassing the portal blood through a branch of the superior mesenteric vein (SMV) to the femoral vein during portal vein resection and reconstruction, or to the intrahepatic portal vein through the umbilical vein in the hepatic round ligament, to prevent both portal congestion and hepatic ischemia during simultaneous resection and reconstruction of the portal vein and hepatic artery (Fig. 20.2) [1–5]. The time limitation on portal occlusion was thus removed, and we have been aggressively resecting pancreatic cancer with portal invasion using catheter bypass of the portal vein [6–9]. When we started performing PD combined with portal vein resection in the 1980s, we routinely used Kocher's maneuver [10] as the first step. However, we sometimes encountered pancreatic cancer with portal vein obstruction and well-developed collateral veins because of cancer invasion. When resecting such cancer using Kocher's maneuver, we experienced massive bleeding. Therefore, we developed isolated PD using a mesenteric approach [11–16] and use catheter bypass of the portal vein if necessary, since 1992.

In cancer surgery, "isolated" means en bloc resection using a non-touch isolation technique. Before manipulation of the pancreatic head cancer, all arteries that supply the pancreatic head region and all drainage veins for this region are ligated and divided (Fig. 20.1). Our first step in performing the PD is a mesenteric approach; we do not perform Kocher's maneuver. This mesenteric approach involves clearing the connective tissue around the SMV and superior mesenteric artery (SMA) in the mesenteric root, which includes systematic lymphadenectomy around the SMA [17]. Resection starts from the noncancerous side and cancer-free surgical margins, and resectability can be diagnosed before proceeding. The inferior pancreaticoduodenal

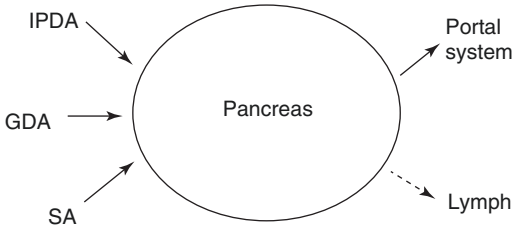

Fig. 20.1 Pancreatic blood supply. *IPDA* inferior pancreaticoduodenal artery, *GDA* gastroduodenal artery, *SA* splenic artery

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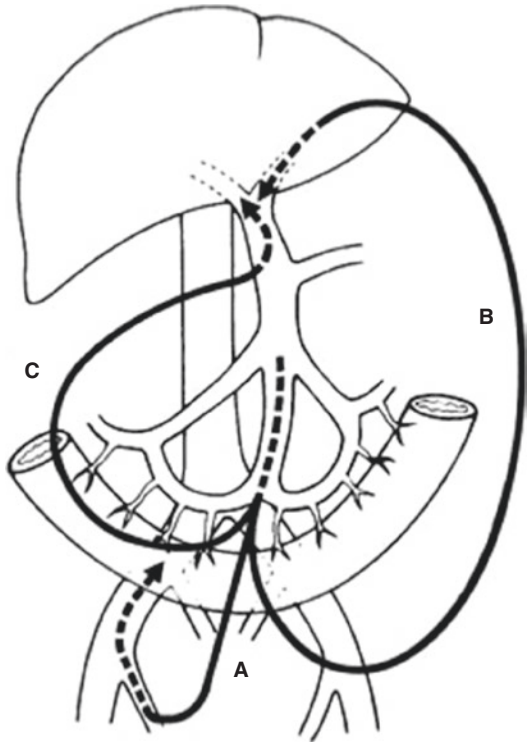

Fig. 20.2 Catheter bypass of the portal vein: (*A*) bypass between the mesenteric and femoral veins, (*B*) bypass between the mesenteric and umbilical veins, (*C*) bypass between the mesenteric and hepatic hilar portal veins (From reference No. [5])

artery (IPDA) arising from the SMA is ligated and divided first. This approach makes it possible to perform total mesopancreas [18] excision, meaning total excision of the second portion of the pancreatic head nerve plexus (PLphII) (Fig. 20.3) [19, 20]. This approach facilitates reconstruction of the portal vein by end-to-end anastomosis.

20.2 Surgical Techniques in Isolated PD Using the Nakao Mesenteric Approach

20.2.1 Mesenteric Incision

After laparotomy by upper midline skin incision, the abdominal cavity is examined using ultrasound and washing cytology. The first step in the mesenteric approach is incision of the mesentery from the ligament of Treiz to the lower border of the second portion of the duodenum using electrocautery (Fig. 20.4). The surface of the mesentery is incised until the anterior walls of the SMV and SMA are exposed. With this approach, Kocher's maneuver is not performed.

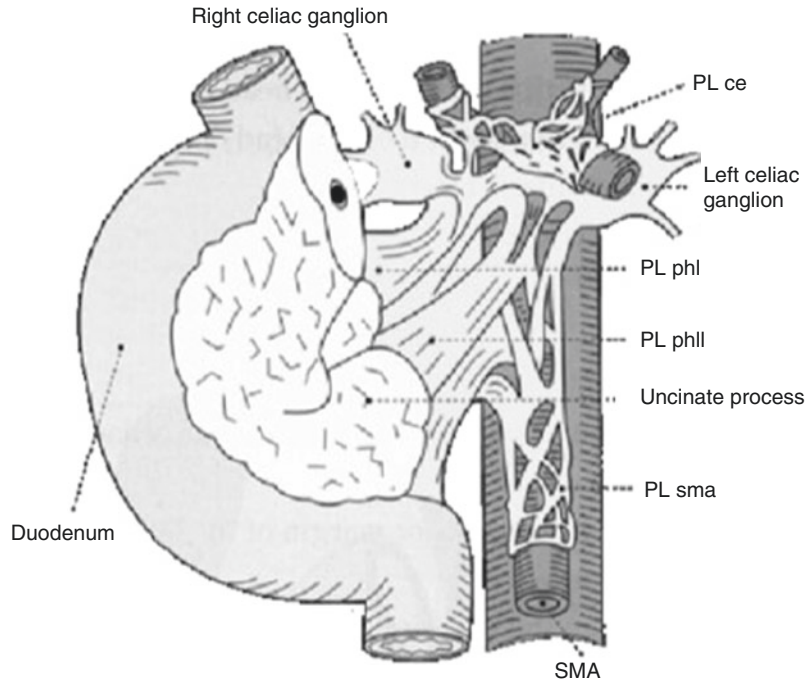

Fig. 20.3 Extrapancreatic nerve plexus (From JPS. Classification of pancreatic carcinoma. 3rd English ed.)

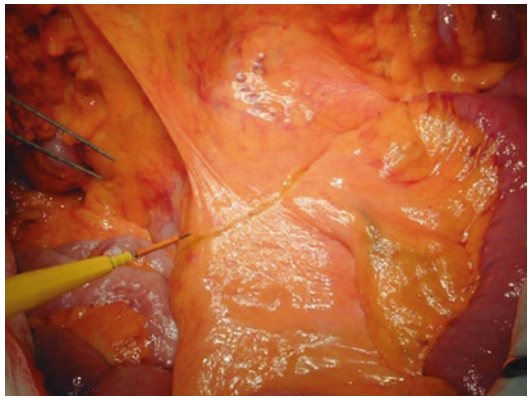

Fig. 20.4 Incision in the mesentery from the ligament of Treiz to the lower border of the second portion of the duodenum

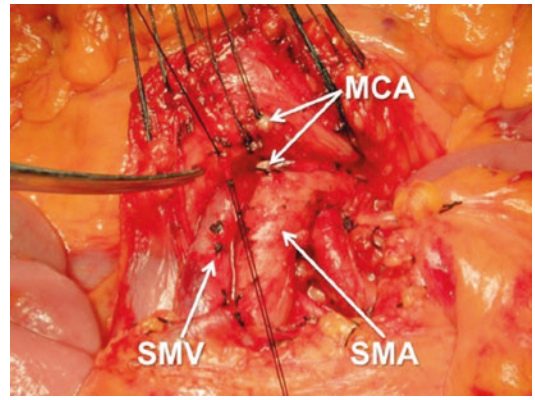

Fig. 20.5 Connective tissue clearance around the superior mesenteric vein (*SMV*) and superior mesenteric artery (*SMA*) and division of the middle colic artery (*MCA*)

20.2.2 Connective Tissue Clearance Around the SMV and SMA

All of the connective tissues, including the lymph nodes around the SMV and SMA (No. 14d lymph nodes) [17], are dissected to the lower border of the pancreatic head (Fig. 20.5). If no cancer invasion of the second portion of the PLphII is observed, the nerve plexus around the SMA (PLsma) [19, 20] is completely preserved. If cancer invasion into the PLphII or the PLsma is detected, the PLsma is resected to obtain cancer-free surgical margins. If it is difficult or impossible to obtain cancer-free surgical margins, we stop the radical resection. We also stop the radical resection if we determine that reconstruction of the SMV is impossible because of severe cancer invasion into the peripheral branches of the SMV.

20.2.3 Division of the Middle Colic Artery

The middle colic artery is exposed at the anterior side of the SMA. The middle colic artery is generally ligated and divided at the root (Fig. 20.5), which facilitates connective tissue clearance around the root of the SMA (No. 14p lymph nodes).

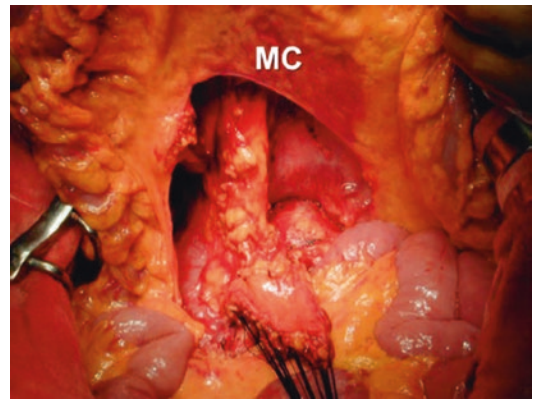

Fig. 20.6 Incision in the mesocolon (*MC*)

20.2.4 Division of the Gastrocolic Ligament

The gastrocolic ligament is incised near the transverse colon, and the epiploic sac is opened. By opening the epiploic sac, the mesocolon can be examined from both the anterior and posterior sides, and the anterior surface of the pancreas can be visualized.

20.2.5 Incision of the Mesocolon

The root of the mesocolon is horizontally incised and resected, preserving the arcade of the middle colic artery (Fig. 20.6). This makes it easier and

safer to perform connective tissue clearance around the root of the SMA through the large opening in the mesocolon.

20.2.6 Connective Tissue Clearance Around the Root of the SMA

Connective tissue clearance around the SMV and SMA proceeds to the roots of the SMV and SMA. All connective tissues of the mesenteric root are dissected, including the lymph nodes (No.14 d, p lymph nodes).

20.2.7 Exposing the Mesopancreas

The PLphII is exposed between the uncinate process of the pancreatic head and the SMA (Fig. 20.7). There is no precise anatomical definition for the mesopancreas [18]. In the Japanese classification of pancreatic cancer [19, 20], the anatomy of the extrapancreatic nerve plexuses is described (Fig. 20.3), and Japanese pancreatic surgeons know this anatomy well. I propose that mesopancreas excision means excision of PLphII (Fig. 20.3) and recommend the term PLphII instead of mesopancreas.

20.2.8 Exposure of the Jejunal Arteries and the IPDA, and Total Mesopancreas Resection

The first branch of the jejunal artery lies behind the SMA, and the IPDA is a branch of the first branch of the jejunal artery that lies within the region of the mesopancreas (Fig. 20.8). There are many variations of IPDA anatomy. Ligation and division of the IPDA, and total excision of the PLphII and the first portion of the pancreatic head nerve plexus (PLphI) from the attachments of the SMA and celiac axis, complete the mesenteric approach (Fig. 20.9). This approach results

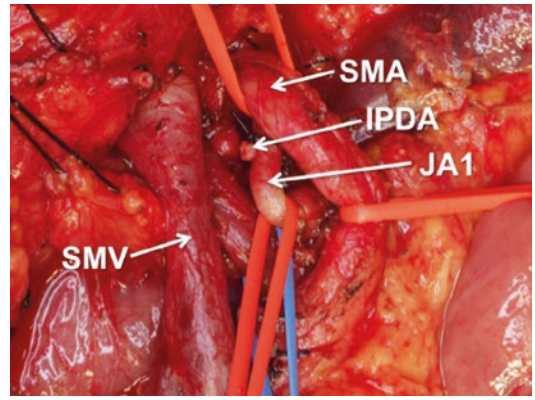

Fig. 20.8 Exposure of the first branch of the jejunal artery (*JA1*) and division of the inferior pancreaticoduodenal artery (*IPDA*)

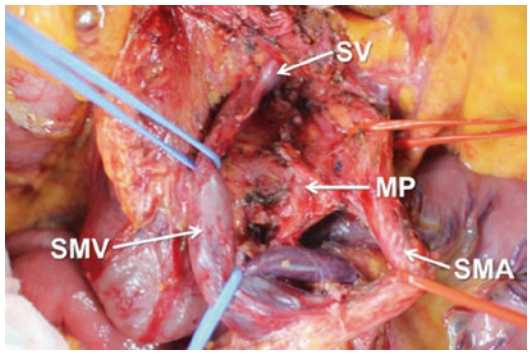

Fig. 20.7 Exposure of the mesopancreas (*MP*)

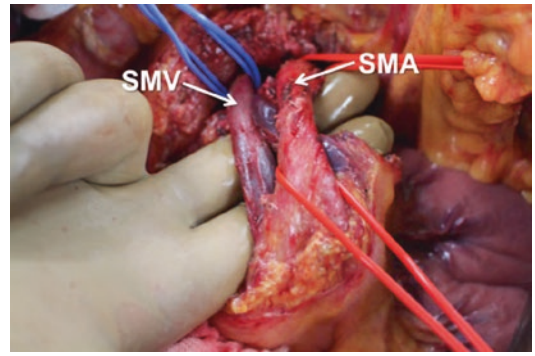

Fig. 20.9 Completion of total mesopancreas resection

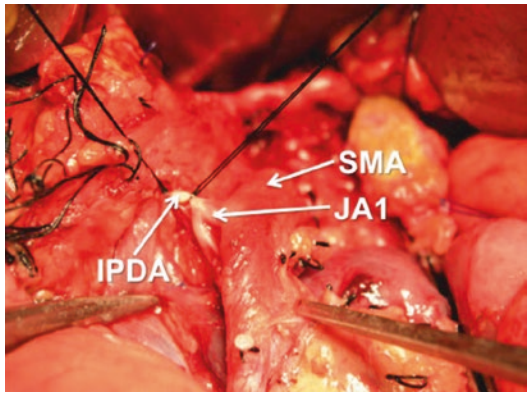

Fig. 20.10 Exposure of the inferior pancreaticoduodenal artery (*IPDA*) arising from the first branch of the jejunal artery (*JA1*) after dividing the pancreas along the line of the superior mesenteric artery (*SMA*)

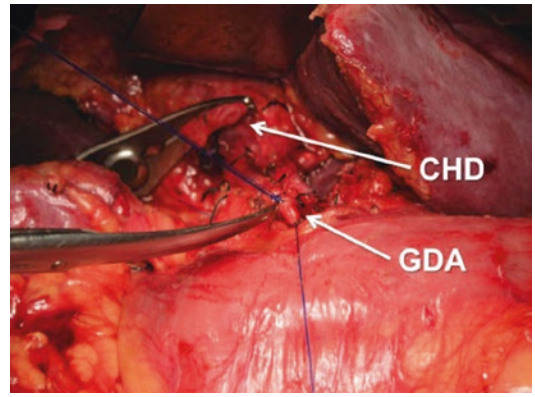

Fig. 20.11 Division of the gastroduodenal artery (*GDA*). Common hepatic duct (*CHD*)

in total resection of the PLphI and PLphII. In patients with more locally advanced cancer, excision of the first and second branches of the jejunal artery may be necessary. If it is difficult to expose the IPDA or the first branch of the jejunal artery via the mesenteric approach, these vessels can be exposed by dividing the pancreas along the line of the SMA (Fig. 20.10).

20.2.9 Typical Procedures After the Mesenteric Approach

After completing the mesenteric approach, the gallbladder is resected along with the common hepatic duct. Clearance of the hepatoduodenal ligament is performed, and the gastroduodenal artery (GDA) is ligated and divided (Fig. 20.11). The stomach is divided at the prepylorus, and lymph node dissection around the common hepatic artery and celiac artery is performed. The PLphI is also dissected. If cancer invasion into the portal vein is observed, the portal vein is resected and reconstructed. If the time to resect and reconstruct the portal vein is expected to be prolonged, catheter bypass of the portal vein using an antithrombogenic catheter is performed. These procedures complete isolated PD by the mesenteric approach. The intention of isolated PD is to reduce operative blood loss by first ligating the IPDA and GDA and prevention of distant metastasis by ligation of the drainage veins from the pancreatic head region before manipulation of the tumor.

20.3 Discussion

In the past, Kocher's maneuver has been the first step in PD. Based on extensive experience with vascular resection in PD, I developed a mesenteric approach [11, 12] in 1992. In our opinion, isolated PD using this mesenteric approach is the ideal surgery for pancreatic head cancer from both oncological and surgical points of view. The mesenteric approach allows dissection from the non-cancer infiltrating side and initial determination of cancer-free margins and resectability, followed by systematic lymphadenectomy around the SMA. This approach also enables early ligation of the IPDA, which reduces venous congestion of the pancreatic head region, along with ligation of the GDA and total mesopancreas excision. The term "mesopancreas" has no precise

anatomical definition; I offer that it can be defined as the PLphII according to the classification of pancreatic carcinoma edited by the Japan Pancreas Society [19, 20]. The Nakao mesenteric approach has been gradually adopted throughout Japan. By mastering this mesenteric approach, surgeons can control pancreatic cancer surgery in all patients.

Conclusion

We presented the concepts, intentions, and precise surgical procedures of isolated PD for pancreatic head cancer using the Nakao mesenteric approach.

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Role of Extended Resection in Pancreatic Cancer

21

Jin-Young Jang

21.1 Introduction

Pancreatic ductal adenocarcinoma (PDAC) is a malignant neoplasm with the poorest prognosis among the periampullary cancers with a 5-year survival rate of approximately 20% even after curative resection. PDAC is a well-known systemic disease, but definitive systemic therapy is currently lacking [1–3].

Many surgeons have tried to increase the survival of PDAC patients with aggressive surgery. Following Fortner's regional pancreatectomy, several surgical methods have been applied to increase the extent of surgery aiming to increase curability [4–6].

Extended surgery has improved resectability followed by promising outcomes in some retrospective studies; however, there was no reliable report in prospective studies that shows increased long-term survival [7, 8].

Although the definition of extended resection is not clear, many surgeons use "extended resection" when performing wider extent of lymphadenectomy with resection of peripancreatic nerve plexus while some define extended surgery when performing vessel resection around the pancreas. In this chapter, the role of extended resection based on recent evidences is described.

21.1.1 Rationale for Dissection of Lymph Node and Nerve Plexus

Pancreatic cancer is a well-known highly aggressive neoplasm. Even for a small-sized tumor, lymph node metastasis is frequently detected in the peripancreatic area as well as para-aortic spaces. Lymph node status is one of the most important prognostic factors in patients with pancreatic head cancer [9].

The Japanese Pancreatic Association reported that not only the presence but site of metastatic lymph nodes is prognostic of early recurrence and long-term survival [10].

The high incidence of local recurrence after conventional pancreatoduodenectomy was considered to result from incomplete lymph node clearance, with previous studies showing that standard pancreatoduodenectomy removes 80% of the lymph node sites most frequently involved [8, 11].

These findings suggests that more extensive lymph node dissection may enhance survival outcomes. Some surgeons, especially among the

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Japanese surgeons, suggested en bloc dissection of lymph nodes including the para-aortic spaces could improve survival of the patients with PDAC [6, 11].

Neural invasion is another important prognostic factor in pancreatic carcinoma. The postoperative survival rate for patients with extrapancreatic nerve plexus (PLX) invasion is significantly worse compared with that of patients without PLX invasion. About 60–80% of PDAC has perineural involvement of tumor. In recent literature, the concept of a tumor-neural microenvironment was proposed and the main idea of this concept is that cancer cells and nerves constitute a microenvironment which mutually promotes proliferation and inhibits apoptosis [12].

To improve survival, some surgeons advocate the complete resection of nerve plexus around the pancreas [13].

Also some data show that lymph node metastasis is limited to areas along the superior mesenteric artery (SMA) when PDAC is almost entirely confined to the ventral pancreas; on the other hand, lymph node metastasis is limited to areas along the common hepatic artery and the hepatoduodenal ligament when PDAC is almost entirely confined to the dorsal pancreas. This suggests the necessity to alter the extent of nerve plexus and lymph node dissection according to the location of the primary tumor [13, 14].

Clearing the retroperitoneal nerve plexus, especially the peripheral nerve plexus at the SMA during surgical resection of pancreatic cancer, has a neuroanatomical basis. Analyzing the recurrence patterns of pancreatic cancer after pancreatoduodenectomy and retroperitoneal recurrence caused by perineural invasion is important all aspects except for metastasis. Several surgeons tried to completely remove the connective tissues surrounding the SMA. However, complete removal of the nerve plexus can provoke intractable diarrhea and malnutrition followed by immunologic dysfunction. Considering the quality of life, only right-sided semicircular clearance of the SMA nerve plexus is recommended [15].

21.1.2 Outcomes of Extended Surgery in PDAC

Many pancreatic surgeons have tried to improve resectability and survival by adopting aggressive extended resection in pancreatic cancer such as extended lymphadenectomy or dissection of nerve plexus around the major vessels based on aforementioned theoretical advantages [16–18].

Some retrospective studies showed better survival outcomes by performing extended lymphadenectomy. Ishikawa et al., reported that the 3-year survival rate after radical resection was 38% which is superior to that of standard resection (13%). However, numerous retrospective studies have shown conflicting results.

Five prospective randomized controlled trials (RCTs) compared standard and extended resection mainly focusing on lymphadenectomy. However, the extent of surgery differs between each studies (Table 21.1) [8, 19–23].

In two RCTs, dissection around the SMA was considered as nerve plexus dissection. Diarrhea rates were reported between 42–84% after circumferential dissection and 15% after semicircumferential dissection of the SMA nerve plexus. However, R0 resection rate and overall survival was not affected by the extent of SMA nerve plexus dissection. Therefore, circumferential dissection of the SMA is not oncologically necessary, but only worsens the QOL after pancreatoduodenectomy.

Operative outcomes according to surgical extents are summarized in Table 21.2. Mean operative time was significantly longer in extended pancreatoduodenectomy (EPD) in four studies. Blood transfusion rate was higher in extended surgery compared to standard pancreatoduodenectomy (SPD) in one trial. R0 resection rates were similar in the SPD (72.5–94.1%) and EPD (78.0–93.0%) groups. In all five studies, the number of retrieved lymph nodes was significantly higher in the EPD than in the SPD group. However, lymph node metastasis rates in all five studies were similar in patients who underwent EPD (43.2–68.0%) and SPD (45.9–68.7%) [8, 19–23].

Table 21.1 Extent of lymph node and nerve plexus dissection in five randomized controlled trials

	Pedrazzoli et al.	Yeo et al.	Farnell et al.	Nimura et al.	Jang et al.
Standard operation	Anterior/posterior pancreatoduodenal Pyloric Biliary duct Superior/inferior pancreatic head and body	Anterior/posterior pancreaticoduodenal Hepatoduodenal ligament Right lateral aspect of the SMA and SMV	Gastric lesser/greater curvature Pyloric Right of the hepatoduodenal ligament Anterior/posterior pancreatoduodenal Right of the SMA Anterior to the CHA	Anterior/posterior pancreatoduodenal	Anterior/posterior pancreatoduodenal Bile duct and cystic duct
Extended operation	Hepatic hilum Along the aorta from the diaphragmatic hiatus to the IMA Laterally to both renal hilus	Gastric lesser/greater curvature Superior/inferior pyloric Celiac origin Celiac to left renal vein Left renal vein to IMA	Between bilateral renal hilum Hepatoduodenal ligament skeletonization up to the liver Hepatic artery and celiac axis Paraaortic from celiac axis to IPM Circumferential dissection of the SMA	Common hepatic artery Celiac artery Hepatoduodenal ligament skeletonization SMA Paraaortic from the origin of celiac axis to IMA	Common hepatic artery Celiac axis Hepatoduodenal ligament skeletonization SMA Paraaortic between celiac axis and IMA
Nerve plexus dissection in extended operation				Circumferentially around the CHA and SMA, semicircumferentially on the right lateral aspect of the celiac axis	Right side of the celiac axis and SMA semicircumferentially

Table 21.2 Operative outcome of five RCTs according to type of surgery

		Pedrazzoli et al.		Yeo et al.		Farnell et al.		Nimura et al.		Jang et al.	
		SPD	EPD	SPD	EPD	SPD	EPD	SPD	EPD	SPD	EPD
N		40	41	146	148	40	39	51	50	83	86
Operative time (min)	Mean ± SEM	371.9 ± 49.8	396.7 ± 49.9	354	384	378	450	426	547	355.5 ± 12.4	419.6 ± 13.0
Blood transfusion (U)	Mean ± SD	1.95 ± 0.2	2.07 ± 0.2	0.5 ± 0.1	0.5 ± 0.1	22%	44%	2.1	2.4	0.1 ± 0.05	0.25 ± 0.09
PD/PPPD/SSPPD	*N*	20/20/0	18/23/0	21/125/0	148/0/0	40/0/0	39/0/0	13/19/19	11/23/16	21/62/0	26/60/0
Portal vein resection	*N*(%)	–	–	4(3%)	4(3%)	(23%)	(21%)	24(47%)	24(48%)	17(20.5%)	23(26.7%)
No. of lymph nodes retrieved	Mean	13.3	19.8	17.0	28.5	15	34	13.3	40.1	17.3	33.7
LN(+)(%)	*N*(%)	24(60.0%)	24(58.5%)	67(45.9%)	64(43.2%)	(55%)	(68%)	32(63%)	30(60%)	57(68.7%)	57(66.3%)
R0 resection (%)	*N*(%)	29(72.5%)	32(78.0%)	128(88%)	138(93%)	(76%)	(82%)	48(94.1%)	45(90%)	71(85.5%)	78(90.7%)
Postoperative hospital stay (days)	Mean ± SD	22.7 ± 1.4[a]	19.3 ± 1.1[a]	11.3 ± 0.5[a]	14.3 ± 0.8[a]	13	16	43.8	42.4	19.7 ± 9.4	22.8 ± 17.1

[a]Standard error of means

Meta-analysis of the five RCTs showed that delayed gastric emptying and pancreatic fistula rates tend to be higher in patients who underwent EPD. However, meta-analysis of each morbidity using a random effects model revealed no significant differences. The rate of postoperative diarrhea (17.3% vs. 6.7%, $p = 0.08$) and overall postoperative morbidity (38.8% vs. 30.3%, $p = 0.160$) tended to be higher in patients who underwent EPD (Fig. 21.1). The odds ratio for mortality in the EPD group was 1.02 (95% CI, 0.38–2.69), but the difference was not statistically significant.

Meta-analysis showed that overall survival was not affected by the extent of surgery in pancreatic cancer. The pooled hazard ratio across all five trials was 1.07 (95% CI, 0.89–1.30; $p = 0.460$) (Fig. 21.2).

In all five RCTs, R0 resection rates were similar, suggesting that EPD does not guarantee a more complete tumor removal followed by similar overall survival rates between SPD and EPD. Moreover, adjuvant treatment may improve survival outcomes after curative resection rather than surgical extent itself [23, 24].

21.1.3 Vascular Resection

Since the first reasoning of Dr. Fortner, many surgeons believe that a more radical resection can improve survival by enhanced tumor clearance, especially tumor adhering main vessels such as portal vein/superior mesenteric vein (PV/SMV) or adjacent arteries. Some suggest that aggressive surgery can overcome the barrier of unresectability by en bloc resection of major vessels. A few retrospective data showed promising survival outcomes [25, 26].

In the era of organ transplantation, vessel resection and anastomosis is not greatly challenging.

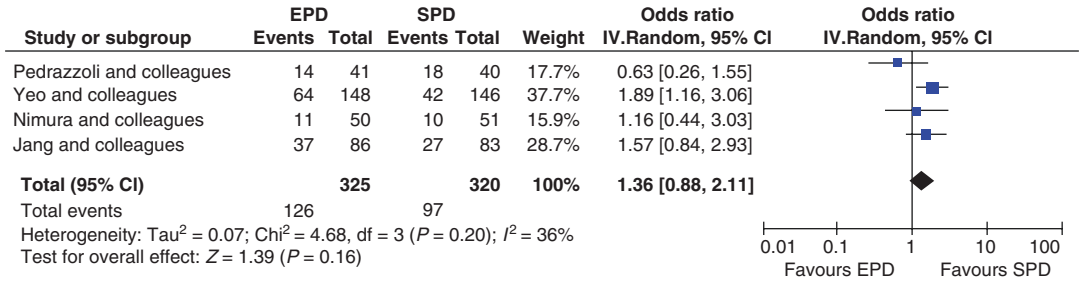


Fig. 21.1 Operative morbidity after SPD and EPD. The rates of overall postoperative morbidity tended to be higher in patients who underwent EPD, but pooled analysis showed no significant difference (38.8% vs. 30.3%, $p = 0.160$)

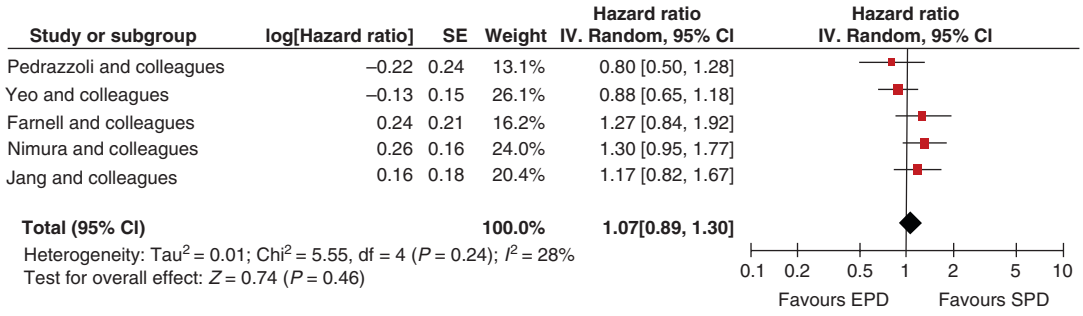


Fig. 21.2 Overall survival after SPD and EPD. Overall survival was not affected by the extent of surgery (pooled hazard ratio 1.07, 95% CI, 0.89–1.30; $p = 0.460$)

Using autologous veins or other materials, long segmental resection is technically possible (Fig. 21.3).

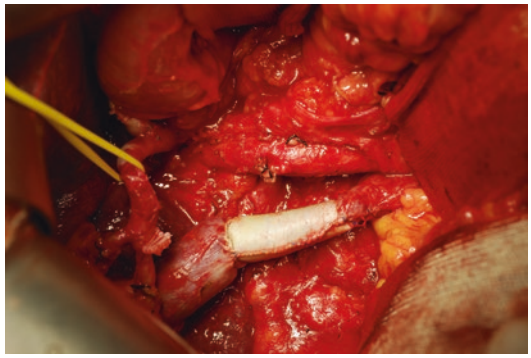


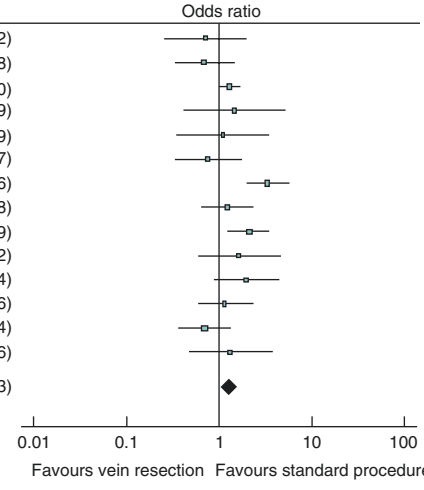
Fig. 21.3 Long segment of PV/SMV was resected and anastomosed using bovine patch graft in patients with PDAC invading SMV and splenic vein confluence

Based on these data, criteria for PV/SMV invasion as advanced T stage was eliminated from the 6th version of American Joint Committee on Cancer (AJCC) staging unlike other GI tract malignancy with a conviction that PV/SMV invasion is a matter of tumor location not tumor aggressiveness. However, recent meta-analysis revealed that patients undergoing PV/SMV resection has an increased risk of postoperative mortality (risk difference (RD) 0.01, 95% CI, 0.00–0.03; $P = 0.02$) and of R1/R2 resection (RD 0.09, 0.06–0·13; $P < 0{\cdot}001$) compared with those undergoing standard surgery. Also 1-, 3-, and 5-year survival rates are worse in the PV/SMV resection group: hazard ratio 1.23 (95% CI, 1.07–1.43; $P = 0.005$), 1.48 (1.14–1.91; $P = 0.004$), and 3.18 (1.95–5.19; $P < 0.001$), respectively [27, 28] (Fig. 21.4).

a

Reference	Overall morbidity: Vein resection	Overall morbidity: Standard procedure	Weight (%)	Odds ratio
Bachellier et *al.*[28]	8 of 21	30 of 66	4.7	0.74 (0.27, 2.02)
Carrère et *al.*[29]	25 of 45	56 of 88	7.1	0.71 (0.34, 1.48)
Castleberry et *al.*[30]	112 of 281	1099 of 3301	14.4	1.33 (1.03, 1.70)
Chakravarty et *al.*[31]	6 of 12	30 of 75	3.5	1.50 (0.44, 5.09)
Fuhrman et *al.*[32]	7 of 23	10 of 36	3.9	1.14 (0.36, 3.59)
Fukuda et *al.*[33]	12 of 37	32 of 84	6.2	0.78 (0.34, 1.77)
Gong et *al.*[46]	28 of 119	37 of 447	9.6	3.41 (1.99, 5.86)
Hartel et *al.*[34]	18 of 68	45 of 203	8.3	1.26 (0.67, 2.38)
Kelly et *al.*[47]	36 of 70	139 of 422	10.1	2.16 (1.29, 3.59)
Kurosaki et *al.*[35]	12 of 35	10 of 42	4.8	1.67 (0.62, 4.52)
Murakami et *al.*[48]	22 of 61	14 of 64	6.5	2.01 (0.91, 4.44)
Ouaissi et *al.*[39]	35 of 59	45 of 82	7.8	1.20 (0.61, 2.36)
Riediger et *al.*[41]	22 of 53	84 of 169	8.4	0.72 (0.38, 1.34)
Shimada et *al.*[42]	9 of 28	12 of 46	4.6	1.34 (0.48, 3.76)
Total	352 of 912	1643 of 5125	100.0	1.34 (1.03, 1.73)

Heterogeneity: $\tau^2 = 0.10$; $\chi^2 = 25.87$, 13 d.f., $P = 0.02$; $I^2 = 50\%$
Test for overall effect: $Z = 2.21$, $P = 0.03$



b

Reference	Log[hazard ratio]	Standard error	Weight (%)	Hazard ratio
Murakami et *al.*[48]	2.186	1.095	5.2	8.90 (1.04, 76.15)
Ouaissi et *al.*[39]	1.515	0.456	29.9	4.55 (1.86, 11.13)
Riediger et *al.*[41]	0.051	0.577	18.7	1.05 (0.34, 3.26)
Shibata et *al.*[43]	1.258	0.367	46.3	3.52 (1.72, 7.22)
Total			100.0	3.18 (1.95, 5.19)

Heterogeneity: $\chi^2 = 5.25$, 3 d.f., $P = 0.15$; $I^2 = 43\%$
Test for overall effect: $Z = 4.64$, $P < 0.01$

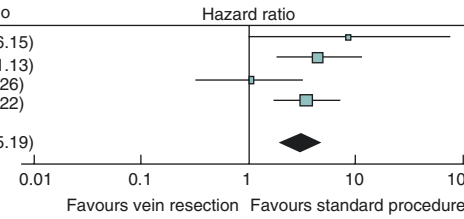


Fig. 21.4 Comparison of morbidity (**a**) and 5-year overall survival (**b**) after pancreatic resection with and without PV/SMV resection (Data from meta-analysis by Giovinazzo et al. [27]) (**a**) Comparison of overall morbidity rates after pancreatic resection with and without portal–superior mesenteric vein resection. (**b**) Comparison of 5-year overall survival after pancreatic resection with and without portal–superior mesenteric vein resection. An inverse-variance fixed-effect model was used for meta-analysis. Hazard ratios are shown with 95% c.i

In high volume centers equipped and staffed for vascular surgery, perioperative mortality and morbidity in PV/SMV resection group might be similar compared to the non-vessel resection group.

However, in cases of histologically confirmed tumor infiltration into the tunica media or intima of PV/SMV, most reported that prognosis is worse and long-term survival can hardly be anticipated [29].

When performing pancreatectomy, indications for PV/SMV resection must be cautiously selected according to the hospitals' facilities and experiences considering morbidity. In case of definite vascular invasion of tumor, neoadjuvant treatment rather than upfront surgery can be a better option to avoid early recurrence and metastasis and to reduce the extent of tumor infiltration into the vessels.

Unlike PV/SMV, resection of hepatic artery, SMA, and celiac trunk is not recommended in spite of technical feasibility. There is lacking data supporting improved survival after arterial resection which inevitably related to high morbidity.

Conclusion

Although achieving R0 resection still remains the most important aspect to guarantee curative surgery and long-term survival in pancreatic cancer, extended surgery alone cannot improve oncological curability. Recent meta-analysis show that SPD with R0 resection is sufficient with comparable survival outcomes and better morbidity, mortality and quality of life compared to EPD in patients with pancreatic cancer. Considering tumor location and severity, there might be some remaining rationale for extended surgery to achieve a margin-negative resection. However, routine extended pancreatic surgery is unnecessary to increase survival. Surgical strategies should be customized considering the patients' general condition and disease all together. Therefore, pancreatoduodenectomy with dissection of peritumoral lymph nodes including lymph nodes number 12, 13, 8, and 17 may be further extended depending on tumor location and severity. For peripancreatic nerve plexus, routine dissection is not needed but can be performed with a maximum of 180° to achieve a R0 resection and preserve postoperative QOL, if the tumor is located near the SMA. In performing pancreatectomy for pancreatic cancer, surgeons must bear in mind that surgery is only part of the multimodality treatments provided in pancreatic cancer. Other than the effort to achieve a R0 resection, surgeons must be judicious to decrease surgical morbidity by avoiding unnecessary extended surgery for early systemic therapy to increase survival.

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Type of Reconstruction After Pancreatoduodenectomy

22

Yi-Ming Shyr and Shin-E Wang

22.1 Introduction

Pancreaticoduodenectomy (PD), introduced by Whipple et al. in 1935 [1] and also well known as Whipple operation, has been the treatment of choice for pancreatic head cancer and a variety of periampullary lesions. Classically, PD includes resection of the head, neck, and uncinate process of the pancreas, all of the duodenum, the bile duct and gallbladder, and distal half of the stomach. However, Whipple procedure was once abandoned during the 1960s and 1970s because of the high operative mortality and virtually no long-term survival for pancreatic head adenocarcinoma [2, 3]. Recently, increased experience and advances in perioperative care have reduced the mortality after PD to less than 5%, even 0–2% in some experienced centers [4–7]. Nevertheless, despite improvements in perioperative outcomes following PD, morbidity remains as high as 30–50% [8–10].

Pancreatic anastomosis has been the Achilles heel of PD, and postoperative pancreatic fistula (POPF) is the leading cause of morbidity such as intra-abdominal hemorrhage, intra-abdominal abscess, prolonged hospital stay, or occasional mortality. In the effort to prevent POPF, various modifications of surgical technique have been proposed, including occlusion of main pancreatic duct with rubber or fibrin glue, pancreaticoenterostomy with the jejunum or stomach (with or without external/internal pancreatic duct drainage, duct-to-mucosa anastomosis or invagination, end to side or end to end, with one- or two-layer suture), and even total pancreatectomy [11, 12].

More than 80 different types of pancreatic reconstruction have been proposed, suggesting the complexity of the pancreatic anastomosis [13]. Ideally, an "optimal" technique for the pancreatic anastomosis should be associated with a zero rate of POPF regardless of pancreatic texture and ductal size and, furthermore, should be easily performed and taught. However, there is currently no universally accepted standard technique for pancreatic reconstruction after PD. Pancreatic fistula after PD is still unsatisfactorily high, at 5–25%, even in high-volume centers [8, 9, 11, 14, 15].

There are two major variants of pancreatic reconstruction after PD: pancreaticojejunostomy (PJ) and pancreaticogastrostomy (PG).

22.1.1 Classic Pancreaticojejunostomy

PJ using a jejunal loop is the most commonly used method for pancreatic anastomosis after PD. There are two main types of PJ: duct-to-mucosa anastomosis and invagination anastomosis [13, 15].

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22.1.1.1 Technique of Pancreaticojejunostomy

For end-to-side duct-to-mucosa PJ, the pancreatic remnant is mobilized for approximately 2 cm to allow the placement of sutures to the posterior surface of the pancreas. The transected jejunal limb is brought upward through retrocolic route or duodenal tunnel (posterior to the mesenteric vessels). A small hole for duct-to-mucosa anastomosis is created on the appropriate antimesenteric site of the jejunal limb. The posterior outer-layer sutures between the jejunal seromuscular layer and the posterior part of the capsular parenchyma of the pancreatic stump are placed with or without tying first, using 3-0 nonabsorbable interrupted or continuous sutures of about 0.5 cm distance from each other. Then, inner-layer duct-to-mucosa sutures are completed with 4-0 absorbable interrupted or continuous sutures. Finally, the anterior outer-layer sutures between the jejunal seromuscular layer and the anterior part of the capsular parenchyma of the pancreatic stump are finished. Pancreatic duct stent is not routinely used, except for the small caliber of pancreatic duct.

22.1.2 Pancreaticogastrostomy

PG has been proposed as an alternative to PJ. A number of theoretical and anatomic advantages of PG have been suggested including (1) pancreatic enzyme inactivation under acid environment due to gastric secretion, (2) absence of enterokinase in the stomach, (3) tension-free anastomosis due to anatomical co-location, (4) excellent blood supply to the stomach, (5) thick stomach wall which is less likely to dehisce, (6) early detection of bleeding from the pancreatic remnant by routine postoperative gastric decompression, (7) direct examination of the anastomosis by endoscopy if necessary, and (8) easy exploration of the anastomosis without disassembling the pancreatic anastomosis by opening the anterior wall of the stomach if bleeding occurs [4, 6, 7, 10, 16].

22.1.2.1 Technique of Pancreaticogastrostomy

For PG reconstruction, the proximal 3–4 cm of the pancreatic remnant is freed from the splenic vein and retroperitoneum. A pancreatic stump is anastomosed and invaginated into the posterior wall of the low body of the stomach. PG is performed with interrupted two-layer sutures, with 3-0 silk for the outer layer placed between the pancreatic capsule and seromuscular layer of the posterior gastric wall and 3-0 polyglactin (Vicryl; Ethicon, Inc., Somerville, NJ, USA) for the inner layer placed between the cut edge of the pancreas and the full thickness of the posterior gastric wall. Pancreatic duct stent is not routinely used.

22.1.3 Blumgart Pancreaticojejunostomy

A novel technique, Blumgart PJ, has recently begun to attract attention with low rates of pancreatic leakage, morbidity, and mortality [9–11, 17]. Blumgart described a simple and effective PJ which combined the principle of duct-to-mucosa anastomosis with jejunal covering over the raw surface of the pancreatic stump [8, 11, 17]. The original Blumgart PJ involves placement of five to six transpancreatic and jejunal seromuscular U-sutures to approximate the pancreas stump and the jejunum. The theoretical advantages of Blumgart PJ include the following: (1) blood flow to the pancreatic stump is not compromised by interrupted transpancreatic mattress U-sutures holding the pancreas in firm opposition to the jejunum; (2) duct-to-mucosa sutures can be easily, accurately, and meticulously placed before securing the posterior and anterior seromuscular jejunum under a tension-free approximation and excellent visualization of the pancreatic duct; (3) tension of the jejunal covering may afford an extra compression on the pancreatic stump and prevent fewer leaks from accessory pancreatic ducts and minor bleeding from the stump; and (4) transpancreatic, full thickness, mattress U-sutures, instead of tangential sutures, could eliminate tangential tension and shear force at the pancreatic stump, particularly during knot tying which might cut through the fragile pancreas [8, 10, 11, 17].

22.1.3.1 Technique of Modified Blumgart Pancreaticojejunostomy

After resection of the periampullary lesion with PD, a pancreatic stump of about 1–2 cm is freed from the splenic artery and vein. The modified

Blumgart PJ is constructed using two to four (usually three, instead of five to six in original Blumgart PJ [11]) transpancreatic U-sutures with 3-0 monofilament synthetic absorbable sutures made of polydioxanone (PDS™), with one or two placed cranial and two caudal to the pancreatic duct (Fig. 22.1a, b). The jejunal limb is brought upward for pancreatic reconstruction in a retrocolic fashion to the right of the middle colic vessels or via duodenal tunnel. The U-sutures, as the outer row, are placed about 8–10 mm from the transected edge of the pancreas and go through the whole pancreas parenchyma from front to back. A seromuscular bite in horizontal mattress fashion, instead of a two vertical mattress described in the original Blumgart PJ [11], over the jejunum near the mesenteric edge, is taken as the posterior outer layer, and the same suture reverts back to front through the whole pancreas again to complete the U-suturing, about 5 mm away from the initial entry point of the suture into the pancreas. Each of the U-sutures is placed at a distance of 5–8 mm to the next one. These sutures with needles on them are not tied at this time, but instead are left loose and kept separately and held with clamps until all of the inner duct-to-mucosa sutures are placed and tied. After creating a small hole on the jejunum opposite the location of the pancreatic duct opening, a series of simple interrupted sutures with 4-0 absorbable synthetic monofilament suture made of polydioxanone (MonoPlus®) are then carefully and accurately placed for duct-to-mucosa anastomosis (Fig. 22.2a, b). These inner sutures are preset without tying and organized in order, usually six sutures for a non-dilated pancreatic duct and eight for a dilated pancreatic duct, using pair-watch

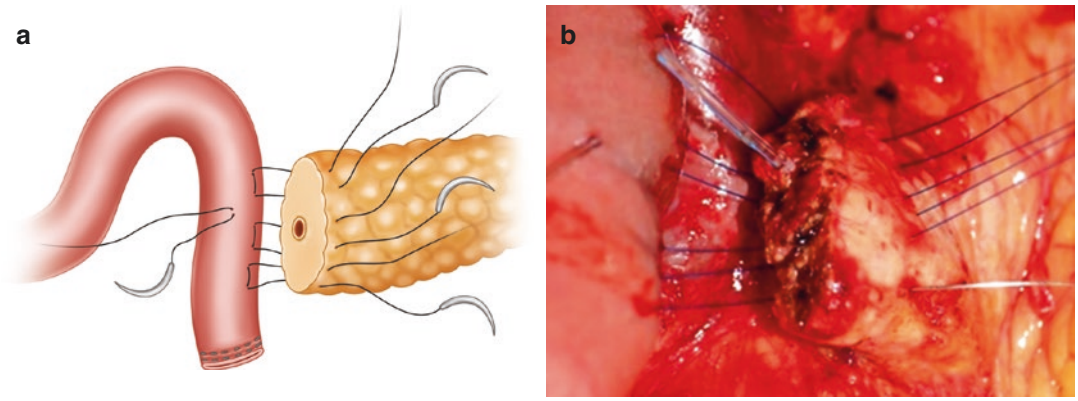

Fig. 22.1 (**a**, **b**) Preset outer-layer U-sutures (three to four sutures) without tying for posterior horizontal mattress sutures on the jejunum

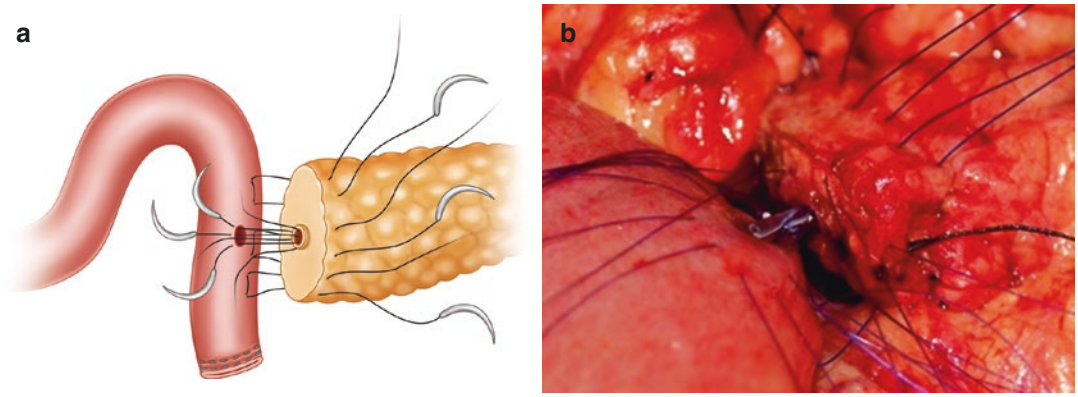

Fig. 22.2 (**a**, **b**) Preset inner-layer sutures (six to eight sutures) without tying for duct-to-mucosa anastomosis using pair-watch suturing technique

suturing technique [13]. Once all duct-to-mucosa sutures are placed, the pancreas and the jejunum are approximated by parachuting the pancreas and the jejunum together along both the outer PDS and inner MonoPlus sutures (Fig. 22.3a, b). After the duct-to-mucosa sutures are tied (Fig. 22.4a, b), the outer anterior horizontal mattress sutures on the jejunum using previously held U-sutures are completed (Fig. 22.5a, b) and tied one by one on the anterior surface of the pancreas. Thus, the pancreatic

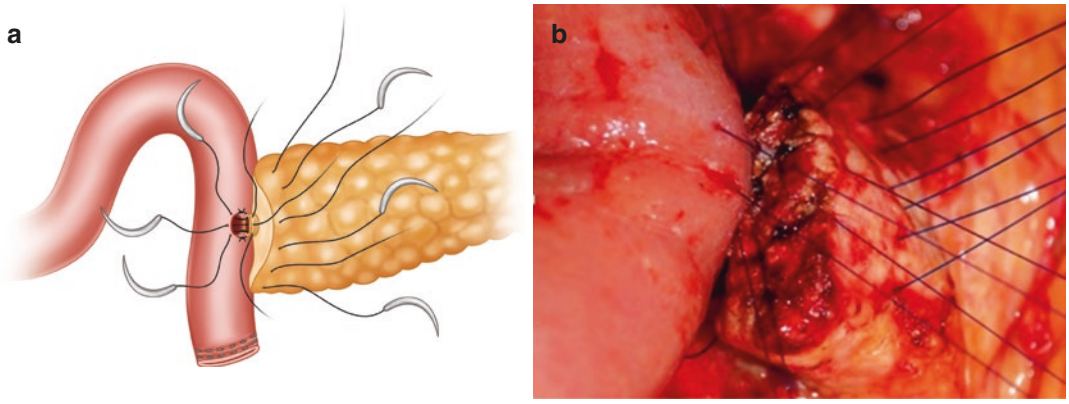

Fig. 22.3 (**a**, **b**) Preset inner-layer sutures (six to eight sutures) with partial tying for duct-to-mucosa anastomosis

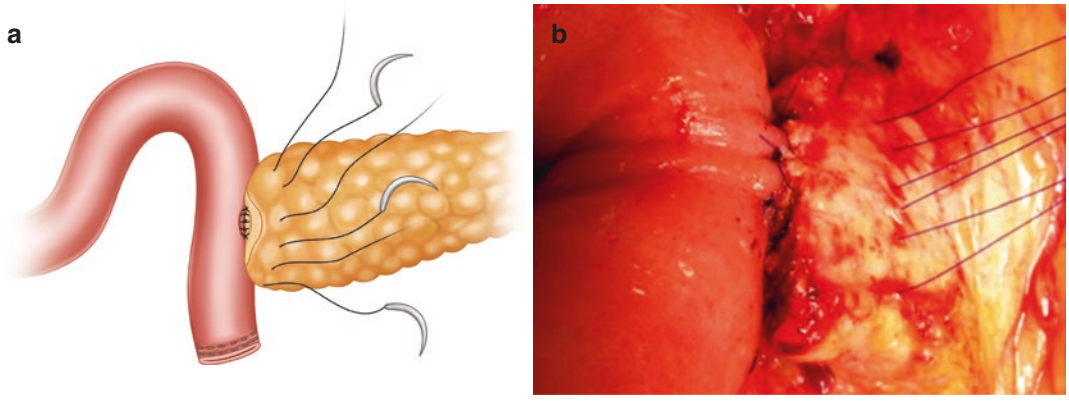

Fig. 22.4 (**a**, **b**) Inner-layer sutures with complete tying for duct-to-mucosa anastomosis

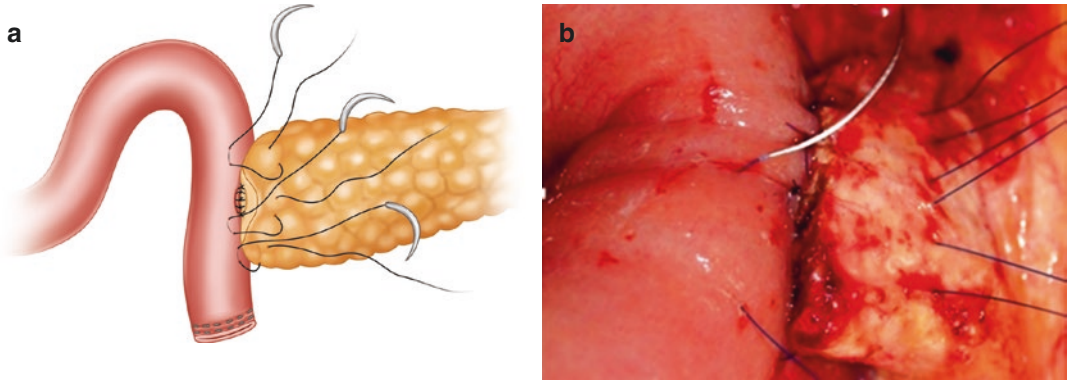

Fig. 22.5 (**a**, **b**) Outer-layer U-suturing for anterior horizontal mattress sutures on the jejunum

remnant is completely covered and compressed by jejunal serosa (Fig. 22.6a, b). Pancreatic duct stents are not routinely used except for a small pancreatic duct using a short internal stent.

22.1.4 Pancreatic Fistula After Pancreatic Reconstructions

POPF has been the leading cause of postoperative morbidity and mortality after PD. The severity of POPF is classified into grades A, B, and C based on the definition of the International Study Group on Pancreatic Fistula (ISGPF) [18]. Grades B and C are clinically relevant postoperative pancreatic fistula (CR-POPF), and grade A is biochemical leakage without clinically relevance. PG has been claimed to be a better pancreatic reconstruction in reducing the incidence and severity of CR-POPF by most retrospective studies [4, 5, 16, 19]. However, not all of the published randomized controlled trials confirm the superiority of PG (Table 22.1). In recent meta-analysis of published randomized controlled trials, PG has been shown

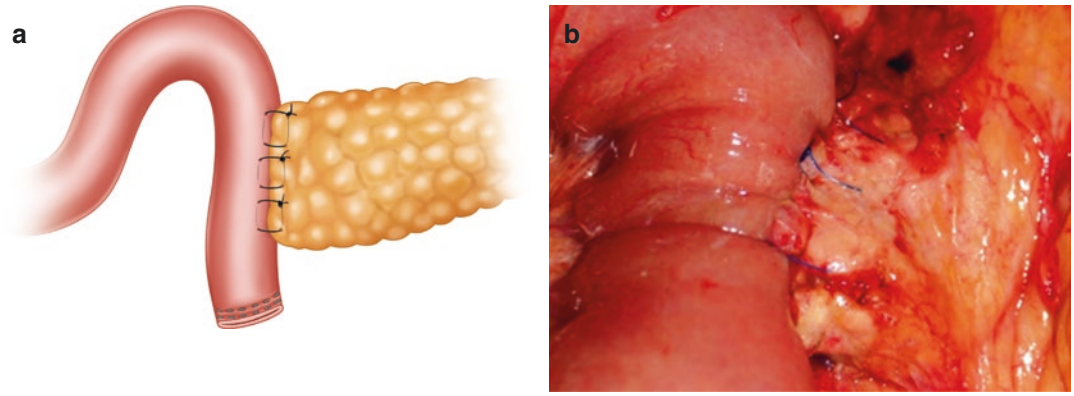

Fig. 22.6 (**a**, **b**) Completed outer-layer U-suturing with tying for anterior horizontal mattress sutures on the jejunum

Table 22.1 Randomized controlled trials for clinically relevant postoperative pancreatic fistula (CR-POPF) after pancreaticoduodenectomy

			CR-POPF		
	Year	*n*	PG[a]	PJ[b]	*P* value
Keck et al. [20]	2015	PG = 149 PJ = 171	20%	22%	NS[c]
Nakeeb et al. [21]	2014	PG = 45 PJ = 45	15.6%	8.9%	NS[c]
Topal et al. [22]	2013	PG = 162 PJ = 167	8.0%	19.8%	0.002
Figueras et al. [23]	2013	PG = 65 PJ = 58	11%	33%	0.006
Wellner et al. [24]	2012	PG = 59 PJ = 57	11%	33%	NS[c]
Fernandez-Cruz et al. [25]	2008	PG = 53 PJ = 55	4%	18%	<0.01
Duffas et al. [26]	2005	PG = 81 PJ = 68	16%	20%	NS[c]
Bassi et al. [27]	2005	PG = 69 PJ = 51	13%	16%	NS[c]
Yeo et al. [28]	1995	PG = 73 PJ = 72	12.3%	11.1%	NS[c]

[a]*PG* pancreaticogastrostomy
[b]*PJ* pancreaticojejunostomy
[c]*NS* not significant

to be associated with lower rate of CR-POPF as compared with classic PJ (Table 22.2). PG had been the procedure of choice for pancreatic reconstruction at the author institute since 1997 [4]. In 2012, the modified Blumgart PJ began to be adopted at our institute and has replaced PG as the technique of choice for pancreatic reconstruction after PD thereafter. With the modified Blumgart PJ, only a 1- to 2-cm free pancreatic stump is needed, as opposed to a 3- to 4-cm free pancreatic stump for PG reconstruction. Moreover, only three or four transpancreatic U-sutures are used for the modified Blumgart PJ, instead of the multiple tangential sutures needed for PG or classic PJ. Blumgart PJ has been reported to decrease the CR-POPF rate to 4.3–6.9%, significantly lower than the 10–20% of other techniques (Table 22.3) [8, 9, 11, 14]. Based on our matched historical control study [33], the modified Blumgart PJ appears to be superior to PG in reducing the incidence and severity of CR-POPF. The modified Blumgart PJ can therefore be recommended as a fast, simple, and safe alternative for pancreatic reconstruction after PD.

"It appears that a standardized approach to the pancreatic anastomosis and a consistent practice of a single technique can help to reduce the incidence of complications after PD," as emphasized by Shrikhande SV [34]. "At present, the only reproducible factor able to significantly reduce the morbidity and mortality rate in pancreatic resections appears to be the establishment of high-volume, regional centers (and surgeons!)", as also stated by Bassi C. [12].

Table 22.2 Meta-analysis of randomized controlled trials for clinically relevant postoperative pancreatic fistula (CR-POPF) after pancreaticoduodenectomy

	Year	*n*	PG[a]	PJ[b]	*P* value
Menahem et al. [29]	2015	PG = 562 PJ = 559	11.2%	18.7%	0.0003
Hallet et al. [30]	2015	PG = 339 PJ = 337	8%	20%	<0.0001
Que et al. [31]	2015	PG = 384 PJ = 382	9.1%	16.5%	0.0001
Liu et al. [32]	2015	PG = 562 PJ = 559	10.6%	20.5%	<0.0001

[a]*PG* pancreaticogastrostomy
[b]*PJ* pancreaticojejunostomy

Table 22.3 Blumgart pancreaticojejunostomy studies for clinically relevant postoperative pancreatic fistula (CR-POPF) after pancreaticoduodenectomy

	Year	*n*	Blumgart PJ[a]	PG[b]	PJ	*P* value
Wang et al. (authors) [33]	2015	B-PJ[c] = 103 PG = 103	7.8%	19.4%		0.007
Fujii et al. [9]	2014	B-PJ[c] = 120 PJ = 120	2.5%		36%	<0.001
Mishra et al. [17]	2011	B-PJ[c] = 98	7.14%			
Grobmyer et al. [11]	2010	B-PJ[c] = 187	6.9%			
Kleespies et al. [8]	2008	B-PJ[c] = 90 PJ = 92	4%		13%	0.032

[a]*PJ* pancreaticojejunostomy
[b]*PG* pancreaticogastrostomy
[c]*B-PJ* Blumgart pancreaticojejunostomy

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The Concept of Customized Pancreatoduodenectomy

23

Sun-Whe Kim

23.1 Introduction

There are still many controversial issues on the pancreatoduodenectomy (PD) in many aspects including the extent of surgery, surgical planes and order, reconstruction method, etc. Surgical decision-making should be based on the principle of cancer surgery and evidence-based surgery. Cancer surgery should be safe and radical enough to get R0. Specimen should be removed in en bloc manner, and the surgeon should minimize touch and spillage of tumor and avoid crossing the potential tumor present area. Meanwhile, the innocent organs and tissues should be preserved with their functions.

Surgical decision should be made on the basis of evidences – evidence-based surgery. There are different levels of evidences with different degrees of recommendation. Randomized controlled trial (RCT) is known as a study providing evidence with the highest level. However, there are some problems with RCTs that cannot be neglected. RCTs mostly compare only two arms that usually have both merit and demerit. On the top of that, even similarly designed RCTs from different centers sometimes show different directions of result. This is why systematic review and meta-analysis are usually needed, although not all of them are conclusive. There could be more than two options for a certain procedure. Usually multicenters or multi-surgeons are supposed to join the RCTs because of the limitation of case number, so that other factors could decrease level of reliability of RCTs. Therefore, pancreatic surgeons cannot simply choose one of the two types of surgery for all patients in order to follow the result of RCT, and PD could be or should be "customized." The word "customized" was chosen among the words with similar meaning, "personalized, individualized, or tailored."

How is PD customized? It can be customized according to tumor factor and patient host factors. Tumor factors include nature, origin, location, and extent of tumor. PD for malignant tumors should be different from PD for benign lesion in terms of the extent of resection. According to the tumor origin, focusing area during PD could be different. Hepatoduodenal ligament dissection (including skeletonization of the portal vein and hepatic artery) might be more important for bile duct cancer than other periampullary cancers. Retroperitoneal pancreatic head nerve plexus and peri-SMA (superior mesenteric artery) nerve plexus have more significance in pancreatic head cancer than others. Peri-SMA lymph node dissection might have more clinical prognostic significance in pancreatic and ampullary cancer than in bile duct cancer. Extent of resection sometimes should be customized according to the location of bile duct cancer or

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the location of pancreatic head cancer [1]. According to the extent of tumor, sometimes resections of other organs or major vessels are needed. For reconstruction, there are many options for pancreatoenterostomy in terms of the site, mode, or order of anastomosis. Different techniques can be applied according to the parenchymal condition and ductal diameter of the pancreas. Host factors including old age and operative risk are the factors that might affect surgical decision also. Abdominal incision can be customized according to the body-belly shape for better exposure.

In this chapter, potential procedures that can be customized mainly for pancreatic head cancer are introduced. Some have evidences and others need evidence.

23.1.1 Access to the Head of the Pancreas

The pancreatic head is fully covered or attached to the surrounding tissues as well as the duodenum (Fig. 23.1). There are some loose connective tissue between the antropyloric area and pancreas. More soft tissues with some small vessels from gastroduodenal artery exist between duodenal bulb and pancreatic head. There are also loose connective tissues at least even between great vessels – the inferior vena cava (IVC) and left renal vein – and posterior surface of the pancreatic head. Omentum and mesocolon are attached to the anterior inferior surface of the head of the pancreas. All of these tissues surrounding pancreatic head are potentially tumor present area according to the tumor location. Because most of the resectable pancreatic head cancers are T3 – tumor invading beyond the pancreas – dissection plane should be carefully determined.

If the tumor is located anterior superior part of the pancreatic head, it would be safe not to try to separate prepyloric stomach from the pancreas head and just not to preserve the pylorus. If the tumor is located anterior inferior head, it would be safe not to separate omentum and mesocolon from the pancreatic head and remove them together (Fig. 23.2). Posteriorly located tumor can be exposed to posterior surface of the pancreatic head and invaded into loose tissue between the pancreas and IVC (Fig. 23.3). So, when the duodenum with pancreatic head is mobilized from retroperitoneum (Kocher maneuver), all the soft tissue between the pancreas and IVC should be completely removed so that IVC is clearly seen without covering any soft tissues.

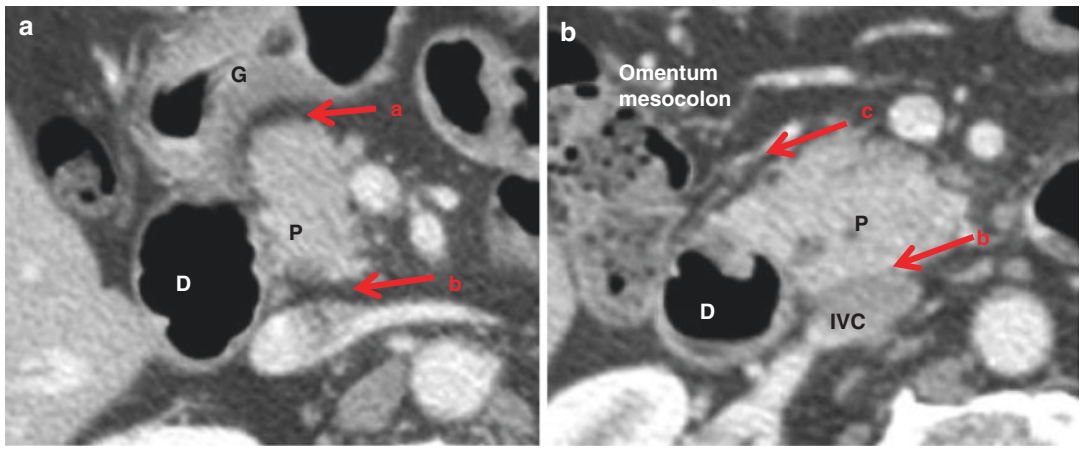

Fig. 23.1 (**a**) Superior part of the pancreatic head. (**b**) Inferior part of the pancreatic head. (*Arrow* **a**) Soft tissue plane between antropyloric area of the stomach and the pancreas, (*Arrow* **b**) soft tissue plane between IVC and the pancreas, (*Arrow* **c**) plane between omentum and mesocolon and anterior inferior surface of the pancreatic head (*D* duodenum, *G* stomach, *P* pancreas, *IVC* inferior vena cava)

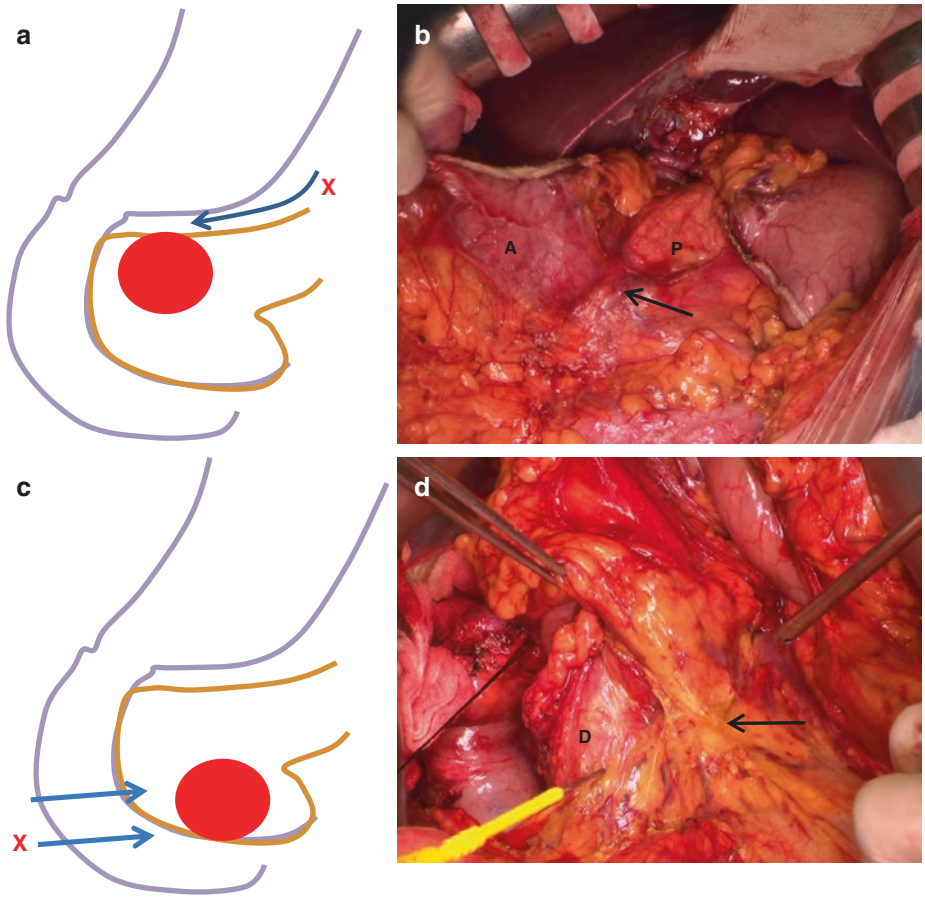

Fig. 23.2 (**a**) For tumors located anterior superior part of the head, it would be safer not to separate prepyloric stomach from pancreas head. (**b**) *Arrow* indicates the intact soft tissue between antropyloric area and pancreatic head. (**c**) For tumors located anterior inferior head, it would be safer not to separate covered omentum and mesocolon from the pancreatic head. (**d**) *Arrow* indicates pancreatic head covered with omentum and mesocolon (*G* gastric antrum, *P* pancreas, *D* duodenum)

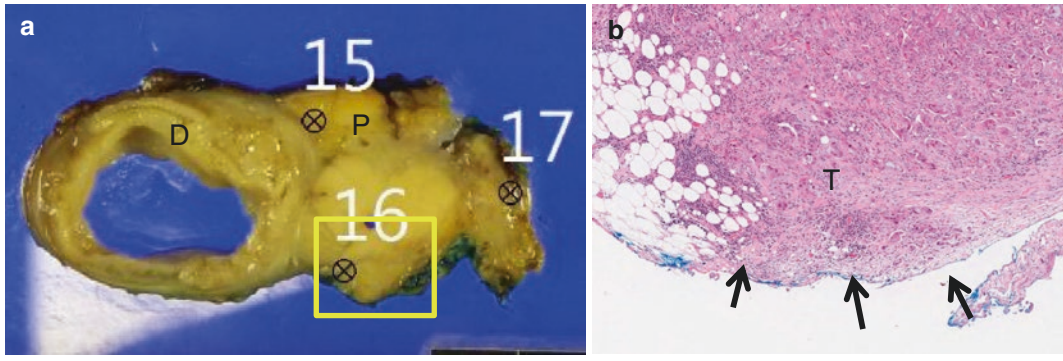

Fig. 23.3 Potential tumor exposure of posterior surface. Posterior-located tumor as seen on the cross-sectional gross photo (**a**) can be exposed (*arrow* indicated) as seen in Fig. (**b**), that is, microphoto of yellow frame area of gross section (**a**). Pathologic report says "Pancreas posterior resection margin: presence of tumor, involved by carcinoma" (*D* duodenum, *P* pancreas, *T* tumor)

23.1.2 Level of Organ Transection

Organs to be resected are the bile duct, gastroduodenal segment, and pancreas. The level of bile duct cutting can be customized according to the tumor origin and location (Fig. 23.4). For pancreatic head cancer, common hepatic duct just proximal to the cystic duct insertion site is recommended. Common bile duct level transaction (distal to the cystic duct) is not recommended because sometimes cystic duct lumen and long redundant common duct make anastomosis complicated, even though its radicality is acceptable for pancreatic cancer. It would be oncologically safer to remove the whole extrahepatic common duct for common bile duct cancer.

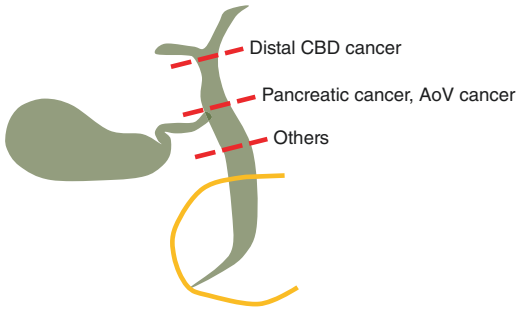

Fig. 23.4 Customized level of bile duct transection according to the tumor origin and proximal extent

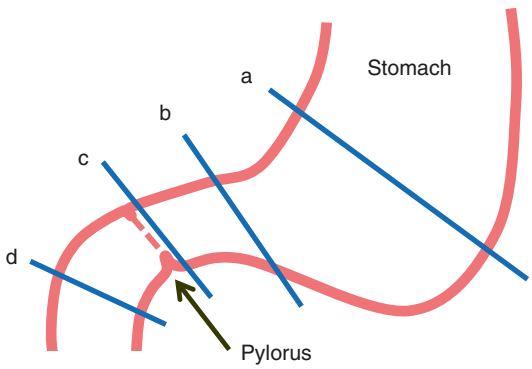

Fig. 23.5 Different options for gastroduodenal transection level between PD and PPPD ((**a**) classical pancreatoduodenectomy (*PD*), (**b**) subtotal gastric-preserving PD, (**c**) pylorus-resecting PD, (**d**) PPPD)

There are some options for gastroduodenal transaction level (Fig. 23.5). In addition to conventional pancreatoduodenectomy and pylorus-preserving pancreatoduodenectomy (PPPD), pylorus-resecting or near total gastric-preserving pancreatoduodenectomy has been introduced recently as another option, mainly for preventing delayed gastric emptying after PPPD [2, 3]. If the pylorus is thought to have a significant physiologic function, it could be the surgeon's choice whether they preserve the pylorus for preventing delayed gastric emptying. In author's institution, PPPD is considered first unless there is any reason to do PD, and then the level of transaction can be customized between PD and PPPD according to various factors. For instance, PD is recommended for the tumor at anterior superior portion of the pancreas, and PPPD is recommended for tumors at inferior portion of the head of the pancreas (Fig. 23.6). If the duodenal perfusion condition is not good enough, other options can be tried, such as pylorus-transecting PD.

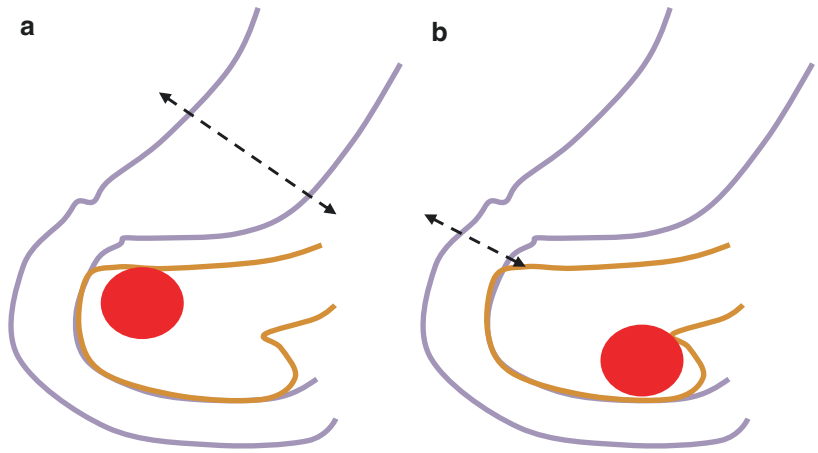

Fig. 23.6 Choice between PD and PPPD. PD is recommended for tumor at anterior superior portion of the pancreas (**a**) and PPPD is recommended for tumors at inferior portion-ventral pancreas (**b**)

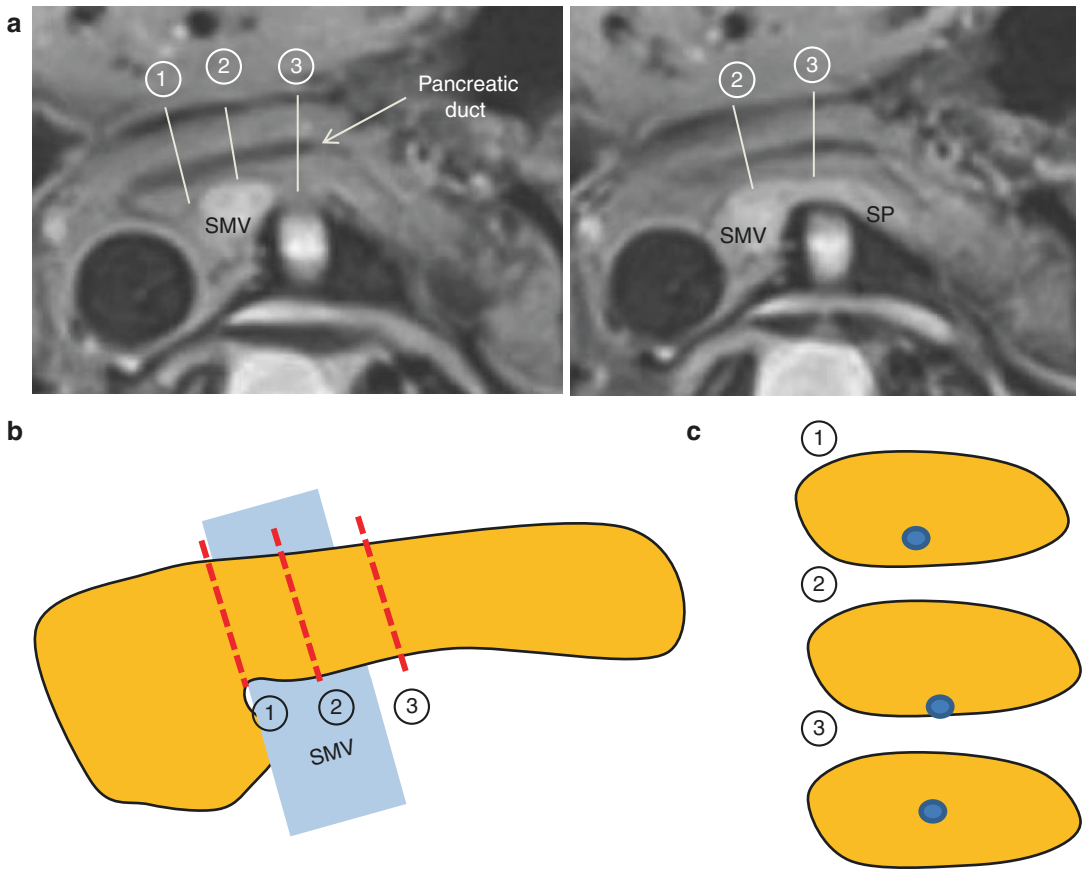

Fig. 23.7 Location of pancreatic duct at the cut section of the pancreatic neck (*SMV* superior mesenteric vein, *SP* splenic vein). (**a**) CT image and transection lines. Respective transection lines (**b**) and duct location on cut sections

Pancreatic neck transaction line should be customized according to the tumor location. A safe length of gross tumor-free segment has not been clearly defined. It would be difficult to define because of infiltrating nature of pancreatic cancer and associated inflammation of the pancreas, especially distal side of the tumor. In order to get free margin, 1 cm margin at least is recommended, so transaction line should be customized according to the tumor location.

Transection line can also be customized for technical reason. Pancreatic duct runs very close to the posterior surface of the pancreatic neck, so that anastomosis is sometimes very difficult. Transection at a little left side of the neck is recommended to get more centrally located duct for easier anastomosis (Fig. 23.7).

23.1.3 Conventional Approach Versus "Artery-First" Approach

Separation of uncinate process from SMA as the first procedure (SMA-first approach) is what many surgeons stress nowadays [4]. Mesenteric approach is the most commonly adopted artery-first approach (Fig. 23.8). Most surgeons are used to conventional right side approach (SMA-last approach), but the mesenteric approach has advantages for the tumors involving uncinate process, especially in the cases of SMV/PV invasion or suspicious SMA invasion. It is considered to make early determination of respectability possible, to be better for complete peri-SMA lymph nodes dissection, and to cause less operative

bleeding despite longer operation time. Other options for approach to SMA have been introduced with potential indications, but any good evidences are not available yet [4].

SMA-last approach is a conventional approach that is more familiar to most surgeons because it is simpler and easier compared to SMA-first approach and it has been working well for most of the periampullary cancers including pancreatic head cancer. So unless pancreatic cancer is located, uncinate process or major vascular invasion – at least abutting – is suspected, and SMA-last approach can be chosen.

If PV/SMV invasion is suspicious and combined vein resection is expected, vein resection should be the last procedure for en bloc removal of the specimen. To make it possible, uncinate process should be divided from SMA first before vein resection (Fig. 23.9).

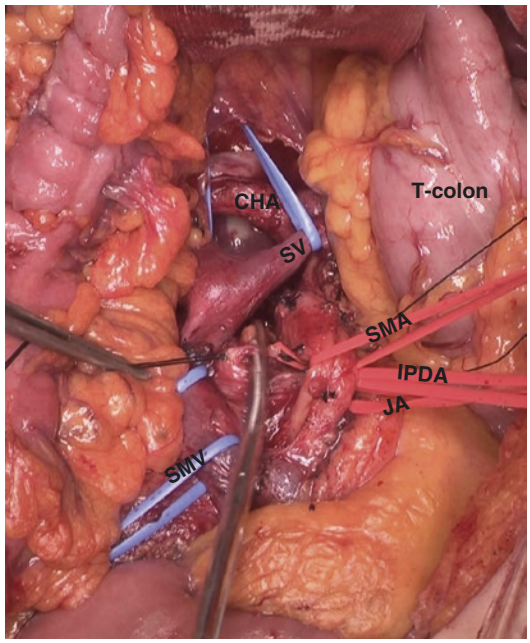

Fig. 23.8 Operative field of mesenteric approach (*T-colon* transverse colon, *SMA* superior mesenteric artery, *SMV* superior mesenteric vein, *JA* jejunal artery, *IPDA* inferior pancreaticoduodenal artery, *SV* splenic vein)

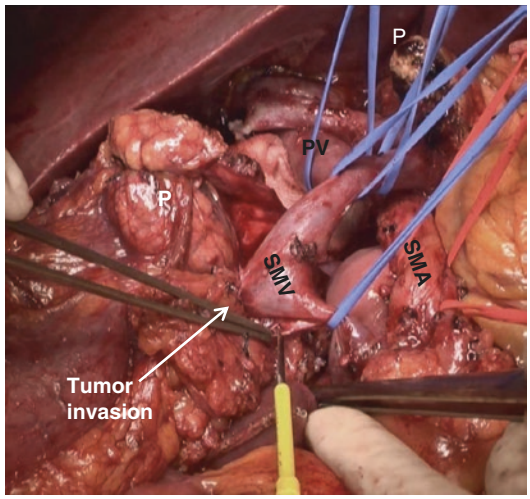

Fig. 23.9 Operative field view just before en bloc removal of specimen in pancreatic head cancer with SMV invasion (*P* pancreas, *SMA* superior mesenteric artery, *SMV* superior mesenteric vein, *PV* portal vein)

23.1.4 Design for Portal Vein Resection

Surgeons should design portal vein resection for those who have suspicious portal vein invasion. Whether wedge resection or segmental resection with or without different types of graft is chosen should be determined according to the site and the extent of invasion. And the order of vessel dissection should be customized as described above. For instance, if there is no vein invasion, SMV can be separated from pancreatic head first, and if invasion is suspected, SMA first with SMV last is recommended for en bloc removal of specimen. Graft that could be used is diverse, autograft, allograft, or xenograft. There are different sources of autograft such as the left renal vein, jugular vein, external iliac vein, saphenous vein, etc. Frozen vessels from organ donor can be used and bovine patch grafts are used.

All the reconstruction procedures are to aim preserving portal blood flow as much as possible. Splenic vein and inferior mesenteric vein are recommended to be preserved unless vascular invasion is suspected. Some surgeons prefer splenic vein cutting for better exposure of the superior mesenteric artery and retroperitoneum (more for vascular resection and reconstruction is covered in other chapters).

23.1.5 Extent of Lymph Node Dissection

Lymph node metastasis has been known strong prognostic factor of pancreatic cancer, and exten-

sive dissection of regional lymph nodes has been considered to bring some survival benefit. To investigate whether extensive lymph node dissection has any beneficial effect on survival in pancreatic head cancer, five randomized controlled trials have been tried to compare between limited LN dissection and extended LN dissection [5–9]. Although there were slight differences in the extent of LN resection (Fig. 23.10 and Table 23.1), all the studies failed to show any survival benefit of extended dissection. Therefore, it has been documented that standard or limited LN dissection is recommended (more for extent of surgery is discussed in other chapters). However, the results of these RCTs have not made most surgeons routinely perform standard limited LN dissection for pancreatic head cancer. Actually in most institutions, the extent of PD is customized between standard PD and extended PD.

For customizing LN dissection, several points should be considered. For R0, LN site of frequent metastasis and recurrence should be considered. There should not be additional morbidity. LN dissection can be done for biopsy purpose.

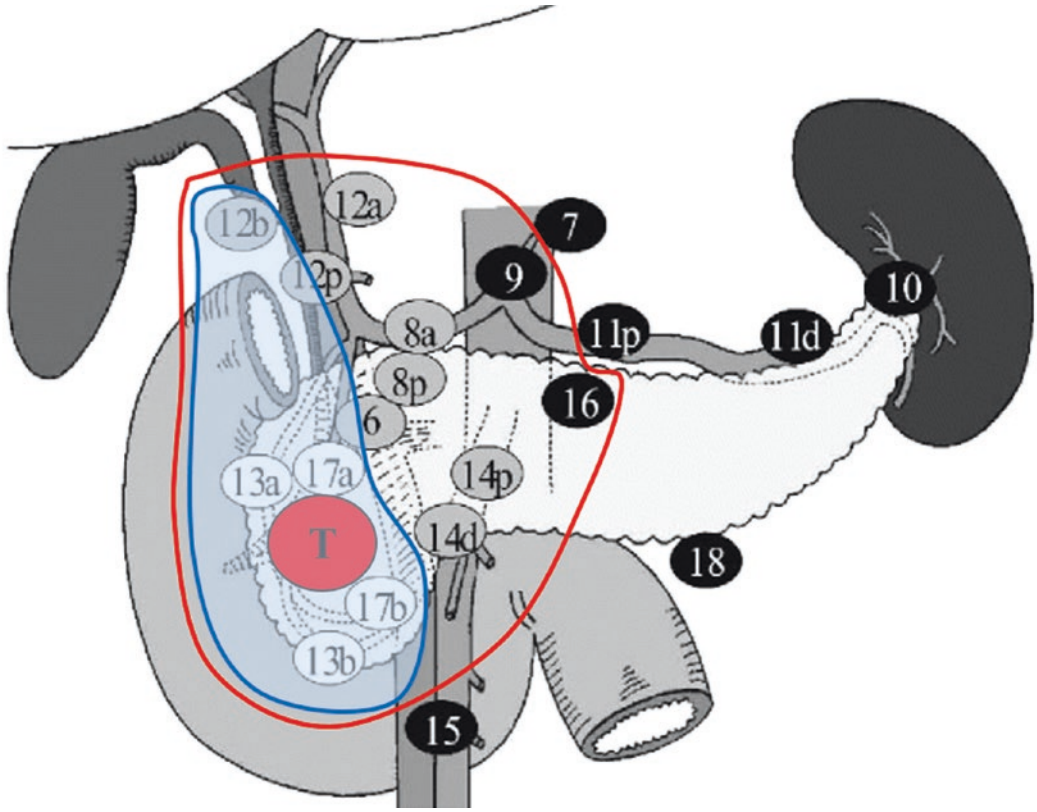

Fig. 23.10 Regional LN for pancreatic head cancer. The figure shows the definition of the extent of LN resection in the author's study, standard (*blue lined area*) and extended (*red lined area*) dissection

Table 23.1 Extent of LN dissection in reported RCTs: standard PD vs extended PD

Standard/Extended	Pedrazzoli (Italy, 1998)	Yeo (JHI-USA, 2002)	Nimura (Japan, 2004)	Farnell (Mayo-USA, 2005)	Jang (Korea, 2013)
Extent of LN dissection	8, 13, 17 vs +9, 12, 14, 16	Regional vs +perigastric, 16a2+b1	13, 17 vs + 8, 9 , 12, 14, 16	12bc,13, 14ab vs +8, 9, 12a, 14cd, 16a, 2b	12b, c, 13, 17 vs + 8, 9, 12a, 14, 16a2, b1
Retrieved LN	13.3/19.8	17/28.5	13.3/40.1	15/36	17.3/33.7

So far, 5 RCTs have compared between limited LN dissection and extended one. And all the studies failed to show any benefit of extended dissection, although there was a little difference in the extent of LN dissection in each study

Prognosis of cases with direct LN invasion has been reported better than that of cases with typical LN metastasis [10]. So LN dissection can be customized according to the tumor location.

SMA LNs (#14) are located around SMA from the origin down to the level of jejunal branches. #14 LNs are located any direction of SMA. Most of LN dissection of the standard PD did not include peri-SMA LNs, although some SMA right side LNs can be removed. However, metastasis to the #14 LN is frequently seen in pancreatic head cancer, especially in uncinated process cancer, either in primary cases or recurrent cases. Prognostic significance of #14-LN metastasis has been reported [11]. So, for the pancreatic head cancer, located near uncinate process, complete LN dissection around SMA including left side of SMA is recommended. When proximal jejunum is mobilized, SMA left side should be exposed not leaving any LNs.

Para-aortic LNs – #16 LNs – can be removed for biopsy purpose by en bloc manner during Kocher maneuver if it is extended up to as far left as possible as shown in Fig. 23.11. Although

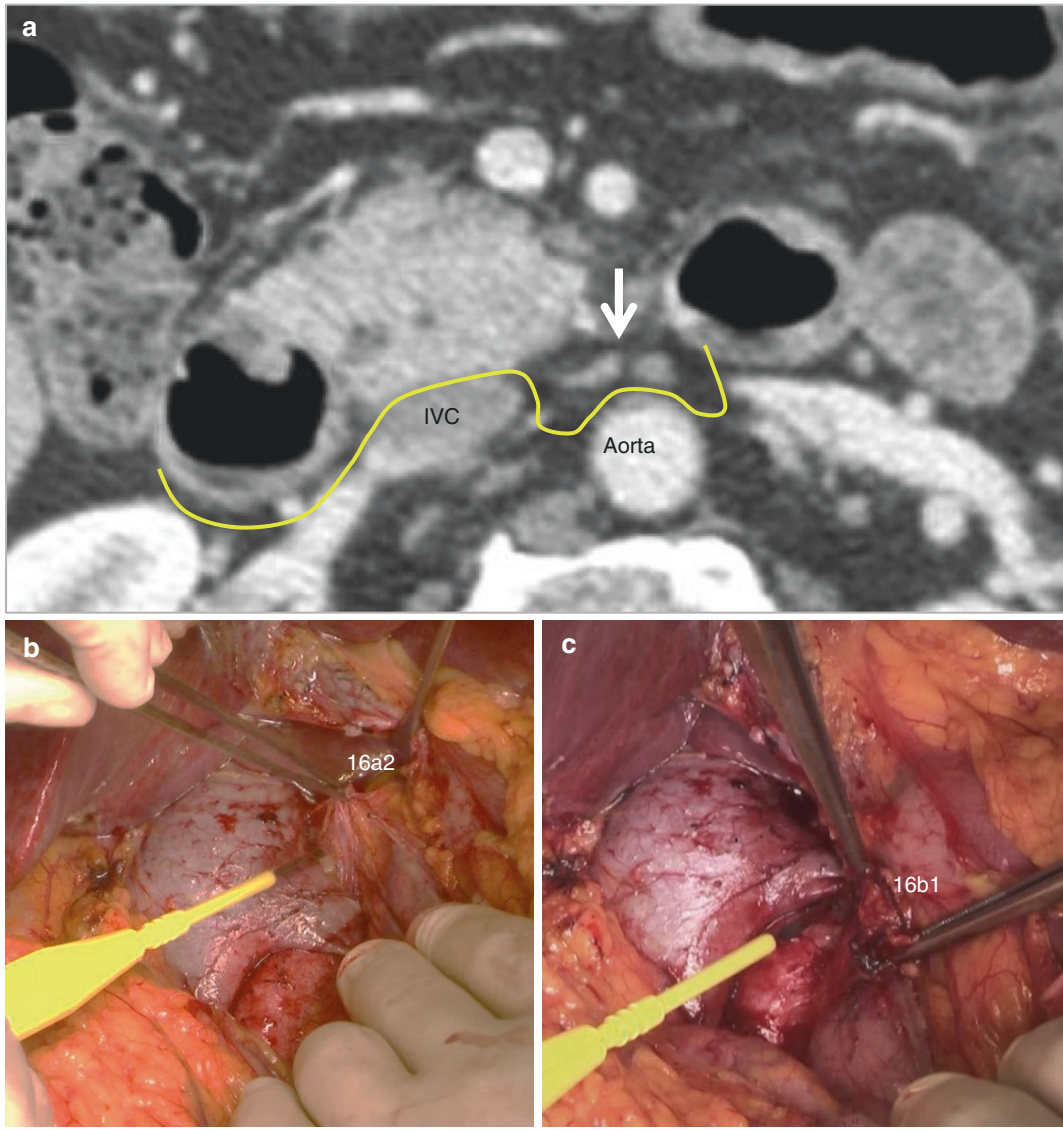

Fig. 23.11 #16 aortocaval LN biopsy by en bloc manner during extended Kocher maneuver. (**a**) *Yellow line* indicates dissection line for extended Kocher maneuver (*Arrow* indicates aortocaval LN). (**b**) Dissection for #16a2 LN. (**c**) Dissection for #16b1 LN

para-aortic LN dissection has no prognostic benefit, it wouldn't increase morbidity and be helpful to estimate prognosis. Usually #16a2 and b1 LNs can be removed by en bloc manner.

There are two types of pattern of LN involvement. As gross and micro cross-sectional image of PD specimen shows (Fig. 23.12), there could be direct peritumoral LN invasion as well as typical standard LN metastasis. Although even single LN metastasis is already associated with a dismal prognosis [12], it has been reported direct LN invasion is associated with better prognosis compared to standard LN metastasis [10]. So, potential direct LN invasion should be considered to determine adequate dissection plane for en bloc specimen removal. In this aspect, some #12 LNs and #8 LNs which are tightly attached to the pancreas should be removed during PD for cancer of the dorsal pancreas. #14 LNs should be removed for cancer of the uncinated process of the pancreas.

Customization of LN dissection for pancreatic head cancer is summarized in Fig. 23.13. In addition to the automatically removed #13 and #17 LNs, additional dissection of #16 LNs for biopsy purpose, #12 and #8 LNs for dorsal pancreas, and #14 LNs for ventral pancreas are recommended (Fig. 23.13).

23.1.6 Nerve Plexus Dissection

It is not clearly documented whether periarterial and retroperitoneal nerve plexus dissection is necessary and what the extent of dissection should be if it is necessary. Peri-SMA nerve plexus has been the site of the most controversial issue. There could be three options for the extent of dissection of the peri-SMA nerve plexus: (1) cutting nerve plexus at the level of pancreatic head plexus (I, II), (2) a half circumferential dissection, and (3) a whole circumferential dissection (Fig. 23.14).

Different extent of nerve plexus dissection has been compared in three RCTs among five (7–9). The figures (Fig. 23.15) from the authors' study show different extents of nerve plexus dissection, SMA covered with plexus in standard surgery and a half dissected SMA in extended surgery. Although the three RCTs tried different extents of nerve plexus dissection, all of them concluded that extended pancreatectomy including extensive nerve plexus dissection would not improve long-term outcome and early recovery with lower morbidity rate is observed with standard pancreatic resection. SMA nerve plexus dissection, which is thought very important as retroperitoneal margin, does not improve survival and is associated with naturally following severe diarrhea. So, it has been recommended that cutting pancreatic head plexus level and preserving SMA nerve plexus should be routine (Table 23.2).

However, there are cases where nerve plexus dissection might be needed to get R0. A half circumferential dissection would not bring any

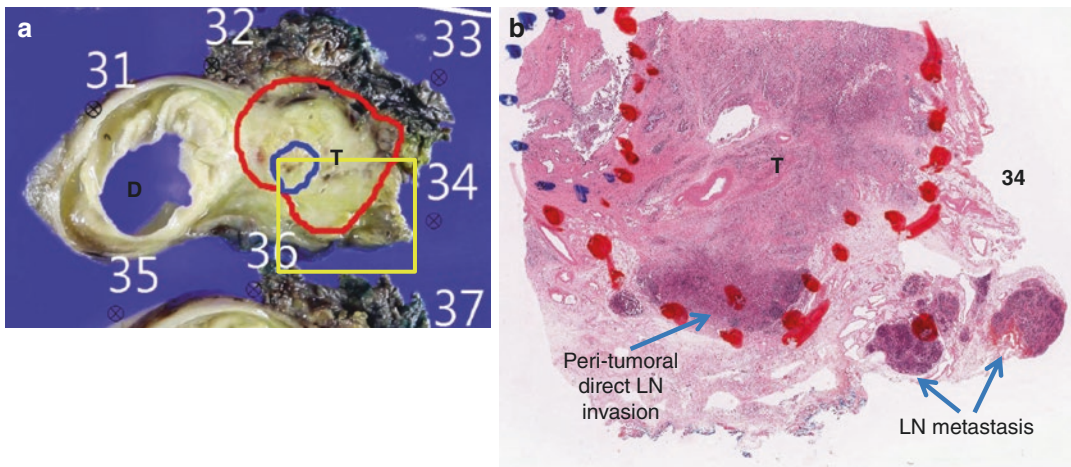

Fig. 23.12 Gross (**a**) and micro (**b**) cross-sectional images of pancreatoduodenectomy specimen. (**b**) is a microphoto of *yellow* frame area of gross photo (**a**). Direct peritumoral LN invasion and standard LN metastasis are shown

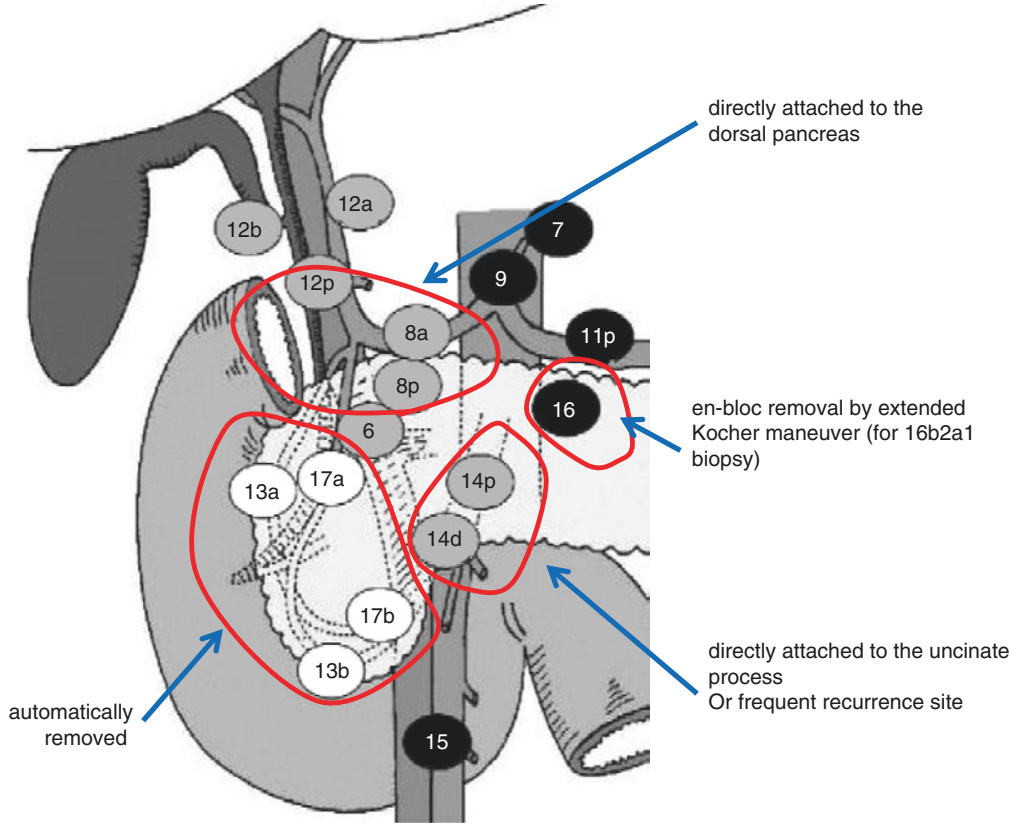

Fig. 23.13 Customized extent of LN dissection

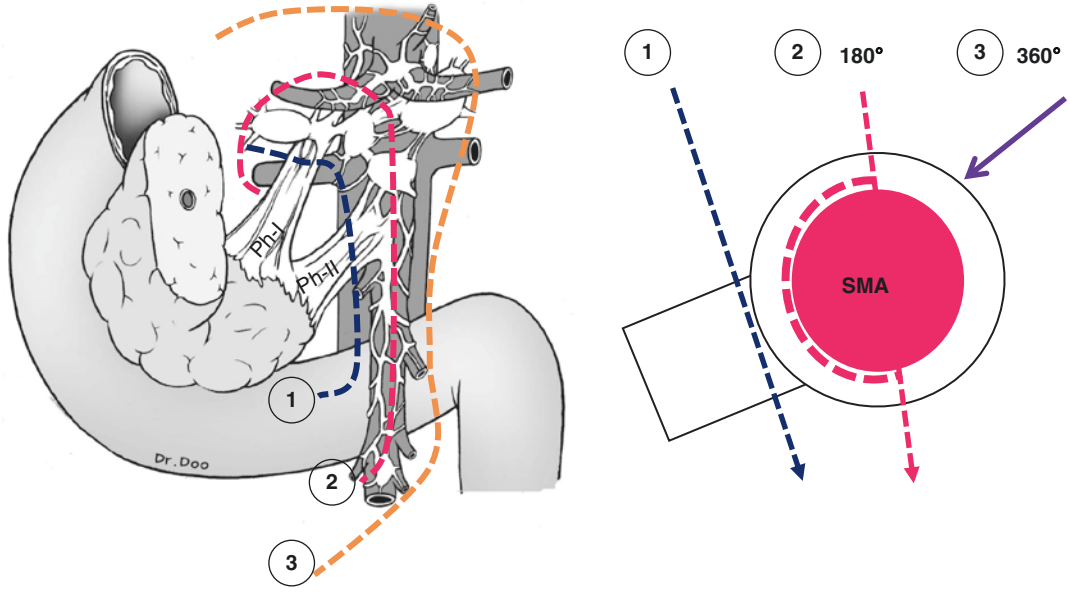

Fig. 23.14 Extent of nerve plexus dissection. There are three options for nerve plexus dissection. (1) Cutting nerve plexus at the level of pancreatic head plexus, (2) a right half removal, (3) a whole circumferential dissection

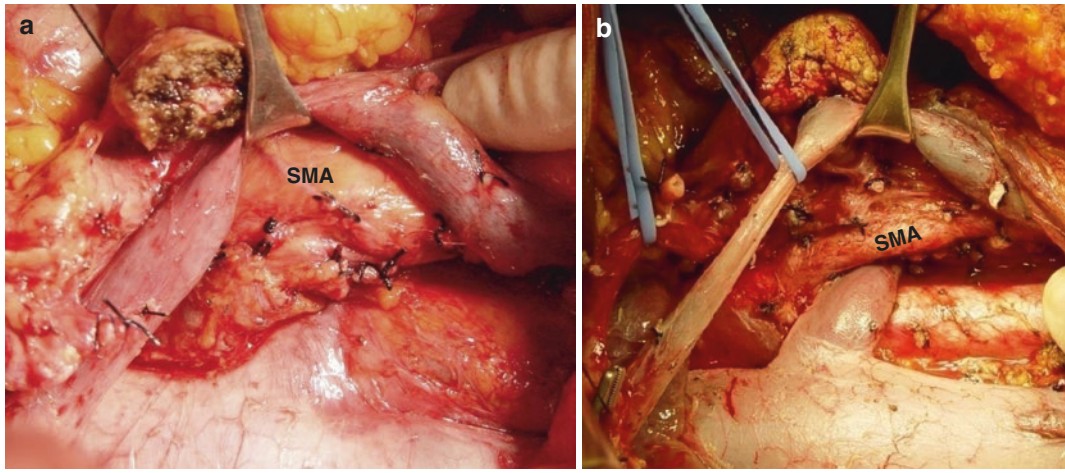

Fig. 23.15 Operative field photos of different extents of nerve plexus dissection. (**a**) Preserving peri-SMA plexus, (**b**) a half nerve plexus dissection around SMA

Table 23.2 Extent of nerve plexus dissection in 3 RCTs and severity of diarrhea after extended surgery

SMA nerve dissection	Nimura (Japan 2004)	Farnell (Mayo 2005)	Jang (Korea 2013)
Standard vs Extended	None vs 360°	Right 180° vs 360°	None vs Right 180°
Diarrhea after Extended	+++	++	±

additional morbidity, and site of nerve plexus invasion can differ according to the tumor location at its early stage at least. Dorsal pancreatic head cancer invades into common hepatic artery (CHA) and hepatoduodenal ligament (HDL) plexus, and ventral pancreatic cancer invades into pancreas head plexus and SMA plexus [13]. Therefore, nerve plexus dissection can be customized according to the tumor location. Although it is true that SMA nerve plexus invasion is dismal prognostic sign, it is advisable that a segmental right side SMA nerve plexus at the tumor level at least should be removed to get R0, which is becoming stricter in terms of the distance from margin.

A half circumferential dissection is not always right half dissection. The neurovascular structures between uncinated process and SMA, including nerve plexus around inferior pancreaticoduodenal artery, move right to posterior caudally as seen in the CTs (Fig. 23.16).

23.1.7 Pancreaticoenteric Anastomosis

Pancreatic leakage risk depends on pancreatic parenchymal condition, ductal diameter, and others. There are different modes of pancreaticoenteric anastomosis, in terms of the site, pancreaticojejunostomy (PJ) vs pancreaticogastrostomy (PG), and stent use: no stent, internal and external stent, and other modes of anastomosis. To find out better way, many RCTs have been performed. Some RCTs have shown no difference but others have shown that PG is better. As a meta-analysis report, PG looks superior when it comes to the leakage risk (Table 23.3) [14]. However, most of the RCTs have not standardized the PJ technique, and long-term outcome of the different techniques has not been considered.

RCTs that have investigated the effect of stent insertion into the pancreaticojejunostomy site were systematically reviewed [15, 16]. All the studies compared two arms among three ways: no stent, internal (lost) stent, and external (long) stent. Meta-analysis shows external stent is better than no stent and no difference between no stent and internal stent (Table 23.4) [15, 16].

So, according to the currently available evidences, in terms of the risk of leakage, PG is the safest method, and PJ with external stent, PJ with internal stent, and no stent are the next. However,

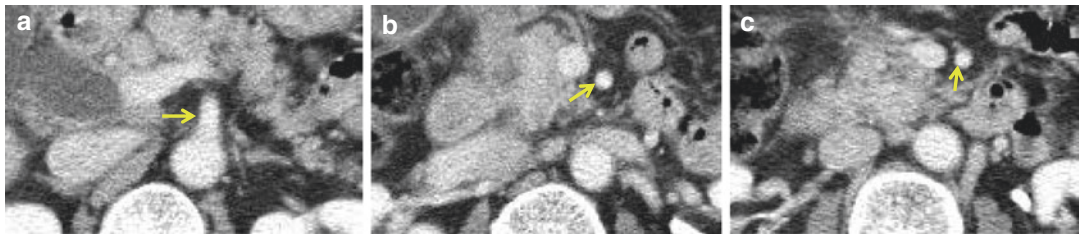

Fig. 23.16 Direction of plexus invasion from pancreatic head. *Arrows* indicate SMA and directions of infiltration. A half plexus to be dissected moves right to posterior caudally as seen in CTs (**a→b→c**: craniocaudal)

Table 23.3 RCT for comparing pancreaticogastrostomy (PG) versus pancreaticojejunostomy (PJ)

Author	Year	Number of cases		Pancreatic fistula	Mortality %
RECOPANC	2014	320	PG 171	20% (B, C)	5.6
			PJ 149	22% (B, C)	
El Nakeeb	2014	90	PG 45	20%	7.8
			PJ 45	22%	
Figueras	2013	123	PG 65	15%	4.9
			PJ 58	34%	
Topal	2013	329	PG 162	8% (B,C)	3.6
			PJ 167	20% (B, C)	
Wellner	2012	116	PG 59	10%	1.7
			PJ 57	12%	
Fernández-Cruz	2008	108	PG 53	6%	0.0
			PJ 55	18%	
Bassi	2005	151	PG 69	13%	0.7
			PJ 82	16%	
Duffas	2005	149	PG 81	20%	11.4
			PJ 68	16%	
Yeo	1995	145	PG 73	12%	0.0
			PJ 72	11%	

Table 23.4 RCTs comparing different types of pancreaticoenteric anastomosis according to the stent use: no/internal/external stent

		Anastomosis	Number of patients			POPF		
			No stent	Internal stent	External stent	No stent	Internal stent	External stent
Poon	2007	DTM-PJ	60		60	20%		6.7%
Pessaux	2011	DTM-PG or PJ	81		77	42.0%		26.0%
Motoi	2012	DTM-PJ	46		47	22%		6%
Kuroki	2011	DTM-PJ	22		23	40.9%		34.5%
Winter	2006	IN or DTM-PJ	119	115		7.6%	11.3%	
Kamoda	2008	IN or DTM-PJ		21	22		33.3%	36.4%
Tani	2010	DTM-PJ		50	50		26%	20%
Chang	2015	DTM-PJ		164	164		18.9% (B, C)	24.4% (B,C)

DTM duct-to-mucosa, *In* invagination, *POPF* postoperative pancreatic fistula

not only risk of leakage but also some potential early and long-term adverse effects of different methods should be considered. These include long-term pancreatic function, incidence of ductal stenosis or pancreatitis, stent-related problems including migration of internal stent into unwanted spaces such as intrahepatic duct and duct of the remnant pancreas, pancreatic duct obstruction due to fixed and plugged internal stent, minor leak after removal of external stent, decreased pancreatic function during early postoperative period due to full diversion of pancreatic enzyme by external stent, etc.

So, method of restoration of pancreatic flow can be customized as below. If the pancreas has hard parenchyma and large duct (>5 mm), PJ with no stent is recommended. If soft pancreas and small duct (<2 mm), PJ with external stent is recommended. For cases between above two groups, PJ with internal stent is recommended. For the cases that leakage is highly probable due to fatty, inflammatory, or bulky pancreas, PG is recommended.

In conclusion, pancreatoduodenectomy for pancreatic head cancer should be customized according to the disease and host factors. Pancreatic surgeons should be familiar with every type of resection and reconstruction method so as to be able to customize pancreatoduodenectomy for each patient.

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24 Distal Pancreatectomy with *En Bloc* Celiac Axis Resection (DP-CAR) for Advanced Pancreatic Body Cancer

Satoshi Hirano

24.1 History and Concepts of Distal Pancreatectomy with Celiac Axis Resection (DP-CAR)

Locally advanced cancer of the body of the pancreas often involves the common hepatic artery (CHA) and/or the celiac axis (CA), with perineural invasion of the nerve plexuses surrounding these arteries. Although this leads to it being regarded as a borderline resectable or unresectable disease according to the NCCN guidelines® Version 2.2015 [1], distal pancreatectomy with celiac axis resection (DP-CAR) may be the only surgical option for treatment of such an advanced disease [2]. An advantage of DP-CAR is reduction in the likelihood of a positive retroperitoneal margin by complete en bloc resection of the distal pancreas, together with the entire surrounding structures, especially the CHA, CA, and the circumferential nerve plexus along the superior mesenteric artery (SMA), without the need for either arterial, pancreatobiliary, or gastrointestinal reconstruction (Fig. 24.1).

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24.1.1 Development of DP-CAR

This procedure was originally designed as en bloc lymphadenectomy combined with total gastrectomy and resection of the celiac axis for advanced gastric cancer by Appleby in 1953 [3]. It was first adopted by Nimura in 1976 [4] for patients with advanced pancreatic body cancer with invasion of the celiac axis. A modification to the procedure with preservation of the entire stomach was made by Ogata and his colleagues [5] in 1991 (in Japanese with English abstract) and Kondo [6] in 2001, which resulted in better postoperative nutritional status. The first report regarding the long-term outcome of DP-CAR was published by Kondo and Hirano in 2007 [7], which included the results of 24 consecutive patients with favorable postoperative survival. Since then, the procedure and the term "DP-CAR" have been widely acknowledged. Nowadays, several pancreatic surgeons have performed this procedure for carcinoma of the body and tail of the pancreas.

24.1.2 Resected and Preserved Organs in DP-CAR

Perineural invasion in patients with pancreatic body cancer can spread toward the celiac plexus and ganglions directly or via the nerve plexuses surrounding the splenic and common hepatic arteries. Although DP-CAR includes en bloc resection of these arteries and plexuses,

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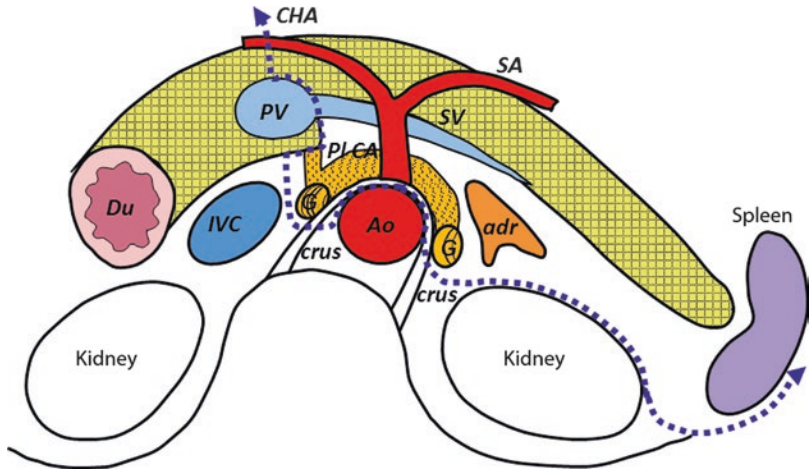

Fig. 24.1 Schematic cross-sectional view demonstrating the resection area of distal pancreatectomy with en bloc celiac axis resection (DP-CAR). The *dotted line* indicates the dissection plane. *adr* adrenal gland, *Ao* aorta, *CA* celiac axis, *CHA* common hepatic artery, *crus* crus of the diaphragm, *Du* duodenum, *g* celiac ganglion, *IVC* inferior vena cava, *pl* celiac plexus, *PV* portal vein, *SA* splenic artery, *SV* splenic vein

reconstruction of the arterial system is not required because of early development of a collateral arterial circulation via the pancreaticoduodenal arcades from the superior mesenteric artery. The entire alimentary tract, including the stomach and bile duct, which are not invaded by the cancer, is preserved. Cholecystectomy is, however, performed for preventing postoperative ischemic rupture of the gall bladder. If the tumor of the pancreatic body invades other organs directly, concomitant resection of the organs, including the alimentary tract, could be performed. However, in the case that a tumor has invaded the stomach to a depth that necessitates full-thickness resection, total gastrectomy should be considered because healing of the anastomosis might be disturbed by an insufficient collateral arterial flow. As far as possible, the entire stomach should be preserved in cases without cancer invasion of the stomach, to maintain the patient's nutritional status and tolerance of oral anticancer agents. SMA preservation, even with complete eradication of the surrounding plexus, is the key feature of this procedure, which maintains arterial supply to the hepatobiliary system and stomach. Resection of the portal vein and middle colic vessels is an optional procedure.

24.1.3 Arterial Supply to the Liver and the Stomach After DP-CAR

After division of the CA with the CHA and splenic artery (SA), the hepatic and gastric arterial flow depend on the flow from the gastroduodenal artery (GDA), which should, therefore, definitely be preserved with the pancreatic head during DP-CAR. The collateral pathways via the SMA, pancreaticoduodenal arcades, and GDA maintain the arterial blood supply to the hepatobiliary system. Since the collateral pathways also ensure arterial flow to the right gastroepiploic artery, the entire stomach can be preserved (Fig. 24.2).

Preoperative coil embolization of the CHA is routinely used to enlarge the collateral arterial pathway, so as to reduce ischemia-related complications such as ischemic gastropathy, liver abscess, and perforation of the biliary system [8] (Fig. 24.3).

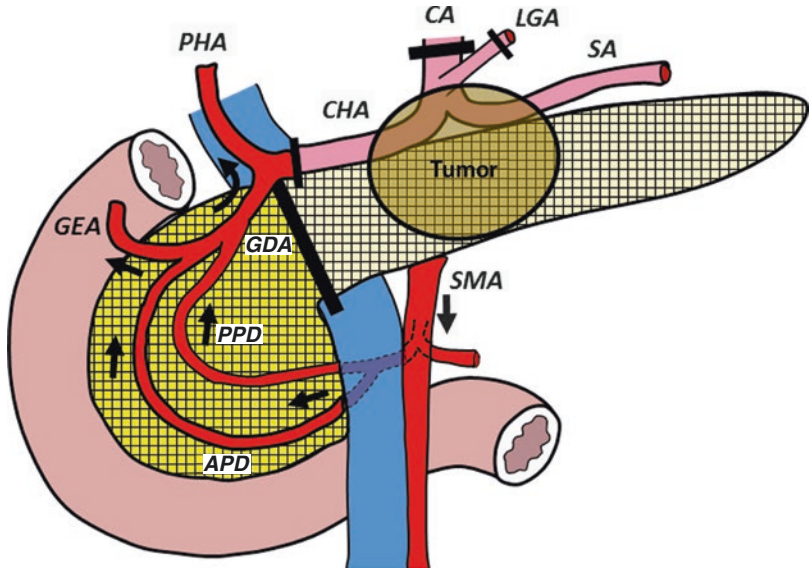

Fig. 24.2 Schematic drawing of collateral arterial pathways via the pancreaticoduodenal arcades from the superior mesenteric artery following DP-CAR. The *arrows* show the direction of arterial flow from the superior mesenteric artery to the liver and stomach via the pancreaticoduodenal arcades. *APD* anterior pancreaticoduodenal arcade, *CA* celiac axis, *CHA* common hepatic artery, *GDA* gastroduodenal artery, *GEA* right gastroepiploic artery, *LGA* left gastric artery, *PHA* proper hepatic artery, *PPD* posterior pancreaticoduodenal arcade, *SA* splenic artery, *SMA* superior mesenteric artery

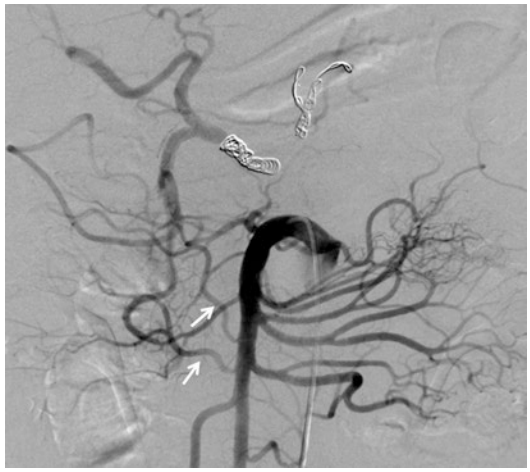

Fig. 24.3 Angiography image of the superior mesenteric artery just after embolization of the common hepatic artery. The *arrows* show the enlarged collateral arterial pathway in the pancreatic head via the posterior and anterior pancreaticoduodenal arteries

24.1.4 Selection of Candidates for DP-CAR

Tumor progression is cautiously evaluated mainly with preoperative multi-detector row computed tomography (MDCT), with supplemental use of magnetic resonance imaging (MRI) and endoscopic ultrasonography (EUS). The indication for DP-CAR is locally advanced ductal adenocarcinoma of the body of the pancreas, such as that involving or abutting the CHA, the root of the SA, and/or the CA, without involvement of the GDA, SMA, and inferior pancreaticoduodenal artery. Patients with involvement of less than approximately half the circumference of the SMA plexus should be considered candidates for DP-CAR because complete dissection of the SMA plexus without exposing the cancer can be achieved by dividing the plexus on the side

opposite to that of the tumor. For oncologically safe ligation and division of the root of the CA in front of the aorta, a 5–7 mm noncancerous length of the CA from the adventitia of the aorta is required.

24.1.5 Surgical Procedure of DP-CAR

DP-CAR usually includes resection of the distal pancreas and the spleen, together with en bloc resection of the celiac, common hepatic and left gastric arteries, the celiac plexus and bilateral ganglions, and the circumferential nerve plexus around the SMA. The left perirenal fat tissue, the left adrenal gland, the entire retroperitoneal fat tissue containing lymph nodes cranial to the left renal vein, the transverse mesocolon covering the body of the pancreas, and the inferior mesenteric vein are also resected (Fig. 24.4).

To achieve R0 resection, a systematic procedure of DP-CAR, which consisted of right and left dorsal (first step), ventral (second step), and medial (third step) approaches, was previously advocated [9]. In the first step (dorsal approach), the lower parts of the SMA are exposed following Kocher's maneuver, with complete eradication of the right celiac ganglion by exposing the right crus of the diaphragm. The plexus of the SMA is first divided at the dorsal end (opposite to the side of the tumor), and the excision is extended by 4–5 cm in the longitudinal direction. The median arcuate ligament has to be divided to expose just the root of the CA where it should be divided. Then, after moving to the left side, en bloc resection of the retroperitoneal fat, together with the upper part of the perirenal fat, including the left adrenal gland cranial to the left renal vessels is performed in exposing the left crus. In this approach, bilateral para-aortic nodes and ganglions are completely dissected. In the second step (ventral approach), transection of the pancreas is performed after dividing the common hepatic artery. When a tumor is located near the GDA, it should be mobilized laterally in order to obtain a cancer-free margin at the site of division of the pancreatic parenchyma. Reconstruction of the portal and/or superior mesenteric vein should be performed in this step, if necessary. In the third step (medial approach), division of the SMA plexus that was performed in the first step is extended longitudinally to just proximal to the inferior pancreaticoduodenal artery (IPDA) to achieve complete resection of the plexus. The procedure is completed after dissecting between the SMA plexus and the uncinate process of the pancreas.

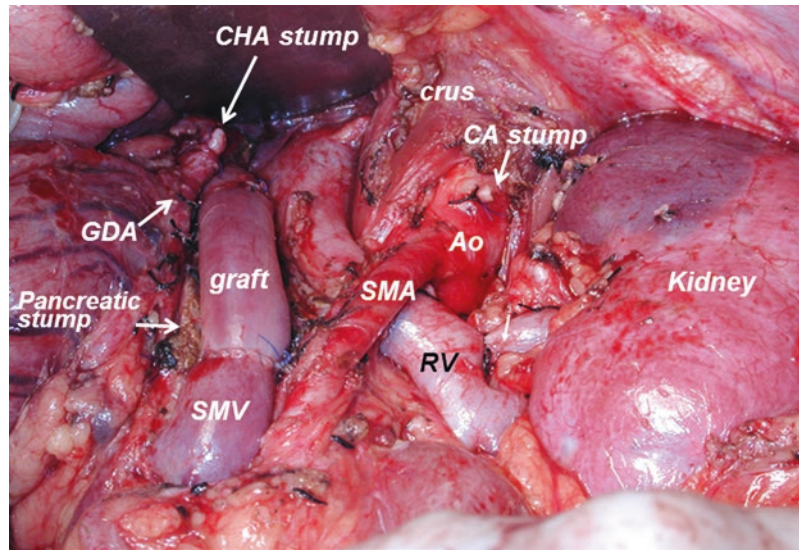

Fig. 24.4 Post-resection view during distal pancreatectomy with en bloc celiac axis resection (*DP-CAR*). *Ao* aorta, *CA* celiac axis, *CHA* common hepatic artery, *crus* crus of the diaphragm, *GDA* gastroduodenal artery, *graft* interposed iliac vein graft, *IVC* inferior vena cava, *RV* renal vein, *SMA* superior mesenteric artery, *SMV* superior mesenteric vein

Accidental injury to the inferior pancreaticoduodenal or gastroduodenal artery compromises collateral blood flow and leads to fatal complications, such as gastric necrosis and/or liver infarction. If this occurs, microscopic anastomosis between the proper hepatic artery and middle colic artery (MCA) [10] or the right gastroepiploic artery and MCA [11] could be a possible option for maintaining arterial flow to both the stomach and the liver.

24.2 Outcomes of DP-CAR

24.2.1 Postoperative Course Following DP-CAR

The most frequent morbidity after DP-CAR is pancreatic fistula, which occurs relatively easily because the pancreatic parenchyma needs to be divided at the pancreatic head in patients with a tumor extending to the proximal end of the pancreas, beyond the portal vein. In such cases, the cut surface of the pancreas becomes wider than that following usual distal pancreatectomy, in which the pancreatic parenchyma is divided at the neck of the pancreas. It is rather important to insert an indwelling drain at an appropriate position beside the pancreatic stump during surgery, so as to avoid postoperative hemorrhage from a pseudoaneurysm in the stump of the CHA. The second most common morbidity is ischemic gastropathy due to decreased gastric blood flow [12]. According to data from 50 consecutive patients who underwent DP-CAR [13], postoperative morbidity occurred in 27 (54%) patients; pancreatic fistula and ischemic gastropathy occurred in 20 (40%) and 6 (12%) patients, respectively. Two patients out of 50 (4%) died in the hospital of myocardial infarction and multiple organ failure due to anastomotic insufficiency following partial resection of the antrum of the stomach. Postoperative hospital stays ranged from 17 to 208 days, with a median of 39 days [13].

One of the other postoperative complications is stubborn diarrhea due to complete dissection of the nerve system around the SMA, CA, and bilateral ganglions. From a published data, approximately half of the patients regularly required antidiarrheal agents, and the remaining half only occasionally required or never used the agents over a median follow-up period of 39 months [12].

Contrary to the adverse effects of resection of nerve tissues, patients enjoy the complete disappearance of pain, even if it has been controlled by opioids just before surgery [14].

Since both the incidence of morbidity and poor quality of life postoperatively are major factors influencing the tolerance of adjuvant treatment, surgeons should make greater efforts to improve these factors following DP-CAR.

24.2.2 Long-Term Outcomes Following DP-CAR

In 2007, the long-term outcomes of DP-CAR were first reported in a series of 23 patients with locally advanced pancreatic body cancer who underwent DP-CAR under a policy of "surgery first" [7]. With R0 resectability in 91% of the cases and a median follow-up time of 27.4 months, the estimated 5-year survival rate was 42%, and the median survival was 21 months. Seven years after the first report, a second report that included 50 patients was published from the same institute, which indicated estimated disease-specific 1-, 3-, and 5-year survival rates of 80.7%, 32.3%, and 24.3%, respectively, and a median survival time of 24.7 months after a median follow-up period of 45.3 months [13]. Despite the excellent local control with an R0 resection rate of more than 90% in the report, early recurrence (predominantly in the liver) occurred after surgery, which resulted in poor survival time [13].

24.3 Modification of the Indications and Procedure of DP-CAR

Some problems concerning difficulty in achieving R0 resection and patient selection have been reported. Some authors believe that DP-CAR should be reserved for patients without tumor infiltration of either the portal vein or artery because the survival rate of patients with these conditions was poor in their series [15]. A recent article revealed that preoperative factors such as CRP, platelet count, and the level of CA19-9 could assist in the selection of patients who could survive long term without recurrence following DP-CAR [13]. To reduce the occurrence of postoperative hepatic metastasis while maintaining the complete local control that is achievable by DP-CAR, the strategy of up-front surgery is most likely to change in the current era of advancements in chemo- and chemoradiotherapy. Long-term survival after DP-CAR might be improved by employing neoadjuvant and/or adjuvant chemotherapy.

Another serious problem of DP-CAR to be resolved is ischemic gastropathy. For this, preserving the left gastric artery in limited cases or reconstruction of the artery might be a possible future modification [16].

Although DP-CAR could be used to treat locally advanced pancreatic body cancer, future prospective studies with a large patient cohort for ensuring adequate patient selection, modification of the procedure, and perioperative treatments are necessary to demonstrate the effectiveness of this innovative surgery.

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Radical Antegrade Modular Pancreato-splenectomy (RAMPS)

25

Julie G. Grossman and Steven M. Strasberg

Adenocarcinoma of the body and tail of the pancreas is a highly malignant tumor. Until recently long-term survival after surgical resection was rare. In 1990 Billesholle et al. were able to identify only five long-term survivors [1]. In the past 25 years, there have been advances in detection, staging, and treatment of these tumors. As a result, a small subset of patients with this disease are now being cured. This article will focus on Radical Antegrade Modular Pancreato-Splenectomy (RAMPS). RAMPS is a promising technique which was designed specifically to treat adenocarcinomas of the body and tail of the pancreas, although it may be used for other tumors. It has been shown to achieve the oncologic goals of a pancreatic resection for cancer [2] RAMPS.

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25.1 History of Left-Sided Pancreatectomy and Development and Rationale of the RAMPS Procedure

The first left-sided pancreatectomies were performed in the late nineteenth century [3] in Europe. The first in the USA was apparently performed by Briggs in St. Louis in 1890 [4]. Distal pancreatectomy was most commonly used for treatment of chronic pancreatitis because cancers were usually too advanced for surgical treatment. It seems incredible that there was no direct way to image the pancreas before advent of computerized tomography. This imaging method dramatically changed management by permitting diagnosis of cancer of the distal pancreas in some patients when it was operable. Until 1999 the standard operation was performed by early ligation of the splenic artery followed by mobilization of the spleen and pancreas, usually from a left-to-right direction [5], much as the operation for benign disease was done, although some authors performed the mobilization right to left [3]. Oncologic goals and the strategies to achieve them, namely, the extent of node dissection and the dissection planes used to optimize margin negativity, were not well defined, possibly since most left-sided resections prior to 1990 were performed for benign disease.

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Radical antegrade modular pancreatosplenectomy (RAMPS) has been performed at Washington University in St. Louis since 1999 [2, 6, 7]. It was designed to establish an operation with good oncologic rationales for the dissection planes used to achieve negative margins and for the extent of node dissection. The extent of the lymph node dissection is based on the anatomic descriptions of N1 node drainage from the body and tail of the pancreas by O'Morchoe [8]. The anatomic plane for the posterior margin of the dissection, which is the margin most frequently positive, is based on the relationship of the fascial planes of the retroperitoneum to the posterior surface of the pancreas, as described by Lei et al. [9]. The plane of the posterior dissection is modular in respect to the adrenal gland and depends upon the position of the tumor in relation to the adrenal gland on preoperative CT scans as explained below. The emphasis on the adrenal gland is due to the fact that it is the organ which most commonly needs to be resected in addition to the distal pancreas and spleen to obtain clear margins. RAMPS is not an "extended" pancreatic resection. Its intention is to bring the oncologic rationales of the modern Whipple procedure – N1 node dissection and dissection technique with the best chance of attaining negative margins to left-sided pancreatectomies.

25.2 Anatomic Basis for the RAMPS Procedure (Fig. 25.1)

25.2.1 Position and Relations

Lei et al. provided a clear description of the fascial spaces in which the retroperitoneal organs lie [9]. The "distal" pancreas (pancreatic body and tail) lies within the *pararenal* fascial space (pararenal means *near* the kidney), i.e., behind the peritoneum, and in front of a distinct layer of fascia called the anterior renal fascia (Fig. 25.1). The kidney and adrenal lie *behind* the anterior renal fascia in the *perirenal* space (perirenal = *around* the kidney), demarcated posteriorly by another layer of fascia – the posterior renal fascia. The contents of the perirenal space are embedded in loose fatty areolar tissue. The connective tissue of the pararenal space is more fibrous in nature. The two peritoneal layers of the mesocolon separate on the anterior surface or inferior border of the pancreas, one leaf passing upward on the retroperitoneum and one downward. This explains why the base of the mesocolon is frequently involved by pancreatic tumors.

Anteriorly, the organ which is most commonly invaded is the stomach since the posterior parietal peritoneum overlying the pancreas is usually in contact with the visceral peritoneum covering the

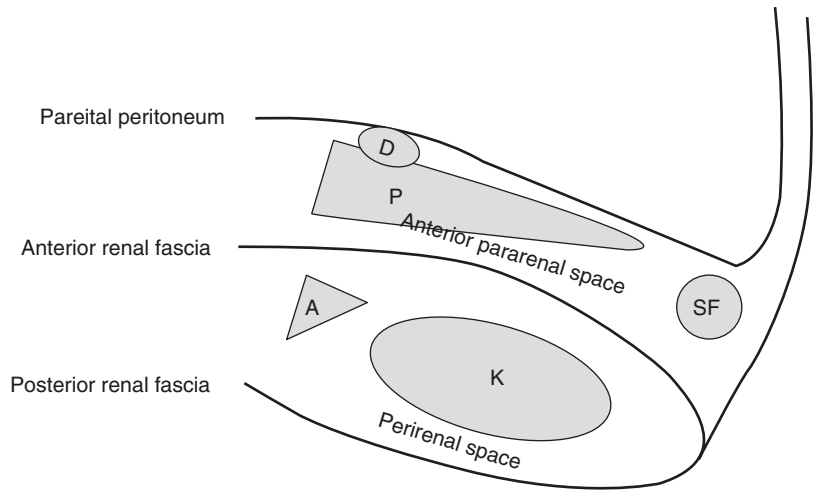

Fig. 25.1 Fascial spaces of the retroperitoneum. *A* left adrenal gland, *D* duodenum, *K* kidney, *P* pancreas, *SF* splenic flexure of the colon

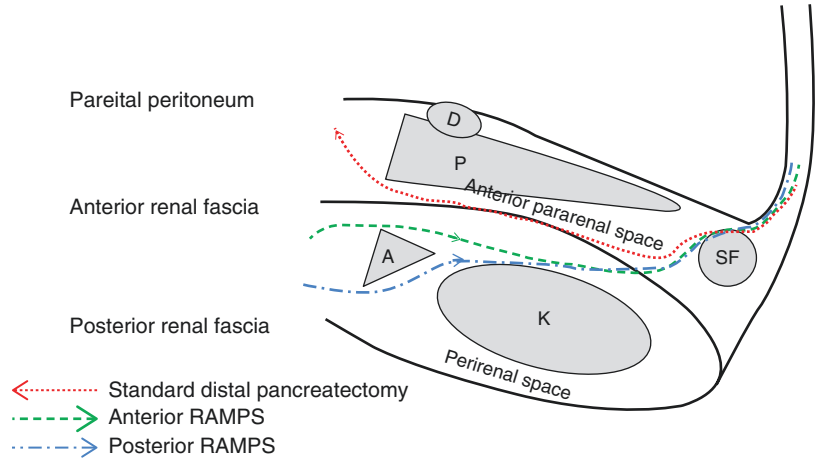

Fig. 25.2 Planes of posterior margin and direction of dissection in different types of distal pancreatectomies

posterior wall of the stomach. Laterally, the spleen is frequently involved by tail lesions. The structures that share the pararenal space with the pancreas on its anteroinferior aspect include the fourth part of the duodenum, the splenic flexure of the colon more laterally, and the root of the mesocolon as noted above. For the surgeon the posterior relationships of the pancreas are the most important since the posterior resection margin is the most common site of a positive margin. Posteriorly and superiorly pancreatic tumors invade the splenic artery, the celiac artery, the common hepatic artery, and sometimes the origin of the left gastric artery. More posteriorly the superior mesenteric artery, aorta, and the confluence of the splenic and superior mesenteric veins may be involved. Pancreatic tumors also invade posteriorly through the anterior renal fascia to involve the adrenal and less commonly the kidney or the vasculature of these organs.

RAMPS attempts to maximize the chance of getting negative tangential margins by placing the resection plane behind the anterior renal fascia when the tumor has *not* penetrated the posterior capsule of the pancreas on preoperative CT scans and behind the adrenal gland and Gerota's fascia when it has penetrated the posterior capsule [6] (Fig. 25.2). The goal is to add an extra margin of safety in resecting these tumors, which can spread microscopically beyond their radiographically visible or palpable margins. In each case the adrenal vein is the intraoperative guide to the position of the margin. In anterior RAMPS the posterior margin is formed by identifying the adrenal vein at its junction with the left renal vein and following its anterior surface retrograde in a right-to-left direction to the left adrenal gland. The posterior margin continues out on the surface of the adrenal and Gerota's fascia. In posterior RAMPS, the adrenal vein is divided at its termination and elevated along with the adrenal to give the posterior margin. Not surprisingly larger tumors require a posterior RAMPS more commonly than small tumors.

25.2.2 Lymph Node Drainage (Fig. 25.3)

Both anatomical and pathological studies have been used to determine the propensity of a cancer to metastasize to specific lymph nodes. Pathological lymph node mapping studies use specimens obtained at surgery or autopsy to determine which lymph nodes are invaded in patients who have a particular tumor type. On the other hand, the anatomical approach uses dissection and injection of markers to identify the primary and secondary nodal drainage stations from particular organs. The aim of the RAMPS

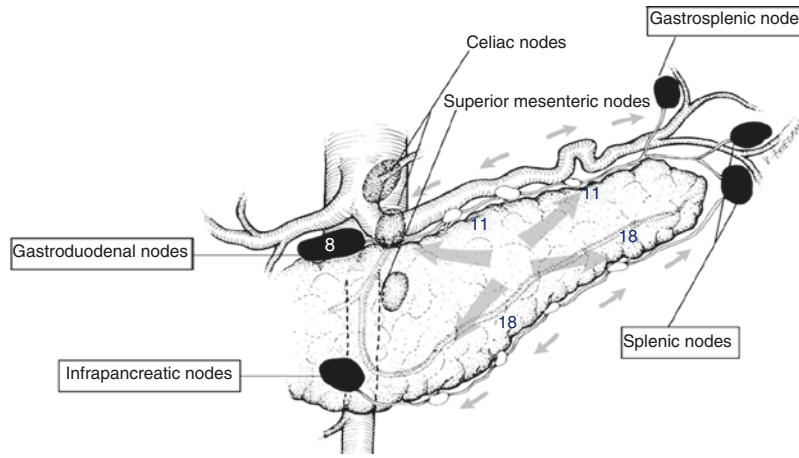

Fig. 25.3 Lymphatic drainage of body and tail of pancreas. The "ring" of nodes is named in *boxes*. The celiac and superior mesenteric nodes make up the "string" of nodes. The gastroduodenal node is node 8 in the Japanese classification, while the node chains on the superior and inferior borders are nodes 11 and 18. These nodes are most commonly involved in carcinoma of the body and tail of the pancreas

procedure is to perform a complete N1 node dissection and not resect N2 or N3 node levels. To do so the position of N1 nodes had to be defined, and we relied on anatomic studies of the lymphatic drainage of the body of the pancreas based on anatomic studies (Fig. 25.3) as summarized in the classic review by O'Morchoe [8].

25.2.3 Summary of Anatomic Studies by O'Morchoe

The *body and tail* of the pancreas has four nearly equally sized quadrants. Lymphatic vessels traveling from the four quadrants connect to lymphatic vessels that lie on the superior and inferior borders of the gland (Fig. 25.3) [8]. Small lymph nodes are situated along these lymphatic vessels, and these are termed the suprapancreatic and infrapancreatic lymph nodes. These are node stations 11 and 18 in the Japanese Pancreas Society (JPS) classification. The lymphatic vessels on the superior and inferior borders of the *left* half of the body and tail drain to *splenic* nodes in the hilum of the spleen (JPS station 10) or to *gastrosplenic* nodes in the gastrosplenic omentum. These nodes lie in the gastrosplenic omentum along the short gastric arteries and correspond to JPS node station 4. O'Morchoe states that these nodes mainly receive lymph from the stomach but may also receive some lymph from the tail and left side of the body of the pancreas [8]. Lymphatic vessels coursing along the superior and inferior borders of the *right* half of the body drain to the *gastroduodenal* nodes (JPS station 8) and *mesenteric* nodes (JPS station 14c). These four sets of nodes form a *ring of nodes* [8] (Fig. 25.3). The efferent lymphatics from the ring of nodes drain into nodes that lie anterior to the aorta in relation to the celiac (JPS 9) and superior mesenteric arteries (JPS 14a), but these nodes, which may be thought of as a *string of nodes,* are not exclusively a N2 node group. Lymphatics from the central part of the pancreatic body enter these nodes directly without first entering a node on the ring [8]. Therefore, they should be considered as N1 as well as N2 nodes. As a result, operations designed to remove N1 nodes should resect both sets of N1 nodes, which we have colloquially referred to the "ring" and the "string" of nodes.

25.2.4 Summary of Pathological Studies

Kayahara et al. performed pathological mapping of nodes in cancer of the body and tail of the pancreas in 20 patients [10]. Three node groups were involved in more than 20% of patients – nodes along the superior and inferior borders of the pancreas (stations 11 and 18 in JPS system, respectively) and the gastroduodenal node (JPS node 8) (Fig. 25.3). These are all resected in the RAMPS operation. Fujita et al. [11] described the results of pathological lymph node mapping in 50 patients with adenocarcinoma of the body

and tail of the pancreas. They identified a group of small lymph nodes attached to the pancreas, seen only on histological slides. These nodes were involved by the cancers in about 75% of patients. However, all other lymph node groups were involved very infrequently, usually in less than 10% of patients. The frequently involved nodes may correspond to the nodes that lie along the superior and inferior borders of the pancreas described in O'Morchoe's study, [8] although those were grossly identifiable as nodes. Whether these nodes are exactly the same as those described by O'Morchoe, they are certainly removed by RAMPS. Kanda et al. studied 78 patients who had resection of the body and tail of the pancreas [12]. They noted that suprapancreatic nodes (21% of patients) and superior mesenteric nodes (10% of patients) were most commonly involved (JPS stations 11 and 14, respectively). Other stations were involved in less than 10%. The results of Fujita et al. and Kanda et al. are interesting, but it is unclear at present whether they apply to patients in Western countries since the incidence of cancer in lymph nodes seems lower than in American patients. Also as we will describe Japanese patients seem to have better differentiated tumors than American patients, a fact that also suggests that the disease may differ significantly in virulence in the two countries.

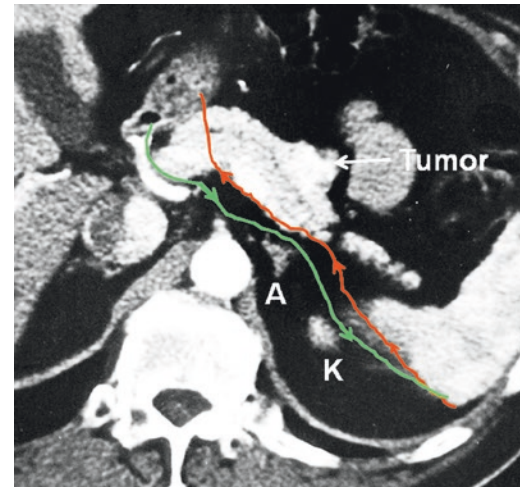

Fig. 25.4 *Green line* shows planned plane of posterior dissection as shown in preoperative computed tomogram in anterior RAMPS in which the tumor has not penetrated the posterior capsule of the pancreas. Note that the plane is on the anterior surface of the adrenal. *Red line* shows possible plane when standard distal pancreatectomy is performed without regard to the position of the anterior renal fascia. *A* left adrenal gland, *K* kidney

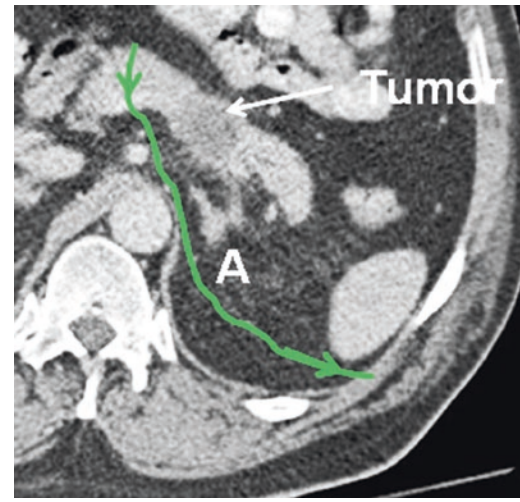

Fig. 25.5 *Green line* shows planned plane of posterior dissection as shown in preoperative computed tomogram in posterior RAMPS in which the tumor has penetrated the posterior capsule of the pancreas. *A* left adrenal gland

25.3 Technique of the RAMPS Procedure [2, 6, 7]

25.3.1 Preoperative Preparation

A recent computed tomogram is used to decide whether to perform an anterior or posterior RAMPS. When a rim of normal pancreas remains posterior to the tumor, the anterior RAMPS is chosen (Fig. 25.4). When the posterior margin of the tumor contacts or appears to break through the posterior capsule of the pancreas, the posterior RAMPS is selected (Fig. 25.5). The latter is more common in large tumors as might be expected. The tumor does not need to be seen to be touching or invading the adrenal for a posterior RAMPS to be selected. It needs only to be seen to have invaded posteriorly out of the pancreas. The principle is that the space between the back of the pancreas and the front of the adrenal is too thin to

reliably attain negative margins when the tumor is present in the space. Of course in some instances when the tumor is very far to the left toward the hilum of the spleen, it is well away from the adrenal. In those cases the perinephric fat down to the level of the left kidney and occasionally the left kidney itself must be removed, and in some of these cases, the left adrenal may be spared. The operation in this respect is modeled around involvement of the left adrenal since it is by far the most common organ that requires resection other than the pancreas and the spleen. In our experience the left adrenal is removed in about 30% of patients.

25.3.2 The Procedure

Staging laparoscopy is performed to detect intra-abdominal metastases, which contraindicate the procedure. In a study published in 2002, we found that 50% of laparoscopically staged patients had metastases [13] although with improved computed tomography techniques that figure is probably much lower today. A left upper quadrant "J" incision or "Mercedes Benz" incision with a longer left limb is used. The abdomen is again explored for evidence of metastases. The greater omentum is freed from the colon. The gastrosplenic ligament is divided taking the short gastric vessels close to the stomach in order to remove the gastrosplenic node group (JPS station 4). The lesser sac is entered much as in performing a Whipple procedure and the middle colic vein traced to the superior mesenteric vein. The neck of the pancreas is elevated off the superior mesenteric and portal veins. The right gastroepiploic vein may be sacrificed if necessary to display the superior mesenteric vein. A wide Kocher maneuver is performed and the anterior surface of the inferior vena cava is exposed. Then the left renal vein is exposed for several centimeters. The plane created on the left renal vein is behind the anterior renal fascia. This is quite useful later in the procedure when the anterior renal fascia has to be divided exposing the renal vein on the left side of the aorta.

The lesser omentum is opened and the right gastric artery is divided. The proper hepatic artery is identified and followed proximally to display the common hepatic artery and gastroduodenal arteries. The gastroduodenal node (JPS node 8) is mobilized from above downward and left attached to the superior border of the pancreas, as the common hepatic artery is displayed. The anterior surface of the portal vein is exposed by retracting the gastroduodenal artery to the right. When the neck of the pancreas is less than 1 cm in thickness, it is divided using a stapler coated with collagen matrix sheets ("Peri-Strips" Baxter, Deerfield IL). When thicker than 1 cm, four stay sutures are placed in the neck of the pancreas, which is then divided with blended cutting cautery. The pancreatic duct is closed with a figure-of–eight 5-0 polypropylene suture (Prolene, Ethicon), and the stump of the pancreas is oversewn with several 2-0 silk full-thickness mattress sutures. Coagulating current is avoided for division of the pancreas because the resultant char may obscure the position of the pancreatic duct which is often of small diameter. Another factor taken into account is the shape of the pancreatic neck which is usually ovoid and of equal thickness in cross-section. However, occasionally the pancreatic neck is triangular in cross-section, and in these cases, stapling is less effective. A celiac node dissection is performed starting by incising the peritoneum over the crus of the diaphragm and progressing anteriorly and inferiorly from that point sequentially gathering lymph nodes, off the celiac artery and the origins of the left gastric and common hepatic and splenic arteries. Note that the origin of the splenic artery is identified as the nodes, and surrounding fat and fibrous tissue are cleared off the celiac artery and surrounding ganglia. The celiac ganglion is not resected. The splenic artery is occluded with a bulldog clamp and the common hepatic artery pulse is checked. The splenic artery is then divided between silk ties. It is our practice to tie and suture ligate the proximal part of the artery before dividing it. Occasionally, when the tumor is close to the origin of the splenic artery, the celiac and common hepatic arteries are occluded with vascular clamps; the splenic artery is cut almost flush with the celiac artery and oversewn with 5-0 polypropylene suture. In deep patients, usually men, the origin of the splenic artery may actually lie posterior to the

pancreas, and it can be difficult to expose in that position until the neck of the pancreas and the termination of the splenic vein are divided. Also the origin of the left gastric artery may be involved and is then sacrificed. This is uncommon and usually occurs when the tumor has become attached to the lesser curvature of the stomach.

The splenic vein is isolated at its junction with the superior mesenteric vein and divided with a vascular stapler. If tumor invasion is present at this site, a resection of the superior mesenteric vein and/or portal vein is performed and repaired primarily or with a vein graft. The right border or the dissection is carried downward in the sagittal plane, dividing fat and fibrous tissue until the left side of the superior mesenteric artery is identified (Fig. 25.6). The artery is followed on its left side, superiorly and posteriorly, down toward the aorta. The lymph nodes anterior and to the left of the superior mesenteric artery are taken with this step.

The next step continues to develop the right border of dissection, which is now carried in the sagittal plane through the anterior renal fascia onto the renal and adrenal veins (Fig. 25.6). This step is facilitated by placing a finger on the anterior surface of the left renal vein behind the previously mobilized duodenum. The finger can be palpated from the left side of the dissection posterior to the superior mesenteric artery. Dividing the intervening tissue (anterior renal fascia) will expose the left renal vein. In the anterior RAMPS, the adrenal vein is identified, and its anterior surface also becomes part of the posterior plane of dissection, as does the anterior surface of the adrenal gland as it is reached (Fig. 25.6). The dissection is continued in a posterolateral direction onto the perinephric fat. The superior and inferior attachments of the pancreas are divided as the dissection proceeds to the left. The inferior mesenteric vein is transected when it terminates in the splenic vein. The remaining short gastric arteries are divided up to the level of the diaphragm. The splenic flexure of the colon is mobilized, and the splenocolic omentum is divided. Retraction of the mobilized colon inferiorly provides a good view of the inferior border of the pancreas as far as the spleen in most cases. If the tumor has involved the transverse mesocolon, a disc of the mesocolon can be excised. Usually, this occurs to the left of the middle colic artery. Division of the lienorenal ligament is the last step in the procedure. In the posterior RAMPS, the adrenal vein is divided at its termination, and the dissection is carried to the left and posteriorly behind the adrenal gland and onto the surface of the kidney (Fig. 25.7). After removal from the patient, the specimen is inked at the pancreatic neck margin as well as on the posterior, superior, and inferior tangential margins using different colored inks, and a frozen section of the neck of the pancreas is obtained.

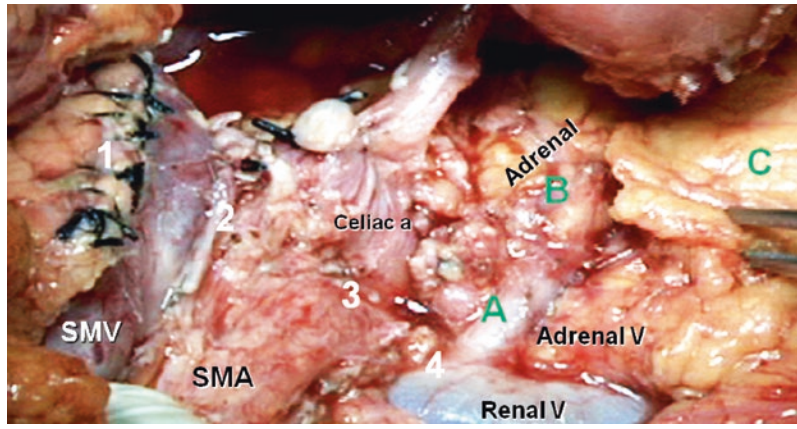

Fig. 25.6 Anterior RAMPS at completion of dissection. Numbers *1–4* show the four levels of the sagittal dissection *1* pancreatic neck, *2* splenic vein, *3* side of celiac and superior mesenteric artery, and *4* renal vein. (*A–C*) Shows the subsequent more coronal dissection. (*A*) Along the adrenal vein; (*B*) on the adrenal gland; and (*C*) along the surface of Gerota's fascia

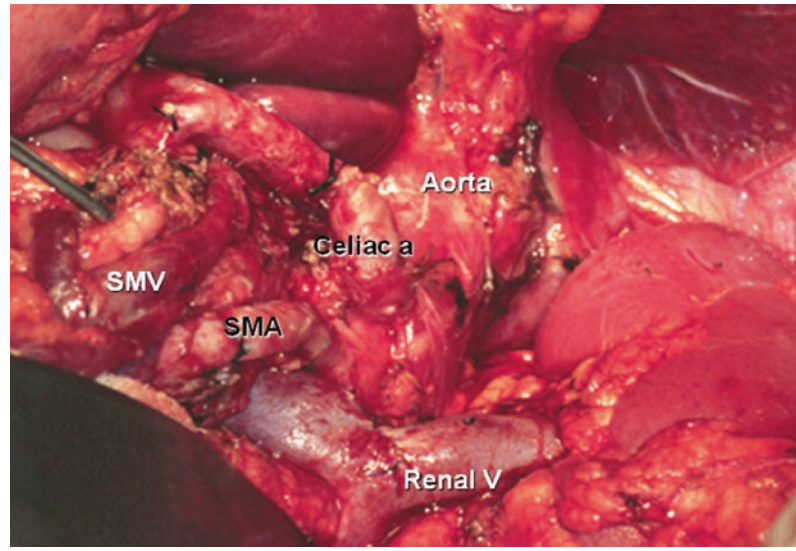

Fig. 25.7 Posterior RAMPS at completion of dissection. Note the deeper level of dissection compared to Fig. 25.6

These tumors may also invade several other organs or tissues in in close relationship to the pancreas. The stomach is the most common additional organ that requires excision other than the adrenal. Formal gastrectomy is usually not required. However, occasionally the upper stomach is involved close to the esophagogastric junction, and a total gastrectomy is needed to resect the tumor. Obviously, this degree of radicality should be reserved for highly selected patients. Resection of the mesocolon does not usually also require resection of the adjacent colon. However, the colon itself may be involved especially at the splenic flexure. Less commonly the kidney or other organs such as a portion the duodenum or small bowel need to be resected. Provided that the disease is local, any of these structures may be resected as in the standard method. The view at the end of the dissection in the two procedures is shown in Figs. 25.6 and 25.7**.**

25.3.3 Variations of the RAMPS Procedure

25.3.3.1 Expanding the Retroperitoneal Dissection

As we have emphasized previously, establishing the dissection plane behind the anterior renal fascia is a key requirement of any RAMPS procedure. We do this by performing duodenal mobilization with exposure of the vena cava and left renal vein as an early step in the operation. This elevates the anterior renal fascia off the veins and puts the plane of dissection behind the anterior renal fascia. Later in the procedure, the now elevated anterior renal fascia is incised in the sagittal plane as the dissection on the side of the SMA continues posteriorly to expose the left renal vein on the left side of the aorta. Kitagawa et al. [14] have described an interesting modification in which the anterior renal fascia is elevated by mobilizing the third portion of the duodenum left to right until the IVC is exposed. The dissection continues cephalad along the IVC and then along the anterior surface of the left renal vein toward the renal hilum and then in the coronal plane to the superior border of the pancreas. This wide exposure of the retroperitoneum behind the anterior renal fascia might be particularly helpful in large or obese patients.

25.3.3.2 Vascular Involvement

Vascular involvement of the borderline type may be present in some patients with centrally placed tumors. In other patients the exact status of the tumor along vessels is uncertain as after pretreatment with chemotherapy or chemoradiation. As noted under “technique,” resection of portions of the SMV and portal vein may occasionally be

necessary in performance of RAMPS. We have undertaken these resections and reconstructions after dividing the neck of the pancreas and the splenic vein. They are generally easier than in a Whipple procedure since the splenic vein is always taken. Two groups have described a modification which is essentially a "SMA-first" approach for left-sided tumors much as Pessaux et al. described for the Whipple procedure [15]. In the technique of Rosso et al. [16], the approach is from the right. The retroperitoneum is first exposed by an extensive Kocher maneuver and reflection of the right colon and mesentery followed by dissection of the SMA toward its origin and cylindrical resection of the SMV/portal vein. This approach has the advantage that the SMA can be proven to be free of tumor before dividing the SMA and portal vein. Kawabata et al. have described a technique with similar intent of SMA first for venous resections [17]. However, in their technique the retroperitoneum is first opened at the duodenojejunal flexure working left to right similar to the technique by Kitagawa, and the SMA is identified by following the middle colic artery to its origin. These authors present an interesting "pancreas-hanging" maneuver by passing a forceps in front of the SMA behind the pancreas and splenic vein. This facilitates exposure of the SMA in order to prove that it is free of tumor. Both of these papers are well illustrated.

25.3.3.3 Laparoscopic RAMPS

Standard distal pancreatectomy has been performed successfully by minimally invasive techniques for more than a decade and has been applied to carcinoma in some centers. A large multi-institutional series found no difference in survival between open and laparoscopic procedures [18]. However, the median follow-up time of 10 months was relatively short, and the survival curve in the laparoscopic group, comprised of only 23 patients, was somewhat immature with only one patient having reached 5 years of survival. The median survival in both laparoscopic and open groups was 16 months [18].

Theoretically the RAMPS procedure can be performed laparoscopically or robotically. However, the celiac node dissection and the formation of the posterior plane right on the renal and adrenal veins will be challenging especially in large, deep patients. Additionally, there have been few studies to support performing laparoscopic RAMPS procedure for pancreatic adenocarcinoma, and those that have been published are limited due to low patient number or short follow-up time [19–21]. Fernandez-Cruz et al. reported results of a slightly modified RAMPS procedure performed laparoscopically on ten patients with negative tangential margins of 90%, but survival was not addressed [20]. Lee et al. used a selective approach employing laparoscopy when an anterior RAMPS was indicated and an open approach when a posterior RAMPS was needed [21]. They reported on 12 patients who underwent laparoscopic or robotic RAMPS, meeting the criteria that (1) the tumor was confined within the pancreas, (2) there was intact fascial layer between the distal pancreas and the left adrenal gland and kidney, and (3) the tumor was located more than 1–2 cm from the celiac axis. They observed negative margins in all patients and a 5-year survival of 56%; however, it is important to note they had a high conversion rate and that tumors resected laparoscopically were statistically smaller than those of the patients undergoing conventional open distal pancreatectomy (2.8 ± 1.3 vs. 3.5 ± 1.9 cm, $p = 0.05$). Song et al. described their experience in 359 laparoscopic left pancreatic resections (for both benign and malignant disease), of whom 24 patients underwent laparoscopic RAMPS for adenocarcinoma. They reported 92% negative resection margin and 2-year survival of 85%. There was limited median follow-up of only 10 months [19].

One concern in using a laparoscopic technique for RAMPS is that Lee et al. and Fernandez-Cruz et al. seem to have performed a more limited dissection in respect to the renal vein [20, 21]. In our technique, we have assured that the plane of the posterior margin is behind the anterior renal fascia by dissecting onto the left renal vein and out along the surface of the adrenal vein. If this step is omitted, it is possible that the plane will be too shallow and anterior to the anterior renal fascia.

Modifications described by Rosso et al. [16] and Kitagawa et al. [14] to facilitate exposure of the left renal vein in the open procedure may aid the laparoscopic approach.

The number of patients requiring RAMPS is too small to consider any kind of trial of open vs. laparoscopic procedure. While the benefits of laparoscopy are attractive, the ability to complete the resection routinely without compromising the oncologic goals of the procedure is the primary consideration. Therefore, at present laparoscopic RAMPS should be attempted in selected patients whose tumor and body habitus are favorable and the operation converted if the oncologic principles are not being achieved.

25.4 Results of the RAMPS Procedure

25.4.1 Surgical Outcomes

Multiple centers internationally have published their experience with RAMPS in patients with adenocarcinoma. Table 25.1 presents results from these studies, all of which are case series. Studies in which RAMPS results were not clearly separated from standard techniques are not shown. Tumor size ranged from 2.6 to 4.7 cm with laparoscopic RAMPS having the smallest tumors [19]. Additionally, the total number of lymph nodes resected was lower in Song et al. (10 lymph nodes) compared to other studies performed open, which ranged from 14 to 26 lymph nodes. Negative resection margin and tangential margin status were comparable. Kawabata et al. reported much poorer resection margin results; however, their series only consisted of patients with borderline resectability. Most studies did not report 5-year overall survival, due to limited follow-up time. Murakawa et al. have reported on 49 patients; however, they have limited follow-up and only include 2-year survival, which was 39% [22].

Our published data in 47 patients is presented in the table [6]. Our latest data is in the process of being compiled for journal submission. Preliminary results in approximately 80 patients are available. The average operative time was about 4 h, and 30% of patients had a posterior RAMPS. The negative tangential margin rate was greater than 90%. There were no 30-day mortalities. Average length of follow-up was about 3 years. The 5-year survival rate was approximately 25%. This is lower than our prior study which reported a 5-year overall survival of 35% in 48 RAMPS-resected patients [6]. This difference in outcome is likely attributable to the larger number of patients within the current study, thus now reaching the true 5-year survival as these higher numbers lead to regression to the mean. Ideally a RCT would be the way to determine the value of RAMPS. However, the number of patients required for a trial would be in the order of 450 in total. It would have to be multicenter and gathered over a number of years. For the present the basis of selecting RAMPS as the method for this tumor must be based on its achievement in the area of excellent margins and adequate node yield.

Table 25.1 Operative, pathologic, and survival data in literature case series of adenocarcinoma of the body and tail of the pancreas resected using RAMPS procedure

First author	Year	Span of series	Country	*n*	No. of open/lap procedures	No. of venous resections	Mean operative time, min	Mean EBL, mL	Mean no. of nodes resected	% patients with positive nodes	Mean tumor size, cm	R0, %	Negative tangential margin, %	Postoperative 30-day mortality	Median survival, month	5-year survival, %
Song	2011	2005–2010	South Korea	24	24 lap	NS	225[a]	NS	10.3	NS	2.6[a]	92	NS	NS	NS	NS
Chang	2012	2005–2009	South Korea	24	24 open	8	305	NS	20.9	71	4.1	92	92	NS	18.2	NS
Rosso	2013	2008–2012	France	10	10 open	10	424[a]	NS	17[a]	70	4.6[a]	90	90	NS	20.5	NS
Park	2014	1995–2010	South Korea	38	38 open	NS	210[a]	325[a]	14[a]	58	3.1[a]	89	NS	0	24.6	40
Kitagawa	2014	2007–2012	Japan	24	24 open	1	387	371	28	54	3.5	88	92	0	NS	53
Murakawa	2015	2000–2014	Japan	49	49 open	NS	278[a]	850[a]	15	55	3.8	84	NS	NS	22.6	NS
Kawabata	2015	2013–2014	Japan	11	11 open	2	423[a]	500[a]	26[a]	91	3.4[a]	77	82	0	NS	NS
Mitchem	2011	1999–2008	USA	47	2 lap/45 open	5	243	744	18	55	4.4	81	89	0	26	36

NS not stated
[a]Median value, mean value not published

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26 Laparoscopic Distal Pancreatectomy in Pancreatic Cancer

Ho-Seong Han

Laparoscopic surgery for benign disease is well established and becoming well accepted in clinical practice. However, there are still debates using laparoscopy in malignant disease of the pancreas. During recent decades, laparoscopic surgery has been applied in various types of malignancy, such as colorectal cancer, gastric cancer, and even hepatocellular carcinoma. Several well-designed randomized studies have shown equivalent outcomes after laparoscopic surgery for colorectal cancer. Recent randomized studies on gastric cancer have shown that laparoscopic surgery is not inferior to open surgery in the treatment of early stage of gastric cancer. There are also numerous studies on the effectiveness of laparoscopic surgery for hepatocellular carcinoma. However, the studies on laparoscopic surgery on pancreatic cancer are still scarce. And there is no randomized controlled trial comparing laparoscopic distal pancreatectomy versus open distal pancreatectomy for patients with pancreatic cancers. The plausible reasons for this paucity of study may be the relative small number of cases of resectable pancreatic cancer, technical difficulty of laparoscopic surgery, and cautious application of this procedure to malignant disease. Therefore, the laparoscopic surgery for pancreatic cancer is not yet well recommended in current situation. Even though the reports on the laparoscopic distal pancreatectomy are still scarce, most of the reports show that outcomes are similar to open surgery. These studies show that laparoscopic distal pancreatectomy is associated with shorter hospital stay than open distal pancreatectomy. However, the advantage in length of hospital stay is meaningful only after it is proved that laparoscopic operation is not inferior to open procedures oncologically (Table 26.1) [1].

In this chapter, we will describe current situation of the laparoscopic distal pancreatectomy for pancreatic cancer.

26.1 Operative Techniques

When distal pancreatectomy is performed in benign disease or low-grade borderline malignancy, splenic preservation is usually recommended. There is a report from Memorial Sloan Kettering Center that the patient group with splenectomy has higher morbidity than non-splenectomy group in open distal pancreatectomy [2]. And spleen has a role in immunology, and there may be a possibility of post-splenectomy sepsis when spleen was removed. There are two methods of preserving the spleen, one is splenic vessel preserving method and another is splenic vessel sacrificing method (Warshaw technique). Splenic vessel preserving operation is associated

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Table 26.1 Laparoscopic distal pancreatectomy compared with open distal pancreatectomy for pancreatic cancer

Outcomes	Illustrative comparative risks[a] (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of evidence (GRADE)
	Assumed risk	Corresponding risk			
	Open distal pancreatectomy	Laparoscopic distal pancreatectomy			
Short-term mortality	10 per 1,000	5 per 1,000 (1–22)	OR 0.48 (0.11–2.17)	1,451 (9 studies)	⊕ Very low[b, c]
Long-term mortality Follow-up: 2–3 years	549 per 1,000	535 per 1,000 (480–590)	HR 0.96 (0.82 to 1.12)	277 (3 studies)	⊕ Very low[b, d]
Serious adverse events (proportion)	51 per 1,000	88 per 1,000 (28–247)	OR 1.79 (0.53–6.06)	206 (3 studies)	⊕ Very low[b, c, d]
Pancreatic fistula (grade B or C)	66 per 1,000	77 per 1,000 (32–175)	OR 1.19 (0.47–3.02)	246 (4 studies)	⊕ Very low[b, c, d, e]
Recurrence at maximal follow-up	495 per 1,000	363 per 1,000 (239–507)	OR 0.58 (0.32–1.05)	184 (2 studies)	⊕ Very low[b, c, d]
Adverse events (proportion)	328 per 1,000	317 per 1,000 (209–448)	OR 0.95 (0.54–1.66)	246 (4 studies)	⊕ Very low[b, c, d]
Length of hospital stay	Mean length of hospital stay in the control groups was 9.4 days	Mean length of hospital stay in the intervention groups was 2.43 lower (3.13–1.73 lower)		1,068 (5 studies)	⊕ Very low[b]
Positive resection margins 184	184 per 1000	143 per 1,000 (99–198)	OR 0.74 (0.49–1.10)	1,466 (10 studies)	⊕ Very low[b, c]

From Riviere et al. [1]
CI, confidence interval, *HR* hazard ratio, *OR* odds ratio
GRADE working group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low quality: We are very uncertain about the estimate
[a]The basis for the assumed risk is the mean control group proportion. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI)
[b]We found no randomized controlled trials. The nonrandomized studies included in this review were at unclear or high risk of bias for most domains
[c]Confidence intervals were wide
[d]Sample size was small
[e]I2 was high and little overlap of confidence intervals was evident

with less complication associated with splenic infarction. However, this procedure is technically more demanding than splenic vessel sacrificing operation. Even after preservation of the splenic vessels, the patency of the vessels may not last long enough. There has been report on high incidence of the splenic venous obstruction compared to open surgery on long-term follow-up of the splenic vessel-preserved patients [3]. Subsequent multi-institutional studies showed that this higher rate of splenic vein patency may be related with technical inadequacy in early period of surgeon's experiences [4]. When preserving splenic vessels is difficult or splenic vessels are injured during operation, Warshaw technique is a useful option. Warshaw technique is easy to perform compared to splenic vessel saving surgery with the advantages of preserving the spleen.

When the patient has aggressive behavioral premalignancy or overt cancer, splenectomy is

usually performed for complete clearance of the lymph node and obtaining adequate margin.

Laparoscopic surgery is well described in many reports that it may be not necessary for the detailed description of the operative procedure. One distinct characteristics of laparoscopy is the more frequent use of endoscopic stapler. By using endoscopic stapler, the operation time can be shortened, as difficult procedure like intracorporeal sewing of pancreatic stump is not needed. One well-randomized study has shown that there is no difference in the rate of pancreatic fistula or any morbidity between using stapler and hand-sewing method during distal pancreatectomy [5].

However, endoscopic stapler does not fit in well if the width of pancreas at resection line is too thick. Therefore, the selection of the well suited is important. For thick pancreas, some surgeons use the way of slow and gradual closure of stapler, to allow the time to decrease the thickness. And when the parenchyma of the pancreas is too soft, it may be crushed easily, which may lead to pancreatic fistula as well. Rate of postoperative pancreatic fistula may be increased in the patients with thick and soft pancreas [6]. It is not clear that reinforcing suture on the stumps will decrease the incidence of pancreatic fistula. There are various methods to lessen the leak from the stump, which include the application of the fibrin glue, mesh, etc. [7].

Operation technique for pancreatic cancer by laparoscopy does not differ from open surgery. The oncologic clearance is mandatory including negative resection margin and adequate lymph node harvest. If there is any possibility of hampering the oncologic safety, the laparoscopic surgery should be converted to open surgery immediately.

Totally laparoscopic distal pancreatectomy is usually performed, although there are very few reports on hand-assisted distal pancreatectomy. By the accumulation of experiences of advanced laparoscopic surgery, total laparoscopic distal pancreatectomy is more adopted. However, when inexperienced surgeons start the program of minimal invasive surgery on pancreas, hand-assisted technique can be a bridge to total laparoscopy. And when the pancreas' tumor size is too large, hand-assisted way can be used for oncologic safety.

Robotic surgery is one variant of laparoscopic surgery using robots. This technique will also be dealt in detail in another chapter.

There has been tendency of performing RAMPS procedure in open surgery of pancreas body or tail cancer. RAMPS procedure is proposed to complete removal of the lymph node. The report stated that antegrade approach provide more visibility, permit more lymph node dissection, and permit adjustment of the depth of the posterior extent of the resection [8]. RAMPS procedure will be dealt in another chapter. Laparoscopic RAMPS operation is also possible in experienced hands.

26.2 Patient Selection

Laparoscopic surgery is reported to have less blood loss, less morbidity, and shorter hospital stay compared to open surgery [9]. Therefore, laparoscopic distal pancreatectomy is recommended for benign disease or low-grade premalignant conditions. This category includes benign cystic tumor, low grade of IPMN, SPN, and low-grade pancreatic neuroendocrine tumor (PNET). If the patients have suspected malignant cystic tumor, malignant IPMN, and high-grade PNET, there are not enough data on the superiority of laparoscopic distal pancreatectomy. For these entities, operation is performed following oncologic principles. In these patients, there will be a dispute over preserving splenic vessels or sacrificing. If there is any possibility of tumor encroaching on the vessels, splenic vessels is rather sacrificed. And if the tumor is close to splenic hilum, the spleen and splenic vessel are removed as en bloc. When the patient has overt pancreatic adenocarcinoma, there is still shortage of evidence whether oncologic outcomes are similar between laparoscopic and open group. There is a saying that biology is the king and will determine the prognosis of the patients, and there are few roles in techniques. However substantial evidence should be accumulated before laparoscopic distal pancreatectomy is well recommended for patients with pancreatic cancer. Even after the oncologic safety has been shown, there are still

shaded areas, where laparoscopic surgery is still too challenging. These are adenocarcinoma with large size, portal vein invasion, and adjacent organs invasions. The patient with severe collateral vessel on hilum area such as portal vein hypertension and portal vein occlusion will also have relative contraindications. Oncologic outcomes will be dealt in another chapter.

26.3 Future Prospects

Penetration of laparoscopic pancreatic surgery is still slow compared to other fields such as colorectal, gastric, and liver. The technique is still requiring high standard of advanced laparoscopic surgery. However, compared to laparoscopic pancreaticoduodenectomy, laparoscopic distal pancreatectomy is well used in many centers in the world. General acceptance has been achieved by numerous reports on the effectiveness and superiority of the procedure when compared to open surgery. It has taken significant time to reach this status. The outcome of distal pancreatectomy for pancreatic adenocarcinoma has not been well documented enough. However many surgeons are trying to prove its oncologic effectiveness. The highest evidence is prospective randomized study. However, randomized study is difficult to perform when comparing two completely different surgical techniques. Besides, the number of cases of resectable pancreatic cancer is limited, which makes this kind of study more difficult. Robot-assisted pancreatic surgery is not different from laparoscopic pancreatic surgery. The procedures will also be useful in distal pancreatectomy if the surgeon gets used to it. Robot-assisted pancreatic surgery will be more used in pancreaticoduodenectomy than distal pancreatectomy for its ergonomic advantages.

Numerous operations have been accepted without randomized study, one of which is laparoscopic cholecystectomy. In this regard, the laparoscopic distal pancreatectomy may well be recommended for any disease of pancreatic body and tail in the future.

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Robotic Application for Pancreatectomy

27

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27.1 Introduction

Surgical intervention for pancreatic diseases has increased substantially over the past several decades. Once thought to be prohibitively morbid, greater understanding of tumor biology, improved diagnostic imaging and staging, and advances in perioperative and postoperative care have significantly decreased the morbidity and mortality associated with pancreatic surgery. Despite this, pancreatic surgery continues to be an especially challenging discipline where increased volume and experience correlate with improved outcome [1, 2].

With the considerable learning curve and inherent limitations of laparoscopy compared to open surgery, the advent of robotic surgery has emerged as a new technology to overcome these barriers. With features such as articulation and three-dimensional binocular vision that simulates the open approach, both demand and acceptance of robotic surgery continue to grow. In this chapter, we will explore the origins of pancreatic surgery and development of minimally invasive approaches and discuss the evolution, outcomes, and future directions of robotic pancreatic surgery.

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27.2 Development of Minimally Invasive Pancreatic Surgery

Since the first reports of totally laparoscopic PD by Gagner and Pomp in 1994 [3], complex pancreatic resections and reconstructions remain limited to select high-volume centers since concerns regarding oncologic efficacy and procedure-related morbidity remain prevalent. However, in a single institutional series by Croome and colleagues, patients undergoing minimally invasive PD demonstrated faster recovery and a significantly shorter hospital stay than their open counterparts [4]. Notably, the minimally invasive group demonstrated a longer progression-free survival, which may be attributable to the fact that a significant proportion of patients in the open resection group either had a delay in initiation of systemic treatment or received no adjuvant therapy at all. Echoing these findings, Correa-Gallego et al. noted in a recent systematic review, which included both laparoscopic and robotic pancreatic resections, reduced blood loss and length of stay, higher lymph node yield, and R0 resection rates among minimally invasive PD cases when compared to the open approach [5]. It should be noted, however, that recent publications have called into question the efficacy of minimally invasive technique in pancreatic surgery, demonstrating increased 30-day mortality and no benefit in terms of time to adjuvant treatment for minimally invasive PD

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compared to open PD [6–8]. Notably, these studies utilized the National Cancer Database data, which included outcomes from low-volume pancreatic surgeons and centers, a factor that may have accounted for the higher mortality observed.

Predictably, minimally invasive distal pancreatectomy (DP) has received wider acceptance. A meta-analysis of 15 studies comprising over 1,400 patients confirmed the safety, feasibility, and advantages of LDP [9]. In a retrospective study from the University of Pittsburgh on 62 consecutive patients, the laparoscopic approach demonstrated shorter hospital stay and lower blood loss, with no difference in major complications [10]. Importantly, a recent National Cancer Data Base review demonstrated no compromise in oncologic outcomes with the laparoscopic approach, while noting shorter overall hospital stay and readmission rates in this group [11]. Comparable findings have been noted in similar reports [12, 13]. Cumulatively, these findings support the increasingly widespread use of minimally invasive approaches to DP.

27.3 Development of Robotic Surgery

The laparoscopic approach to pancreatic resections however is hampered by several limitations including the lack of wristed articulation and three-dimensional depth perception. In an attempt to overcome these impediments, alternative minimally invasive procedures continued to be investigated.

The initial foray into a robotic surgical platform was the Arthrobot. This system, developed in Vancouver, BC, was a bone mountable hip arthroplasty system utilized to improve orientation and surface conformity. This was soon followed by the first documented use of a robotic-assisted surgical procedure in 1985 with the PUMA 560 system, for neurosurgical biopsies [14]. This system was then adapted to use in other fields, with Davies et al. using the PUMA system for a transurethral resection of the prostate [15]. This led to the development of the PROBOT in 1988 at the Imperial College of London specifically for this surgery and ROBODOC®, a system initially designed to machine the femur with greater precision in hip replacement surgery. After a ten-patient feasibility study at Sutter General hospital in Sacramento, California, this system was then installed in two additional hospitals under an expanded Food and Drug Administration (FDA) program, New England Baptist in Boston, MA, and Shadyside hospital in Pittsburgh, PA [16]. This system then became the first FDA-approved surgical robot.

Concurrently, researchers at the Ames Research Center of NASA were working on "telepresence" surgery, a forerunner to robotic surgery. In conjunction with Stanford Research Institute, with funding from the US Army, the ground was laid for the design of a surgical robotic system. In 1990, the AESOP® (Automated Endoscopic System for Optimal Positioning), produced by Computer Motion Inc., became the first system approved by the Food and Drug Administration (FDA) for endoscopic surgical procedures. Integrated Surgical Systems (now Intuitive Surgical) licensed the SRI Green Telepresence System and, after extensive redesign, introduced this as the da Vinci Surgical System in 1999. In 2000, the da Vinci System became the first FDA-approved robotic surgery system for general laparoscopic surgery and in 2002 was approved for cardiac valve replacement surgery. After a merger in 2003 with Computer Motion Inc., Intuitive Surgical is now the sole producer of robotic surgical devices.

27.4 Robotic Pancreas Surgery

With increased acceptance of the robotic platform in urologic and gynecologic surgery, several of the advantages associated with this platform have made it particularly appealing to pancreatic surgeons. In contrast to the laparoscopic approach, robotics affords the surgeon the ability to regain dexterity and range of motion,

which more closely mimics the open approach. Additionally, the three-dimensional binocular visualization and magnification abilities allow for a more intricate dissection in conjunction with the ability to complete complex reconstructions on very delicate tissue. Additionally, improved ergonomics and computer-mediated negation of surgeon tremor allow for unparalleled precision during prolonged surgical procedures (Table 27.1).

Table 27.1 Advantages and disadvantages of robotic surgery

Advantages of robotic surgery	Disadvantages of robotic surgery
3D binocular vision	Loss of haptic feedback
Increased dexterity	Expensive, high maintenance costs
7 degrees of freedom	High start-up costs
Near 540-degree motion	Increased staff requirements
Elimination of tremor	Limited change of patient position
20–30× magnification	Cumbersome
Ability to scale motions	Relatively new technology
Ability to perform micro-anastomoses	Difficulty operating in multiple abdominal quadrants

27.5 Robotic Pancreaticoduodenectomy (PD)

In one of the first large series on robotic PD, Giulianotti et al. reported on 134 robotic pancreatic resections, including 50 robotic PDs [17]. An initial series of 132 RPDs at the University of Pittsburgh reported 30- and 90-day mortality of 1.5% and 3.8%, respectively. Grade 3–4 complications (according to the Clavien-Dindo classification system [18]) were reported at 10% and 11%, respectively. These findings are in line with additional smaller studies, which have demonstrated postoperative morbidity and complication rates similar to open PD [19–21]. Rates of pancreatic fistula seen in these robotic series compare favorably to many of the largest series of patients undergoing open PD [22, 23]. In a very large series from the Johns Hopkins Medical Center, the authors reported a mean operative time of 380 min for the procedure, a mean blood loss of 800 mL, 58% R0 resection, and a mean length of stay of 9 days [24]. As can be seen from the previously noted robotic series and as noted in Table 27.2, outcomes approach equivalence with increasing proficiency. Additionally, oncologic outcomes appear

Table 27.2 Comparison of outcomes of robotic pancreaticoduodenectomy

Series	Year	Patients (*n*)	Malignancy (%)	Time (min)	EBL (ml)	R0 resection (%)	Lymph nodes (*n*)	Length of stay (days)	30-day mortality (%)	Fistula (%)	Conversions (%)
Narula [25]	2010	5	20	420	NR	100	16	9.6	NR	NR	37.5
Giulianotti [17]	2010	50	100	568	394	90	18	22	8	38	22
Buchs [19]	2011	44	75	444	387	90.9	16.8	13	4.5	18	4.5
Zhou [21]	2011	8	100	718	153	87.5	NR	18.4	NR	25	NR
Lai [20]	2012	20	75	491.5	247	73.3	10	13.7	0	35	5
Chalikonda [26]	2012	30	46.7	476.2	485.8	100	13.2	9.79	3	7	10
Boggi [27]	2013	34	64.7	597	220	100	32	NR	0	38.2	0
Zureikat [28]	2013	132	80.3	527	300	87.7	19	10	1.5	17	8
Bao [29]	2014	28	100	431	100	63	15	7.4	7	29	14

to be similar in both open and robotic PD, with one series demonstrating an advantage in lymph node yield with the robotic approach [19].

Having established safety and feasibility of RPD, the Pittsburgh authors sought to identify its learning curve. In a series of 200 consecutive RPDs, the learning curve was found to be 80 cases for operative time (581–417 min), 40 cases for fistula rate (27–14 %), and 20 cases for minimizing blood loss and conversion (600–250 ml and 35–3%, respectively) (all $P < 0.05$) [30].

27.6 Robotic Distal Pancreatectomy (DP)

In comparison to laparoscopic and robotic PD, minimally invasive DP has enjoyed a much broader acceptance, allowing for comparisons between the approaches. In a recent retrospective series of 35 patients comparing robotic and laparoscopic DP, operative time was found to be significantly longer in the robotic approach with no significant difference in overall morbidity rate [31]. However, there were nonsignificant trends favoring the robotic approach in operative blood loss and postoperative stay. A second series by Butturini et al. of 43 patients (21 robotic) confirmed the equivalence of robotic DP in regard to these end points, as well as no significant difference in lymph node yield [32]. In a series from the University of Pittsburgh, a significant decrease in conversion rate to open was noted with robotic DP compared to laparoscopic DP [33]. In this study, which minimized selection bias through propensity matching, the R0 resection rate and lymph node yield favored the robotic approach, while the laparoscopic group had a greater conversion rate despite having less pancreatic cancers compared to the robotic cohort.

Similar to the data on RPD, the Pittsburgh group sought to identify the learning curve associated with RDP. In analyzing the first 100 RDPs, the conversion rates were only 2%, despite a significant proportion (30%) of resections being for pancreatic ductal adenocarcinoma [34]. Significant reductions in operative time were observed after 20 cases, with optimization of performance noted after 40 cases. In a series of their initial 55 robotic DPs, Napoli et al. demonstrated low rates of serious morbidity, no conversions to laparotomy, and a learning curve similar to the experience at the University of Pittsburgh [35]. Additionally, series have also reported improved rates of splenic preservation utilizing the robotic approach [36, 37] (Table 27.3). These findings

Table 27.3 Comparison of outcomes of robotic distal pancreatectomy

Series	Year	Patients (*n*)	Time (min)	EBL (ml)	Fistula (%)	Conversions (%)	Spleen preservation (%)	Lymph nodes (*n*)	LOS (days)	R0 resection (%)	30-day mortality (%)
Waters [38]	2010	17	298	279	0	2	65	5	4	100	0
Giulianotti [17]	2010	46	NR	NR	9	3	50	NR	NR	NR	0
Kang [37]	2011	20	348	372	NR	NR	95	NR	7	95	0
Suman [39]	2013	49	203	100	20	18.4	30	4.5	5	92.5	0
Hwang [40]	2013	22	398	361.3	9.1	0	95.5	NR	7	100	0
Zureikat [28]	2013	83	256	150	43	2	NR	16	6	97	0
Daouadi [33]	2013	30	293	212	13	0	7	18.6	6	100	0
Chen [36]	2015	69	150	100	24.6	0	95.7[a]	15.5	11.6	100	0
Lai [31]	2015	17	221.4	100.3	41.2	NR	52.9	NR	11.4	NR	0
Lee [12]	2015	37	213	193	8	38	8	12	5	100	0

[a]Percent of predetermined attempt at splenic preservation

would seem to support robotic DP as a safe, oncologically sound procedure with a relatively short learning curve.

27.7 Robotic Central Pancreatectomy (CP)

In comparison to DP, CP is less frequently described in the literature. This is potentially due to the high potential for pancreatic fistula with this procedure. However, many lesions including pancreatic neuroendocrine tumors (pNETS) and mucinous cysts may not require extensive pancreatic resections such as PD or DP, allowing for preservation of pancreatic endocrine and exocrine function. Given the relative infrequency with which this procedure is performed, few large series exist for minimally invasive approaches. Since the first reported laparoscopic CP reported by Baca and Bokan for a cystic pancreatic lesion [41], the number of series of minimally invasive CP continues to slowly increase (Table 27.4). In a review of 51 published cases, Machado et al. found the laparoscopic approach to be feasible, with similar rates of complications as compared to the open approach, with fistula being the primary source of clinically significant morbidity [46]. However, due to the technical complexity of this procedure, it remains limited to few specialized centers.

Introduction of the robotic approach has the potential to alter the risk-benefit profile, broadening the indications for CP. In one of the largest single institution series, Abood et al. established robotic CP as a safe and feasible approach for small benign and low-risk pancreatic lesions [44]. In this study, all patients underwent an R0 resection, validating the oncologic equivalency of the robotic approach. Median estimated blood loss was 190 milliliters, and one conversion to the open approach was noted due to poor visualization. The vast majority of patients experienced no or mild postoperative complications, with only 11% experiencing Clavien-Dindo grade III or greater. Although pancreatic fistula occurred in 78%, only two were clinically significant grade B or C, according to ISGPF definitions [47]; both of these were managed nonoperatively. At 30 days postoperatively, no patients experienced pancreatic exocrine or endocrine insufficiency. These results compare favorably to the open approach in regard to surgical outcomes. With further published studies, robotic CP may become the preferred approach for lower-risk pancreatic lesions.

27.8 Additional Robotic Pancreatic Procedures

With increasing experience in the use of the robotic platform, indications and potential applications for its use in pancreatic surgery continues to expand. Enucleation of small pancreatic lesions, such as neuroendocrine tumors and insulinomas, continues to be reported in increasing numbers. In a recent report by Shi et al., robotic enucleation was compared directly to the open approach [48]. In this single institution report of 26 robotic procedures, morbidity, postoperative stay, and fistula rate were similar between the two

Table 27.4 Comparison of outcomes of robotic central pancreatectomy

Series	Year	Patients (*n*)	EBL (ml)	Time (min)	Conversion (%)	30-day mortality (%)	Pancreatic fistula (%)	Length of stay (days)	R0 resection (%)	Lymph nodes (*n*)	Endocrine/ exocrine insufficiency (%)
Giulianotti [42]	2010	3	233	320	0	0	33.3	9–27	NR	NR	0
Kang [43]	2011	5	275	432	NR[a]	0	20	14.6	NR	NR	NR
Abood [44]	2013	9	190	425	11.1	0	78	10	100	NR	0
Zhan [45]	2013	10	158	219	0	0	70	26.3	NR	NR	NR

[a]Two procedures performed via hybrid approach

groups. Interestingly, mean operative time and intraoperative blood loss were significantly less in the robotic group. These authors echo the known advantages of the robotic system in their application to this procedure. The stability and elimination of tremor allow for a precise, parenchyma-sparing procedure, while the high-resolution optics of the robotic system afford improved visualization of the pancreatic duct and adjacent vascular structures.

Additionally, the robotic approach has been applied to pancreatic procedures with benign indications. In a retrospective review of robotic cyst gastrostomy and necrosectomy for sterile, walled-off pancreatic necrosis, the robotic approach proved comparable to endoscopy in terms of outcomes and overall cost [49]. Importantly, the authors noted that in cases that need concomitant cholecystectomy, the robotic approach provides a significant advantage.

Further expansion of robotic pancreatic resections has been demonstrated in limited numbers for total pancreatectomy and auto-islet cell transplantation, establishing feasibility and reproducibility [50, 51]. Additionally, establishment of the feasibility of the robotic approach for lateral pancreaticojejunostomy has been demonstrated in small series [17, 28].

27.9 Controversies in Robotic Pancreatic Surgery

Although it is generally accepted that there is increased cost associated with robotic pancreatic surgery, there is limited data available to quantify this. Dedicated staffing and longer operative times factor into the expenditures associated with robotic surgery, as well as the approximately $1.2 million initial investment in acquiring the console. Additionally, there remains a $100,000–150,000 yearly maintenance cost related to upkeep and limited life span of robotic instrumentation. Despite these costs, the robotic system has been demonstrated to be profitable to healthcare systems [52]. In a single institution study examining the costs associated with robotic hysterectomy, no significant cost difference was noted as compared to the laparoscopic approach once the surgeon was beyond their initial learning curve, after adjusting for patient related covariates [53]. Similarly, in a retrospective analysis comparing costs of open, laparoscopic, and robotic DP, direct hospital costs were similar among all groups [38]. Notably, there was a reduced length of stay in the minimally invasive groups, and this benefit may negate the additional costs associated with the robotic system. As familiarity and experience in robotic pancreatic surgery increases, reduced operative times, decreased morbidity, shorter hospital stays, and faster return to work may further justify the cost-effectiveness of this platform. Additionally, more widespread utilization of the robotic platform and introduction of competing systems to the market are anticipated to lower the cost associated with this platform.

One of the greatest hurdles to adoption of any surgical technology is its safe dissemination. Despite widespread formal integration of laparoscopic programs worldwide, only a few surgeons have demonstrated the technical ability to safely and efficiently perform laparoscopic PD. Since the robotic platform possess features that mimic open surgery, including stereotactic vision and endowrist capability, it may ultimately be easier to disseminate. Moreover, robotic simulators have proven to be intuitive and user-friendly and offer increasing levels of complexity approaching pancreas-specific procedures while providing performance feedback in real time. Multiple simulator systems have been developed, and the face, content, construct, and validity of these systems have been established [54–56]. Additionally, simulator training appears to be the most useful training method for trainees at beginner skill level [57]. In a study by Hung et al., 15 expert surgeons determined the simulation training to be very useful for residents and fellows [58]. Dry lab exercises have been similarly validated, demonstrating moderate correlation with virtual reality simulation performance [59].

Additionally, the presence of a dual console allows the trainee to transition to operative

procedures, while retaining the ability of the attending surgeon to rapidly assume control during instances of bleeding or difficult dissections. At our institution, trainees begin to gain their familiarity with the robotic platform utilizing simulators and progress through a structured course of biotissue models that mimic essential steps in PD reconstruction. With a structured format and stepwise increments in trainee participation, oncologic fellows completing this program gain the ability to safely and efficiently perform multiple pancreatic operations.

27.10 Future Directions

As increasing number of surgeons gain experience with the robotic platform, both the diversity of surgical procedures and the corresponding demand for technologic advances will likely continue to grow. One such area is the introduction of single-incision robotic procedures. In a multicenter retrospective review of 465 consecutive robotic single-incision cholecystectomy, this approach proved feasible, with a 2.6% overall complication rate [60]. Similarly, the single-site robotic approach has been described for colon [61], gynecologic [62], and adrenal surgery [63]. Development of system software, remote center technology, and minimized size of the robotic arms will continue to broaden the application of this approach.

Additionally, the development of robotic stapling devices and dedicated ports allows for primary surgeon control of larger vessels and tissue without the need for reliance of approaching from an assistant port. Further development of improved energy devices will provide the surgeon with increased options for tissue and vascular dissection. Further technologic advances include the Firefly Fluorescence Imaging System® for the Xi platform. After intravenous injection of indocyanine green, activation of the fluorescence mode provides enhanced, real-time visualization of critical structures and blood vessels. This approach may have potential to reduce inadvertent injuries and improve surgical outcomes.

In terms of training and accreditation, we anticipate a steady movement toward standardization of robotic training. Since 2009, the American Board of Surgery has required all general surgery residency graduates to successfully complete the Fundamentals of Laparoscopic Surgery (FLS) exam [64]. Currently, no such standardized evaluation exists for robotic surgery. One group has demonstrated construct validity for robotic suturing based on the FLS model [65]. With increased prevalence and standardization, these training systems will better prepare surgeons to perform increasingly complex robotic pancreatic procedures.

Conclusion

Pancreatic surgery has changed radically over the past century. Improved outcomes and understanding of pancreatic diseases have provided pancreatic surgeons the opportunity to perform safer and more effective operations. Although still in its infancy, the application of the robotic platform to pancreatic resections appears to be a safe and feasible approach for a wide variety of pancreatic procedures. Additionally, defined procedure-specific learning curves and demonstration of safe dissemination of this technology enhance its appeal for an increasing number of surgeons and trainees. Although early reports provide support for its use, long-term outcomes will be necessary to fully evaluate the benefit of robotic pancreas surgery.

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Organ-Preserving Pancreatectomy

28

Wooil Kwon and Sun-Whe Kim

28.1 Introduction

The standard operative method of pancreatic cancer is pancreatoduodenectomy, distal pancreatectomy including radical antegrade modular pancreatosplenectomy, and total pancreatectomy depending on the location and nature of the lesions. These operations are destructive but offer radicality, and radicality is very important in terms of oncologic outcome.

Organ-preserving pancreatectomy is less destructive and considers functional outcome after surgery. But because organ-preserving pancreatectomy does not guarantee radicality, it is not suitable for pancreatic cancer. However, organ-preserving pancreatectomy may be considered for pancreatic lesions which are not cancer but have malignant potential at the time of operation. In this chapter, the conditions and indications in which organ-preserving pancreatectomy may be considered will be explored. Then different types of organ-preserving pancreatectomy will be discussed.

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28.2 Indications (Table 28.1)

28.2.1 Low-Grade Malignant Neoplasms

Basically, organ-preserving pancreatectomy is indicated in benign or low-grade malignant neoplasms. These include mucinous cystic neoplasm (MCN), intraductal papillary mucinous neoplasm (IPMN), solid pseudopapillary neoplasm (SPN), and small pancreatic neuroendocrine tumor (PNET). The detection of low-grade malignant

Table 28.1 Possible indications for organ-preserving pancreatectomy

Indicated disease	Conditions
MCN	<4 cm without mural nodules
IPMN	Branch duct type
	Asymptomatic
	No elevation of CA19-9
	Cyst size over 2 cm
	No mural nodules
SPN	Well-demarcated small mass
PNET Nonfunctioning Functioning	Asymptomatic and ≤2 cm Small tumors without vascular involvement
Metastatic tumors	Renal cell carcinoma
	Colorectal cancer
	Melanoma
	Sarcoma

MCN mucinous cystic neoplasm, *IPMN* intraductal papillary mucinous neoplasm, *SPN* solid pseudopapillary neoplasm, *PNET* pancreatic neuroendocrine tumor

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neoplasms of the pancreas has increased recently with advances in imaging technologies even in young or otherwise healthy population [1, 2]. Many of these low-grade malignant neoplasms require surgical interventions. Although conventional pancreatectomy may be performed with minimal perioperative morbidities and mortalities nowadays [3], these operations seem to be excessive in some cases since they result in considerable functional loss and decreased quality of life. Considering that most of the patients have long life expectancy, the preservation of function and quality of life is important in patients with low-grade malignant neoplasm. In this respect, organ-preserving pancreatectomy is an attractive option for low-grade malignant neoplasms [4].

28.2.1.1 Candidates in MCN

MCNs are typically detected in pancreas tail of women in their fourth to fifth decade. They may be easily detected on CT or MRI scans as cystic mass. They usually present as unilocular or multilocular cystic mass without evidence of connection to the main duct of pancreas. If the size of MCN is less than 4 cm without mural nodules, organ-preserving pancreatectomy may be considered [5–7]. Large MCNs and MCNs with nodules harbor risk of malignancy and thus should be precluded from undergoing organ-preserving pancreatectomy

28.2.1.2 Candidates in IPMN

It is well known that IPMNs undergo adenoma-to-carcinoma progression. The frequencies of malignancy vary according to the morphological types. The malignancy frequency is reported to be around 60% for the main duct-type IPMN, and standard resection is recommended for all main duct-type IPMN [7]. On the other hand, the branch duct-type IPMNs are more complicated. Their mean malignancy frequency is 17.7%. Thus, not all branch duct-type IPMNs are indicated for operation, and only those at high risk for malignancy are indicated for surgery which is constantly controversial [7]. According to the International Consensus Guideline, organ-preserving pancreatectomy may be considered for branch duct-type IPMN without clinical, radiologic, cytopathologic, or serologic suspicion of malignancy [7]. Asymptomatic patient without elevated tumor markers whose IPMN is over 2 cm and without mural nodule on image studies may be a candidate for organ-preserving pancreatectomy.

28.2.1.3 Candidates in SPN

SPN is seen predominantly in young women and is an indolent tumor with malignant potential. About 15% of resected cases show malignant features but death resulting from SPN is rare [8, 9]. Malignancy predictive factors differ among investigators, and most of them are histological features which can be determined only after resection. Thus, a compromised indication for organ-preserving pancreatectomy may be well-demarcated small SPNs without metastasis.

28.2.1.4 Candidates in PNET

The indication of organ-preserving pancreatectomy in PNET is an ongoing debate. PNETs are usually graded using the World Health Organization (WHO) system which grades PNETs based on Ki-67 and mitotic count [10]. The WHO grade is the most consistent predictive factor for malignancy [11]. But this grade can be obtained after surgical removal of the tumor and cannot be used to establish treatment strategy preoperatively. There are several reports indicating that small size is a predictive factor for either malignancy or high WHO grade [12–17]. Despite ongoing controversies, size is often used to determine treatment strategy. For nonfunctioning PNETs, the most often referenced indication for organ-preserving pancreatectomy is asymptomatic small (≤2 cm) PNETs [18]. For functioning, small tumors especially insulinoma without vascular involvement may be a candidate [4].

28.2.2 Metastatic Tumors

Metastasectomy is known to have benefit for some cancers. Metastatic colorectal cancer, gastrointestinal stromal tumors, neuroendocrine cancers, renal cell cancers, and sarcomas are some of the representative cancers that benefit from metastasectomy. The role of metastasectomy for metastasis to pancreas is yet unknown. And given the rarity of pancreatic metastases, it will be very

difficult to analyze the benefit of metastasectomy in pancreatic metastases. The most common pancreatic metastasis is renal cell carcinoma consisting about 60% of all reported pancreatic metastases. Others in literatures include colorectal cancer, melanoma, and sarcoma [19, 20].

The guidelines from the European Organisation for Research and Treatment of Cancer's Genito-Urinary group on the management of metastatic renal cell carcinoma recommended metastasectomy in all possible cases for clinical benefit without reference to the site of metastasis [21]. Although there is no concrete evidence to demonstrate benefit of metastasectomy in pancreatic metastasis of renal cell carcinoma, the consensus from most of the articles is that patients with renal cell carcinoma to the pancreas benefit from resection [19].

Metastasectomy of colorectal cancer pancreas metastasis demonstrated comparable survival outcome to metastasectomy of colorectal cancer liver metastasis [20]. For melanoma, given the improved survival with metastasectomy in other gastrointestinal sites, pancreatic metastasectomy should also be considered for resection [20].

Organ-preserving pancreatectomy is reported to have comparable outcome to standard resection [22, 23]. Considering the similar surgical outcome and possible multiplicity of metastatic lesions, organ-preserving pancreatectomy should be considered whenever feasible.

28.3 Types of Organ-Preserving Pancreatectomy (Table 28.2)

28.3.1 Enucleation

Although the actual history may be older than the reported history, the first enucleation of pancreas was reported in 1898 by Ernesto Tricomi in Italy [24]. The biggest advantage of enucleation is that pancreatic parenchyma can be preserved as much as possible, and other organs such as pancreas need not to be sacrificed. For enucleation to be possible, there are several conditions that need to be met:

1. The lesion needs to be determined as benign or low-grade malignant neoplasm during preoperative evaluation.
2. Signs of malignancy such as vascular involvement or infiltration of other organs must be absent.
3. No evidence of distant metastasis demonstrated at preoperative images.
4. Sufficient distance from the main pancreatic duct must be secured.

Table 28.2 Summary of organ-preserving pancreatectomy in lesions without evidence of malignancy

Operation	Location	Conditions
Enucleation	Anywhere	2–3 mm distance from the main pancreatic duct
DPPHR	Head	Preservation of posterior arcade of PD vessels
PHRSD		Failed DPPHR due to margin or ischemia
Ventral pancreatectomy	Head	Limited to uncinate process
Pancreas head excavation	Head	Limited to pancreas head
		Preservation of vasculature
Central pancreatectomy	Neck and proximal body	Adequate proximal and distal margin
		Preservation of splenic vessels
Spleen-preserving distal pancreatectomy	Body and tail	No evidence of malignancy
		Sufficient distance from spleen
Middle-preserving pancreatectomy	Head and tail	Multiple lesions in head and tail
		No lesion in body
Dorsal pancreatectomy	Anywhere except ventral pancreas	Multiple lesions anywhere other than ventral pancreas
		Pancreas divisum

DPPHR duodenum-preserving pancreatic head resection, *PHRSD* pancreatic head resection with segmental duodenectomy

There is no consensus on the absolute value of distance from the tumor to the main pancreatic duct. Distance of at least 2–3 mm is often dictated reference but the evidence is low [25]. Some tips to ensure safety of main pancreatic duct when conducting enucleation include utilizing intraoperative ultrasonography (US) and insertion of pancreatic drainage tube through endoscopic retrograde cholangiopancreatography preoperatively.

Before conducting enucleation, the abdominal cavity should be thoroughly explored to rule out any unexpected discrepancy with preoperative work-up findings such as seeding, distant metastasis, regional lymph node metastasis, or adjacent organ invasion. Any enlarged lymph node should be resected for intraoperative frozen biopsy. If the biopsy turns out to be metastatic lymph node, enucleation should be abandoned and converted to conventional pancreatectomy with standard lymph node dissection.

Intraoperative US is particularly helpful during enucleation. It can identify the targeting lesion and morphology and also evaluate its distance from the main pancreatic duct [26, 27]. In addition, additional multifocal lesions may be incidentally detected during intraoperative US especially in patients with multiple endocrine neoplasia (MEN) type 1 [28].

When performing enucleation, the most important thing to consider is to remove the tumor completely without disrupting the capsule. Meticulous dissection is essential with ligation of small vessels. When ligating the vessels, any of surgical ties, clips, electrical coagulation device, or harmonic scalpel may be used. However, operator should take caution when using electrical coagulation device or harmonic scalpel, since they may inflict thermal injury to the main pancreatic duct. Drain should be placed and positioned in the proximity of enucleated site to monitor postoperative bleeding or pancreatic fistula.

The enucleated mass should be sent for frozen biopsy to ensure that it is not malignant. If it is found to be malignant, then conventional pancreatectomy needs to be performed. If it is found to be malignant or to have inadequate margin at permanent pathologic report, reoperation should be considered.

The major drawback of enucleation is relatively high incidence of postoperative pancreatic fistula. The postoperative pancreatic fistula rate is reported to be around 30% with clinically relevant fistula (i.e., International Study Group on pancreatic fistula grade B and C) rate of 15% [29–31]. However, most of the fistulae are known to resolve without operative intervention. The overall morbidity of enucleation is acceptable compared to the conventional pancreatectomy [32]. Recurrence is rare after enucleation when the patients are carefully selected. More importantly, exocrine/endocrine insufficiency is very low with 0–6% incidence rate [4, 32–34].

28.3.2 Partial Pancreatectomy According to the Location of Target Lesion

28.3.2.1 Head

Pylorus-preserving pancreatoduodenectomy may be considered to be "organ"-preserving pancreatectomy in relation to Whipple's operation. Since the two operative techniques have similar radicality and outcome, these two operations will be regarded as conventional pancreatectomy.

Duodenum-Preserving Pancreatic Head Resection (DPPHR) and Pancreatic Head Resection with Segmental Duodenectomy (PHRSD)

Beger et al. [35] first introduced DPPHR on a patient with chronic pancreatitis and inflammatory mass in the head of the pancreas. Since then, various modified techniques have been developed to fit resection of benign or low-grade malignant neoplasms of pancreas head [36, 37]. The potential benefits of DPPHR are the improved quality of life through the preservation of digestive tract and bile duct integrity, and the preservation of whatever amount of pancreas head parenchyma may be possible [38, 39]. While DPPHR may offer more conservative treatment, the procedure is very complex and demanding.

The technique involves division of pancreas over the portal vein and subtotal resection of the pancreatic head. In the process, preserving the

posterior arcade of pancreaticoduodenal artery is important to maintain blood flow to the duodenum. The common bile duct is skeletonized semi or full circumferentially according to the amount of pancreatic rim on the duodenum that can be preserved. The remnant pancreas can be anastomosed to Roux-en-Y jejunal loop, duodenum, or posterior wall of the stomach [36, 37, 40].

The reported overall complication rate is estimated to be 46%, ranging from 24% to 55% [39, 40]. Mortality is rare. Although postoperative outcome is acceptable, there are some unique concerns for DPPHR. One is uncertainty of complete excision due to remnant pancreatic rim or main duct. Another is the risk of ischemia of duodenum, ampulla of Vater, and bile duct. Thus preservation of posterior arcade of pancreaticoduodenal artery is essential. PHRSD was devised by Nakao et al. [41, 42] in 1994 to avoid these problems. All pancreaticoduodenal arcades are sacrificed except for anterior inferior pancreaticoduodenal artery which is needed to supply the third portion of duodenum. Then second portion of duodenum and distal common bile duct are resected along with pancreas head. While PHRSD can save time of vessel preservation, extra time is consumed for additional choledochoduodenostomy and duodenoduodenostomy, resulting in similar operation time with DPPHR. The complication rate of PHRSD is similar to that of DPPHR. Therefore, when risk of ischemia or positive resection margin is concerned with DPPHR, PHRSD may be a reasonable alternative.

The complication rate and postoperative fistula rate of DPPHR and PHRSD are similar to that of pylorus-preserving pancreatoduodenectomy [43]. But at the same time, DPPHR and PHRSD offer better exocrine and endocrine pancreatic function [44–46]. Therefore, DPPHR and PHRSD may be performed instead of conventional pancreatectomy in carefully selected indicated patients.

Ventral Pancreatectomy

Ventral pancreatectomy, also known as inferior head resection, was first reported by Takada in 1993 [47]. The uncinate process and pancreatic tissue around the Wirsung's duct are resected. Kocher maneuver should not be performed in order to preserve small vessels to duodenum. The pancreaticoduodenal arcades are all preserved, and only the branches of inferior pancreaticoduodenal vessels are ligated. Parenchyma is divided so that half of distal common bile duct becomes exposed. After excision of the inferior head of the pancreas, the duct of Wirsung is anastomosed to the third portion of the duodenum in an end-to-side fashion [48].

Although there are not many reports on the outcome of ventral pancreatectomy, a recent report indicated 67% morbidity rate without any mortality. The pancreatic fistula rate was 47%. No impairment in exocrine and endocrine pancreatic function was noted in 15 patients. The efficacy of ventral pancreatectomy still needs further investigation [49].

Pancreatic Head Excavation

Andersen et al. [50] reported this modification of DPPHR in 2004. Proximal pancreatic duct or central core of the pancreatic head is excised using ultrasonic dissection, and longitudinal side-to-side Roux-en-Y pancreaticojejunostomy is performed. Analysis of five cases revealed 33% complication rate without mortality [51]. The feasibility remains to be investigated.

28.3.2.2 Neck and Body

Central pancreatectomy is also known as median pancreatectomy, middle pancreatectomy, or middle segment pancreatectomy. This operation was first reported by Guillemin and Bessot [52] in 1957 to treat chronic pancreatitis patient. This operative technique is suitable for lesions located in the neck or proximal body of pancreas which are not amenable by enucleation. Central pancreatectomy allows preservation of the spleen as well as normal pancreas parenchyma. But in order for central pancreatectomy to be done safely and successfully, certain conditions must be met:

1. Possibility of malignancy must be ruled out at preoperative studies.

2. Adequate margins need to be obtained both proximally and distally.
3. Portal vein, splenic vein, and splenic artery should be preserved.

Frozen biopsy on main tumor and any enlarged lymph node should be performed, and if it turns out to be malignant, conventional pancreatectomy (i.e., subtotal pancreatectomy or extended pancreatoduodenectomy) should be performed. Proximal and distal margin of at least 1 cm is often recommended as adequate safe margin. Any lesion adherent to splenic vessels or failure to preserve splenic vessels during dissection will usually result in distal pancreatectomy. Therefore, thorough pre- and intraoperative evaluation as well as meticulous dissection is essential for successful central pancreatectomy.

After exploring the abdominal cavity, lesser sac is entered exposing pancreas. Intraoperative US is helpful to localize the tumor, to exclude other multifocal lesions, and to evaluate the relationship with vascular structures [53]. The posterior aspect of the pancreas is dissected away from the superior mesenteric vein and the portal vein. The posterior aspect dissection is continued distally ligating branches of splenic vessels. The proximal is transected either sharply or with linear stapler. When transected sharply pancreas duct and parenchyma are oversewn. Distal is transected sharply and pancreaticojejunostomy with Roux-en-Y jejunal loop is created. An alternative to pancreaticojejunostomy is pancreaticogastrostomy to the posterior wall of the stomach [54]. Some prefer to create a double pancreaticojejunostomy on both proximal and distal pancreatic stump [55]. After placing a drain at the site of pancreatic transection, the operation comes to an end.

The major concern with central pancreatectomy is the high rate of complications, especially postoperative pancreatic fistula. In a literature review, the overall morbidity was 48% (range 0–92%), and pancreatic fistula was the most common complication occurring in 31.6% with a range of 0–62% [39]. However, most of the pancreatic fistulae closed spontaneously or with only conservative treatment. The perioperative mortality was 0.7%. Lee et al. [43] reported comparable postoperative outcome of central pancreatectomy with conventional distal pancreatectomy through a direct comparison.

Despite the relatively high perioperative morbidity, central pancreatectomy is a valid option for low-grade malignant neoplasms considering long-term endocrine and exocrine function preservation.

28.3.2.3 Body and Tail

Lesions in body and tail that are not a suitable candidate for enucleation have been subject to distal pancreatectomy with concomitant splenectomy traditionally. For low-grade malignant lesions, radicality is not the greatest issue. Rather, organ and function preservation may be more of an importance. The role of the spleen is yet unclear, but there are reports that the spleen may have a role in preventing infection and malignancy [56]. For such reason, it may be worthwhile to preserve the spleen whenever feasible.

The most important thing to determine in order to proceed with spleen-preserving distal pancreatectomy is whether the lesion is malignant or not. Malignancy must be excluded. The relationship with the splenic vessels is not as important as in central pancreatectomy. Splenic vessels may be either preserved or sacrificed depending on the situation or surgeon's preference.

Splenic vessel preservation, refined and popularized by Kimura et al. [57], is more physiologic and ideal. However, based on the anatomic knowledge that vasculatures of spleen can be maintained through short gastric vessels, Warshaw [58] described spleen preservation with ligation and transection of splenic vessels. It is still controversial which technique is superior.

For Warshaw's technique, the procedure is similar to conventional distal pancreatectomy. One important point in performing Warshaw's technique is to make certain that the short gastric and left gastroepiploic vessels are well preserved. If splenic infarction after removing pancreas is extensive, splenectomy should be considered.

When preserving splenic vessels, finding the plane between pancreas and the splenic, portal,

or superior mesenteric veins is important. Then, meticulous ligation of branches of splenic vein and artery should be performed. Pancreas can be dissected in either retrograde or antegrade fashion. Even while preserving splenic vessels, short gastric and gastroepiploic vessels should be left intact in case of compromised splenic vessels during dissection.

The overall complication rate and pancreatic fistula rate are similar between spleen-preserving distal pancreatectomy and conventional distal pancreatectomy [43, 56, 59, 60]. Therefore, spleen-preserving distal pancreatectomy is a safe and feasible alternative to conventional distal pancreatectomy in benign and low-grade malignant neoplasms occurring in body or tail of pancreas

28.3.2.4 Multifocal

Multifocal lesions may be present in MEN type 1 syndrome, multifocal branch duct-type IPMNs, or multiple pancreatic metastases. In these cases, operations should be customized to the location of targeting lesions. Multiple enucleation may be performed if feasible, or combination of different organ-preserving pancreatectomies may be performed according to the locations. Among pancreatectomies that were not mentioned, middle-reserving pancreatectomy and dorsal pancreatectomy can also be an option in multifocal lesions.

28.4 Minimally Invasive Surgery of Organ-Preserving Pancreatectomy

Laparoscopic surgery is becoming ever popular and pancreas is not an exception. Laparoscopic enucleation, laparoscopic central pancreatectomy, and laparoscopic spleen-preserving distal pancreatectomy are minimally invasive organ-preserving pancreatectomy that are relatively frequently performed.

There are several reports on early experiences with laparoscopic enucleation for insulinoma or nonfunctioning PNETs [61–63]. In these reports typical advantages of laparoscopic surgery such as reduced blood loss and hospital stay was demonstrated with no difference in morbidity. Although more evidence needs to be accumulated, laparoscopic enucleation seems to be safe and feasible in well-selected cases.

Laparoscopic surgery has also been reported in central pancreatectomy [64, 65]. Morbidity rate of 33% and no mortality were reported in nine case series [65]. These results are only preliminary, and further studies are warranted, but the safety and feasibility were demonstrated nonetheless.

Laparoscopic spleen-preserving distal pancreatectomy has been widely performed and has been shown to be safe and feasible [66]. Both Warshaw's technique and splenic vessel preservation are technically possible in laparoscopic spleen-preserving distal pancreatectomy, and either method has comparable result with conventional laparoscopic distal pancreatectomy in terms of early and late clinical outcomes and quality of life [56]. With accumulating evidences, laparoscopic spleen-preserving distal pancreatectomy may become more popular in the future than open surgery.

Conclusion

There are various types of organ-preserving pancreatectomy ranging from simple enucleation to complex DPPHR. These organ-preserving pancreatectomies lack radicality and are unsuitable for pancreatic cancer. However, there are many borderline malignant neoplasms that harbor possibility of malignant transformation in pancreas. In this respect, knowing the treatment strategy for the borderline malignant neoplasms is almost as important as knowing the treatment strategy of overt pancreatic cancer. With this in mind, this chapter presented various feasible organ-preserving pancreatectomy.

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Minimally Invasive Surgery for Pancreatic Cancer

29

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29.1 Minimally Invasive Surgery for Pancreatic Cancer

The most common procedures for pancreatic cancer are pancreaticoduodenectomy (PD) and distal pancreatectomy (DP), depending on the location of the lesion. PD involves resection of the pancreatic head, duodenum, gallbladder, and common bile duct. DP is the resection of the part of the pancreas located to the left side of the portomesenteric vein. Pancreatic cancer currently represents the fourth and fifth leading cause of cancer deaths in women and men, respectively. These poor survival outcomes can be partially attributed to late onset of symptoms, resulting in only 20% eligibility rate for surgery among patients with pancreatic cancer. After curative surgery of pancreatic cancer, median survival varies between 20 and 24 months, with a reported 5-year survival of approximately 20%. Poor survival and substantial risk of perioperative mortality and morbidity remain the major concerns in pancreatic resection. Today, minimally invasive surgeries (MISs) have become a routine part of management of some abdominal malignancies such as stomach and colon cancers. They have been introduced in reliable surgical specialties, usually with improved postoperative outcomes, shorter length of hospital stay (LOHS), and faster recovery. However, their adoption for pancreatic surgery has lagged. This is likely due to the perceived technical difficulty associated with pancreatic MIS, in part due to the retroperitoneal location of the pancreas, its proximity to major vascular structures, and the potential for perioperative morbidity and mortality. Since the first pancreatic MIS was reported [1], the implementation of MIS was initially slow, and increasing interest and wide adoption only started to appear 10 years later. There seems to be a sharp increase in the interest for MIS, potentially due to ongoing centralization of pancreatic surgery in specialized large-volume centers, which has enabled technical developments.

29.2 Laparoscopic Distal Pancreatectomy (LDP) for Pancreatic Cancer

DP lends itself to easier adoption of MIS techniques compared with PD because it does not require complicated dissection and laborious reconstruction. Since the first LDP was performed in 1996 by Cuschieri [2], it has been increasingly performed for lesions in the left side of the pancreas. Several studies have compared perioperative and oncological outcomes for LDP

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and open distal pancreatectomy (ODP) for various pathologies. Sufficient evidence support the use of the laparoscopic approach for resection of benign left-sided pancreatic lesions. When adopting the laparoscopic approach for the resection of any malignancy, initial concern about oncological safety and feasibility remains, including other considerations such as risks of postoperative morbidities and quality of life (QoL).

29.2.1 Indication and Incidence of LDP for Pancreatic Cancer

Currently, reported series on LDP for pancreas cancer are influenced by selection bias because most centers are still in the learning curve of LDP, and during that phase, only ideal patients are selected. The factors to consider when selecting patient for LDP include body mass index (BMI), history of previous laparotomy, need for major vascular invasion and multivisceral resection, and history of neoadjuvant therapy. Although current literature does not provide any clear contraindications for LDP, these possibly depend on the surgeon's skills and experience. With increasing surgical experience, the indication of LDP is extended to nearly all left-sided pancreatic cancer.

According to the National Cancer Database (NCDB), LDP was used in 31% of all DP in the United States in 2010–2011 [3]. Recently, the number of published series of LDP significantly increased, suggesting increasing interest and utilization. In a meta-analysis of 1814 patients pooled from 18 studies, Venkat et al. [4] found that LDP was used in 43% of all DP for benign and malignant disease.

29.2.2 Perioperative and Oncological Outcomes of LDP for Pancreatic Cancer

29.2.2.1 Perioperative Outcomes

To date, a large number of institutional or multicenter series, either clinical series or case-match studies, have compared LDP with ODP. Jayaraman et al. [5] reported the perioperative outcomes of a total of 343 DPs (107 LDP and 236 ODP) during a 7-year study observation period. LDP resulted in better outcomes, less blood loss, and shorter hospital stay compared with ODP in a matched analysis. However, the operative times were longer, and the specific incidence of postoperative pancreatic fistula (POPF) was similar in the two groups. In this study, the conversion rate was 30%. They recommended careful patient selection because patients who required conversion experienced higher rates of complications and POPF.

One of the largest multicenter comparative studies was published by Nakamura et al. [6]. From 2006 to 2013, 2010 patients in 69 institutes in Japan were enrolled in this study and divided into two groups: LDP and ODP. Perioperative outcomes were compared between the groups using unmatched and propensity-matched analysis. LDP was associated with favorable perioperative outcomes compared with ODP, including higher rate of preservation of spleen; lower rates of intraoperative transfusion, clinical relevant POPF (International Study Group on Pancreatic Fistula [ISGPF] grades B and C), and morbidity; and shorter hospital stay, but a longer operative time.

A recent meta-analysis, including 3,701 patients from 29 observational studies, showed the superiority of LDP in terms of blood loss, time to first oral intake, and LOHS. All other parameters of operative morbidity and safety showed no difference [7].

POPF is the most common complication and remains a problem that can prolong hospital stay after DP. In almost all published comparative and meta-analyses [5–9], clinically relevant POPF (ISGPF B or C) seems to be the same for LDP and ODP.

Generally, LDP is associated with shorter LOHS and lower blood loss in comparison to the open approach. One of the consistently reported advantages of LDP over ODP in the literature is shorter LOHS. In most studies, LOHS was shorter after LDP than after ODP [5–9]. It is also associated with shorter time to first flatus and oral intake. Blood loss is lower for LDP compared

with ODP. Less blood loss is one of the most important results of the advances in surgical techniques and laparoscopic system in terms of magnification and high-definition view that have increasingly augmented the safety of LDP.

In a different series, the operating time of LDP is reported as longer, similar, or shorter compared with the open approach. This may be explained by the difference in the learning curve of the surgeons and the surgical team. The largest single-center study to date was described by Song et al. [10], in which 359 consecutive patients underwent LDP. The authors reported that operation times for LDP are reduced when surgeons with adequate experience perform the surgery.

Usually, the learning curve of an operation refers to operative time. An individual surgeon, a surgical team, or an institution needs an adequate number of operations to achieve proficiency. This process is influenced by many factors, including innate abilities, and is difficult to define. Some studies showed that the learning curve for LDP can decrease the operative time and the conversion rate to open. They also reported that the minimum number of LDP required to achieve an optimal result is between 10 and 20 [11, 12].

The conversion rate varies from 0% to 15% in major LDP series [5–8]. The difference in conversion rates also has been attributed to the learning curve of the surgeon in obtaining proficiency. Generally, mortality is rare (<1%) for LDP.

Current literature suggests significantly better QoL outcomes after LDP [13]. However, randomized trials on this subject with a long-term follow-up are needed to determine the potential QoL advantages of LDP.

In terms of costs of LDP, outcomes varied from no statistically significant cost reduction to statistically significant 20–30% cost reduction in the case of LDP. The reduction in LOHS after LDP seems to be the major contributing factor to reduced overall costs [13–15].

29.2.2.2 Oncological Outcomes

To adopt LDP for pancreatic cancer, the minimum prerequisite is to maintain the same oncological outcomes of ODP, including overall survival and progression-free survival. Surrogate parameters, such as the number of harvested lymph nodes and the negative margins of resections, should also be taken into consideration.

The status of the resection margin and metastasis of lymph nodes is well documented to be an important predictor of outcome after resection of pancreatic cancer. LDP may demonstrate oncological advantages over ODP in well-selected patients and achieve a similarly high rate of R0 resection and lymph node retrieval for patients with pancreatic cancer. However, large studies on the oncological efficiency of LDP versus ODP are rare.

In a multi-institutional study by Kooby et al. [16], 667 DPs were performed from 2000 to 2008, with 24% LDP and 76% ODP. Short- (node harvest and margin status) and long-term (survival) oncological outcomes were assessed. A 3:1 matched analysis was performed for ODP and LDP cases using age, the American Society of Anesthesiologists class, and tumor size. LDP provides similar short- and long-term oncological outcomes as compared with ODP, with potentially shorter hospital stay.

Magge et al. [17] reported that LDP achieved the same rates of margin-positive resections and numbers of retrieved lymph nodes without difference in long-term survival compared with ODP in patients with pancreatic cancer.

Shin et al. [18] specifically compared LDP and ODP in 150 patients operated on for pancreatic cancer after using unmatched and propensity score-matched analyses. The two groups did not differ significantly in terms of primary outcomes of operative time, number of harvested lymph nodes, resection margin status, and secondary outcomes of frequency of POPF and other complications. The two groups also had comparable patient survival.

These studies suggest that LDP for pancreatic cancer is feasible, with comparable oncological outcomes as reported for open approaches [16–18] (Table 29.1).

Radical antegrade modular pancreatosplenectomy (RAMPS) for left-sided pancreatic cancer was first described in 2003 [20]. RAMPS aims to facilitate radical tumor resection combined with extensive lymph node dissection along the celiac axis, the hepatic artery, and the retroperitoneal

Table 29.1 Large studies comparing LDP and ODP for pancreatic cancer [19]

	Type of procedure	Shin et al. [18]	Magge et al. [17]	Kooby et al. [16]
Inclusion period		2006–2013	2002–2010	2000–2008
Patients, n	LDP	70	28	23
	ODP	80	34	189
Operative time, min	LDP	239	317	238
	ODP	254	294	230
EBL, ml	LDP	–	290[a]	422[a]
	ODP	–	570[a]	790[a]
Tumor size, mm	LDP	30[a]	37	35
	ODP	35[a]	45	45
R0 resection rate, %	LDP	76	86	74
	ODP	84	88	73
Resected LN, n	LDP	12	11	14
	ODP	10	12	13
Adjuvant CTx, %	LDP	79	89	57
	ODP	68	85	70
Median survival, months	LDP	33	19	16
	ODP	29	19	16

EBL estimated blood loss, *CTx* chemotherapy, *LDP* laparoscopic distal pancreatectomy, *ODP* open distal pancreatectomy
[a]Difference between groups with *P* value <0.05

region, including the anterior renal fascia (anterior RAMPS) and, optionally, the left adrenal gland (posterior RAMPS). Laparoscopic RAMPS is also feasible, but long-term oncological outcomes are yet to be determined, and the true oncological and survival benefits of this procedure have not yet achieved generalized consensus [21].

Involvement of other organs, such as the adrenal glands, kidney, colon, or stomach, is relative but not absolute contraindication for the laparoscopic approach, as concomitant organ resection is possible during laparoscopic RAMPS. However, evidence of multivisceral resection by laparoscopic approach in left-sided pancreatic cancer is low.

The potential benefits of LDP include the prompt instigation of adjuvant therapy, compared with ODP, which may have a role in determining long-term outcome and improving overall survival.

29.2.3 Conclusion

LDP seems to be a technically safe and feasible approach, providing favorable perioperative outcomes in terms of reduced estimated blood loss and shorter LOHS compared with ODP. LDP demonstrates short- and long-term oncological outcomes similar to those after ODP in patients with pancreatic cancer. Although no randomized trial has been performed to date, many centers consider LDP as the "gold standard" approach for left-sided pancreatic tumors in selected patients except for locally advanced cancer.

29.3 Robot Distal Pancreatectomy (RDP) for Pancreatic Cancer

Conventional laparoscopic surgery exhibits its own limitations, including reduced freedom of movement within the abdominal cavity, reduced precision, and poor ergonomics. These limitations translate into a long learning curve, which requires longer time and more effort to develop and maintain such advanced laparoscopic skills. Therefore, since the first LDP was reported by Cuschieri in 1996, it remains not widely adopted. By contrast, robotic system allows complex dissections, and this method is performed more easily and precisely. In 2003, Giulianotti et al. [22] completed the first robot-assisted pancreatic resection. Since then, more investigations have been made on the applications of various surgical resection procedures for pancreas using robotic surgical systems.

Robotic surgical systems exhibit several advantages over conventional laparoscopic instrumentations. Robotic surgical systems provide reduced operator fatigue, motion stabilization by improved dexterity of wristed instruments, and magnified three-dimensional (3D) imaging, and they have been demonstrated to be superior to laparoscopic surgery when performing complex surgical maneuvers. These advantages facilitate hemostasis, as well as control of the spleen artery, venous mesenteric and portal regions, and small vascular plexus surrounding the pancreas.

29.3.1 Perioperative and Oncological Outcomes of RDP for Pancreatic Cancer

29.3.1.1 Perioperative Outcomes

Centers performing both laparoscopic and robot-assisted pancreatic surgery remain scarce; thus, limited comparative evidence exists. Only a handful of studies to date have attempted to compare the outcomes of RDP versus LDP [23–26]. Most of these studies demonstrated comparable outcomes between RDP and LDP, such as postoperative morbidity including POPF rates and LOHS. However, in general, RDP appeared to be associated with a longer operation time and increased rate of spleen preservation compared with LDP. In several studies, operative time was longer in RDP than in LDP. It can be explained by the longer docking time of the robotic system than the laparoscopic system and the burden of learning curve. Docking and undocking of the robot can be time-consuming especially for surgical teams during their learning phase. However, some large series reported shorter operation times with RDP compared with LDP after the learning curve [24]. The spleen should be preserved as much as possible in the case of benign or borderline diseases because spleen-preserving distal pancreatectomy offers patients other clinical benefits as well, such as lower morbidity, shorter hospitalization time, and prevention of life-threatening sepsis by splenectomy [27]. Others have demonstrated higher rates of POPF with splenectomy during distal pancreatectomy [28]. However, concomitant en bloc splenectomy is performed with distal pancreatectomy mainly for technical reasons, such as to make resection easier, shorten operative time, and minimize bleeding from dissecting splenic vessels. Spleen-preserving LDP is relatively time and labor consuming. RDP was associated with a significantly higher spleen-preserving rate, which resulted from the fact that the robotic approach was more effective at controlling splenic vessel bleeding due to the good flexibility of instruments and high-definition view in this system [29]. The cost-effectiveness of RDP is inconclusive, and the added benefit of the robot-assisted technique remains controversial to date.

29.3.1.2 Oncological Outcomes

Compared with LDP for pancreatic cancer, RDP appears capable of finer lymph node dissection and more radical dissection. Concerning pancreatic cancer, Daouadi et al. [24] retrospectively compared 94 LDP with 30 well-matched RDP patients. The oncological outcomes were superior for RDP, with higher rates of margin-negative resection and improved lymph node clearance. Nevertheless, randomized clinical trials demonstrating that these potential advantages correspond to an actual superiority of RDP over LDP are still lacking.

29.3.2 Conclusion

Robot-assisted platforms aim to improve technical ability during a surgical procedure by providing highly defined 3D vision, eliminating tremor, and improving surgeon ergonomics. RDP can be safely adopted for left-sided pancreatic cancer by appropriate patient selection. RDP was similar to LDP in terms of most operative outcomes such as postoperative morbidity, POPF, blood loss, rate of blood transfusion, and LOHS. It was also associated with high rate of spleen preservation but longer operation time. RDP is associated with similar short-term oncological outcomes, such as margin-positive rate and numbers of lymph nodes harvested, compared with LDP. However, long-term results in terms of oncological adequacy of RDP for pancreatic cancer are not yet available. The main limitation associated with RDP is its greater costs. Other limitations of RDP include the potential need for more ports and the lack of tactile feedback. They are important barriers to widespread implementation of RDP. However, robotic technology has some nonmeasurable benefits: It is ergonomically more comfortable; it gives a feeling of stability and security; the surgeon feels that each surgical step of the procedure is safer and faster. The actual benefits of RDP over LDP are still under investigation.

29.4 Minimally Invasive Pancreaticoduodenectomy (MIPD) for Pancreatic Cancer

PD is considered one of the most challenging and complex operations in abdominal surgery. It is a highly demanding surgical operation because it needs very delicate manipulation during resection and very laborious reconstruction, which are the reasons for the extremely low diffusion and some degree of skepticism over the minimally invasive approach in the era of pancreatic head resection.

29.4.1 Indication and Incidence of MIPD for Pancreatic Cancer

The indications are the same as for the open pancreaticoduodenectomy (OPD) for surgeons experienced in MIPD, whereas surgeons with limited experience should exclude obese patients and limit the procedure to small pancreatic cancer confined to the pancreatic head without suspicion of vascular involvement.

According to the NCDB, of the 4421 patients who underwent PD in 2010 and 2011, 4037 (91%) patients underwent OPD and 384 (9%) underwent laparoscopic pancreaticoduodenectomy (LPD); 75.7% of hospitals performed OPD only and 1% of all centers performed ≥10 LPDs [30]. The limited incidence of pancreatic tumors reduced the number of the centers with sufficient caseload. Published clinical series of experience with MIPD have been limited so far to reports from high-volume institutions.

29.4.2 Perioperative and Oncological Outcomes of MIPD for Pancreatic Cancer

29.4.2.1 Perioperative Outcomes

Although MIPD is still not universally practiced, it is now receiving more interest with increasing proficiency in the laparoscopic skills of surgeons and advances in technology, including surgical robotics. In recent years, a large number of single-institution series of MIPD have been performed, and a variety of studies have been reported. On these series comparing LPD and OPD, LPD seems advantageous over OPD in terms of estimated intraoperative blood loss, but it results in longer operative time. The rate of postoperative complications, POPF, including clinically relevant POPF, and delayed gastric emptying are comparable following OPD and LPD. However, the latter is associated with shorter LOHS (Table 29.2).

Croome et al. [32], in large single-center study comparing 108 LPD and 214 open OPD cases well matched for pathologic parameters, reported a less intraoperative blood loss and shorter LOHS in the LPD group. The other perioperative outcomes, including PF, were similar.

Notably, LOHS and blood loss were significantly lower in patients who underwent MIPD in large single-institutional comparative study. LOHS reflects the incidence and severity of postoperative complications and is influenced by the health insurance system, culture, and enhancing recovery program of the each center. LOHS varied markedly in reported series. However, in the single-center study, we used the same criteria to determine the discharge, and the differences in LOHS between the LPD and the OPD groups might be reliable.

The less intraoperative blood loss in MIPD is often attributed to the magnified view afforded by laparoscopy and the robotic system, which enhances the surgeon's view of the structures surrounding the specimen, allowing precise dissection along appropriate planes. Because blood loss during MIPD can obscure the laparoscopic view and the robot, the surgeon needs to perform more careful dissection during MIPD.

29.4.2.2 Oncological Outcomes

For patients with pancreatic cancer, MIPD has several theoretical advantages. We will expect any long-term oncological benefits indirectly from other advantages of MIS, such as decreased inflammation, faster recovery, and increased access to postoperative multimodality therapies. There has been substantial interest in whether MIPD may lead to increased use and earlier

Table 29.2 Large single-center series comparing LPD and OPD

	Type of procedure	Song et al. [31]		Croome et al. [32]	Asbun et al. [33] (2012)
Inclusion period		2007–2012		2007–2012	2005–2011
Patients, n	LPD	93	11	108	53
	OPD	93	261	214	215
Operative time, min	LPD	483[a]		379	541[a]
	OPD	348[a]		388	401[a]
EBL, ml	LPD	570		492[a]	195[a]
	OPD	609		867[a]	1032[a]
Conversion rate, %		–		6.5	15
POPF, %	LPD	7 (B+C)		11 (B+C)	9.5 (B+C)
	OPD	7 (B+C)		12 (B+C)	9 (B+C)
DGE, %	LPD	1 (B+C)		9 (B+C)	9.5 (B+C)
	OPD	2 (B+C)		18 (B+C)	9.8 (B+C)
Morbidity, %	LPD	8 (CD>2)		5.6% (CD≥3b)	24.5 (CD>2)
	OPD	5 (CD>2)		13.6% (CD≥3b)	24.7 (CD>2)
LOHS, days	LPD	14[a]		6[a]	8[a]
	OPD	19[a]		9[a]	12.4[a]
Mortality, %	LPD	0 (30 days)		1% (in hospital)	5.7 (100 days)
	OPD	0 (30 days)		2% (in hospital)	8.8 (100 days)
Cancer, %	LPD	0	100	100	46.5
	OPD	0%	100	100	41.5
Tumor size, mm	LPD		28	33	27
	OPD		30	33	31
R0 resection rate, %	LPD		72.7	77.8	94.9
	OPD		81	77.6	83
Resected LN, n	LPD		15	21.4	23.4[a]
	OPD		16.2	20.1	16.8[a]
Time until adjuvant CTx, days	LPD		–	48[a]	58.6
	OPD		–	59[a]	64.1
Adjuvant CTx, %	LPD		81.8		76
	OPD		69.7		57
Progression-free survival	LPD		LPD = OPD	LPD > OPD[a]	–
Overall survival	LPD		LPD = OPD	LPD = OPD	–

B+C ISGPF grade B and C complications, *CD* Clavien-Dindo classification of surgical complications, *CTx* chemotherapy, *DGE* delayed gastric emptying, *EBL* estimated blood loss, *LDP* laparoscopic distal pancreatectomy, *LOHS* length of hospital stay, *ODP* open distal pancreatectomy, *POPF* postoperative pancreatic fistula

[a]Difference between groups with *P* value <0.05

initiation of postoperative chemotherapy, which, theoretically, is secondary to faster recovery time. Interestingly, Croome et al. [32] found earlier start of adjuvant therapy and longer progression-free survival in the LPD patients, although the overall survival was similar between the two groups. The assessment of new minimally invasive techniques for patients with malignant disease must consider oncological outcomes. The surrogates of oncological outcomes are typically assessed, which include number of lymph nodes harvested, rate of margin positivity, and long-term survival. Song et al. [31], in a large single-center case-control study comparing LPD and

OPD, reported no difference in either the number of retrieved lymph nodes or the rate of R0 resection between the two groups. However, long-term oncological outcomes were not addressed in this study. In another comparative study, Asbun et al. [33] included 39 patients who underwent LPD and 100 patients who underwent OPD for pancreatic cancer. They showed no difference in R0 resection and a higher mean number of lymph nodes harvested in the LPD group. Buchs et al. [34] compared 33 patients who underwent RPD with 27 patients who underwent OPD. They demonstrated no difference in R0 resection and a higher mean number of nodes harvested in the robotic group than in the OPD group.

Chalikonda et al. [35] compared 14 patients who underwent RPD and 14 patients who underwent OPD. This group demonstrated a lower proportion of patients with margin-positive resection in the robotic group than in the OPD group, with no significant difference in the mean number of harvested lymph nodes.

The large single-institutional data suggest that MIPD is feasible, with outcomes that are comparable to OPD for a select group of patients. However, these data are from high-volume institutions with highly experienced pancreatic surgeons.

Increasing surgeon experience and hospital volume is significantly associated with reduced morbidity and mortality after PD [36–38]. Therefore, interpretation of data from a single-institution series with regard to outcomes from MIPD is potentially limited by lack of generalizability. Adam et al. [39], for example, demonstrated that short-term mortality after MIPD is substantially higher among less experienced centers. MIPD is only safe if surgeons are experienced in pancreatic and minimally invasive surgery in high-volume centers. The use of a robotic platform has already shown several potential advantages, such as magnified intraoperative imaging, increased range of motion within narrow and deep spaces, and enhanced surgical dexterity, which afford optimal control during surgical dissections and reconstructions. Several limitations of LPD have been partially overcome by robot-assisted surgery, but the actual benefits of RPD for patients are still under investigation.

Conclusion

MIPD is not only technically feasible and safe in pancreatic cancer but may also provide advantages such as shorter LOHS and quicker recovery. In recent years, a large number of single-institution series of MIPD have been performed, and a variety of studies have been reported. However, there is currently no powerful evidence that informs the advantages of using MIPD over conventional OPD. Considering the complexity and the lack of long-term oncological outcomes of MIPD, we suggest that it should be performed in a high-volume pancreatic surgery center in patients with small pancreatic cancer distant from the major vessels. Further studies, randomized trials, or high-quality nonrandomized prospective studies comparing MIPD and OPD are needed to expand the scope of MIPD with firm conclusion.

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Part V

Morbidity and Perioperative Care of Pancreatectomy

Pancreatic Fistula

30

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30.1 Definition, Diagnosis, and Grading

Postoperative pancreatic fistula (POPF) represents the complication that predominantly influences the perioperative outcome in pancreatic surgery. Its incidence ranges between 5% and 30% [2] of pancreatic resections performed at high-volume centers. The complexity of patients developing a POPF requires a highly qualified multidisciplinary approach for its diagnosis and management. Most of these patients can be successfully treated conservatively. However, even when adequately managed, POPF has always the potential to lead the patient to severe clinical condition and eventually death. Even if the meaning of the term "pancreatic fistula" could be intuitive, the appropriate medical definition able to discriminate between an "innocent" pancreatic spilling and a "clinically significant" leak has represented a matter of debate for many years.

The International Study Group on Pancreatic Fistula (ISGPF) has proposed in 2005 a unique definition of POPF that has been then widely approved and used by the entire international surgical community. Thanks to this contribution, common criterion to define POPF is now available, resulting in the possibility to compare outcomes and surgical experiences among different centers worldwide [3]. The ISGPF defined POPF as "an abnormal communication between the pancreatic ductal epithelium and another epithelial surface containing pancreas-derived, enzyme-rich fluid" [1]. This condition might be either due to a leak from the pancreaticojejunostomy or as consequence of pancreatic surface damage. In addition to this pathophysiological mechanism, the ISGPF defined the diagnostic criteria of POPF as an "output via an operatively placed drain (or a subsequently placed, percutaneous drain) of any measurable volume of drain fluid on or after postoperative day 3, with an amylase content greater than 3 times the upper normal serum value."

Since this definition meets a wide spectrum of different clinical conditions, from asymptomatic to critical patients, the ISGPF introduced different grades of POPF based on clinical and radiological criteria (Table 30.1). The *grade A* represents a biochemical fistula without corresponding clinical symptoms. The patient is orally fed, without signs of infection, and appears generally well; for this status no specific treatments are required. The *grade B* fistula requires a change in the management from the usual

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Table 30.1 Parameters for postoperative pancreatic fistula grading

Grade	A	B	C
Clinical condition	Well	Often well	Ill appearing/bad
Specific treatment[a]	No	Yes/no	Yes
US/CT (if obtained)	Negative	Negative/positive	Positive
Persistent drainage[b] (after 3 weeks)	No	Usually yes	Yes
Reoperation	No	No	Yes
Death related to POPF	No	No	Possibly yes
Signs of infections	No	No	Yes
Sepsis	No	Yes/No	Yes/No
Readmission	No	Yes/No	Yes/No

Reproduced from Bassi et al. [1]
US ultrasonography, *CT* computed tomographic scan
[a]Partial (peripheral) or total parenteral nutrition, antibiotics, enteral nutrition, somatostatin analogues, and/or minimal invasive drainage
[b]With or without a drain in situ

postoperative pathway. Although this patient might appear in good condition, he needs specific treatment to enhance the fistula closure. These treatments may include either parenteral or enteral nutrition and the administration of somatostatin analogues. When signs of infections are present, antibiotics are needed, and abdominal imaging, such as CT or US, might show a collection that potentially requires drainage. Many patients with grade B fistula need long-standing intra-abdominal drainage that could remain in place even after the hospital discharge. The *grade* C is defined when major changes in the clinical management from the normal clinical pathway are necessary. The cross-sectional imaging usually detects one or more peripancreatic fluid collections that must be drained since conditioning the clinical condition of the patient. A POPF-related sepsis syndrome is present and this might require ICU staying. If the clinical condition is critical, a surgical re-exploration might be warranted. Grade C POPF is a life-threatening condition and it is associated with a 30–35% mortality rate [4, 5].

Of note, the POPF grade can be assessed only retrospectively after the complete resolution of the clinical condition. This reflects the aim of ISGPF classification to provide a reliable definition and grading of POPF, without an actual prognostic value while the condition is ongoing.

30.2 Clinical Presentation

POPF is defined by an initial amylase-rich effluent, as well as the presence of clinical signs and symptoms or radiological evidence of peripancreatic fluid collections [5, 6]. Patients with clinically relevant fistulas (both B and C grades) usually show specific clinical manifestations since the first postoperative days. However, in a minority of cases, symptoms can be non-specific and leading to a late identification of the fistula. Non-specific symptoms can be abdominal pain, nausea, vomiting, and failure to pass flatus or stool. Clinical manifestations include fever greater than 38 °C; postural hypotension; a tender, distended, or rigid abdomen; localized abdominal or wound erythema; and warmth or swelling [1, 5, 6]. Both the quality and the quantity of drain emission are important diagnostic parameters. When a fistula occurs, the effluent is usually defined as "sinister" [1], and its appearance depends on the pancreatic juice activity on the surrounding tissues and on the presence of an anastomotic dehiscence. Quality can be classified as "pure" when the effluent constituted exclusively of pancreatic juice or "mixed" when pancreatic juice is combined with bile or enteric fluid [5]. Many other definitions are present in the literature including "Coca-Cola-like," "murky," "whitish," "bilious," "bloody," "purulent," and "foul smelling" when a infection occurs [4].

Moreover, POPF can be classified as of "low" or "high output," depending on whether the daily volume of fluid exceeds the 200 ml. Based on the timing of manifestation, POPF can be defined as "early" if it occurs within the first week after surgery or "latent" when an initial low drain amylase activity occurs, but ultimately the patient exhibits the clinical or radiological findings of a POPF (about 5% of all resections) [5, 6]. In contrast with an early POPF, latent is usually more severe and twice as likely to be infected. In these cases hospital readmission is required, and the duration of the staying is significantly longer and associated with higher costs [6].

30.3 Risk Factors

The POPF development is related to a multifactorial condition, where the major role is played by patients, pathological, and surgical factors [7]. The most significant risk factors for the development of POPF after pancreaticoduodenectomy (PD) are a soft pancreatic parenchyma and a non-dilated main pancreatic duct [8, 9], as both affect the reconstruction of the pancreatic-enteric anastomosis. It is well established that a "healthy" pancreatic parenchyma without fibrotic modifications is more susceptible to injury during the operative dissection and the anastomosis confectioning. In this case, the texture is friable, and sutures are more vulnerable to tear through the parenchyma as well as through a fragile duct lining. Moreover, a small pancreatic duct is more challenging to be reconstructed, with a significant probability to occlude or dehisce once the anastomosis is performed. The pathophysiological mechanism behind the POPF development is related to the exocrine function that is generally preserved in soft pancreatic glands, resulting in a preserved secretion of the pancreatic juice rich in proteolytic enzymes. Neoplasms that infiltrate the main pancreatic duct determining upstream chronic pancreatitis, such as adenocarcinoma, are often associated with a harder parenchyma and a dilated main pancreatic duct (MPD). Conversely, masses that do not occlude the MPD like cystic, neuroendocrine, and ampullary tumors are considered as risk factors for POPF.

Other factors are associated with POPF and include age, comorbidities, body mass index, jaundice, neoadjuvant chemotherapy, pancreatic steatosis, intraoperative blood loss, and operative technique [7]. Based on these factors, several predictive scores have been developed to stratify the patient's risk to develop POPF after PD [7, 8, 10–12]. In particular, Callery et al. [8] proposed a risk score that considers the preoperative diagnosis and other intraoperative data such as the gland texture, the pancreatic duct diameter, and the intraoperative blood loss (Table 30.2). The assessment of these factors into scores has been used to assign each patient into a risk zone: negligible (0 points), low (1–2 points), moderate (3–6 points), and high (7–10 points), with a good correlation with POPF development [13]. Determining the pre- or intra-operative POPF risk allows clinicians to a proper informed consent, as well as to individualize operative and postoperative conduct. Recent evidences [14] suggest that these scores may help to recognize low-risk patients suitable for no drain placement, as well as high-risk patients in which additional treatment should be advocated. Specifically, in

Table 30.2 FRS for the prediction of CR-POPF after pancreatoduodenectomy

Risk factor	Parameter	Points
Gland texture	Firm	0
	Soft	2
Pathology	Pancreatic adenocarcinoma or pancreatitis	0
	Ampullary, duodenal, cystic, islet cell, etc.	1
Pancreatic duct diameter	≥5 mm	0
	4 mm	1
	3 mm	2
	2 mm	3
	≤1 mm	4
Intraoperative blood loss	≤400 ml	0
	401–700 ml	1
	701–1000 ml	2
	>1000 ml	3
		Total 0–10 points

Reproduced from Callery et al. [8]

these patients clinicians may decide to start a prophylactic treatment with somatostatin or its analogues. In addition, they might consider other intraoperative strategies such as an upfront total pancreatectomy, to perform a pancreaticogastrostomy over than a classical pancreaticojejunostomy, the placement of intraductal stents, or a feeding jejunostomy [8, 15, 16].

30.4 Treatment

The early treatment of POPF is conservative. This consists in limiting the oral intake, administering somatostatin analogues to inhibit the pancreatic exocrine secretion, and providing adequate nutritional support and, if necessary, antibiotics. If this first-line management fails and imaging demonstrates non-drained abdominal collections, interventional procedure might be warranted. Finally, a reoperation may be required in selected critical patients whenever minimally invasive approaches fail to improve the clinical condition.

30.4.1 Somatostatin and Its Analogues

As previously stated, the active exocrine secretion of pancreatic enzymes has a key role in the development of POPF. During the last decade, several pharmacological approaches have been investigated in order to successfully inhibit the pancreatic exocrine secretion. Somatostatin is a 14-amino acid peptide that has an active role on the digestive system by inhibiting pancreatic exocrine, biliary, and small bowel secretions and increasing the water absorption [18]. When any digestive fistula occurs, somatostatin reduces its output with potential positive effects on its natural course. The major limitation of somatostatin is its very short half-life (1–2 min), necessitating for continuous intravenous infusions. In order to avoid long infusions, synthetic analogues such as octreotide and pasireotide are nowadays available (with a half-life of 120 min and 11 h, respectively) [18, 19]. These analogues allow for intermittent subcutaneous dosing schedules and differ from each other in the binding profile for somatostatin receptors [18, 19].

Several randomized controlled trials were conducted with the aim to demonstrate the effectiveness of somatostatin and its analogues on POPF mitigation, but results are conflicting [20, 21]. The main bias of these trials was substantially represented by the heterogeneity with respect to the definition of POPF, the type of analogues administered, the pancreatic resection performed, and the timing of the treatment. In 2013, a Cochrane systematic review [21] compared the use of somatostatin analogues with a no-somatostatin group in pancreatic surgery. Authors reported no differences in the incidence of clinically significant POPF and in the length of staying, but with lower overall postoperative complications in the interventional group. Authors concluded that considering the lack of serious adverse effects and the relatively low costs, somatostatin analogues should be recommended routinely in pancreatic surgery [21]. Recently, another randomized controlled trial considering only high-risk patients failed to demonstrate the aforementioned benefits for the octreotide group [22]. Interesting results have been reported by Allen et al. [19] in a randomized, double-blind placebo-controlled trial on pasireotide. Authors demonstrated a significant reduction of clinically relevant POPF in the pasireotide group (7.9% vs 16.9%) with no grade C fistula occurring in this cohort [19]. After over 20 years and many studies, there are still no definitive conclusions on this matter. For these reasons, further high-quality RCTs are necessary before considering somatostatin and its analogue as standard treatment in pancreatic surgery.

30.4.2 Parental and Enteral Nutrition

Nutritional support is an essential element in the management of patients with clinically relevant POPF, either through parental nutrition (PN) or enteral nutrition (EN). Most of these patients need to be kept with “nothing by mouth” as the oral food intake enhances the pancreatic juice secretion [1]. In addition, artificial nutrition could improve the wound healing necessary for the anastomotic leak closure [23]. Postoperative malnutrition may be associated with high-output

POPF (>200 mL of daily exocrine secretion), leading to a significant loss of fluid and electrolyte imbalance [24]. In this matter, EN is considered by the last evidences as the nutritional support of choice, avoiding the well-known disadvantages related to long-term PN such as infections (septicemia, wound infections) and metabolic complications (hyperglycemia) [24–27]. EN prevents the atrophy of gastrointestinal mucosa and preserves the intestinal bacterial flora architecture, resulting in the inhibition of the microbial translocation from the gut to the bloodstream [23, 28]. In addition, an open-label randomized controlled clinical trial by Klek et al. [27] demonstrated that EN, compared to PN, is associated with an increased faster rate of POPF closure and with a lower rate of nutrition-related complications.

In case of clinically relevant POPF, EN is administered via a nasal-jejunal tube or a jejunostomy tube. The rationale consists in a continuous feeding of the distal jejunum, allowing for a resting in the exocrine pancreatic secretion [29]. For this reason, the tube must be placed distal to the pancreas, below the Treitz's ligament or, in case of a PD, distal to entero-enteric anastomosis [17, 29].

Of note, the EN therapy for POPF needs to be adjusted according to the course of the complication and the intestinal tolerance. The ESPEN guidelines suggest an energy supply that should not exceed 20–25 kcal/kg BW/day during the acute and initial phase of critical illness, which can be increased up to 25–30 kcal/kg BW/day during the anabolic recovery phase. If these target values are not reached, supplementary PN should be added [30]. In elective upper gastrointestinal surgical patients, EN with immune-modulating formulae (enriched with arginine, nucleotides, and omega-3 fatty acids) is superior to standard enteral formulae [30]. Currently there is no agreement on routine use of tube feeding in pancreatic surgery [31, 32], but an intraoperatively prophylactic placement should be at least considered in patients with high risk to develop POPF [8].

30.4.3 Interventional Radiology and Endoscopic Therapy

The role of interventional radiology in the POPF treatment is becoming increasingly relevant. Currently, around 7–12% [33, 34] of pancreatic resections are complicated by abdominal fluid collections, and these are mostly due to POPF that are not properly drained. These collections are rich in amylase and may lead to potentially fatal complications. Patients might be initially asymptomatic or suffer from mild abdominal discomfort and pain. Subsequently, the typical signs of infections might develop despite the antibiotic therapy, such as fever and leukocytosis, eventually leading to sepsis [35]. In the most serious cases, if the patient is hemodynamically stable, imaging-guided percutaneous drainage may offer a safe alternative to surgical exploration, as it is less invasive, requires shorter recovery time, and is associated overall to a lower morbidity [36]. In recent series, the 5–7% of PD and up to 14–20% of distal pancreatectomy (DP) [34, 37–39] developed intra-abdominal collections requiring a percutaneous drainage. This procedure might be either ultrasound (Fig. 30.1) or computed

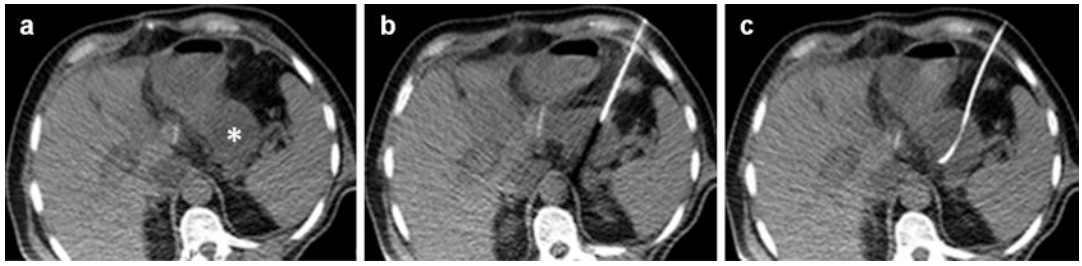

Fig. 30.1 Computed tomography-guided percutaneous drainage of a large collection from a pancreaticojejunostomy leak. (**a**) Large retro-gastric collection (*) from pancreatic anastomosis leak. (**b**) The collection is punctured using the Seldinger technique. (**c**) A pigtail drain is placed into the collection

tomography guided, according to the operator expertise, and mostly using the Seldinger or the tandem-trocar technique [36, 37, 40]. The aspirated fluid must be sent for amylase value assessment and microbiology cultures. The catheter should be as large as possible since the collected fluid is often viscous and hard to drain. The cause of this viscosity might be related to the presence of pus and bile or to the local fat necrosis due to the pancreatic juice leak [37]. Imaging-guided percutaneous drainage is associated with high technical success rates (95–100%) [37, 40, 41]. However, more than 30% of patients require a second procedure (catheter exchange, increase in catheter size, catheter repositioning, additional catheter) [37]. The related morbidity is low but not negligible, and it includes bleeding and visceral perforation [36, 40, 41]. Recently, endoscopic ultrasound (EUS)-guided drainage has become a viable alternative for the treatment of peripancreatic fluid collections. EUS drainage avoids the implications of external drainage such as the frequent need for maintenance, the risk of local skin irritation and infection, and the electrolyte loss, resulting in an improving of quality of life. The procedure is performed under sedation or general anesthesia, using standard endoscopic supplies. The drainage is achieved by passing through the gastric or the duodenal wall and controlled, thanks to the high-resolution and real-time imaging of the pancreas and the surrounding vasculature. The tract is then safely dilated, and one or more double pigtail stents are left in place, allowing for a rapid fluid evacuation [41, 42]. Although the experience is still limited, the reported technical success rate is around 100% with a clinical success rate of 93–97%, even though one out of three patients would require a second EUS drainage [41, 42]. Most of these experiences refer to patients who underwent DP [41, 42] although series including more challenging PD cases exist [41, 43]. The interventional timing could be another limiting factor for EUS-guided drainages, as a thicker wall surrounding the collection is needed. However, while most of the studies excluded patients with fluid collection less than 4 weeks old because of the presumed lack of the collection wall [40, 42], Tilara et al. [35] recently reported a series of 17 patients who underwent early drainage (<30 postoperative days) showing that EUS-guided drainage is feasible and safe.

Finally, in case of refractory POPF after DP or enucleation (e.g., patients without signs of improvement after prolonged drainage placement) may benefit from sphincterotomy and pancreatic duct stenting, in the attempt of decompressing the pancreatic duct and promoting the physiologic discharge of pancreatic fluid. The experience with this technique is still limited, and because of the potential risk for acute pancreatitis, it should be nowadays employed only in highly selected cases [44–46].

30.4.4 Surgical Therapy

Despite the efficacy of a minimally invasive first-line management, more than half the patients with C grade POPF would require a surgical reintervention [4]. These patients frequently develop warning signs such as elevated white blood cell count, fever, tachycardia, abdominal pain, or distension [4, 47]. The drain output is usually "sinister" or suddenly no longer present due to drainage dislocation. In the most worrisome setting, a late bleeding can occur as a consequence of a ruptured pseudoaneurysm caused by pancreatic juice erosion. The decision whether to operate is often difficult, but it could be triggered whenever the state of illness is supported by an intra-abdominal collection non suitable for percutaneous drainage, in case of peritonitis or perforation [48]. The relaparotomy for POPF is a challenging operation. Usually, the patient is in a life-threatening condition, and the surgical procedure is made more difficult by adhesions, inflammation, and loss of typical surgical landmarks. The tissues are fragile, and the risk of collaterally damaging the other biliary or digestive anastomosis is relevant. The pancreatic stump may be compromised by necrosis, and resulting crumbly, with tendency to bleed. In these cases the surgeon has to choose between the preservation of the pancreatic remnant and a rescue completion pancreatectomy (RCP). Because it

eliminates the risk of a new leakage, some authors advocate RCP as the standard of care [49]. On the other hand, RCP might result technically difficult and leads to an irreversible endocrine and exocrine insufficiency. Unfortunately evidences in this regard come from small retrospective series, and data about RCP morbidity and mortality (ranging from 24% to 71%) are contradictory without a common agreement [49–52]. Depending on the experience of the surgeon, RCP should be reserved to selected cases. RCP could not be avoided whenever the distal pancreatic remnant is replaced by necrosis, if the pancreatic anastomosis is largely disrupted with difficulty to detect the main pancreatic duct on the pancreatic stump, and finally every time the splenic artery ligation is warranted to ensure hemostasis [48].

Pancreas-preserving approaches are technically easier than RCP and have the advantage of sparing the pancreatic function. However, should keep in mind that further surgical operations may be required to control the persistence of the POPF and its complications [50, 53, 54] (Fig. 30.2).

The pancreas-preserving procedures can be categorizing as follows:

- Debridement and drainage of peripancreatic collections (Fig. 30.2a)
- Attempt to repair or re-perform pancreatic anastomosis (Fig. 30.2b–c)
- Pancreatic remnant abandonment (Fig. 30.2d–e)

The debridement and drainage without reconfectioning the pancreatic anastomosis might be performed electively if the pancreatic anastomosis is in good condition. Another scenario is whenever the local conditions are particularly challenging and the pancreatic remnant (PR) handling is dangerous due to the risk to damage the surrounding viscera and vessels. In this latter setting, the surgical drainage may be the only possible option.

The attempt to repair the pancreaticojejunal anastomosis is rarely successful and limited to small and localized anastomotic injuries and when the pancreatic stump is firm enough to hold additional sutures. [55]. Whereas the anastomosis is largely disrupted but the PR is suitable, a new anastomosis can be performed after an additional short resection (of about 1 or to 2 cm). If the main pancreatic duct is small or not detectable, a pancreaticogastrostomy might be suitable (Fig. 30.2b) [56]. Alternatively, it is possible to perform a new "bridge" stenting anastomosis with (Fig. 30.2c) or without disconnection of PR [48, 54]. This bridge consists of a 5- or 8-Fr plastic tube stent that is placed between the jejunal enterotomy and the pancreatic duct and secured with an absorbable suture at both the extremities. On the jejunal side, the stent can be placed through the enterotomy employed for the original anastomosis. The bridge stents could be internal or alternatively externalized through the jejunal wall in a Witzel fashion and then through the abdominal wall [54]. A similar technique was described by Paye et al. [48], consisting in the placement of an exteriorized pancreatic stent and either staple or exteriorize the jejunal stump. Restorative laparotomy can be performed >3 months after the salvage procedure, with the stent being used as a guide to re-perform the pancreatic anastomosis. Finally, if the anastomosis is largely disrupted and the PR conditions are unfavorable, the remnant can be abandoned without internal connections. In these cases the PR can undergo a subtotal resection (by the preservation of a small tract of approximately 4 cm), and/or the pancreatic duct is closed either by suturing or injection of biological glue, or it is drained by external wirsungostomy [50, 57, 58] (Fig. 30.2d–f). In details, the wirsungostomy consists in the placement of a stent into the pancreatic duct that is passed through the abdominal wall and stitched to the skin, developing a "controlled" pancreaticocutaneous fistula (Fig. 30.3) [57]. All these techniques include the resection of the dehiscent jejunal loop with the aim to convert a "mixed" POPF into a "pure" POPF, avoiding the activation of pancreatic enzymes by the bilioenteric secretions. In spite of the theoretical long-term advantages of the pancreas preservation, this choice should be made always considering the high risks of a long-standing POPF [50]. Regardless of the specific surgical approach, it

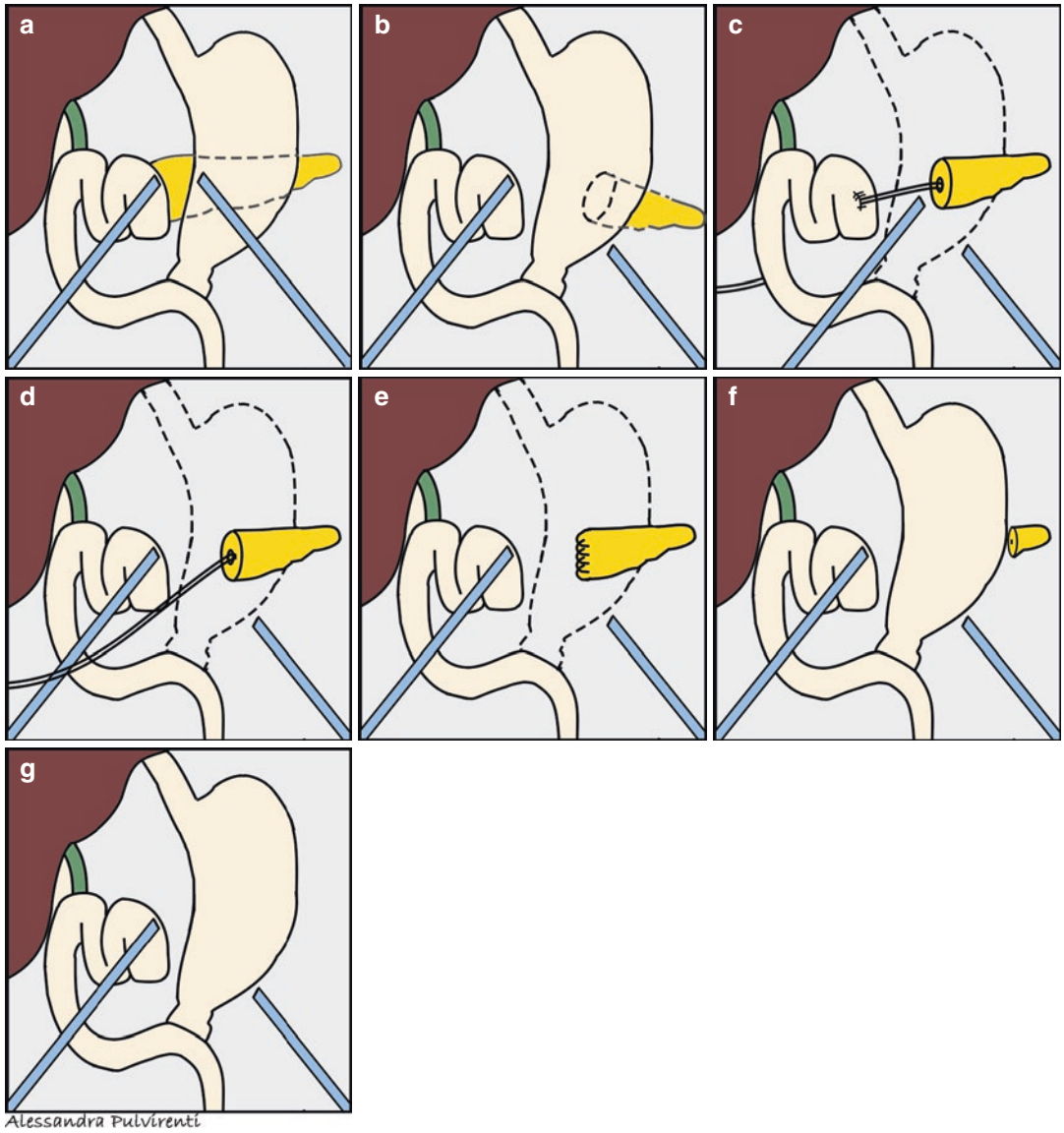

Fig. 30.2 Surgical options for C grade POPF. (**a**) Pancreaticoduodenectomy with pancreaticojejunal reconstruction, drainage of peripancreatic collections. (**b**) Conversion from pancreaticojejunostomy to pancreaticogastrostomy. (**c**) Bridge stenting anastomosis with external wirsungostomy. (**d**) Pancreatic remnant abandoning with main pancreatic duct external drainage by wirsungostomy. (**e**) Pancreatic remnant abandoning and main pancreatic duct closure by suturing. (**f**) Pancreatic remnant abandoning with subtotal resection. (**g**) Rescue completion pancreatectomy

has been shown that subsequent operations are required in nearly 50% of patients that undergo a second laparotomy for POPF. These patients might develop septic complications requiring further open abdominal lavage and secondary abdominal wall closure [55]. A surgical option for external refractory POPF is fistula-jejunostomy. The surgical repair consists in the identification of the established fistula tract around a drainage tube (distant from the pancreatic gland) and its eventual anastomosis with a Roux-en-Y jejunal loop. This technique is associated with a very high rate of success, despite the very limited indications [59, 60].

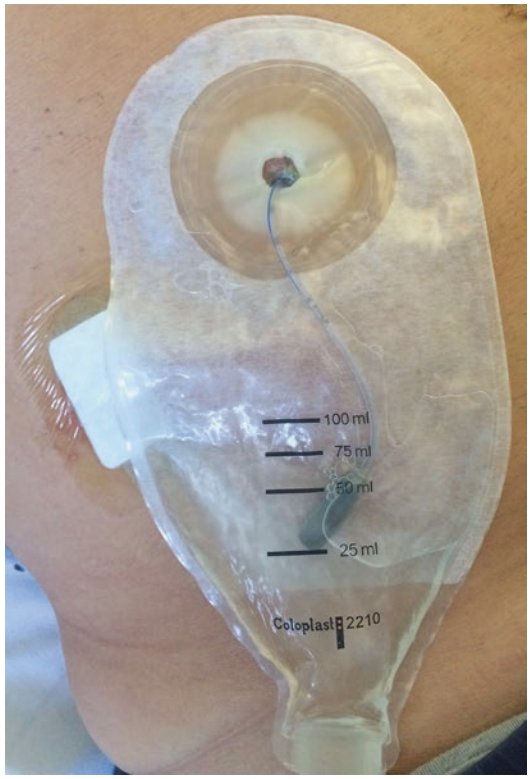

Fig. 30.3 External wirsungostomy and pure pancreaticocutaneous fistula with "spring-water" (*) appearance

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Delayed Gastric Emptying

31

Masaji Tani

Pancreaticoduodenectomy (PD) is the standard procedure for pancreatic head and periampullary diseases. PD is an aggressive surgery, and some persistent complications of PD have been reported, which include pancreatic fistula, intra-abdominal abscess, intra-abdominal hemorrhage, and delayed gastric emptying (DGE). Especially, pancreatic fistula is associated with all of these postoperative complications and contributes to overall morbidity and mortality [1–4].

Conventional PD was combined with distal gastrectomy with or without truncal vagotomy. Distal gastrectomy was common to prevent postoperative peptic ulcers at the anastomosis of gastrojejunostomy, in the era of no anti-peptic agent, which represented H2-receptor antagonists and proton pump inhibitors. DGE is not always associated with postoperative pancreatic fistula and has been a frustrating complication for which the mechanism has not been fully clarified. Although DGE is not life threatening and can be treated conservatively, it results in discomfort and significant prolongation of the hospital stay that adds to hospital costs [5], impaired oral intake, and delayed initiation of postoperative adjuvant therapy. A grade C DGE patient incurs more than three times the cost incurred by a patient without DGE [5]. Therefore, DGE is an important complication and needs to be minimized in patients who have undergone PD.

Traverso and Longmire reported success with pylorus-preserving pancreaticoduodenectomy (PPPD); however, PPPD was performed for the patients with chronic pancreatitis [6]. PD patients easily develop postoperative nutritional insufficiency due to diarrhea, dumping, dyspepsia, post-gastrectomy syndrome, and small bowel absorption. Aggressive operations have been developed to treat abdominal diseases. Additionally, an aggressive curative operation was indicated for the surgical treatment of malignant diseases. On the other hand, aggressive operations take over a lot of physical functions and are risky due to complications including operation-related death. Organ preservation has become widely popular in the abdominal operations. Stomach preservation is increasing in pancreatic head resection for not only benign diseases but also malignant diseases. PPPD has been widely performed without enough evidence of postoperative outcome when compared to PD, especially, the survival benefit, without waiting for clinical trials including randomized controlled trials (RCTs). Surgeons were dissatisfied with the postoperative course after conventional PD.

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31.1 RCTs on PD Versus PPPD

Gastric emptying physiologically requires coordination of the gastric antrum, pylorus, and duodenum via paracrine messages and extrinsic stimulations from the vagal nerve. The pathogenesis of DGE after PPPD has been speculated to include several factors such as local ischemia of the antrum, the absence of duodenal motilin [7], gastric atony caused by vagotomy [8], and gastric dysrhythmias secondary to other complications like pancreatic fistula and abscess [9]. Moreover, univariate analyses have indicated that other factors associated with DGE after PPPD could be the length of the preserved proximal portion of the duodenum, the volume of gastric juice, the duration of gastric tube placement, or administration of cisapride [10]. On the other hand, DGE sometimes occurred in PD patients too. Which is a better technique?

Four RCTs have been conducted to reveal the superiority of PPPD over PD, revealing that the outcome of PPPD is similar to that of PD [11–14]. Table 31.1 shows the summary of results in RCTs. Lin and Lin showed the tendency of increasing DGE in PPPD compared to PD (38% vs 7%, $P = 0.08$); however, this RCT did not investigate survival [11]. All of the RCTs showed that PPPD had decreased intraoperative bleeding compared to PD. Moderate quality evidence suggests that PPPD is a faster procedure with less blood loss compared to PD.

In all of the RCTs, it was possible that underpowered trials had overestimated the results due to small scale studies, and it was concluded that large absolute differences in other key outcomes are unlikely; excluding relatively small differences will, however, require larger, stronger methodologies [15].

Table 31.1 Summary of four prospective RCTs to compare between PD and PPPD

Author	Lin	Seiler	Tran	Seiler
Year	1999	2000	2004	2005
Country	Taiwan	Switzerland	Netherlands	
	Switzerland			
Operation (PD/PPPD)	15/16	49/37	83/87	66/64
Operation time (minutes)				
PD	237	476	200	449
PPPD	215	404	300	382
Estimate blood loss (ml)				
PD	687	2096	2000	1500
PPPD	451	1453	2000	1196
DGE				
PD (%)	7	45	23	45
PPPD (%)	38	37	22	31
Pancreatic fistula				
PD (%)	13	2	14	2
PPPD (%)	0	3	13	3
Mortality				
PD (%)	0	5	7	3
PPPD (%)	7	2.7	3	2
Survival				
PD	NA	16 m[a]	14 m[b]	ND
PPPD		24 m[a]	15 m[b]	

NA not available, *ND* not different
[a]Median survival
[b]Median disease free survival

Diener reported the Cochrane Database systematic review. A total of 465 participants demonstrated vast heterogeneity with regard to the quality of the methodology and outcome parameters. The incidence of DGE showed no significant difference between PD and PPPD. Hospital mortality, morbidity, and overall survival also showed no significant differences. However, the operating time (95% CI −105.70 to −30.83; *P* value 0.0004) and intraoperative blood loss (95% CI −0.96 to −0.56; *P* value <0.00001) were significantly reduced in the PPPD group rather than PD group. All significant results are associated with low quality of evidence, and as determined on the basis of this, no evidence suggests relevant differences in mortality, morbidity, or survival between the two operations [16].

31.2 Pylorus-Resecting Pancreaticoduodenectomy (PRPD)

The gastrectomy site might affect the rate of occurrence of DGE and survival of cancer patients; however, there is no data on the gastrectomy site. At what distance is the gastrectomy performed from the pylorus ring? How much stomach is remnant? All of the four RCTs demonstrated that the incidence of DGE in PPPD was similar to that in PD [11–13]. If only extended gastrectomy patients were included in those studies, those RCTs might demonstrate other results. Kawai et al. reported the result of an RCT focused on the pylorus ring, PPPD versus pylorus-resecting PD (PRPD), with near total stomach preservation. They gave it the name of pylorus-resecting PD (PRPD) and proposed this as a new procedure [17]. It was determined that the incidence of DGE was 4.5% in PRPD and 17.2% in PPPD, with a significant difference. This RCT is an epoch to determine whether the pylorus ring affects the occurrence of DGE or not, and it revealed that the pylorus ring is the deciding factor in the occurrence of DGE.

31.3 Subtotal Stomach-Preserving Pancreaticoduodenectomy (SSPPD)

Japanese surgeons have previously performed SSPPD, which is PD combined with an intended antrectomy; however, SSPPD does not clearly define the gastrectomy site [18]. A meta-analysis demonstrated that the occurrence of DGE favors SSPPD compared to PPPD (odds ratio 2.75, 95% CI 1.75–4.30, $P < 0.00001$) [19]. However, PRPD was included in the SSPPD group in this meta-analysis. Distal gastrectomy in PD is associated with gastric emptying via gastroenteric hormones [20], and the RCT (PPPD vs. PRPD) has clarified the importance of the antrum [20]; therefore, the concept of PRPD is different from that of SSPPD.

31.4 Reconstruction Route of PPPD

Reconstruction route was previously thought to be important in the occurrence of DGE. Two reconstruction routes are usually considered for duodenojejunostomy, the antecolic route or the retrocolic route in PPPD. However, Tani et al. paid attention to the reconstruction, and an RCT was conducted to analyze whether or not an antecolic route reduces the incidence of DGE compared to a retrocolic route. DGE occurred in 5% of patients with the antecolic route for duodenojejunostomy versus 50% with the retrocolic route ($P = 0.0014$). Those with the antecolic route had a significantly shorter duration of postoperative nasogastric tube drainage than did those with the retrocolic route (4.2 days versus 18.9 days, respectively, $P = 0.047$). This result demonstrated the superiority of the antecolic route in prevention of DGE by interim analysis [21]. Therefore, this RCT investigated a small cohort of patients, although this RCT was statistically planned for 140 patients. Table 31.2 shows the summary of RCTs focused on only PPPD assigned into two groups: antecolic reconstruction and retrocolic reconstruction.

Table 31.2 Summary of four prospective RCTs to compare between antecolic reconstruction and retrocolic reconstruction in PPPD patients

Author	Tani	Tamandl	Imamura	Eshuis
Year	2006	2014	2014	2014
Country	Japan	Austria	Japan	Netherlands
Operation (ante/retro)	54/57	20/20	36/28	60/60
DGE				
Antecolic (%)	5*	17	12	58
Retrocolic (%)	50	24	20	54

*$P = 0.0014$

Recently, a meta-analysis of 6 RCTs consisting of 588 patients evaluated the effect of antecolic gastroenteric reconstruction compared to retrocolic gastroenteric reconstruction (DGE antecolic 32.5%, retrocolic 39.9%; odds ratio 0.57; 98% CI 0.23–1.43; $P = 0.23$) and analyzed the benefit of antecolic gastroenteric reconstruction after PPPD [22].

Gastro-scintigraphy demonstrated that the route of gastroenteric anastomosis after PD does not influence DGE, and this study was thought to be important to assess the gastroenteric movement in the solid phase. In addition, the quality of life was also similar after operations via the antecolic and retrocolic routes [22]. Imamura et al. demonstrated that the incidence of DGE was similar in antecolic and retrocolic duodenojejunostomy after PPPD; however, the DGE that occurred in the retrocolic group was twice as high as that in the antecolic group. Moreover, both Tmax and T1/2 of the antecolic group were significantly better than those of the retrocolic group [23]. These results suggest recommending antecolic reconstruction after PPPD.

It is important to consider the reason why the incidence of DGE is significantly lower in an antecolic route than a retrocolic route. What is the advantage of an antecolic reconstruction after PPPD? The antecolic route has two advantages compared to the retrocolic route on the occurrence of DGE; one is the vertical straight form of the stomach after reconstruction, and another is the distance between the site of pancreaticojejunostomy and the stomach. The vertical straight form of the stomach supports gastric emptying by passive movement due to gravity force. Stomach of antecolic route is separated from pancreaticojejunostomy by transvers colon. Even if the clinical pancreatic fistula is not shown, subclinical pancreatic fistula might affect surround organs including stomach adversely, and it is thought that the separation of the stomach from pancreatico-jejunostomy is effective to prevent the occurrence of DGE. When expert pancreatic surgeons follow the two concepts of vertical straight form and separation of the stomach from pancreatico-jejunostomy, it might remove an advantage of an antecolic reconstruction

31.5 Billroth II or Roux-En-Y

There have been no studies that compare the incidence of DGE in terms of the reconstruction method. The objective of the RCT was to evaluate the superiority of Billroth II (B-II) over Roux-en-Y (R-Y) reconstruction on decreasing the incidence of DGE after SSPPD. DGE occurred in 5.7% of patients in the B-II group and in 20.4% of patients in the R-Y group ($P = 0.028$). Patients in the B-II group had a significantly shorter hospital stay after the operation than did patients in the R-Y group (31.6 ± 15.0 days versus 41.4 ± 20.5 days, $P = 0.037$). This RCT met a primary endpoint, and this result exposed the weakness in R-Y stasis. In terms of postoperative complications, the incidence of pancreatic fistula was significantly higher in patients with DGE (38.5%) than in patients without DGE (14.8%) ($P = 0.037$) [24]. On the other hand, in the RCT on isolated R-Y and B-II that focused on pancreatic fistula, there was no significant difference between the two groups in the incidence of DGE (B-II 12%, isolated R-Y 15%, $P = 0.609$), although this RCT was conducted to evaluate the incidence of pancreatic fistula [25]. Even the R-Y

reconstruction is the subtle difference, and the incidence of DGE is different. The RCT was conducted to evaluate the superiority of Billroth II (B-II) over Roux-en-Y (R-Y) reconstruction on decreasing the incidence of DGE after SSPPD. DGE occurred in 5.7% of patients in the B-II group and in 20.4% of patients in the R-Y group (P = 0.028). Patients in the B-II group had a significantly shorter postoperative hospital stay than did patients in the R-Y group (31.6 ± 15.0 days versus 41.4 ± 20.5 days, P = 0.037). This RCT met a primary endpoint. In terms of postoperative complications, the incidence of pancreatic fistula was significantly higher in patients with DGE (38.5%) than in patients without DGE (14.8%) (P = 0.037) [24]. On the other hand, the RCT focused on pancreatic fistula (isolated R-Y versus B-II) demonstrated no significant difference between the two groups in the incidence of DGE (B-II 12%, isolated R-Y 15%, P = 0.609) [25].

31.6 Other Clinical Approach for DGE

Braun enteroenterostomy performed between the afferent and efferent limbs is a traditional technique, and it might be useful for decreasing the postoperative complications. A meta-analysis reported the relationship between clinically relevant DGE and Braun enteroenterostomy following PD; it consisted of 1,369 patients (Braun: 806 vs. non-Braun: 563), reported that Braun enteroenterostomy has a tendency to decrease the incidence of clinically relevant DGE ($P = 0.082$) [26]. However, the length of the jejunal loop affected the occurrence of DGE. Retrospectively, antecolic and long jejunal loop reconstruction showed the lowest incidence of DGE [27]. Patients with a long jejunal loop were suitable to a combination of Braun enteroenterostomy [28]. Therefore, performing Braun enteroenterostomy does not achieve consensus on prevention of DGE.

An RCT was conducted comparing circular stapler and hand-sewn anastomosis in PPPD, and there was no significant difference between the two anastomotic procedures in all grades of DGE; however, this RCT revealed that the clinically relevant grade B/C DGE was remarkably decreased by circular stapler anastomosis compared to hand-sewn anastomosis (8.9% vs. 16%, $P = 0.015$) [28]. This result suggests that the uniform shape of an anastomotic hole has an advantage in gastric emptying; however, this study has a limitation of confounding bias, which is hand-sewn anastomosis consisting of three types of reconstructions. In addition, the incidence of pancreatic fistula was high compared to that in other reports.

Conclusion

PD is an aggressive operation and an important one to achieve good quality of life and better survival. Postoperative adjuvant chemotherapy is necessary to improve the survival in pancreatic cancer patients, and preservation of the whole stomach might affect the dose intensity of postoperative chemotherapy. A lot of problems remain to be solved, and surgeons need to improve the outcomes of the pancreatic resection through the results of highly qualified clinical trials.

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Postoperative Bleeding

32

Dong Wook Choi and Huisong Lee

32.1 Introduction

Although the mortality rate following pancreatectomy has been decreased steadily over the past several decades and is reported less than 5%, PPH is associated with life-threatening morbidity [1]. The morbidity rate after pancreatectomy still remains high at 30–40%, especially following pancreaticoduodenectomy (PD) [2–4]. The common complications of pancreatectomy include postoperative pancreatic fistula (POPF), delayed gastric emptying (DGE), intra-abdominal infection, and PPH. Among them, the PPH is relatively rare but a lethal complication that makes patients lead to death.

PD is a challenging procedure associated with significant morbidity and mortality. The pancreatico-enteric anastomosis (PEA) is thought to be the Achilles' heel of PD. PPH following POPF is an important cause of postoperative mortality following PD. POPF is often associated with other complications such as intra-abdominal infection, abscesses, and sepsis. Those complications are associated with erosion of vessels and bleeding from major arteries and suture lines. This chapter describes the definition and diagnosis of PPH and also treatment and prevention of early and late PPH, respectively.

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32.2 Definition and Classification of PPH

The International Study Group of Pancreatic Surgery (ISGPS) defined grades and classifications of PPH (Tables 32.1 and 32.2) [5]. The PPH was classified on the basis of three criteria: (I) time of onset, (II) location and cause, and (III) severity.

Time of onset (I). PPH is differentiated into early- and late-onset hemorrhage. If the onset of PPH is ≤24 h after the index operation, the PPH is classified into early PPH. Early PPH is usually caused by a technical failure of hemostasis during the initial operation or an underlying coagulopathy. Late-onset PPH (>24 h after the index operation) is associated with erosion of a peripancreatic vessel secondary to pancreatic fistula and arterial pseudoaneurysms [2, 5].

Location and cause (II). PPH may arise from the various sites: (a) arterial or venous, (b) suture lines of the anastomoses (e.g., gastroenteric, duodenoenteric, jejunojejunal, or pancreaticoenteric), (c) areas of resection (e.g., pancreas stump, retroperitoneum), (d) gastric/duodenal

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Table 32.1 International Study Group of Pancreatic Surgery (ISGPS) definition of postpancreatectomy hemorrhage (PPH) [5]

Time of onset
Early hemorrhage (≤24 h after the end of the index operation)
Late hemorrhage (>24 h after the end of the index operation)
Location
Intraluminal (intraenteric, e.g., anastomotic suture line at stomach or duodenum, or pancreatic surface at anastomosis, stress ulcer, pseudoaneurysm)
Extraluminal (extraenteric, bleeding into the abdominal cavity, e.g., from arterial or venous vessels, diffuse bleeding from resection area, anastomosis suture lines, pseudoaneurysm)
Severity of hemorrhage
Mild
Small or medium volume blood loss (from drains, nasogastric tube, or on ultrasonography, decrease in hemoglobin concentration <3 g/dl)
Mild clinical impairment of the patient, no therapeutic consequence, or at most the need for noninvasive treatment with volume resuscitation or blood transfusions (2–3 units packed cells within 24 h of end of operation or 1–3 units if later than 24 h after operation)
No need for reoperation or interventional angiographic embolization; endoscopic treatment of anastomotic bleeding may occur provided the other conditions apply
Severe
Large volume blood loss (drop of hemoglobin level by ≥3 g/dl)
Clinically significant impairment (e.g., tachycardia, hypotension, oliguria, hypovolemic shock), need for blood transfusion (>3 units packed cells)
Need for invasive treatment (interventional angiographic embolization, or re-laparotomy)

Table 32.2 International Study Group of Pancreatic Surgery (ISGPS) classification of postpancreatectomy hemorrhage: clinical condition and diagnostic and therapeutic consequences [5]

Grade	Time of onset, location, severity, and clinical impact of bleeding		Clinical condition	Diagnostic consequence	Therapeutic consequence
A	Early, intra- or extraluminal, mild		Well	Observation, blood count, ultrasonography, and, if necessary, computed tomography	No
B	Early, intra- or extraluminal, severe	Late, intra- or extraluminal, mild[a]	Often well/ intermediate, very rarely life-threatening	Observation, blood count, ultrasonography, computed tomography, angiography, endoscopy[b]	Transfusion of fluid, intermediate care unit (or ICU), therapeutic endoscopy[b], embolization, re-laparotomy for early PPH
C		Late, intra- or extraluminal, severe	Severely impaired, life-threatening	Angiography, computed tomography, endoscopy[b]	Localization of bleeding, angiography and embolization, (endoscopy[b]) or re-laparotomy, ICU

ICU Intensive care unit, *PPH* postpancreatectomy hemorrhage

[a]Late, intra- or extraluminal, mild bleeding may not be immediately life-threatening to patient but may be a warning sign for later severe hemorrhage ("sentinel bleed") and is therefore grade B

[b]Endoscopy should be performed when signs of intraluminal bleeding are present (melena, hematemesis, or blood loss via nasogastric tube)

ulcer or diffuse gastritis, (e) eroded and ruptured pseudoaneurysm, or (f) hemobilia from previously placed endobiliary stents. In addition, PPH can be grouped into intraluminal and extraluminal according to the definite location. Peripancreatic vascular structures that may be the source of PPH are the stump of the gastroduodenal artery, splenic artery, branches of the superior mesenteric artery

(SMA), the splenic vein stump, or, rarely, an intrapancreatic artery (Figs. 32.1 and 32.2) [5–7].

Severity (III). The severity of bleeding can be differentiated into two categories based on the amount of blood loss or transfusion requirements: (a) mild (no clinical impairment and transfusion requirements less than three units of packed cells) or (b) severe (more than four or six units of packed cells transfused within 24 h, a decrease in hemoglobin of more than 4 g/dl, or need for re-laparotomy or interventional angiographic therapy due to severe blood loss).

To summarize the ISGPS classification of PPH based on three main parameters (time of onset, location, and severity of hemorrhage): (1) onset is either early (≤24 h after end of the index operation) or late (>24 h); (2) location is either intraluminal or extraluminal; (3) severity of bleeding may be mild or severe (Table 32.1).

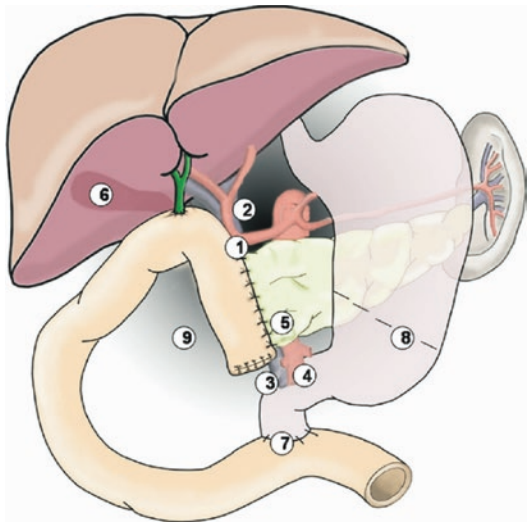

Fig. 32.1 Some potential bleeding sites after right-sided pancreatic resections. *1* Stump of gastroduodenal artery. *2* Tributaries of the portal vein and branches from the hepatic artery. *3* Tributaries of the superior mesenteric vein, including uncinate vessels. *4* Branches of the superior mesenteric artery, including jejunal mesenteric arterial branches to the left and inferior pancreaticoduodenal artery to the right. *5* Pancreatic cut surface and suture line of the pancreaticojejunostomy (PJ) site. *6* Gallbladder fossa after cholecystectomy. *7* Suture line of the duodenojejunostomy after pylorus-preserving pancreaticoduodenectomy. *8* Suture line of the gastrojejunostomy after classical pancreaticoduodenectomy. *9* Area of resection (retroperitoneum) (Reproduced from Wente et al. [5])

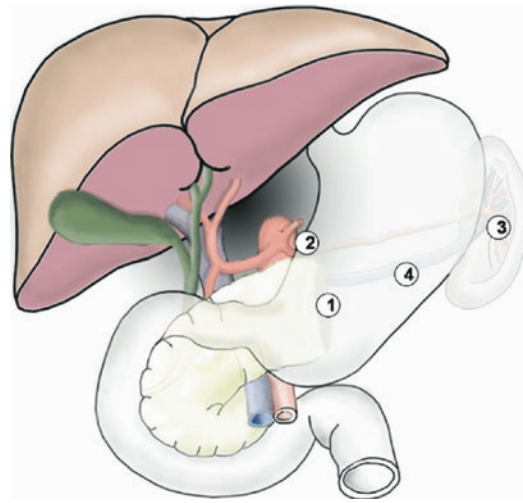

Fig. 32.2 Some potential bleeding sites after left pancreatic resection. *1* Pancreatic stump. *2* Tributaries of the splenic artery. *3* Splenic hilus (in case of spleen preservation)/tributaries of the splenic vein stump. *4* Area of resection (Reproduced from Wente et al. [5])

ISGPS also established a clinical grading system with three different grades of PPH (grades A, B, and C) considering the cumulative overall risk and clinical severity of the hemorrhage (Table 32.2). PPH grade A results only in a temporary and marginal variation of the standard postoperative course of the patient after pancreatectomy. In general, PPH grade A has no major clinical impact, and its occurrence should not be associated with a major delay of the patient's hospital discharge. PPH grade B requires adjustment of a given clinical pathway, including further diagnostics and intervention; this grade of PPH will lead to therapeutic consequences such as the need for transfusion, the readmission to an intermediate or intensive care unit, and potential invasive therapeutic interventions, such as re-laparotomy or embolization. Most likely, the occurrence of PPH grade B will prolong the patient's hospital stay. PPH grade C leads to severe impairment of the patient and should always be considered potentially life-threatening. Immediate diagnostic and therapeutic consequences are mandatory and often needed. The hospital stay of this group of patients is always prolonged and sometimes necessitates that the patient stays longer in the intensive care unit [5].

32.3 Incidence and Mortality

The incidence of PPH is 2–12%. PPH occurs in 4–16% of cases after a PD, in 1–3% of cases after a distal pancreatectomy (DP), and in 6% of cases after enucleation [8–15]. The mortality rate is 6–34% in the case of PPH grade B or C, and the PPH is the leading cause of mortality following PD and accounts for 11–38% of overall mortality [2, 5, 6, 12, 16–19].

Grutzmann et al. [6] reported the incidence and mortality rates according to the ISGPS definition; PPH occurred in 1.7% (grade B) and 4.0% (grade C) of total 945 patients who underwent pancreatic surgery, respectively. They also reported that one (6.2%) mortality in PPH grade B and 13 (34.2%) mortalities in PPH grade C. In our center, 42 (2.2%) patients of total 1,905 patients who underwent PD experienced the delayed arterial hemorrhage between 1995 and 2012. And 12 (28.6%) patients of 42 patients died during admission period. Choi et al. reported 22 cases of delayed hemorrhage after PD, of which the bleeding site could be verified by surgery or angiography in 17 patients. The sites of bleeding in 14 patients with arterial bleeding were five gastroduodenal artery stumps, three common hepatic arteries, three branches of SMA, one proper hepatic artery, one right hepatic artery, and one short gastric artery bleeding [14].

Rebleeding is common after a first radiologic intervention, 20–40% of the patients requiring an additional intervention or surgery a median of 2 days after the first procedure [20, 21].

32.4 Diagnosis

PPH becomes apparent due to one or more of the following signs: blood loss through abdominal drains or nasogastric tube, hematemesis or melena, clinical deterioration of the patient, unexplained hypotension or tachycardia, or laboratory findings such as a decreasing hemoglobin concentration. Sentinel bleeding is a small amount of blood loss via abdominal drains or nasogastric tube several hours before massive hemorrhage, may be present (30–100%); recognizing this event as a sentinel bleed in a timely fashion may prevent severe and fatal outcomes.

32.4.1 Diagnosis of Early-Onset PPH

Early PPH is usually the result of technical failure during the index operation and can be divided into extraluminal bleeding into the abdominal cavity and intraluminal bleeding into the gastrointestinal tract. Various shortcomings during the index operation might lead to early postoperative hemorrhage irrespective of the potential site of the bleeding such as wide distances between successive suture lines, incomplete trans-fixation sutures, or slippage of ligatures. In addition, postoperative relief of vasospasm in smaller blood vessels, which remain undetected as potential bleeding sites during the operation, should be taken into account. Sometimes, an upper digestive hemorrhage originating from a gastric submucosal vessel can benefit from endoscopic hemostasis, but most surgeons would have some concerns about performing an early endoscopy after a pancreatic resection with an anastomosis in situ. They may require additional surgery to maintain hemostasis [2, 8, 21].

32.4.2 Diagnosis of Late-Onset PPH

Late PPH is often associated with POPF or biliary fistula. Accumulation or erosive damage to the vessels leads to pseudoaneurysm formation and may present as sudden hypotension or massive bleeding. If patients with suspected hemorrhage were hemodynamically stable, computed tomography (CT) angiography is the first diagnostic option. And then in case that arterial hemorrhage is suspected or pseudoaneurysm is detected, radiologic intervention should be performed. However, if the patient is hemodynamically unstable, diagnostic and therapeutic angiography should be performed immediately. The therapeutic angiographic techniques categorized into three groups: selective embolization, distal to proximal embolization, and stent graft insertion [8, 20–28].

32.4.2.1 CT

Contrast-enhanced CT scan of the abdomen can provide information regarding pseudoaneurysms, intra-abdominal fluid collections, and abscesses much more reliably than a ultrasonography (US) examination. Hence, it is the investigation of

choice in hemodynamically stable patients, especially if features of sepsis are also present. However, if the size of pseudoaneurysm is small, it can be missed especially in the presence of inflammation. Therefore, a strong index of suspicion is important and should prepare for an emergency angiography even if the CT scan is negative.

32.4.2.2 Angiography

Angiography can make an accurate diagnosis of the site and cause of hemorrhage and resolve the PPH at the same time even in a hemodynamically stable patient. Angiographic evaluation should include the celiac axis and the superior mesenteric artery and their branches. In the presence of pseudoaneurysm, angiography gives a positive result even if active bleeding is not present. However, angiography may give false negative occasionally, because the pattern of delayed hemorrhage is intermittent and the amount is small in early stage. Therefore, early diagnostic angiography is recommended after sentinel hemorrhage occurs. Moreover, the utility of angiography is also dependent on the cause of bleeding. If the bleeding focus is the disrupted suture lines, angiography may give a negative result even in the presence of ongoing ooze.

32.4.3 Sentinel Bleeding

Sentinel bleeding was described by Brodsky and Turnbull in 1991 [29]. By ISGPS definition, sentinel bleeding is defined as a small amount of blood loss before massive hemorrhage via abdominal drains or nasogastric tube. Especially, if a patient with pancreatic fistula had sentinel bleeding, a diagnostic angiography may be necessary. Tien et al. reported that sentinel bleed was detected in 20 (7.1%) patients of 283 patients who underwent PD. In seven (35.0%) patients of 20 patients, angiography detected pseudoaneurysm. Therefore, prompt angiography should be performed for every detected sentinel bleed after PD [22]. However, sentinel hemorrhage is not necessarily present in all patients with delayed hemorrhage.

Tien et al. found sentinel hemorrhage in only three of ten patients, and Rumstadt et al. reported it in only 3 of 11 patients with delayed hemorrhage. In our center, 22 (52.4%) of 42 patients with delayed arterial hemorrhage patients represented sentinel bleeding signs. Sentinel bleeding group had lower mortality rate than without sentinel bleeding group (22.7% vs 35.0%) [3, 30]. Not all sentinel hemorrhage will go on to have massive bleeding. The exact natural history of sentinel hemorrhage remains unknown in view of the limited information available. De Castro et al. reported 11 patients with delayed massive hemorrhage after PD. They reported that nine patients had sentinel hemorrhage prior to massive bleed, but there were four other patients who had sentinel hemorrhage that was not followed by major bleeding [2].

Late-onset PPH sometimes appears as bleeding in two stages, with initial minimal bleeding that stops spontaneously (sentinel bleeding) followed by a significant recurrence of the hemorrhage associated with shock. In cases of sentinel bleeding, contrast-enhanced CT scanning is recommended to make an early diagnosis of a pseudoaneurysm and the usually associated complication of abdominal infection. The CT scan should be followed by specific treatment of the abdominal complication along with an angiography to provide endovascular treatment, which has an efficacy of approximately 80% [21, 22]. Radiological hemostasis can be obtained through the use of either coils or covered stents, allowing for the treatment of pseudoaneurysm without a collar [8, 20, 23–28].

32.5 Treatment

32.5.1 Initial Assessment

The early diagnosis and appropriate management of bleeding are essential to reduce the mortality rate. Continuous and close postoperative observation of the patient is mandatory to detect PPH immediately. Tachycardia and low blood pressure are reliable bedside indicators of progressive hypovolemia associated with significant PPH and should put the nursing and surgical team on high alert. Additionally, persistent bloody aspirate from a nasogastric tube or melena is a certain sign of intraluminal bleeding, and the volume of aspirate should be monitored at short and regular intervals since its primary detection. Furthermore, an assessment of the intra-abdominal drainage

output, both in terms of quantity and quality, is critical to reach a clinical, bedside decision whether the hemorrhage is only intraluminal, extraluminal, or both, as can happen when anastomotic suture line bleeding results in anastomotic disruption with extravasation of blood into the peritoneal cavity. In these situations, all laboratory tests are mandatory on an emergency basis. They serve to correct hypovolemia, coagulation abnormalities, and electrolyte disturbances associated with major hemorrhage.

Rapid decision-making is essential when bleeding stigmata such as pseudoaneurysm on CT and sentinel bleeding are noted. Prompt operation for early bleeding and angiographic embolization for late bleeding are recommended.

32.5.2 Management of Early PPH

Signs of progressive abdominal distension and blood gushing from intra-abdominal drains are an indication for immediate re-laparotomy to identify and control the bleeding source. As a general rule, early severe hemorrhage is managed with re-exploration, as a surgically correctable source of bleeding is likely to be found. The best treatment option remains controversial, and surgery is usually considered the first-line treatment. This is especially true for early bleeding (i.e., occurring less than 24 h after the end of the surgical procedure); because early hemorrhage usually results from incomplete bleeding control, it is treated by reoperation (Fig. 32.3) [20, 23, 31, 32].

The gastroduodenal artery, inferior pancreaticoduodenal artery, splenic artery, and the superior mesenteric and portal veins are the main sources of major intraperitoneal PPH. If the clinical condition is not stabilized after conservative management, re-laparotomy should be undertaken immediately. If massive bleeding is anticipated, blood clot removal should be performed carefully. The surgeon could identify the bleeding site though an abdominal wash with warm saline and careful suctioning. The surgical team has to examine carefully for all the potential sites of rebleeding and place drains to detect any rebleeding that may occur later on [33].

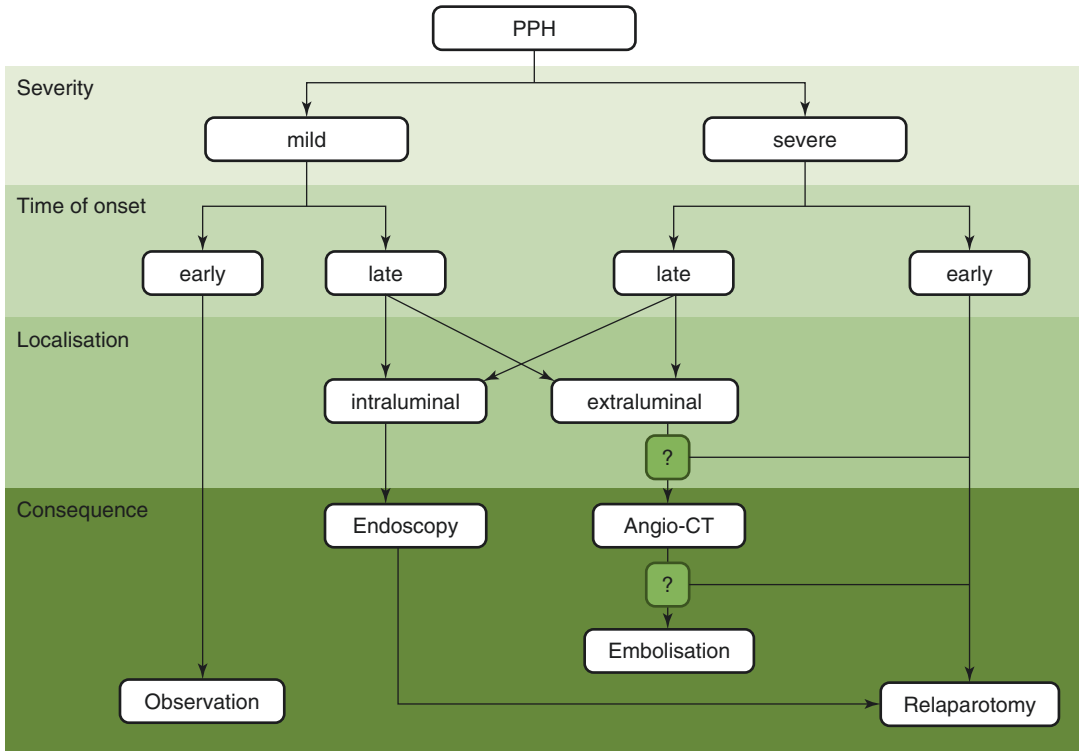

Fig. 32.3 Proposed algorithm for diagnosis and treatment of PPH (Reproduced from Grutzmann et al. [6])

32.5.3 Management of Late PPH

32.5.3.1 Interventional Radiology

Recently, the recommended management of late PPH has been changed from surgery to radiological intervention, such as transarterial micro-coil embolization or the use of a stent graft (Fig. 32.3). Endovascular embolization of the hepatic artery trunk can be securely performed only if blood flow to the liver by an alternate route is confirmed. To reduce mortality of PPH patients, it is necessary to prevent other complications associated with pancreatic fistula following hemostasis. Proactive surgical intervention such as abscess drainage or remnant pancreatectomy is a key consideration [24–28, 31, 34–38].

The technique of transarterial intervention has achieved remarkable development in recent years due to the availability of a variety of fine angiography catheters that allow selective and even super-selective catheterization. Transarterial target artery embolization has an 83–100% hemostasis success rate [28, 39]. The liver has dual blood supply system from the right and left hepatic artery and portal vein. There are also collateral vessels. However, embolization of hepatic artery has a risk of hepatic ischemia. When the collateral flow is not sufficient, severe ischemia of the liver has been reported to lead to liver failure and even death. Liver abscesses may occur after embolization.

Stent graft is a recent approach that manages arterial hemorrhage after PD (Fig. 32.4). It is an ideal method that can preserve organ perfusion and control bleeding simultaneously. There are a few reports that covered stent for delayed bleeding after PD had favorable outcome [28, 39]. Although a covered stent has these advantages, there are some limitations. It is more expansive than embolization method and cannot be applicable in cases that have arterial tortuosity or thin diameter. Furthermore, stent thrombosis may lead to the fatal liver necrosis although it is less frequent compared with embolization.

Sometimes, bleeding can occur from other arteries such as the right or left hepatic arteries, aberrant hepatic arteries, splenic artery, or superior mesenteric artery. The principles of transarterial intervention remain the same for all sites. Where there is effective collateral blood supply, the treatment should consist of distal and proximal embolization. However, an end artery such as the superior mesenteric artery, which has no effective collaterals, cannot be embolized. In such cases, an alternative is to deploy polytetrafluoroethylene (PTFE)-covered stents over the defect to stop the hemorrhage.

However, there are still clinical questions for interventional angiography and stent graft

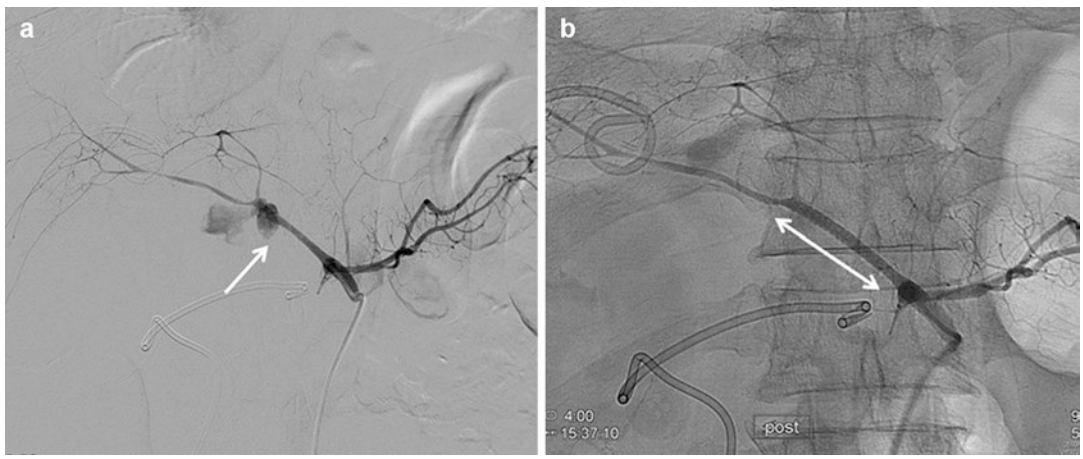

Fig. 32.4 Ruptured pseudoaneurysm treated by covered stent insertion in common hepatic artery. (**a**) Ruptured pseudoaneurysm of common hepatic artery. (**b**) Post-radiologic intervention. The bleeding was well controlled, and the blood flow to the liver is preserved

insertion. Is the CT angiography necessary prior to interventional angiography? If the portal venous flow is intact and there are collateral arteries, is the coil embolization safe? Stent graft could reduce the incidence of hepatic necrosis. However, it also has stent stenosis or thrombosis. The selection of aneurysmal sac is technically demanding especially if the artery is tortuous and the length of aneurysmal neck is long. Moreover, the stent graft insertion is difficult for pseudoaneurysm of thin diameter artery, and there is risk of iatrogenic injury.

32.5.3.2 Endoscopy

Anastomotic suture lines are the main source of intraluminal PPH. Intraluminal PPH can occur at the site of PEA, gastrojejunostomy, or duodenojejunostomy suture lines. If there is small oozing at the gastrojejunostomy or duodenojejunostomy suture lines, upper gastrointestinal endoscopy with adrenaline injection or electric coagulation might be helpful. In case of a PJ site bleeding, endoscopic approach is impossible, and surgical bleeding control may be necessary (Fig. 32.3).

32.5.3.3 Surgery

Operation for late PPH is a technically demanding procedure and should be attempted only by surgeons experienced in pancreatic surgery. The indications of surgery are massive hemorrhage leading to collapse and significant intra-abdominal sepsis associated with hemorrhage. The basic principles of surgery are hemostasis and wide drainage. Hemostasis is best obtained by lighting the offending vessel proximally and distally, preferably away from infected regions where the tissues may be inflamed and very friable. Direct suturing of an eroded artery with friable tissues usually fails, leading to rebleeding, and should be resorted to when dealing with important end arteries such as the superior mesenteric artery. If the site of hemorrhage is not found and the stumps of ligated vessels have been carefully inspected, enterotomy should be considered to look at one or more of the several suture lines, which may be the source of bleeding.

Disrupted PEA can be managed with in one of the following ways. Re-suturing is not recommended in presence of edematous friable tissues. Second option is dismantling the anastomosis completely, closing the jejunal loop and providing drainage of the pancreatic duct, often with a laparotomy to ensure free drainage [3]. This procedure brings out pancreatic fistula but helps to control the sepsis. The other option is complete total pancreatectomy to remove the focus of sepsis altogether [40]. This procedure is associated with the problems of postoperative brittle diabetes and combined complications. Hence it should be resorted to only in cases with a necrotic pancreas with extensive retroperitoneal sepsis. Regardless of what surgical procedure is chosen, effective drainage of fluid collection and abscess is important.

32.5.3.4 Surgery Versus Angiographic Intervention

Over the last decade, angiographic intervention has made rapid strides due to the wider availability of technology and trained personnel. Angiographic intervention suffers from the problems of being technology intensive, being expensive, requiring experience, and having a low but definite morbidity and mortality. The problem of embolization leading to distal ischemia may be sorted out by preserving blood flow with covered vascular stents. But the experience has been limited; these vascular stents are expensive, and questions remain about their placement in a infected operation field. The advantages of interventional angiography are that it is less invasive than surgery, it has a lower morbidity, and vessels can be embolized far away from the infected surgical site, with theoretically lower risk of rebleeding.

Surgery has higher morbidity and mortality as compared to angiographic intervention. In the setting of a bleeding hemodynamically unstable patient with inflamed friable tissue, surgery should not be taken lightly. However, it has the advantages of taking care of disrupted anastomoses, collections, and abscesses at the same time and providing free drainage.

Angiography and embolization is the first choice. However, control of sepsis with percutaneous or surgical drainage should also be given equal importance. In patients where

initial angiography is negative, consideration should be given to a repeat angiography if the sepsis can be easily controlled and the hemorrhage is continuing. However, if the angiography is negative in presence of hemorrhage and continuing sepsis, patients are better served by surgical drainage and hemostasis.

32.5.3.5 Results of Treatment for Late PPH

The endovascular procedures have been shown to be associated with a high rate of clinical success, as well as lower morbidity and mortality, especially for delayed bleeding. In selected series, the success of transarterial embolization and stent graft insertion in achieving hemostasis varies from 63% to 85% [9, 13, 20, 28, 31, 34, 35]. Thus results of radiologic intervention would depend not only on experience and availability of improved technology but also on the bleeding site. Highest success would be achieved with pseudoaneurysms. However, the success rates would be lower in series of patients with other sources of hemorrhage. Late PPH following PD has been associated with high mortality ranging from 11% to 38%. The important causes of mortality are hemorrhagic shock, septic shock with multi-organ failure, and liver failure with ischemia followed by hepatic artery embolization or stent graft thrombosis. Selective embolization for arterial aneurysm had higher rebleeding rate than total embolization or stent graft. Stent graft insertion for arterial hemorrhage is the ideal method, but stent occlusion and rebleeding are still problematic.

32.5.4 Management of Patients with Rebleeding

During interventional angiography, the absence of flow in the eroded segment should be confirmed at the end of the procedure. However, rebleeding can occur after embolization because of several reasons. Recanalization of the pseudoaneurysms from collateral arteries has been reported. Ineffective control of sepsis can lead to further erosion, and rebleeding has been reported from the same or other arteries. Hence, in selected cases, the artery can be blocked far away from the septic focus, thereby theoretically reducing the chances of rebleeding. Re-laparotomy is sometimes inevitable for control of bleeding that was technically impossible to stop by angiography or for recurrent bleeding after coil embolization (Fig. 32.5) [41].

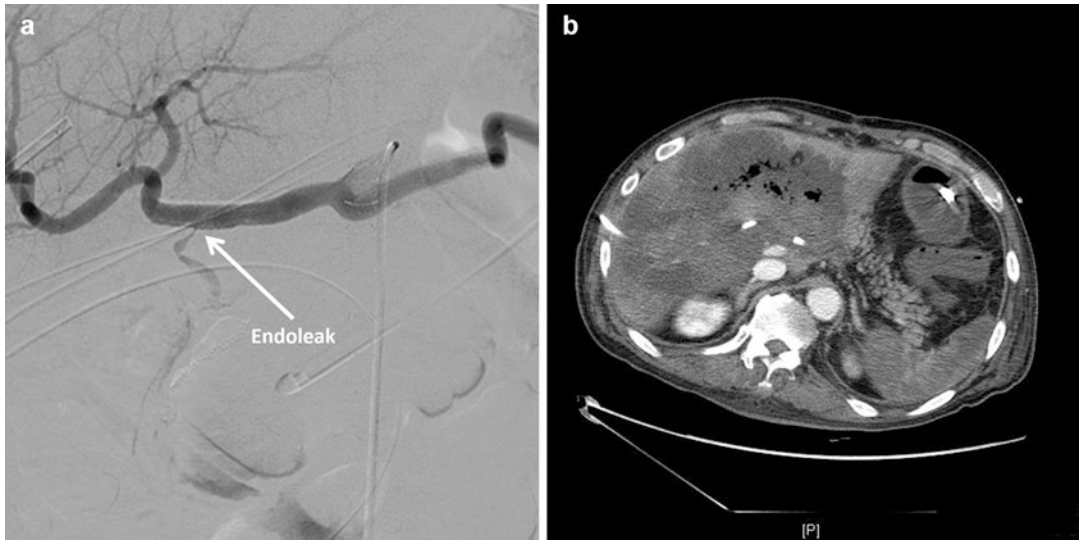

Fig. 32.5 Complications after stent graft insertion for hepatic arterial bleeding. (**a**) Rebleeding with endoleak. (**b**) Massive hepatic necrosis with stent occlusion

Undrained abscesses and intra-abdominal infection can lead to further erosion of vessels. Ligation of the bleeding artery should be done away from abscesses and complicated fluid collections. Angiographic embolization is recommended to treat recurrent hemorrhage after surgery.

32.6 Risk Factors of PPH

POPF is a well-known and potentially most important risk factor. There are many reports that POPF was associated with PPH. In patients with POPF, the incidence of PPH is 12.4% although the incidence is 5% without POPF. The incidence of grade C PPH is 6.8% in patients with POPF and 0.9% in patients without POPF [17]. Biliary fistula is also associated with PPH and had a synergic effect combined with POPF for PPH [3, 9].

Intra-abdominal infection is also a powerful risk factor. Most patients with PPH had intra-abdominal infection combined with pancreatic fistula [42]. Perioperative antithrombotic treatment is an independent risk factor for PPH in patients undergoing pancreatic surgery, although this treatment effectively prevents postoperative thromboembolic events [43]. Age, obesity, portal vein resection, extensive lymph node dissection, soft pancreas, nutritional risk index, malignant disease, preoperative intensive chemotherapy, and radiotherapy are significantly associated with PPH. On the other hand, intraoperative transfusion is associated with low incidence of PPH after PD. However, there is still controversy that PJ compared with pancreaticogastrostomy, jaundice, and preoperative biliary drainage is associated with PPH [16, 17, 42, 44, 45].

32.7 Prevention of PPH

32.7.1 Prevention of Early PPH

Properly done operation with perfect hemostasis is the best way to avoid PPH. Loosening of surgical knot and relieving of vasospasm of small vessels from the pancreatic cut surface cause early PPH. As far as prevention of extraluminal hemorrhage is concerned, major vessels such as the gastroduodenal and inferior pancreaticoduodenal arteries should be gently ligated. Sometimes, the artery stump fracture occurs especially in patients with calcified vessels. Aggressive lymph node dissection might lead to the injury of adventitia of major arteries vulnerable to POPF. Surgeon should carefully inspect the area around the superior mesenteric vessels where the uncinated process of the pancreas has been dissected off during a PD prior to the PJ anastomosis. Similarly, the retro-pancreatic space around the Treitz ligament should be carefully examined for any potential bleeding source from communicating vessels between the superior mesenteric vessels and the proximal jejunum.

The secure approximation of the pancreatoenteric anastomosis with successive sutures is important. The main branch vessels of pancreatic stump are usually located near superior and inferior border of the pancreas. Thus, it appears that a meticulous surgery performed with care should substantially reduce the risk of early hemorrhage from pancreatic anastomosis suture lines. Stress ulcers and erosions of anastomotic site can be prevented by perioperative administration of proton pump inhibitors and octreotide analogues.

Late PPH is correlated with POPF, biliary fistula, surgical site infection including intra-abdominal abscess, or generalized sepsis. The main pathophysiology of PPH is pseudoaneurysm formation. Various pancreatic exocrine enzymes (trypsin, elastase, and so on) are associated with digestion of major vessels secondary to a pancreatic leak. Intra-abdominal infection and bile leakage promote the activity of pancreatic enzymes. There are a variety of chemical materials that have been tested in the attempt to prevent POPF. The fibrin sealant patch was applied to reduce pancreatic fistula; however, it had no significant effect on the rate of POPF after DP [46–48]. Octreotide has been also used to decrease the incidence of leak and the severity of POPF. Although its usefulness is controversial, octreotide may be used in high-risk situations such as a soft pancreas and non-dilated pancreatic duct and in surgical units where the incidence of POPF is more than 10% [49, 50].

Gastroduodenal artery stump is the most common site of pseudoaneurysm formation and should be carefully handled to decrease the incidence of problem. Various measures that have been suggested include leaving a stump of at least 2 cm, suture ligation with monofilament suture, and covering the stump with omentum or other prosthetic materials. Recent studies reported that the vascularized omental flaps around various anastomoses after PD can reduce the incidences of POPF, biliary fistula, and also PPH. This flap lies in front of the gastroduodenal stump and can be a mechanical barrier from erosive injury caused by a POPF [51–54].

A high index of suspicion should be kept for postoperative complications. It is recommended to check the amylase level of serum and drain fluid on postoperative days 1, 3, and 5 in patients following PD. If POPF is suspected, combined infection should be controlled to prevent sepsis as early as possible. Follow-up CT scan may be done to look for fluid collections and abscesses. Drainage of complicated fluid collections and irrigation of abscess cavities along with intravenous culture-based antibiotics should be done. Finally, if there is sentinel bleeding, early angiography should be done to find out the bleeding focus. If the source can be localized, prophylactic embolization or stent graft insertion should be done to prevent life-threatening PPH.

Conclusion

PPH is associated with major morbidity and mortality. Therefore, proper operation with perfect hemostasis is always essential. If the PPH is detected within 1 day from the index operation, immediate reoperation should be considered. However, late PPH is usually related to POPF and intra-abdominal sepsis. Erosion of peripancreatic arteries can lead to pseudoaneurysm formation and massive life-threatening hemorrhage. If there is sentinel bleeding, early detection is most important to make a timely intervention. Angiography is the best diagnostic and therapeutic modality in the setting of late PPH. Surgery is limitedly useful and should be carried out by an experienced surgeon. The role of angiography and surgery may be complementary to manage PPH appropriately.

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Rare Complications After Pancreatectomy

33

Dong-Sup Yoon

33.1 Introduction

With recent progresses in surgical technique and advances in anesthesia as well as in antibiotics, complications after pancreatic resection decreased, but pancreatic resection remains the surgical procedure with highest complication rate.

As described in the previous chapter, pancreatic fistula, delayed gastric emptying, and postoperative bleeding are well-known complications with fatal outcomes for the patient.

For selection of studies for unusual complications after pancreatectomy, multiple databases, including MEDLINE (PubMed), EMBASE, EBSCO, OVID, and Web of Science, were searched with the following Mesh search headings: unusual, rare, and uncommon complication and pancreaticoduodenectomy, Whipple's operation unusual complication, and pancreaticoduodenectomy. Citations were limited to those published on humans and in English language. A search was also performed for reference lists of the retrieved relevant articles for additional trials. The last search was run on January 10, 2016. Publications were excluded if (1) the reports are about an unusual or rare indication of pancreaticoduodenectomy or (2) rare complication but related with chemotherapy rather than pancreaticoduodenectomy or (3) the articles focused on surgical site infection or on pancreatic fistula or delayed gastric emptying without any comments about other complications. The electronic database search of MEDLINE (PubMed), EMBASE, EBSCO, OVID, and Web of Science resulted in the identification of 890 relevant citations. A total of 127 records remained after duplicate citations were removed or after title and abstract review for meeting exclusion criteria were excluded.

The searched complications were divided in vascular complications and nonvascular complications as follows (Table 33.1). From the above complications, pathogenesis, diagnosis, and treatment of complications which are important according to author's experience will be focused on.

Table 33.1 Rare complications after pancreatectomy

I. Vascular complications	SMV or portal vein thrombosis
	Bowel ischemia
	Hepatic ischemia
	Omental infarction
II. Nonvascular complications	Anastomosis site leakage (except Pancreaticoenteric anastomosis)
	Anastomosis site ulcer
	Perioperative catheter related—PEG or feeding tube
	A-loop syndrome
	Ascites and chyle ascites
	Bilio-enteric anastomosis strictures
	Cholangitis and hepatic abscesses
	Cholelithiasis

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33.2 Portal Venous System Thrombosis

Portal venous system thrombosis (PVST) is a rare but potentially lethal complication after pancreatic resections. Since the symptoms range from asymptomatic patients to rapid progression with bowel necrosis, prompt diagnosis and appropriate treatment are essential. However, because of low incidence, there is no opportunity to experience; period of treatment can be missed and led to death.

Depending on operative procedure, rates were highest in total pancreatectomy with splenectomy, followed by pancreaticoduodenectomy and distal pancreatectomy. Vascular injury or portal vein reconstruction during surgery increases the risk of postoperative thrombosis formation.

The pathogenesis of PVST after pancreatic surgery is probably multifactorial. (1) Surgery increases the risk of thrombosis by causing endothelial damage or by decreasing blood flow in the portal vein and its branches. For example, splenectomy has been shown to lead to a high incidence of portal system thrombosis [1, 2]. However, this was not observed in the present study. (2) Malignancy induces a hypercoagulable state, and tumor recurrence after pancreatic surgery is not uncommon. (3) Inflammatory conditions before surgery (e.g., chronic pancreatitis) and after surgery (e.g., abscesses/pancreatitis) may promote thrombus formation.

Symptoms can range from abdominal pain, fever, fatigue, nausea and vomiting, and abdominal distention to shortness of breath. If PVST occurs, ascites, liver abscess, and sepsis and pulmonary embolism can be observed as complications.

Computed tomography and ultrasonography (US) are important in the detection of PVST. Contrast enhanced computed tomograpy (CECT) was used for diagnosing PVST in most patients and has a sensitivity of 90% and high diagnostic specificity (99%) [3]. Color Doppler imaging can be also used, and it has higher sensitivity (93%) and equal specificity (99%) [3]. The surgeon, therefore, can utilize a multimodality approach as it relates to the workup of this potentially lethal complication.

One of questions behind one study was if—and then how—thrombosis after surgery in the portal vein system should be treated [4]. Generally, when PVST was diagnosed, therapy was usually initiated with therapeutic doses of LMWH (dalteparin sodium 200 U/kg body weight/day) if the patients had no severe obstructive signs of the portal vein system, such as bowel wall edema. For severe occlusion, thrombectomy might be performed immediately as a second surgery. The importance of expeditious treatment with systemic anticoagulation is widely recognized for venous thrombosis in general, and recanalization of acute portal venous system thrombosis may occur in most patients following treatment (Fig. 33.1). However, the treatment was not universally effective in all patients.

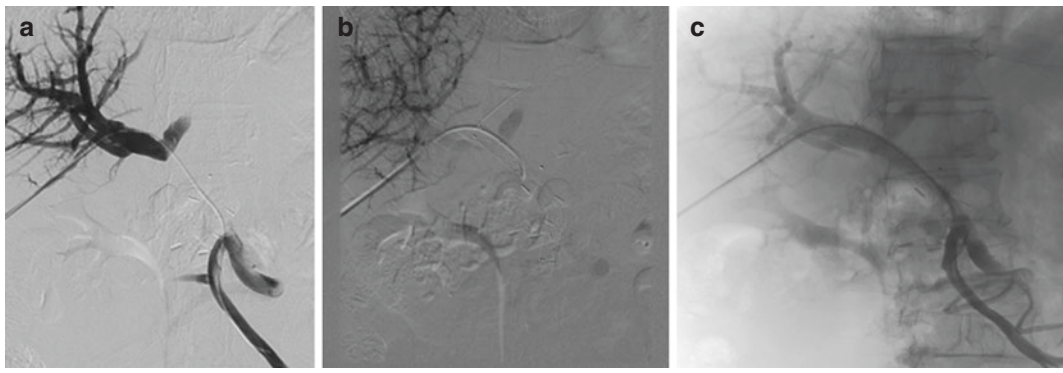


Fig. 33.1 Recanalization of acute portal venous system thrombosis may occur by portal vein stenting. (**a**) Development of portal vein thrombosis after operation. (**b**) Portal vein stenting. (**c**) Recanalization of portal vein flow after stenting

33.3 Marginal Ulcer

Marginal ulcer (MU) is a well-known and morbid complication of pancreaticoduodenectomy (PD), pylorus-preserving pancreaticoduodenectomy (PPPD), and total pancreatectomy (TP). In the past, since the incidence of marginal ulcer was insignificant among patients who underwent pancreaticoduodenectomy with vagotomy, while the incidence was nearly 50% among patients without vagotomy, vagotomy was strongly recommended [5].

In the noughties, it was reported that in patients after pancreaticoduodenectomy or total pancreatectomy without vagotomy, marginal ulcer occurred in 11.7% [6]. Recently with the development of antisecretory medication, there have been many changes in ulcer treatment. Thus during PD or PPPD, vagotomy is usually not performed. However, there is no accurate report about recent incidence of marginal ulcer nor prescription of antisecretory medication.

The recent report of Zyromski et al. showed a mean incidence of ulceration after PD or PPPD of 2.5% (confidence interval (CI) 1.8–3.2%) with a median time to diagnosis of 15.5 months [7]. Pylorus preservation was associated with an MU rate of 2.0% (CI 1.0–2.9%), while classic PD procedures report an overall rate of 2.6% (CI 1.6–3.6%). Documented use of postoperative antisecretory medication was associated with a reduced rate of 1.4% (CI 0.1–1.7). Etiologic factors affecting the occurrence of MU are related to altered gastrointestinal anatomy: duodenal resection removes the thick, alkaline-rich mucus buffer provided by Brunner's glands, and unbuffered gastric content can be ulcerogenic to the bowel wall.

Most of practiced pancreatic surgeons have the experience of severe epigastric pain, panperitonitis due to perforation, or bleeding (dizziness, melena, hematemesis) due to marginal ulcer after PD or PPPD (Fig. 33.2). In these cases, ulcer medication, vigorous endoscopic treatment, or surgical treatment will be conducted. In cases where severe bleeding or panperitonitis due to free perforation occurs, mortality rate over 20% is reported; if there is high risk of marginal ulcer before surgery, if the patient has peptic ulcer disease history, or if the patient has favorable prognosis and potential for long-term survival, bilateral truncal vagotomy can be considered.

33.4 Chyle Ascites

Chyle leak complicating pancreatic resection is reported to occur in 1.3–10.8% of cases [8–10]. Postoperative intra-abdominal chyle leak is most likely secondary to surgical disruption of the cisterna chyli or one of its major lymphatic tributaries [11]. Predisposing factors of chyle leak include more radical lymphadenectomy [8], concomitant vascular resection [8], and early institution of enteral nutrition [9]. Chyle leak imposes the additional morbidity of large fluid volume losses together with protein, electrolyte, immunoglobulin, and lymphocyte depletion on already debilitated patients [8]. Recently many experienced surgeons insist that enteral nutrition should be used whenever possible even in patients undergoing pancreatic surgery [12]. I experienced draining fluid milky color change sometimes after starting enteral tube feeding. So early EN correlated with an increase in chylous drainage [9].

The diagnosis of CL was made clinically after observation of a milky appearance of drain fluid at volumes greater than 200 ml/day (Fig.33.3). In cases which CL was suspected but clinical features were equivocal, CL was diagnosed in the presence of drain fluid triglyceride concentration twice that of serum or >110 mg/dL [13]. In addition, the definition of chyle leak shows some differences depending on the researcher. The incidence differs depending on surgical extent, but there are also differences depending on how chyle leak is defined, so that efforts should be make on finding a consensus between researchers. No patient required lymphangiography or any other radiological test for confirmation of diagnosis.

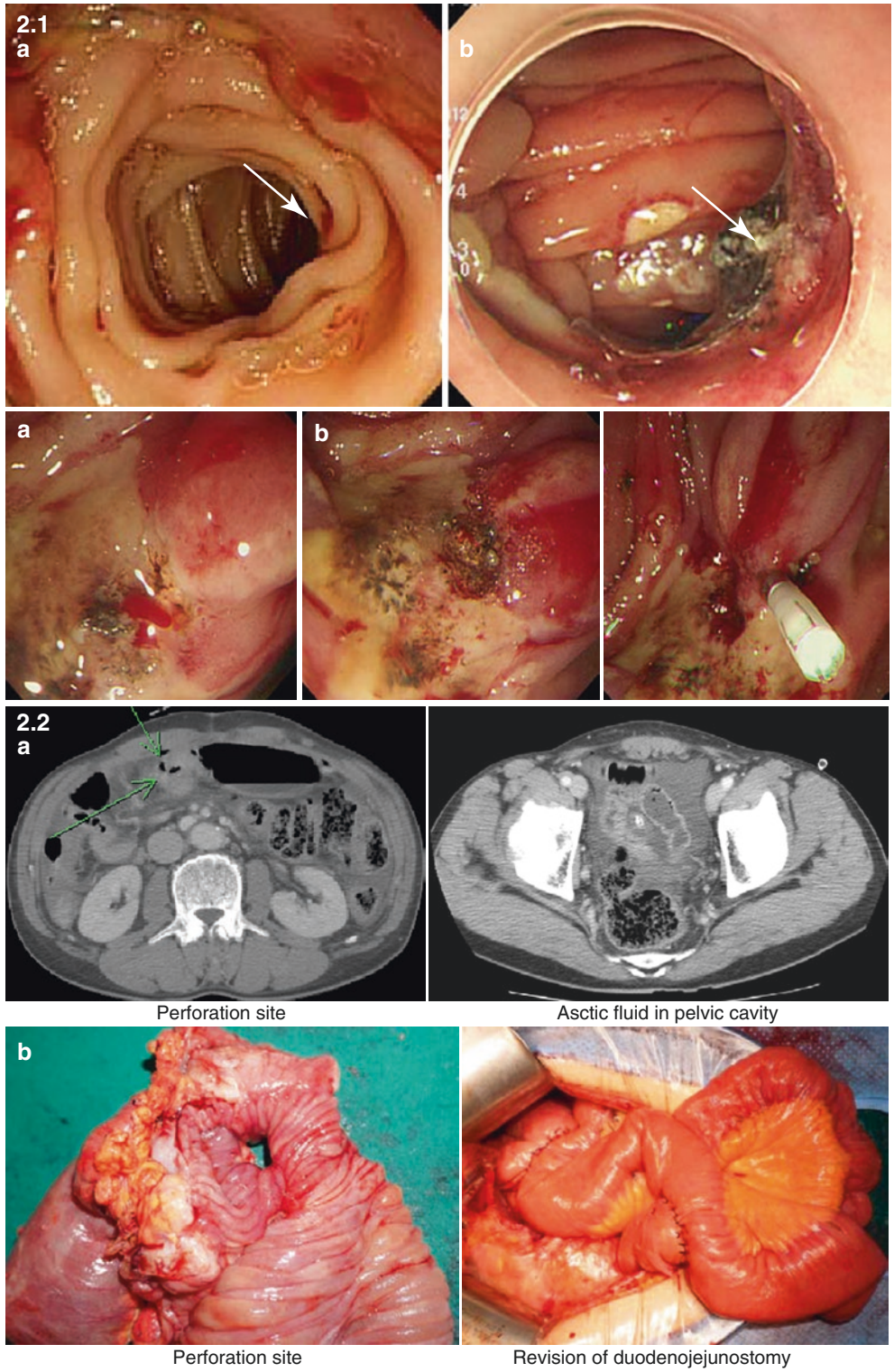


Fig. 33.2 Recurrent bleeding or free perforation from marginal ulcer developed after PD or PPPD. **2-1** Recurrent bleeding from marginal ulceration and it was controlled by coagulation or clipping. (**a**) Bleeding from marginal ulceration. (**b**) Bleeding control by endoscopic therapy (ulceration). **2-2** Free perforation from marginal ulceration and its treatment. **2-2** (**a**) Preoperative CT finding of marginal ulcer perforation. **2-2** (**b**) Operation finding

Treatment can include dietary modification, enteral nutrition (EN) with fat content modification, bowel rest with parenteral nutrition (PN), octreotide administration, and surgery.

According to the severity of CL, we can choose one of above treatments. Most of chyle leaks after pancreas surgery are successfully controlled by bowel rest with parenteral nutrition or conservative measures, including conversion to an MCT enteral feeding regimen and careful fluid balance monitoring with supplemental intravenous rehydration up to 80%. Miyazaki group [13] recommended treatment of algorithm of postoperative chylous ascites, and it seems to be reasonable (Fig. 33.4). Once oral intake was established, patients with CL were maintained on an oral MCT diet until drain output ceased.

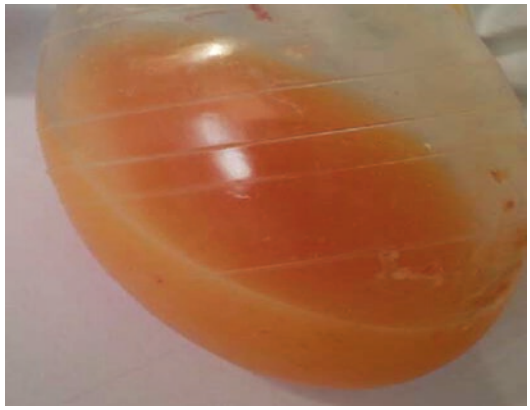


Fig. 33.3 The diagnosis of chyle leak was made clinically after observation of a milky appearance of drain

33.5 Omental Infarction

Omental infarction is a rare entity which occurs because of focal torsion or lack of blood flow to a portion of the omentum. Signs and symptoms can mimic other acute intra-abdominal conditions. Although a benign condition, typical symptoms are severe and can prolong return to activities of daily living for many weeks.

Omental infarction due to pancreatectomy can occur. As a part of the standard procedure, anterior leaf of the greater omentum (gastrocolic ligament) was divided using the high-energy device. This division of the vessels has the potential of disrupting the downstream blood supply of the divided portion of the omentum. In a more traditional method of entering the lesser sac, the posterior leaf of the greater omentum is divided along the avascular plain as it inserts on the transverse mesocolon, leaving the blood supply of the omentum intact. The classical open technique divides the greater omentum along an avascular margin; however, though possible in the laparoscopic approach, the lesser sac is more frequently entered through

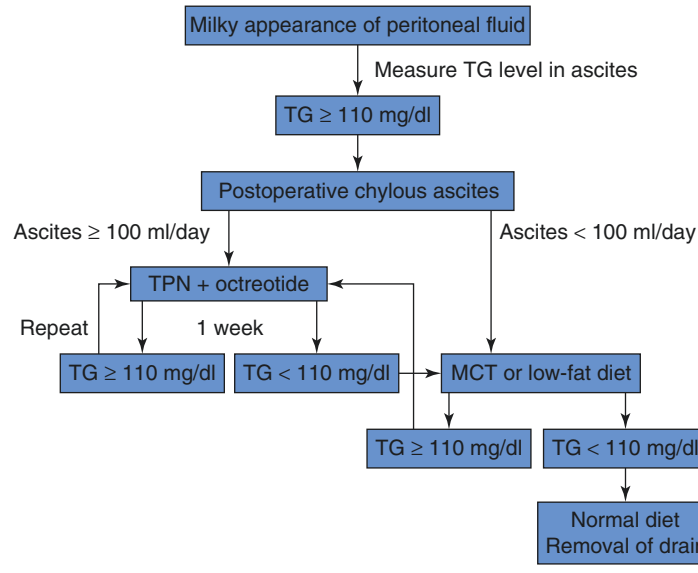


Fig. 33.4 Algorithm for the treatment of postoperative chylous ascites. *TG* triglyceride level, *TPN* total parenteral nutrition, *MCT* medium-chain triglyceride

the anterior leaf of the omentum midway between the greater curve of the stomach and the colon, to avoid thermal injury to the colon by high-energy devices. By dividing the anterior leaf of the greater omentum, the short gastric arteries are divided, and part of the omentum that loses its blood supply is not resected. Based on this hypothesis, we believe that this complication can be prevented by careful inspection of the omentum after its division. All devitalized portions of the omentum should be identified and resected [14]. If these portions are removed, the probability of a postoperative omental infarction in our opinion should reduce considerably.

This condition is often self-limiting and can be managed conservatively. The conservative treatment is an appropriate first line of treatment for the first 24–48 h while resuscitation is initiated and antibiotics are administered. However, if the diagnosis is in doubt, or if conservative treatment fails, then laparoscopy should be performed without delay. We were forced to intervene laparoscopically because of intractable pain and nagging doubts about the diagnosis. Laparotomy or open surgery should only be necessary where good-quality imaging and laparoscopy are not available or rarely if laparoscopic resection is not possible.

33.6 Bilio-enteric Anastomosis Failure

Bilio-enteric anastomosis failure is composed of two types: one is HJ leak which develops in immediate postoperative period, and the other is HJ stricture which is a late complication.

Hepaticojejunostomy (HJ) leak is rare after PD, but it is (also called bile leaks) the second most common type of leak, behind pancreaticojejunostomy leak. HJ leaks occur with an estimated frequency between 3% and 8% [15–18]. The risk factors associated with HJ leak are preoperative hypoalbuminemia, chemoradiotherapy, endoscopic biliary drainage, and high body mass index. The impact of this complication on postoperative recovery ranges from trivial to severe; many leaks resolve on their own and minimally affect outcome. Rarely, a leak can lead to death [15, 19–21].

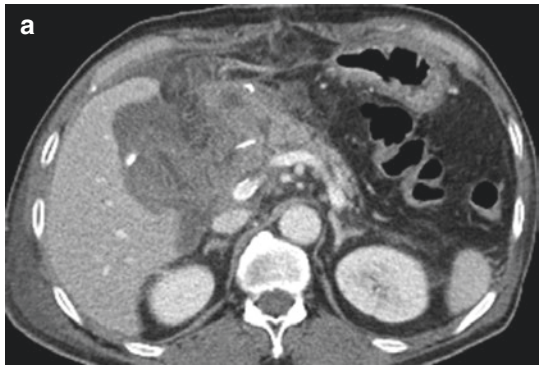
The most common clinical signs associated with an HJ leak included bilious (greenish colored) drainage in the drains placed at surgery (retrograde bile leaks through dehiscence of the pancreaticojejunostomy in patients with pancreatic fistula were excluded), leukocytosis, abdominal pain or distention, and fever typically presented during the first postoperative week.

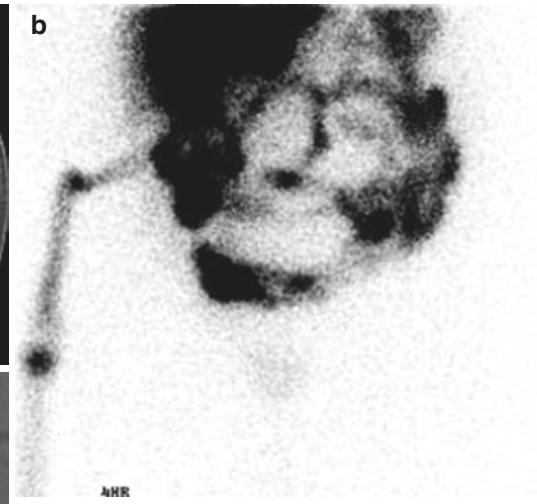
In case bile-stained discharge from drain is observed or in case there are suspicious signs of bile leak, CT scan should be performed to check the overall intra-abdominal status. Once bile leak is confirmed, the site of leakage should be identified because there are three sites of anastomosis in PPPD. Performing DISIDA scan, contrast drain study (sinogram), or percutaneous transhepatic cholangiogram, the exact location of bile leak can be found (Fig. 33.5) [22–24].

If bile leak is confirmed, principles of treatment should be decided depending on the severity.

For the management of HJ leak, PCD is required to drain any collection; a minor HJ leak may stop on its own. If the leak is large or persists, percutaneous transhepatic biliary drainage (PTBD) may be required. Most HJ leaks will respond to PTBD; reoperation is very rarely required. In this setting, the cooperation between surgeons and interventional radiologists seems to be crucial in order to establish the best, less-invasive approach to managing complications in order to decrease the need for re-intervention [25].

HJ stricture is a common complication after liver transplantation in early period, but it is uncommon after PPPD. Once HJ stricture occurs, assessment if it is benign or malignant is necessary. If it is due to cancer recurrence, stent insertion and radiation therapy should be conducted; if it is benign stricture, site of stricture should be widened with balloon dilatation after PTBD (Fig. 33.6). In such cases, if the duration of treatment is very long, it can be difficult to remove PTBD catheter. Recently, a therapeutic method using magnet is developed and used.





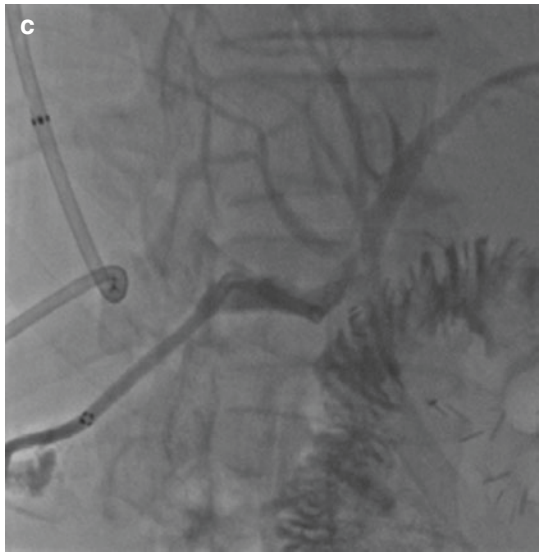
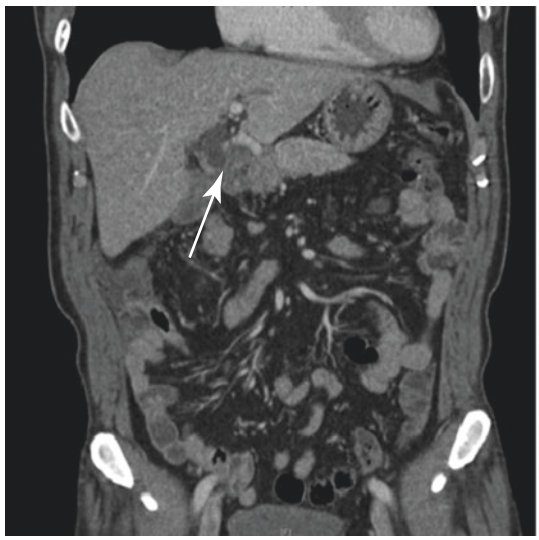


Fig. 33.5 Hepaticojejunostomy site leakage. (**a**) *CT finding*. Fluid collection with hemorrhage in subhepatic space, anastomosis site leakage. (**b**) *Hepatobiliary scan (DISIDA scan)*. Activities along the drainage catheter on 4 h image. Excretion of biliary radiotracer to small bowel. (**c**) *Sinogram (contrast injection study)*. Injected dye reveals intrahepatic duct and jejunum through perforation site of HJ



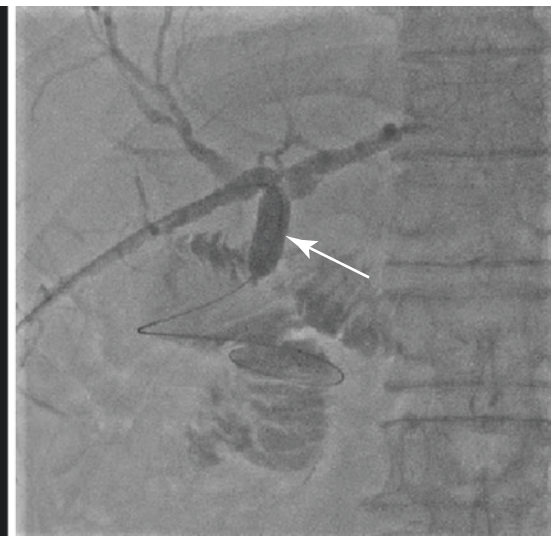


Fig. 33.6 Anastomosis site stricture. Hepaticojejunostomy site stricture. Stricture of hepaticojejunostomy. Intrahepatic/hilar bile duct dilatation (CHD 1.5 cm). Ballooning with catheter in anastomosis site

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Late Metabolic Complications After Pancreatectomy

34

Yoo-Seok Yoon

The ongoing improvements in perioperative care and the introduction of effective chemotherapies for pancreatic cancer have increased the life expectancy of patients after resection of pancreatic cancer. Accordingly, clinicians are now recognizing the importance of the patient's quality of life. Although there are several long-term complications associated with the physiological and anatomical changes after pancreatectomy, abnormal glucose metabolism-related disorders, especially new onset or worsening of diabetes mellitus (DM), have significant impacts on the patient's quality of life [2, 9]. Post-pancreatectomy DM is generally more difficult to treat than type 1 DM (T1DM) and type 2 DM (T2DM). This is because post-pancreatectomy DM is associated with frequent hypoglycemic episodes resulting from the loss of pancreatic counter-regulatory hormones such as glucagon and pancreatic polypeptide, as well as impaired nutrient absorption related to exocrine pancreatic insufficiency. These features may negatively affect the oncologic outcomes because poorly controlled hyperglycemia may delay the initiation of adjuvant therapy or lead to its early termination [19, 32]. Moreover, in the longer term, patients with post-pancreatectomy DM have a similar risk of developing long-term diabetic complications (nephropathy, neuropathy, and retinopathy) to that in patients with T2DM if glycemic control remains poor [5, 43]. Therefore, it is essential to understand the clinical significance of altered glucose metabolism in patients undergoing pancreatectomy for pancreatic cancer. This chapter describes the effects of pancreatectomy on glucose metabolism, the prevalence and clinical characteristics of post-pancreatectomy DM, and the special considerations relevant to treating this disease.

34.1 Effects of Pancreatectomy on Glucoregulatory Hormones

The pancreas is responsible for the regulation of glucose metabolism by the interactions of pancreatic hormones with the liver and peripheral tissues. The key hormones are insulin, glucagon, and pancreatic peptide (PP), which regulate blood glucose concentrations by controlling hepatic glucose production and the utilization of glucose by peripheral tissues [40]. Pancreatectomy deteriorates glucose metabolism by disturbing the balance between the production and utilization of glucose owing to partial or complete deficiency of these hormones. In addition to the decreased insulin secretory capacity, post-pancreatectomy DM is characterized by decreased or absent glucagon and PP secretion because of the loss of the pancreatic parenchyma.

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34.1.1 Insulin

Insulin, which is secreted from β cells distributed evenly throughout the pancreas, decreases blood glucose concentrations by suppressing hepatic gluconeogenesis and glycogenolysis and by facilitating hepatic glycogen synthesis [22]. Fasting insulin and C-peptide concentrations decrease after pancreatectomy, whereas patients with T2DM have normal or elevated insulin concentrations. Consequently, peripheral sensitivity to insulin and the insulin-binding capacity of red blood cells are increased after pancreatectomy [25, 28]. The increase in insulin-binding capacity was due to an increase in peripheral insulin-binding sites rather than an increase in receptor affinity. Although insulin secretion is also reduced in T1DM, the insulin-binding capacity and insulin sensitivity are usually unchanged in these patients.

34.1.2 Glucagon

Glucagon is secreted from α-cells predominantly located in the body and tail of the pancreas, and it is critical for controlling glucose production and in the normal counter-regulation of hypoglycemia [42]. During fasting, glucagon enhances hepatic glycogenolysis and gluconeogenesis, whereas glucose administration suppresses glucagon secretion, thereby avoiding hyperglycemia [17]. Pancreatectomy reduces fasting glucagon concentrations, causing a blunted compensatory response to hypoglycemia. Glucose-induced glucagon suppression is also impaired after pancreatectomy, as in T2DM [38]. With unsuppressed glucagon secretion, the increased hepatic sensitivity to glucagon after pancreatectomy causes hyperglycemia in insulin-deficient states [22].

34.1.3 Pancreatic Polypeptide

PP is secreted by PP cells, which are predominantly located in the head of the pancreas, in response to nutrient ingestion. This hormone plays a role in glucose control by modulating hepatic sensitivity to insulin by regulating hepatic insulin receptor availability [40]. PP deficiency after pancreatectomy leads to increased hepatic glucose production as a consequence of the decrease in hepatic insulin receptor expression. Despite the increase in peripheral insulin availability, post-pancreatectomy DM is associated with a decrease in hepatic insulin availability. Clinical studies have revealed that hepatic sensitivity and glucose tolerance are enhanced after PP infusion in patients with PP deficiency caused by pancreatectomy or chronic pancreatitis [4, 39]. These findings indicate that PP deficiency may be reversed in patients with post-pancreatectomy DM.

34.2 Characteristics of DM After Pancreatectomy

DM after pancreatectomy is classified by the American Diabetes Association (ADA) as a subtype of type 3 DM (T3cDM), which is generally called “pancreatogenic DM” [1]. T3cDM refers to DM associated with, or as a consequence of acute, relapsing and chronic pancreatitis, cystic fibrosis, hemochromatosis, pancreatic cancer, and pancreatectomy. Clinicians are well aware of T1DM and T2DM, but T3cDM is often underdiagnosed or misdiagnosed. According to a recent large-scale study, approximately 9% of patients with DM were found to have T3cDM. Chronic pancreatitis was the most common cause, and pancreatectomy accounted for 2–10% of cases of T3cDM [11, 14].

The clinical and metabolic features of T3cDM are quite distinct from those of T1DM and T2DM owing to decreased circulating concentrations of glucagon, PP, and insulin [36, 40] (Table 34.1). Unlike patients with T1DM, patients with pancreatogenic DM rarely develop ketoacidosis, and hyperglycemia is relatively mild in most cases. Unlike patients with T2DM, which is characterized by profound insulin resistance, patients with pancreatogenic DM are at high risk of severe hypoglycemia after administration of exogenous insulin owing to the increased peripheral sensitivity to insulin and the deficiency of counter-regulatory glucagon secretion. Patients with pancreatogenic DM also have lower insulin

Table 34.1 Characteristics of pancreatogenic DM in comparison with T1DM and T2DM

	T1DM	T2DM	Pancreatogenic DM
Hormone levels			
Insulin	Low	High	Low/absent
Glucagon	Normal/high	Normal/high	Low/absent
Pancreatic polypeptide	Normal/low (late)	High	Low
Insulin sensitivity			
Peripheral	Normal/high	Low	High
Hepatic	Normal	Normal/low	Low
Clinical features			
Hyperglycemia	Severe	Usually mild	Mild
Hypoglycemic episodes	Common	Rare	Common
Ketoacidosis episodes	Common	Rare	Rare

Adopted from Scavini et al. [36]

concentrations, unlike patients with T2DM, whose insulin concentrations are typically normal or elevated, and show little or no insulin response to feeding. Hepatic insulin resistance and unsuppressed glucose production dues to a deficiency in PP secretion are other features of pancreatogenic DM. Therefore, severe T3cDM is often associated with the development of so-called brittle DM because the blood glucose concentration fluctuates from hyperglycemia, due to unsuppressed hepatic glucose production, to severe hypoglycemia due to exaggerated sensitivity to exogenous insulin. This condition is also exaggerated by the nutritional deficiencies and weight loss associated with pancreatic exocrine insufficiency that frequently occur after pancreatectomy [31, 41].

However, post-pancreatectomy DM is not always associated with poor glycemic control. The derangements in glucose metabolism after pancreatectomy range from mild impairments to severe impairments characterized by frequent episodes of hypoglycemia, depending on the extent of resection and the underlying pancreatic disease. Up to 25% of patients with post-pancreatectomy DM have severe glucose metabolic abnormalities [36]. The number of metabolic abnormalities increases greatly as the extent of pancreatectomy increases. In addition, the manifestation of glucose metabolic abnormalities after pancreatectomy may be determined by the relative deficiencies of insulin, glucagon, and PP according to the extent and region of resection. Resection of the pancreatic head is more likely to result in PP deficiency together with hepatic insulin resistance and fasting hyperglycemia. Resection of the distal pancreas is likely to result in glucagon deficiency and a high risk of hypoglycemia [40].

34.3 Prevalence of Post-pancreatectomy DM

In the past, the incidence of DM after partial pancreatectomy has been underestimated. It was though that DM develops if more than 80% of a normal pancreas or 50% of a diseased pancreas are resected. However, recent studies have shown that DM might occur more frequently after partial pancreatectomy than was originally believed, suggesting that this post-pancreatectomy DM might be underestimated and underappreciated [36]. While total pancreatectomy causes pancreatogenic DM in all cases, the incidence of DM after partial pancreatectomy varies according to the underlying pancreatic disease, the type of surgery, and the extent of resection [12, 40].

34.3.1 Prevalence of DM After Pancreatoduodenectomy

There are limited data on the incidence of DM after pancreatoduodenectomy in patients with benign or malignant tumors. Fewer patients (18–27%) without preoperative DM develop DM after pancreatic resection for benign or malignant

pancreatic tumors compared with patients with chronic pancreatitis [22, 32]. The impact of the anastomotic method on postoperative endocrine function is controversial. Although patients who underwent pancreaticogastrostomy experienced marked pancreatic exocrine insufficiency, the extent of impaired endocrine function was similar to that in patients who underwent pancreaticojejunostomy [13, 37]. The decline in glucose tolerance after pancreatoduodenectomy is apparently dependent on a low endocrine functional reserve of the remnant pancreas rather than the anastomotic procedures.

34.3.2 Prevalence of DM After Distal Pancreatectomy

Distal pancreatectomy involves the resection of the pancreatic body and tail, and the volume of resection is dependent on tumor location. The incidence of DM after distal pancreatectomy ranged from 5% to 42% in previous studies [8, 22]. A recent systematic review revealed that, after distal pancreatectomy for benign or malignant tumors, the cumulative incidence of DM was 14%, which is significantly lower than the corresponding value of 39% in patients with chronic pancreatitis [8]. However, a specific limitation of interpreting the results of previous studies is that the volume of the resected pancreas varied considerably, ranging from 10% to 90%, or was not specified. This may contribute to the varying incidence of DM. Recently Kang et al. [15] reported that resection of more than 25% of the total pancreas volume was a significant and independent risk factor for impaired endocrine function after distal pancreatectomy. They also showed that the percentage of patients with impaired endocrine function increased with increasing resection volume. These results suggest that clinicians should recognize the risk of DM, especially in patients with pancreatic cancer who require resection of a greater volume of the pancreas parenchyma for oncologic safety.

Most of the previous epidemiologic studies on the incidence of DM after pancreatectomy have several limitations, which included (1) a retrospective design; (2) heterogeneous criteria for establishing DM without biochemical criteria; (3) no information on preoperative glucose metabolism, such as impaired glucose tolerance or undetected DM; and (4) different follow-up times. Therefore, a prospective observational study with strict diagnostic criteria is needed to estimate the incidence of DM developing after pancreatectomy.

34.4 Special Considerations in the Treatment of Post-pancreatectomy DM

34.4.1 Treatment Guidelines

Limited data are available to guide the development of treatment guidelines specific to pancreatogenic DM, especially post-pancreatectomy DM. Thus, despite its distinct features to those of T1DM and T2DM, post-pancreatectomy DM is often treated according to the best practice recommendations for T1DM and T2DM [24, 27]. The primary target of the treatment of post-pancreatectomy DM, like T1DM and T2DM, is to maintain hemoglobin (Hb)A1c at <7% in order to minimize the risk of microvascular and macrovascular complications [7, 34]. This is because the risks of long-term DM-related complications in patients with T3cDM are similar to those in patients with T1DM and T2DM [5, 43].

In all patients with post-pancreatectomy DM, the initial treatment should begin with efforts to correct the lifestyle factors that contribute to hyperglycemia and to minimize the risk of hypoglycemia. Weight loss in obese patients, daily exercise, low-carbohydrate diet, abstinence from alcohol, and smoking cessation should be encouraged [7]. The therapeutic agents typically used for the treatment for DM after pancreatectomy are the same as those used for T2DM. The choice between insulin or non-insulin drugs as initial therapy depends on the patient's clinical presentation [7, 27]. Insulin is usually preferred for patients with severe hyperglycemia. Because patients

with post-pancreatectomy DM show enhanced peripheral sensitivity to insulin, the dose of insulin required to achieve and maintain glycemic control may be significantly less than that required by other insulin-dependent patients. For patients without severe hyperglycemia, orally administered drugs can be initiated. Metformin is commonly used as the initial oral drug. If hyperglycemia is not well controlled, other orally administered drugs such as a thiazolidinedione or an α-glucosidase inhibitor can be added to metformin. Sulfonylureas and incretin-based drugs (GLP-1 analogs and DPP-4 inhibitors) should not be prescribed to patients with post-pancreatectomy DM because of the increased risks of severe hypoglycemia and pancreatitis, respectively. If hyperglycemia persists despite maximum doses of orally administered drugs, the treatment should be switched to insulin. Metformin should be continued during insulin therapy because it may reduce the daily insulin requirement [21].

PP administration may improve glycemic control in patients with impaired glycemic control despite insulin therapy. As described in Sect. 1.3, the impairment of glucose control associated with hepatic insulin resistance caused by PP deficiency can be reversed by PP administration. A recent study shown that concurrent infusion of PP enhanced insulin sensitivity and reduced insulin requirements in patients with long-standing T1DM or T3cDM who were on insulin pump therapy [33]. Further clinical trials are needed to determine the benefit of PP administration in the treatment of post-pancreatectomy DM.

34.4.2 Treatment of Pancreatic Exocrine Insufficiency

Uniquely, post-pancreatectomy DM is associated with pancreatic exocrine insufficiency, unlike T1DM or T2DM. Although the impact of pancreatic exocrine insufficiency after pancreatectomy has been underestimated, recent clinical studies with functional tests indicate that most patients experience some degree of malabsorption. A recent systemic review indicated that pancreatic exocrine insufficiency is preoperatively present in approximately half of patients with periampullary cancer and that the prevalence of pancreatic exocrine insufficiency markedly increased after resection [41]. The median prevalence of pancreatic exocrine insufficiency at least 6 months after resection was 36–100% after pancreatoduodenectomy and 67–80% after distal pancreatectomy.

It may be difficult to achieve glycemic control in patients with DM and pancreatic exocrine insufficiency. Malnutrition and unpredictable glucose absorption due to rapid intestinal transit increase the likelihood of significant glucose fluctuations and iatrogenic hypoglycemia [20]. There is no definite evidence regarding the beneficial effects of pancreatic enzyme supplementation on fasting glucose or HbA1c. However, oral pancreatic enzyme replacement is likely to improve postprandial glucose tolerance and reduce the incidence of hypoglycemia in patients with pancreatogenic DM [10, 18, 22]. Therefore, the possibility of coexisting pancreatic exocrine dysfunction should be recognized in patients with pancreatogenic DM, and adequate pancreatic enzyme replacement therapy should be initiated promptly in order to control the symptoms of pancreatic exocrine insufficiency and improve glycemic control.

34.4.3 DM After Total Pancreatectomy

DM developing after total pancreatectomy is generally considered to be difficult to treat. However, several recent studies have shown that patients with DM after total pancreatectomy do not necessarily have poor glycemic control [3, 6, 9, 26, 35]. Glycemic control, as represented by HbA1c, was better in these studies than in earlier studies. The rates of hospitalization secondary to hypoglycemic complications and DM-specific quality of life were similar to those in patients with insulin-dependent DM from other causes. There are several explanations for the improvements in glycemic control over time [36]. Hyperglycemia and nutrient malabsorption related to exocrine insufficiency can now be

controlled more effectively with new medications than was historically possible. In addition, increased patient awareness and compliance, self-monitoring of blood glucose, and increasing referrals to a diabetes center may contribute to the improvements in glycemic control. However, in clinical practice, the treatment of patients who develop brittle DM after total pancreatectomy is very complicated. Hypoglycemia-related mortality and long-term complications, such as nephropathy, neuropathy, and retinopathy, should also be taken into consideration [22]. Therefore, after evaluating the true incidence of brittle DM after total pancreatectomy, further studies are needed to determine the optimal management strategy for patients brittle DM after total pancreatectomy to prevent these complications.

34.5 Resolution of Preoperative DM After Pancreatectomy in Patients with Pancreatic Cancer

Improvements in endocrine function have been reported after pancreatectomy in patients with pancreatic cancer [16, 23, 29, 30, 44]. A recent review, which included 440 patients from eight studies, revealed that preoperative DM resolved after pancreatectomy in 29% of patients with pancreatic cancer [32]. Pannala et al. [30] reported that nearly 75% of patients with preoperative DM and pancreatic cancer had new-onset DM (<2 years' duration). Although DM resolved in almost 60% of patients with new-onset DM, its prevalence was unchanged in patients with long-standing DM. The authors concluded that removing a diabetogenic factor secreted by pancreatic cancer may contribute to the resolution of new-onset DM. Wu et al. [44] also reported a higher resolution rate of DM after pancreatoduodenectomy in patients with new-onset DM (51%) than in patients with long-standing DM (10%), but this phenomenon was similar in patients with and without pancreatic cancer. Based on these results, the authors proposed that the anatomical changes after pancreatoduodenectomy may play a role in the resolution of DM. Kang et al. [16] reported that resolution of DM was more frequently observed after pancreatoduodenectomy (40%) than after distal pancreatectomy (13%). Furthermore, based on the results that BMI and baseline insulin secretion showed similar decreases after pancreatoduodenectomy and distal pancreatectomy, they suggested that the physiological and anatomical changes in the gastrointestinal tract after pancreatoduodenectomy may help resolve DM independently of the changes in body weight.

Several possible reasons for the resolution of DM after pancreatectomy have been suggested in previous studies, including (1) removal of diabetogenic factors secreted by pancreatic cancers, (2) improvement in inflammation caused by obstructive lesions of the pancreas, (3) postoperative weight loss, (4) delayed gastric emptying, and (5) altered gastrointestinal tract anatomy after pancreatoduodenectomy.

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Enhanced Recovery Program After Pancreatectomy

35

Sang-Jae Park

35.1 Introduction

ERAS (enhanced recovery after surgery) was initially developed by Henrik Kehlet in 2001, which was first to describe and implement such a multimodal care protocol successfully in colonic surgery [1]. Subsequently, many studies have been published on this topic, not only in colonic surgery but also in many other fields of surgery (e.g., musculoskeletal [2], breast [3], aortic [4, 5], bariatric [6, 7], and prostate surgery [8]). ERAS has been used with other terms like "fast track" or "critical or clinical pathway." The purpose of ERAS is not a simple early discharge but with supplying the most appropriate perioperative management by evidence-based medicine, to reduce surgical stress and maintain patient homeostasis therefore to reduce surgical morbidity and hospital stay and cost, and to improve quality of life. With an ERAS program, the patients can reduce the unnecessary stressful routines such as nasogastric tube insertion, preoperative bowel preparation, long perioperative nil by mouth, long prophylactic antibiotics, etc. and can quickly restore the homeostasis with pain control, early ambulation, enhancement of gut function, perioperative nutritional support, psychological support, etc. To maintain ERAS, multidiscipline approach is mandatory including surgeon, physician, anesthesiologist, nurse, dietician, etc.

Pancreatic surgery traditionally has been considered as a high-risk abdominal surgery associated with high morbidity and mortality rates. As advances in diagnostic and surgical techniques and ICU care in the past decades have led to better outcomes after pancreatic resection, mortality rate has decreased markedly, while morbidity remains still high [9]. In high-volume specialized centers, mortality for the most common pancreatic resection, pancreaticoduodenectomy (PD), is now less than 2–5% [10]. However, morbidity remains high at a rate over 50% [10, 11]. Postoperative hospital stay after PD ranges from 14 to 20 days in various studies [11–13]. Complications, such as pancreatic fistula, bile leakage, and delayed gastric emptying (DGE), are the main reasons for delayed recovery and frequent need for additional radiological or surgical interventions [14]. As pancreatic surgery still combines with frequent complications with long hospital stay, there has been a pessimistic atmosphere for the actual benefit of ERAS program for PD. However, factors other than morbidity also seem to delay recovery from PD, such as pain, gut dysfunction, and immobility. Through the supplement of evidence-based best perioperative care program so far, post-PD complications could be minimized, and recovery and

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discharge could be fastened with decreased cost. Though several protocol elements of an ERAS program already have become the standard practice in many hospitals during the last decade (e.g., thromboprophylaxis, prevention of hypothermia, early mobilization) for PD, substantial heterogeneity in the content of ERAS protocols exists [14, 15]. A meta-analysis with ten studies [16–25] of ERAS programs after pancreatectomy (three prospective and seven retrospective studies) published in 2015 suggested the shortened hospital stay without increased morbidity or readmission rate [15]. In 2013, a comprehensive guideline with 27 items for perioperative care for PD was published by ERAS® society [26]. Many items in this guideline for PD were originally suggested in other guidelines for elective colonic surgery [27, 28], rectal/pelvic surgery [29], and gastrectomy recommended from ERAS® Society [30]. As well-designed studies of ERAS for PD are very rare, many of items suggested in this guideline don't have high evidence levels.

35.2 Basic Concept and Pathophysiology of ERAS

Compared with traditional perioperative care, ERAS program represents a fundamental shift in the process of care, by multidisciplinary interventions that attenuate surgical stress, maintain physiological function, and expedite return to baseline [31]. While each intervention has a small effect, all together they have a stronger synergistic impact (Fig. 35.1) [32]. Preventing stress and thus minimizing this adverse response represents the central mechanism around which the concept of ERAS is based. This response encompasses all elements associated with surgery such as anxiety, fasting, tissue damage, hemorrhage, hypothermia, fluid shifts, pain, hypoxia, bed rest, ileus, and cognitive imbalance [31]. Such significant changes in metabolic and physiological homeostasis represent a threat to the body and mind that need to be treated for a successful recovery after operation. Evidence suggests that this phenomenon, if left untreated, can lead to increased morbidity and mortality [31, 33].

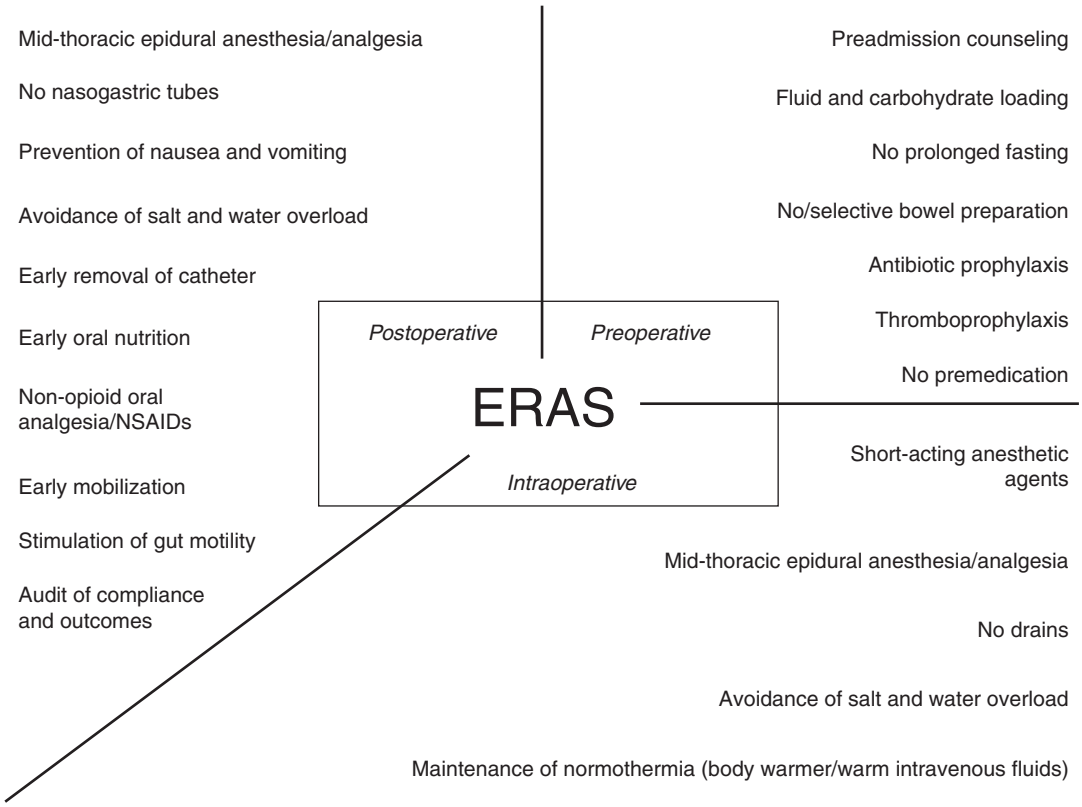

Fig. 35.1 ERAS elements [32]

Major abdominal surgery induces an immune-inflammatory response, which is accompanied by the production of reactive oxygen species (ROS) at the site of injury causing direct cellular injury, and several stress hormones and cytokines appear to amplify the inflammatory cascades. The resulting impaired vascular permeability together with excessive fluid administration can lead to fluid overload, interstitial edema, and therefore delayed recovery of gastrointestinal function and impaired anastomotic healing [34].

Traditional strategy for perioperative fluid management composed of overnight NPO with bowel preparation, sufficient fluid supply intra- and postoperatively to keep intravascular volume enough. However, fluid balance is a very important point in ERAS because salt and water overload results in prolonged ileus and increased postoperative complications including anastomotic leakage which leads to prolonged hospital stay and increased cost [34, 35]. The principle of maintaining a patient in the zone of normovolemia is to maintain a normal intravascular volume and avoid gaining weight due to excessive administration of fluid. Generally, it has been shown that postoperative complications increase when the weight gain in the postoperative period exceeds 2.5 kg (indicative of a 2.5 L cumulative fluid overload) [36]. Preoperative adequate hydration without bowel preparation, intraoperative and postoperative fluid management avoiding fluid overload, and early establishment of oral intake allow the patients to be normovolemic with zero balance [31]. Moreover, preoperative minimal NPO with carbohydrate loading and early feeding can reduce hunger, thirst, and anxiety of the patients as well as decrease postoperative insulin resistance and improve glucose control. The concept of zero-balance fluid management comes from the recent advancement in the surgical techniques allowing less bleeding with fast operation and also in the perioperative care.

Early oral feeding is a key component in ERAS. The risk factors of postoperative ileus have been identified which include increasing age, male gender, low preoperative serum albumin, acute and chronic opioid use, previous abdominal surgery, preexisting airways and vascular disease, long duration of surgery, emergency surgery, blood loss, and salt and water overload. Most of these factors increase the inflammatory response, and inflammation and edema play a major role in reducing intestinal smooth muscle contractility [37]. A number of strategies have been suggested to prevent postoperative ileus, and these have been reviewed recently and are summarized in Table 35.1 [37].

Table 35.1 Strategies to prevent postoperative ileus [37]

Intervention	Mechanism	Benefit
Salt and fluid restriction	↓ gut edema and stretch	++
Carbohydrate loading	↓ insulin resistance	±
Routine nasogastric tubes	Prophylactic drainage of stomach	–
Intravenous lidocaine	Anti-inflammatory; opioid-sparing	+
Coffee	Stimulatory effect	+
Chewing gum	Stimulatory effect	+
NSAIDs	Opioid sparing; anti-inflammatory	++
Early enteral nutrition	Anabolic; ↓ insulin resistance stimulatory	++
Enhanced recovery programs	Multimodal effect	++
Laparoscopic surgery	↓ tissue trauma; ↓ bowel handling; ↓ inflammatory reaction	++
Alvimopan	μ-opioid receptor antagonist	++
Mid-thoracic epidural anesthesia	↓ inflammatory response ↓ sympathetic stimulation ↓ opioid requirement	++
Early mobilization	? anabolic effect	+/±
Nicotine	Colonic prokinetic	+
Daikenchuto	Anti-inflammatory on acetylcholine receptors	+
Magnesium sulfate	Anesthetic effect	+
Prokinetics	Prokinetic effect	±

++ definite benefit, + possible benefit, ± no benefit, – possible harm

In the context of the ERAS program, the adaptation of multimodal analgesic strategies aims not only to improve postoperative pain control and reduce surgical stress but also to attenuate the multiorgan dysfunction induced by unrelieved pain, reduce opioid side effects, facilitate early resumption of oral diet and early mobilization, and ultimately accelerate surgical recovery [31]. For the last decades, minimally invasive surgery (MIS) has been expanding to change the paradigm of the surgical principles dramatically. As MIS can reduce the surgical stress with less incision and pain, postoperative restoration of homeostasis can be achieved fast resulting in early discharge. Expanding MIS is a very strong supporter for ERAS program in the future.

35.3 ERAS for PD

Although still there is a concern about the real benefit of ERAS for PD, positive results with ERAS programs after PD have been published [14–25]. A meta-analysis with ten studies of ERAS programs after pancreatectomy suggested the shortened hospital stay without increased morbidity or readmission rate [15]. One systemic review analyzing eight studies reported that implementation of an ERAS protocol led to a significant decrease in length of stay, complications, and cost without increase of morbidity and mortality [14]. The reductions in hospital stay seen in ERAS studies for PD do not compare with the impressive reductions reported in ERAS studies for colorectal or liver resections. It could be argued that this reflects the high rate of morbidity following PD relative to the acknowledged lower rate of complications following colorectal and standard liver resections [23]. The reported series in ERAS studies for PD employed different protocols, respectively. In fact, the individual items of ERAS can be modified according to the diverse situations of each institute or each surgeon. In Table 35.2, the items of ERAS protocol of the author's institute are suggested. ERAS® Society, European Society for Clinical Nutrition and Metabolism (ESPEN), and International Association for Surgical Metabolism and Nutrition (IASMEN) presented a comprehensive guideline of consensus for optimal perioperative care after PD in 2013 (Table 35.3) [26]. Available evidences and recommendations are summarized for 27 care items. As well-designed studies are very rare, many items suggested in this guideline don't have high evidence levels. In the following session, several important items will be discussed in detail. Issues concerning pancreatic

Table 35.2 ERAS protocol for PD of National Cancer Center, Korea

Before operation
Nutritional assessment (preoperative nutritional support if needed)
Counseling for psychology, rehabilitation and diabetes, etc.
Epidural catheter insertion (till POD #7)
Day of operation
Oral carbohydrate loading until 2 h before operation
No enema
Preoperative heparin, 5,000 units subcutaneously (till POD #7)
Nasogastric tube after induction of anesthesia (removal after operation)
Perioperative antibiotics (single shot after anesthesia)
Somatostatin analogue (till POD #3)
One Jackson-Pratt (JP) drains
POD 1
Start sips of water
POD 2
Free sweet fluid (juice or water with honey)
Removal of Foley
Start ward ambulation
POD 3–4
Semifluid diet (150 Cal/day)
Reduce IV fluid (<1.5 L)
Removal of JP drain (if drain amylase <1,000 iu)
POD 5–6
Semisolid diet (400 Cal/day)
Reduce IV fluid (<1 L)
POD 7–8
Semisolid diet (800 Cal/day)
Stop IV fluid
POD 9–10
Semisolid diet (1,200 Cal/day)
Counseling for psychology, rehabilitation, and diabetes
Nutritional assessment
Check dynamic CT
Consider discharge

Table 35.3 Guideline for perioperative care for PD. ERAS® Society recommendation [26]

Item	Summary and recommendations	Evidence level	Recommendation grade
Preoperative counseling	Patients should receive dedicated preoperative counseling routinely	Low	Strong
Perioperative biliary drainage	Preoperative endoscopic biliary drainage should not be undertaken routinely in patients with a serum bilirubin concentration <250 μmol/l	Moderate	Weak
Preoperative smoking and alcohol consumption	For alcohol abusers, 1 month of abstinence before surgery is beneficial and should be attempted. For daily smokers, 1 month of abstinence before surgery is beneficial. For appropriate groups, both should be attempted	Alcohol abstention: low	Strong
Preoperative nutrition	Routine use of preoperative artificial nutrition is not warranted, but significantly malnourished patients should be optimized with oral supplements or enteral nutrition preoperatively	Very low	Weak
Perioperative oral immunonutrition (IN)	The balance of evidence suggests that IN for 5–7 days perioperatively should be considered because it may reduce the rate of infectious complications in patients undergoing major open abdominal surgery	Moderate	Weak
Oral bowel preparation	Extrapolation of data from studies on colonic surgery and retrospective studies in PD show that MBP has no proven benefit. MBP should not be used	Moderate	Strong
Preoperative fasting and preoperative treatment with carbohydrates	Intake of clear fluids up to 2 h before anesthesia does not increase gastric residual volume and is recommended before elective surgery. Intake of solids should be withheld 6 h before anesthesia. Data extrapolation from studies in major surgery suggests that preoperative oral carbohydrate treatment should be given in patients without diabetes	Fluid intake: high Solid intake: low Carbohydrate loading: low	Fasting: strong Carbohydrate loading: strong
Preanesthetic medication	Data from studies on abdominal surgery show no evidence of clinical benefit from preoperative use of long-acting sedatives, and they should not be used routinely. Short-acting anxiolytics may be used for procedures such as insertion of epidural catheters	No long-acting sedatives: moderate	Weak
Anti-thrombotic prophylaxis	LMWH reduces the risk of thromboembolic complications, and administration should be continued for 4 weeks after hospital discharge. Concomitant use of epidural analgesia necessitates close adherence to safety guidelines. Mechanical measures should probably be added for patients at high risk	High	Strong
Antimicrobial prophylaxis and skin preparation	Antimicrobial prophylaxis prevents surgical-site infections, and should be used in a single-dose manner initiated 30–60 min before skin incision. Repeated intraoperative doses may be necessary depending on the half-life of the drug and duration of procedure	High	Strong

(continued)

Table 35.3 (continued)

Item	Summary and recommendations	Evidence level	Recommendation grade
Epidural analgesia	Mid-thoracic epidurals are recommended based on data from studies on major open abdominal surgery showing superior pain relief and fewer respiratory complications compared with intravenous opioids	Pain: high Reduced respiratory complications: moderate	Weak
		Overall morbidity: low	
Intravenous analgesia	Some evidence supports the use of PCA or intravenous lidocaine analgesic methods. There is insufficient information on outcome after PD	PCA: very low I.V. Lidocaine: moderate	Weak
Wound catheters and transversus abdominis plane block	Some evidence supports the use of wound catheters or TAP blocks in abdominal surgery. Results are conflicting and variable, and mostly from studies on lower gastrointestinal surgery	Wound catheters: moderate TAP blocks: moderate	Weak
Postoperative nausea and vomiting (PONV)	Data from the literature on gastrointestinal surgery in patients at risk of PONV show the benefits of using different pharmacological agents depending on the patient's PONV history, type of surgery, and type of anesthesia. Multimodal intervention during and after surgery is indicated	Low	Strong
Incision	The choice of incision is at the surgeon's discretion, and should be of a length sufficient to ensure good exposure	Very low	Strong
Avoiding hypothermia	Intraoperative hypothermia should be avoided by using cutaneous warming, i.e., forced-air or circulating-water garment systems	High	Strong
Postoperative glycemic control	Insulin resistance and hyperglycemia are strongly associated with postoperative morbidity and mortality. Treatment of hyperglycemia with intravenous insulin in the ICU setting improves outcomes but hypoglycemia remains a risk. Several ERAS protocol items attenuate insulin resistance and facilitate glycemic control without the risk of hypoglycemia. Hyperglycemia should be avoided as far as possible without introducing the risk of hypoglycemia	Low	Strong
Nasogastric intubation	Pre-emptive use of nasogastric tubes postoperatively does not improve outcomes, and their use is not warranted routinely	Moderate	Strong
Fluid balance	Near-zero fluid balance, avoiding overload of salt and water results in improved outcomes. Perioperative monitoring of stroke volume with transesophageal Doppler to optimize cardiac output with fluid boluses improves outcomes. Balanced crystalloids should be preferred to 0.9% saline	Fluid balance: high esophageal Doppler: moderate Balanced crystalloids vs. 0.9% saline: moderate	Strong

Table 35.3 (continued)

Item	Summary and recommendations	Evidence level	Recommendation grade
Perianastomotic drain	Early removal of drains after 72 h may be advisable in patients at low risk (i.e., amylase content in drain <5,000 U/L) for developing a pancreatic fistula. There is insufficient evidence to recommend routine use of drains, but their use is based only on low-level evidence	Early removal: high	Early removal: strong
Somatostatin analogues	Somatostatin and its analogues have no beneficial effects on outcome after PD. In general, their use is not warranted. Subgroup analyses for variability in the texture and duct size of the pancreas are not available	Moderate	Strong
Urinary drainage	Suprapubic catheterization is superior to transurethral catheterization if used for >4 days. Transurethral catheters can be removed safely on postoperative day 1 or 2 unless otherwise indicated	High	For suprapubic: weak Transurethral catheter out POD 1–2: strong
Delayed gastric emptying (DGE)	There are no acknowledged strategies to avoid DGE. Artificial nutrition should be considered selectively in patients with DGE of long duration	Very low	Strong
Stimulation of bowel movement	A multimodal approach with epidural and near-zero fluid balance is recommended. Oral laxatives and chewing gum given postoperatively are safe, and may accelerate gastrointestinal transit	Laxatives: very low Chewing gum: low	Weak
Postoperative artificial nutrition	Patients should be allowed a normal diet after surgery without restrictions. They should be cautioned to begin carefully and increase intake according to tolerance over 3–4 days. Enteral tube feeding should be given only on specific indications, and parenteral nutrition should not be employed routinely	Early diet at will: moderate	Strong
Early and scheduled mobilization	Patients should be mobilized actively from the morning of the first postoperative day and encouraged to meet daily targets for mobilization	Very low	Strong
Audit	Systematic improves compliance and clinical outcomes	Low	Strong

fistula, delayed gastric emptying, intra-abdominal drain management, etc. will be discussed in other chapters of this book.

35.3.1 Preoperative Biliary Drainage (PBD)

PBD has long been considered a routine to reduce jaundice in patients with bile duct obstruction. Several retrospective studies have suggested that PBD could reduce morbidity and mortality after PD [38–40]. However, since the 1990s, despite effective reducing jaundice, several large-scale retrospective studies reported that PBD did not only failed to show a clinical benefit but also associated with an adverse impact on perioperative outcome, especially increasing infectious complications [41–43]. These findings were repeatedly confirmed in several meta-analysis [44–46], and the latest one published in 2015 including 6,286 cases (8 RCTs, 13 prospective,

and 20 retrospective studies) demonstrated that PBD resulted in a significant increase in the risk of postoperative infectious complication, wound infection, and delayed gastric emptying compared with non-PBD [38]. Recently, more elaborated RCT comparing PBD (endoscopic biliary stent of 7-Fr. plastic stent) with non-PBD published in 2010 has suggested that PBD was associated with more serious complications (74% vs. 37%) and therefore should not be performed routinely [47]. Nevertheless, PBD has been incorporated before PD in many centers which is partly because several limitations of previous studies make to draw a conclusion difficult, heterogeneity of study design, types of disease, types of PBD routes or drainage duration, etc. In case of poor patient's condition, presence of cholangitis or jaundice complications such as pruritus, coagulation/nutrition/renal problems, or anticipating neoadjuvant treatment, PBD (endoscopic or percutaneous) should be considered. Compared with PTBD, endoscopic stent shows more procedure failure, procedure-related complications such as pancreatitis and cholangitis, and stent occlusion which can be decreased in self-expandable metal stent (SEMS). PTBD has a big concern about tract seeding which was reported to be 5.2% in a large-series study [48]. In conclusion, PBD before PD should not be a routine any longer when early operation is possible.

35.3.2 Preoperative Fasting and Preoperative Carbohydrate Loading

Preoperative fasting from midnight has long been a standard practice in elective surgery because of the fear for aspiration. However, it was reported that 2 h after clear fluid and 6 h after solid food, gastric residual volume is less than 5% [49]. Overnight fasting increases thirst, hunger, and anxiety as well as insulin resistance and glucose imbalance [50, 51], and intake of a clear carbohydrate-rich drink until 2 h before operation has been shown to improve the clinical course and quality of life [52–54]. Guidelines recommend the intake of clear fluid until 2 h before the induction of anesthesia as well as a fasting period of 6 h for solids [55]. Earlier resumption of gut function after colorectal surgery has also been suggested [56], and an RCT including some PD patients concluded that oral carbohydrate treatment may preserve skeletal muscle mass [57]. With above knowledge, the patients should be allowed to drink clear carbohydrate fluid until 2 h before pancreatectomy.

35.3.3 Perioperative Nutritional Support

According to ESPEN guideline for surgery, preoperative nutritional support is indicated with severe nutritional risk for 10–14 days prior to major surgery even if surgery has to be delayed, weight loss >10–15% within 6 months, BMI <18.5 kg/m^2, Subjective Global Assessment (SGA) Grade C, and serum albumin <3.0 mg/dl (with no evidence of hepatic or renal dysfunction) [58]. And patients after pancreatic surgery also have high tendency of malnutrition postoperatively due to slow return of gut function, high rate of complications including delayed gastric emptying, pancreatic fistula and infection, and long hospital stay [58]. For long time, the fear that early feeding could increase the complication rate by stimulating pancreatic secretion led surgeons to maintain patients nil by mouth after PD [20]. A recent large multicenter RCT in patients undergoing only major upper gastrointestinal and hepatopancreaticobiliary surgery (including >80 patients undergoing PD) investigated this issue and concluded that allowing early diet is safe for these patients and that enteral tube feeding did not confer benefit [59]. There are no data to support the idea that a surgeon-controlled stepwise increase from spoonfuls of water to a normal diet is safer than a patient-controlled routine as long as patients are informed about the potential of impaired gut function in the early postoperative period. Enteral or parenteral nutritional support will often be necessary if major complications develop [26]. Parenteral nutrition is indicated only in patients who cannot eat and

drink normally and who cannot tolerate enteral nutrition [60]. For the feeding routes after PD, five routes (oral, nasojejunal tube, gastrojejunal tube, feeding jejunostomy, TPN) were compared in systemic review in 2013. Fifteen studies were included. For the length of stay, oral, gastrojejunal route was better than NJ > TPN, feeding jejunostomy. For the normal oral intake, oral and NJ were better. For morbidity, NJ and GJ have high mortality. For mortality, NJ and TPN have high mortality [61].

35.3.4 Fluid Management

"Enough, not to be little" had long been the principle of perioperative fluid management until excessive overload of salt and water in the perioperative period reported to increase postoperative complication rates and delay the return of gastrointestinal function [34, 62–64]. Recently, several studies reported that "restricted" fluid management after major elective gastrointestinal surgery improved the outcome reducing peripheral edema, hyponatremia, vomiting, confusion, and readmission within 30 days [35, 64–66]. However, there are some reports that excessive perioperative fluid restriction does not reduce complications [67, 68] and even bring about harmful effects [69]. Therefore, the basic principle of perioperative fluid therapy is "not too much and not too little" to make the near-zero fluid balance. The most studies concerning restricted fluid management were for upper or lower gastrointestinal tract, and in case of pancreatic surgery which accompanies huge surgical stress of large dissection field, considerable bleeding and transfusion risks, long operation time, and high rate of complication, it may often be difficult to keep "restricted" perioperatively. To date, a very few studies evaluating the effect of "restricted fluid management" in pancreatic surgery have been reported [70]. In conclusion, there is still no evidence that "restricted fluid management" can be feasible and improve the outcome after pancreatic surgery; therefore, well-designed studies with advanced perioperative management can draw a conclusion about this point in the future.

35.3.5 Pain Control

Surgical pain can be somatic, visceral, or neuropathic depending on the type of surgery and on the surgical approach [71, 72]. The purpose of multimodal analgesia is to control pain with different classes of medications acting on multiple sites [73]. In the context of the ERAS program, the adaptation of multimodal analgesic strategies aims not only to improve postoperative pain control and reduce surgical stress but also to attenuate the multiorgan dysfunction induced by unrelieved pain, reduce opioid side effects, facilitate early resumption of oral diet and early mobilization, and ultimately accelerate surgical recovery [74].

A meta-analysis showed that continuous epidural analgesia with or without opioids provided significant improvement in postoperative pain control compared with parenteral opioids or patient-controlled intravenous opioid analgesia in open abdominal surgery [74, 75]. With respect to complications after abdominal or thoracic surgery, a meta-analysis [76] concluded that epidural analgesia was associated with a significantly decreased risk of postoperative pneumonia, as well as an improvement in pulmonary function and arterial oxygenation. A retrospective study comparing epidural analgesia with intravenous analgesia after PD found that patients with epidural analgesia had lower pain scores but significantly higher rates of major complications [77]. It has been suggested that thoracic epidural analgesia after PD may be associated with hemodynamic instability, which might compromise enteric anastomoses, intestinal perfusion, and recovery of gastrointestinal function [78].

35.4 Summary

Although some items have considerable agreement for ERAS program for PD, others still do not have the enough support for the general practice. And the individual items of ERAS can be diversified or modified depending on the situation of each institutes or surgeons. ERAS program is not set in stone, rather it is dynamic with audit

and is a continuously evolving process where novel treatments are evaluated and brought into practice to help improve the outcome [26]. As new concept or practice will come from the well-designed powerful studies to find the better way for enhanced recovery after PD, the management guideline will change continuously, and PD will become safer and more effective. Standardized multicenter and multinational prospective studies of a unified and comprehensive perioperative care protocol in patients undergoing PD are warranted.

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Drain Management After Pancreatectomy

36

Manabu Kawai and Hiroki Yamaue

36.1 Introduction

Randomized clinical trials have demonstrated that prophylactic drains have not decreased the incidence of postoperative complications in elective hepatectomy, colectomy, and cholecystectomy [1–4]. However, the morbidity rate after pancreatic surgery still remains high in the range of 15–41%, although mortality has decreased to less than 5% due to recent advances in surgical techniques and perioperative management [5–10]. In particular, pancreatic fistula is one of the most severe postoperative complications after pancreatectomy. Pancreatic fistula is reportedly associated with a higher incidence of life-threatening complications, such as intra-abdominal abscess, intra-abdominal hemorrhage, and sepsis. It has been considered that routine intraperitoneal drain after pancreatectomy could provide monitoring of the early warning sign of intra-abdominal bleeding, as well as the detection of the pancreatic fistula. Therefore, intraperitoneal drains routinely have been inserted after pancreatectomy, even in high-volume centers of pancreatic surgery. In this chapter, the impacts of routine intraperitoneal drain after pancreatectomy and drain management were reviewed from current studies.

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36.2 The Impact of Routine Intraperitoneal Drain After Pancreatectomy

Table 36.1 summarized outcomes of several studies to evaluate the impact of routine intraperitoneal drain after pancreatectomy. In 2001, one randomized controlled trial has reported that the presence of drains failed to reduce the rate of either mortality (drain group 2% vs. no drain group 2%) or severe complications associated with pancreatectomy (drain group 22% vs. no drain group 12%) [11]. It was concluded that routine placement of drain should not be considered mandatory after pancreatectomy. Afterward, four large cohort studies comparing drain with no drain after pancreatectomy were published, although these studies were retrospective studies [12–15]. All of four studies have demonstrated that routine intraperitoneal drain did not decrease severe postoperative complications after pancreatectomy and mortality. Therefore, it was concluded that routine intraperitoneal drains may be not required after pancreatectomy. However, when the available results are carefully considered, we get noticed some points. Fisher et al. have reported that no drain group was associated with decreased delayed gastric emptying compared to drain group (9% vs. 24%, $P = 0.02$) and a tendency toward a lesser rate of wound infection (2% vs. 12%, $P = 0.054$). However, readmission rate (17% vs. 9%, $P = 0.007$) and interventional drainage (11% vs. 2%, $P = 0.001$)

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Table 36.1 Outcomes of several studies to evaluate the impact of routine intraperitoneal drain after pancreatectomy

Authors	Year	Study design	Procedure	Variable	Sample size	Morbidity[a] (%)	Pancreatic fistula[b] (%)	Re-drainage (%)	Reoperation (%)	Readmission (%)	Mortality (%)
Conlon et al. [11]	2001	RCT	PD and DP	Drain	88	22	12.5	13	9	NA	2
				No drain	91	12	0	8	4	NA	2
Fisher et al. [12]	2011	Retrospective study	PD and DP	Drain	179	21	12	2*	4	9*	1
				No drain	47	15	11	11	0	17	2
Mehta et al. [13]	2013	Retrospective study	PD	Drain	251	36.3	16.3	8.4	5.6	17.5	2.0
				No drain	458	30.2	7.6*	6.3	5.7	16.8	2.5
Correa-Gallego et al. [14]	2013	Retrospective study	PD and DP	Drain	553	33	20	19	<1	27	1
				No drain	569	26*	16*	15	<1	20*	2
Adham et al. [15]	2013	Retrospective study	PD and DP	Drain	130	29.4	9.2	14.6	NA	NA	5.4
				No drain	112	42.9	11.4	20.5	NA	NA	4.5
van Buren et al. [16]	2014	RCT	PD	Drain	68	28	10	9*	3	16	3
				No drain	69	41	20	23	9	12	12

PD pancreaticoduodenectomy, *DP* distal pancreatectomy, *RCT* randomized controlled trial, *NA* not available

*A significant reduction was observed ($P < 0.05$)

[a]Morbidity was identified as Clavien IIIa or more

[b]Pancreatic fistula was identified as clinically relevant pancreatic fistula

were significantly higher in no drain group than drain group. On the other hand, Adham et al. have reported that intraperitoneal drains did not decrease the requirement for interventional procedure (drain group 14.6% vs. no drain group 20.5%, $P = 0.15$) after pancreatectomy. A recent largest retrospective study ($n = 709$) by Mehta et al. also has demonstrated that routine intraperitoneal drains after pancreaticoduodenectomy did not decrease the requirement for interventional procedure (drain group 8.4% vs. no drain group 6.3%, $P = 0.358$) and the rate of readmission (drain group 17.5% vs. no drain group 16.8%, $P = 0.892$). Rather, this study has reported that routine intraperitoneal drains after pancreaticoduodenectomy may be associated with increased clinically relevant pancreatic fistula (drain group 16.3% vs. no drain group 7.6%, $P < 0.01$).

It had remained still controversial whether routine intraperitoneal drains decrease the postoperative complications after pancreatectomy. In 2014, a multicenter randomized controlled trial in the USA has evaluated whether pancreaticoduodenectomy without routine intraperitoneal drains does not increase the incidence of severe postoperative complications [16]. One hundred thirty-seven patients who underwent pancreaticoduodenectomy were enrolled in this study; 68 patients were randomized to drain group, and 69 patients were randomized to no drain group. The primary endpoint for this a multicenter randomized controlled trial was the 60-day grade II or greater complication rate. This study has demonstrated that pancreaticoduodenectomy without intraperitoneal drainage was associated with increased 60-day grade II or greater complication rate, which was the primary endpoint for this a multicenter randomized controlled trial (drain group 52% vs. no drain group 68%, $P = 0.047$). Moreover, no drain in this study significantly increased gastroparesis (drain group 24% vs. no drain group 42%, $P = 0.021$), intra-abdominal abscess (drain group 12% vs. no drain group 26%, $P = 0.033$), diarrhea more than grade II (drain group 3% vs. no drain group 17%, $P = 0.005$), abdominal fluid collection (drain group 2% vs. no drain group 12%, $P = 0.033$). The most important point was that the study was stopped early by the Data Safety Monitoring Board although this study were planned to require a total of 752 patients for the two groups at first. Because mortality in no drain group was 12% which was a fourfold increase compared to 3% in drain group after 90-day follow-up. This study concluded that pancreaticoduodenectomy without intraperitoneal drainage significantly increased the incidence of severe complications and contributed to increased mortality.

36.3 The Impact of Early Removal Drain After Pancreatectomy

What is appropriate drain management after pancreatectomy? The period of drain insertion is the most important point regarding drain management after pancreatectomy. Table 36.2 summarized two studies which have reported the association between early drain removal and pancreatic fistula. One prospective study and one randomized controlled trial have been designed to clarify whether the intended period of drain insertion influenced postoperative complication rates after pancreatectomy. The study by Kawai et al. prospectively assigned the patients who underwent PD into two groups: group I ($n = 52$, drain to be removed on postoperative day (POD) 8) and group II ($n = 52$, drain to be removed on POD 4). The incidence of pancreatic fistula was significantly lower in POD 4 (3.6%) than in POD 8 (23%) ($P = 0.0038$) [17]. The incidences of intra-abdominal infections, including intra-abdominal abscess and infected intra-abdominal collections, were significantly reduced in POD 4 (7.7%) compared with POD 8 (38%) ($P = 0.0003$). Moreover, drain removal on POD8 was the only independent risk factor for intra-abdominal infections by multivariate analysis (odds ratio: 6.7). This study has concluded that postoperative complications rates including pancreatic fistula and intra-abdominal infections were significantly lower when the prophylactic drains were to be removed on POD 4.

Table 36.2 Studies to evaluate the association between early removal drain and pancreatic fistula

Authors	Year	Study design	Procedure	Variable	Sample size	Pancreatic fistula[a] (%)	Intra-abdominal infection (%)	Reoperation (%)	Readmission (%)	Mortality (%)
Kawai et al. [17]	2006	Prospective study	PD	Early drain removal on POD4	52	3.6*	7.7*	0	0	0
				Late drain removal on POD8	52	23	38	0	0	1.9
Bassi et al. [18]	2011	RCT	PD and DP	Early drain removal on POD3	57	1.8*	NA	0	0	0
				Late drain removal on POD5 or beyond	57	26	NA	1.8	8.8	0

PD pancreaticoduodenectomy, *DP* distal pancreatectomy, *RCT* randomized controlled trial, *NA* not available

*A significant reduction was observed ($P < 0.05$)

[a]Pancreatic fistula was identified as clinically relevant pancreatic fistula

Also, a prospective randomized clinical trial conducted by Bassi et al. evaluated whether early drain removal (POD 3) is associated to a lower rate of pancreatic fistula and abdominal complications after pancreatectomy compared to late drain removal (POD 5 or beyond) in patients with amylase value in drains less than 5,000 U/L [18]. This study has reported that early drain removal was significantly associated with a decreased rate of pancreatic fistula ($P = 0.0001$), abdominal complications ($P = 0.002$), and pulmonary complications ($P = 0.007$). One prospective study and one randomized controlled trial have concluded that drain removal as early as POD 3–4 results in a significant reduction of postoperative complications compared to late removal drain. Early removal drain after pancreatectomy is essential to reduce postoperative complications as an appropriate timing to remove drain after pancreatectomy.

36.4 Drain Management to Predict Pancreatic Fistula

In 2005, the International Study Group of Pancreatic Fistula (ISGPF) proposed a consensus definition and clinical grading about postoperative pancreatic fistula [19]. The development of pancreatic fistula has been reported to be a potentially life-threatening complication after pancreatectomy. It remains still unclear what predictive risk factor can be used to precisely detect pancreatic fistula in the early postoperative period. The current issue regarding drain management after pancreatectomy is whether drain amylase value in the early period after pancreatectomy can predict developing of pancreatic fistula. Several studies have emphasized the impact of drain amylase value on POD 1 to precisely detect pancreatic fistula [20–22]. A meta-analysis demonstrated that evaluation of drain amylase levels on POD 1 is highly accurate to predict pancreatic fistula after pancreatectomy [23]. Table 36.3 summarized several studies which have reported the association between the drain amylase value on POD 1 and pancreatic fistula. In fact, Molinari et al. proposed that amylase value in drains on POD 1 of more than 5,000 U/L was a significant predictive factor for the incidence of all grades of pancreatic fistula after PD [20]. Similarly, the Japanese Society of Hepato-Biliary-Pancreatic Surgery (JSHPBS) has reported that amylase value more than 4,000 U/L in drains on POD 1 was correlated with a predictive risk factor for developing clinically relevant pancreatic fistula (grade B/C) by performing a survey of high-volume PD centers in Japan [21]. In the meta-analysis, a cutoff value of drain amylase value by the pooled was identified as 5,000 units/l, which had the highest specificity (0.91) to detect the patients at high risk of pancreatic fistula. The identification of high risk of pancreatic fistula can offer useful information to tailor the postoperative management including drain management and administration of antibiotics, a protease inhibitor, octreotide, or enteral nutrition.

On the other hand, exclusion of pancreatic fistula in the early period would allow earlier drain removal. Fong et al. have reported that a cutoff value of 600 U/L to detect low risk of pancreatic fistula was utilized. In the validation cohort of enrolled 369 patients with PD, 229 (62.1%) patients had drain amylase value less than 600 U/L on POD 1, and pancreatic fistula occurred in only 2 (0.9%) patients [24], whereas, in 140 patients who had drain amylase value more than 600 U/L on POD 1, pancreatic fistula occurred in 44 (31.4%) patients (OR = 52). Also, Sutcliffe et al. have reported that a cutoff value of 350 U/L of drain amylase on POD 1 predicted low risk of pancreatic fistula [26]. Afterward, a validation study has reported that the incidence of pancreatic fistula was significantly lower in low-risk patients (9 vs. 45%, $P = 0.0001$) [27]. They concluded that exclusion of pancreatic fistula based on stratifying likelihood of developing pancreatic fistula in the early period would accelerate enhanced recovery after pancreatectomy.

Table 36.3 Outcomes of several studies to evaluate the association between the drain amylase value on POD 1 and pancreatic fistula

Authors	Year	Setting	Procedure	Sample size	All grade of pancreatic fistula (%)	Clinically relevant pancreatic fistula (%)	Prediction of pancreatic fistula	Cutoff value of drain amylase	Sensitivity (%)	Specificity (%)	Accuracy (%)
Molinari et al. [20]	2007	Single center	PD and DP	137	19.7	10.9	High-risk group	5,000 U/L	93	84	NA
Kawai et al. [21]	2011	Multi center	PD	1,239	30	14	High-risk group	4,000 U/L[a]	62	89	85
Ansorge et al. [22]	2014	Single center	PD	315	NA	18.7	High-risk group	1,322 U/L[a]	NA	NA	88.5
Fong et al. [24]	2015	Single center	PD	495	12.5	6.3	Low-risk group	600 U/L	93	79	86
Israel et al. [25]	2014	Single center	PD and DP	63	43	40	Low-risk group	100 U/L	96	69	NA
Sutcliffe et al. [26]	2012	Single center	PD	70	13	10	Low-risk group	350 U/L	100	79	NA

PD pancreaticoduodenectomy, *DP* distal pancreatectomy, *NA* not available

[a]This cutoff value of drain amylase level on POD 1 predicts the development of clinically relevant pancreatic fistula

Conclusion

No routine intraperitoneal drainage significantly increases morbidity and mortality after pancreatectomy. Although routine intraperitoneal drainage after pancreatectomy is required, early removal drain is essential to prevent postoperative complications. Assessment of drain amylase value on POD1 could provide an early stratification of patients at low risk or high risk of developing pancreatic fistula. The identification of high risk of pancreatic fistula in the early period can offer useful information to tailor postoperative management after pancreatectomy. However, a furthermore prospective validation study for a cutoff of drain amylase value on POD1 would be required to precisely detect the risk of pancreatic fistula.

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Part VI

Nonoperative Therapy

Chemotherapy in the Management of Pancreatic Cancer

37

Nai-Jung Chiang and Li-Tzong Chen

37.1 Primary, Palliative Chemotherapy in Advanced and Metastatic Pancreatic Cancer

In the basence of breakthrough improvement in the screening, diagnosis, and management strategies, the incidence and mortality of pancreatic cancer increased significantly in the past several decades. Since majority of patients are being diagnosed with advanced stage diseases, and the rest with resectable diseases will eventually succumb to distant dissemination or local progression after surgery, systemic chemotherapy remains as the main strategy in the management of all staged pancreatic cancer. After the approval of gemcitabine by US FDA in 1996, there have been only five superiority and one non-inferiority positive randomized phase III trials to bring new treatment options for patients with advanced pancreatic cancer, including frontline erlotinib/gemcitabine, nab-paclitaxel/gemcitabine, FOLFIRINOX, and Asia-restricted S-1 for chemo-naïve patients, and oxaliplatin/5-FU/LV (OFF) and nano-liposomal irinotecan/5-FU/LV for gemcitabine-based therapy refractory patients. In this chapter, we shall review and discuss the progress of chemotherapy for metastatic pancreatic cancer and their future impact on the multidisciplinary care for locally advanced and resectable diseases.

37.1.1 Gemcitabine: First Approved Agent for Advanced Pancreatic Cancer

Pancreatic cancer is a detrimental malignant disease. The number of annually newly diagnosis cases and related mortality are nearly identical with overall 5-year survival rate ranged from 5 to 7% globally [1, 2]. Aggressive tumor biology, relatively asymptomatic in early stage, difficulty in detection by regular imaging modality, and lack of awareness of the disease are all potential causes of the delay diagnosis of this highly malignant tumor. At time of diagnosis, 80–85% of patients presented with unresectable locally advanced or metastatic diseases, while majority of the rest 15–20% of patients who underwent curative surgical resection would suffer from systemic dissemination and/or local relapse. Thus, majority of pancreatic cancer patients require palliative treatment at certain time points of their diseases. However, only limited treatment options are available for such a setting. In a pivotal, phase III trial conducted between July 1992 and March 1994, Burris III et al. demonstrated the superiority

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of the classical gemcitabine monotherapy (1,000 mg/m^2, 30-min infusion weekly, 7 weeks on/1 week off followed by 3 weeks on/1 week off) over bolus 5-FU (600 mg/m^2 30-min infusion weekly, 4 weeks per cycle), in terms of clinical benefit response (the primary endpoint, 23.8% vs. 4.8%, $p = 0.0022$) and median overall survival (5.65 versus 4.41 months, $p = 0.0025$) in patients with advanced pancreatic cancer [3]. The results has led to the approval of gemcitabine monotherapy by FDA and become the standard of care for advanced pancreatic cancer since 1996. For the modest antitumor activity of gemcitabine against pancreatic cancer, 5% of objective tumor response rate and 5.6 months of median overall survival, numerous preclinical and clinical studies have been conducted aiming to find more active agent(s) or combination(s) to further improve the clinical outcomes of patients with advanced pancreatic cancer afterward. Table 37.1 summarized those phase III trials of frontline chemotherapy in advanced pancreatic cancer after the introduction of gemcitabine [3–27]. However, perhaps owing to the existence of intrinsic drug resistance, the hamper of blood flow and thus drug delivery by the dense fibrotic tissue (desmoplasia) in tumor microenvironment, and less delineated molecular mechanisms of the pathogenesis in pancreatic cancer, majority of the trials have failed. It is also important to noted that the median overall survival of patients receiving gemcitabine alone generally ranged between 5.5 to 6.5 months in those randomized phase III trials. However, other than the original trial for gemcitabine [3], there are only six positive randomized phase III trials that led to new agent/regimen approval or evidence-based off-labeled use in patients with advanced pancreatic cancer in the past two decades [4, 13, 16, 20, 28, 29].

37.1.2 Erlotinib Plus Gemcitabine: Approved Combination with Limited Activity

Based on the findings of prognostic significance of EGFR overexpression in pancreatic cancer and the growth inhibition activity of EGFR blockage either alone or in combination with gemcitabine on pancreatic cancer cells [30–33], a phase III trial comparing the effect of gemcitabine with and without erlotinib as frontline therapy in patients with advanced pancreatic cancer was launched in October 2001. A total of 569 patients were enrolled into PA.3 trial, which was co-sponsored by both industry and the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) [20]. Survival analysis showed gemcitabine plus erlotinib at a dose of 100 or 150 mg daily could achieve a statistically significant survival benefit over gemcitabine alone, with a median overall survival of 6.24 months vs. 5.91 months (estimated HR = 0.82 [95% CI, 0.69–0.99]; $P = 0.038$) and median progression-free survival of 3.75 months vs. 3.55 months (estimated HR = 0.77 [95% CI, 0.64–0.92]; $P = 0.004$). Of the 282 patients with erlotinib treatment, the median overall survival of the 101 patients (36%) with grade 2 or more skin rash was 10.5 months vs. 5.3–5.8 months in those with less severe skin rash, $P < 0.001$ [20]. Erlotinib became the first FDA-approved drug in combination with gemcitabine for the treatment of advanced pancreatic cancer in November 2005. Gemcitabine/erlotinib combination became a new standard treatment option for patients with advanced pancreatic cancer. It served as the control arm in a July 2005-launched randomized phase III trial to evaluate the effect of add-on bevacizumab in patients with metastatic pancreatic cancer [21]. The new trial completed 607 patients recruited within 14 months. Despite such enthusiasm for the effectiveness of the control and experimental arm, add-on bevacizumab did not provide significant survival benefit as compared to gemcitabine/erlotinib alone in patients with metastatic pancreatic cancer. Of note, the median progression-free survival and overall survival of patients receiving gemcitabine/erlotinib alone were 3.6 months and 6.0 months, respectively [21]. In addition, gemcitabine/erlotinib combination also served as the experimental arm vs. standard gemcitabine control in LAP07 trial for locally advanced pancreatic

Table 37.1 Multicenter, randomized, phase III trials with gemcitabine-based therapy for advanced pancreatic cancer

Study/authorpublication year	Launched date	Study design	N	LAPDAC (%)	Gem DI (%)	Median (95% CI) survival, months		
						ORR (%)	PFS	OS
I. *Gemcitabine vs. non-gemcitabine-containing regimens in advanced pancreatic cancer*								
Burris et al. [3]	1992.07	Gem 1 g/m^2 × 7/8 weeks → 3/4 weeks	63	28	–	5	2.2	5.6
(JCO 1997)		5-FU 600 mg/m^2 × 3/4 weeks	63	24	–	0	1.0	4.4
ACCORD 11 study [4]	2005.12	Gem 1 g/m^2 × 7/8 weeks → 3/4 weeks	171	0		9	3.3 (2.2–3.6)	6.8 (5.5–7.6)
(NEJM 2011)		Oxo/CPT-11/5-FU 85/180/400/2,400 mg/m^2, q 2 weeks	171	0		32	6.4 (5.5–7.2)	11.1 (9.0–13.1)
II. *Gemcitabine vs. gemcitabine-based combinations in advanced pancreatic cancer*								
II-1. *Combined with cytotoxic agents*								
Platinums								
Heinemann et al. [5]	1997.12	Gem 1 g/m^2 × 3/4 weeks	98	21	95	8	4.7	6.0
(JCO 2006)		Gem 1 g/m^2 + cisplatin 50 mg/m^2, q 2 weeks	97	20	95	10	7.2	7.5
GIP-1 [6]	2002.04	Gem 1 g/m^2 × 7/8 weeks → 3/4 weeks	199	17	95	10	3.9	8.3
(JCO 2010)		Gem 1 g/m^2 + cisplatin 25 mg/m^2, × 3/4 weeks	201	15	83	13	3.8	7.2
GERCOR/GISCAD [7]	2001.03	Gem 1 g/m^2 × 7/8 weeks → 3/4 weeks	156	30	81	17	6.7	7.1
(JCO 2005)		Gem 1 g/m^2 + oxaliplatin 100 mg/m^2, q 2 weeks	157	32	91	27	8.5	9.0
ECOG E6201 [8]	2003.03	Gem 1 g/m^2 × 7/8 weeks → 3/4 weeks	275	10	–	6	2.6	4.9 (4.5–5.6)
(JCO 2009)		Gem 1.5 g/m^2, 10 m/m^2/min × 3/4 weeks	277	11	–	10	3.5	6.2 (5.4–6.9)
		Gem 1 g/m^2 + oxaliplatin 100 mg/m^2, q 2 weeks	272	11	–	9	2.7	5.7 (4.9–6.5)
Fluoropyrimidines and antifolate								
ECOG E2297 [9]	1998.04	Gem 1 g/m^2 × 3/4 weeks	162	10	–	6	2.2	5.4
(JCO 2002)		Gem 1.25 g/m^2 + 5-FU 600 mg/m^2 × 3/4 weeks	160	11	–	7	3.4	6.7
Swiss/Austria [10]	2001.06	Gem 1 g/m^2 × 3/4 weeks	156	21	95	8	3.9 (3.6–5.3)	7.2 (6.5–8.3)
(JCO 2007)		Gem 1 g/m^2 + cap 650 mg/m^2 bid, × 2/3 weeks	159	20	97	10	4.3 (3.7–5.3)	8.4 (6.3–9.8)
Cunningham et al. [11]	2002.05	Gem 1 g/m^2 × 7/8 weeks → 3/4 weeks	266	29	–	12	3.8 (2.9–4.8)	6.2 (5.5–7.2)
(JCO 2009)		Gem 1 g/m^2 + cap 830 mg/m^2 bid, × 3/4 weeks	267	30	–	19	5.3 (4.5–5.7)	7.1 (6.2–7.8)

(continued)

Table 37.1 (continued)

Study/authorpublication year	Launched date	Study design	N	LAPDAC (%)	Gem DI (%)	Median (95% CI) survival, months		
						ORR (%)	PFS	OS
Oettle et al. [12]	2001.10	Gem 1 g/m^2 × 3/4 weeks	273	9	95	7	3.4 (2.5–3.6)	6.3 (5.4–6.9)
(Ann Oncol 2005)		Gem 1.25 g/m^2 × 2/3 weeks + PTX 500 mg/m^2 D8	273	10	97	15	3.9 (3.3–4.7)	6.2 (5.4–6.9)
GEST study [13]	2007.07	Gem 1 g/m^2 × 3/4 weeks	277	24	83	13	4.1 (3.0–4.4)	8.8 (8.0–9.7)
(JCO 2013)		S-1 alone 80 mg/m^2 qd, × 4/6 weeks	280	24	–	21	3.8 (2.9–4.2)	9.7 (7.6–10.8)
		Gem 1 g/m^2 + S-1 80 mg/m^2 qd, × 2/3 weeks	275	25	83	29	5.7 (5.4–6.7)	10.1 (9.0–11.2)
Topoisomerase I inhibitors								
Rocha Lima et al. [14]	2000.02	Gem 1 g/m^2 × 7/8 weeks → 3/4 weeks	180	13	76	4	5.9	6.6
(JCO 2004)		Gem 1 g/m^2 + CPT-11 100 mg/m^2, × 2/3 weeks	180	15	82	16	5.4	6.3
Alou-Alfa et al. [15]	2001.08	Gem 1 g/m^2 × 7/8 weeks → 3/4 weeks	174	22	92	5	3.8 (3.0–4.3)	6.2 (5.2–7.5)
(JCO 2006)		Gem 1 g/m^2 + exatecan 2 mg/m^2, × 2/3 weeks	175	21	91	7	3.7 (2.7–4.7)	6.7 (5.4–7.9)
Anti-microtubular agent								
MPACT study [16]	2009.05	Gem 1 g/m^2 × 7/8 weeks → 3/4 weeks	430	0	85	7	3.7 (3.6–4.0)	6.7 (6.0–7.2)
(NEJM 2013)		Gem 1 g/m^2 + nab-paclitaxel 125 mg/m^2, × 3/4 weeks	431	0	71	23	5.5 (4.5–5.9)	8.5 (7.9–9.5)
Hypoxia-driven cytotoxic agent								
MAESTRO study [17]	2012.12	Gem 1 g/m^2 × 3/4 weeks	347	21	–	9	3.7 (3.6–3.8)	7.6 (6.7–8.3)
(ASCO GI 2016)		Gem 1 g/m^2 + evofosfamide 340 mg × 3/4 weeks	346	22	–	15	5.5 (4.8–5.6)	8.7 (7.6–9.9)
II-2. *Combined with targeted agents, including biologic agents*								
RAS signaling pathway inhibitors: farnesyltransferase inhibitors and RAS mimic								
Van Cutsem et al. [18]	1999.11	Gem 1 g/m^2 × 7/8 weeks → 3/4 weeks	347	23	~90	8	109 days	182 (155–202) days
(JCO 2004)		Gem + tipifarnib (200 mg BID)	341		~80	6	112 days	193 (176–218) days
ONTRAC study [19]	2011.05	Gem 1 g/m^2 × 3/4 weeks	54	0	–	13	3.4	6.4
(Ann Oncol 2015)		Gem + rigosertib 1,800 mg/m^2 BIW × 3/4 weeks	106	0	–	19	3.4	6.1
Anti-epidermal growth factor receptor agents								
NCIC CTG PA.3 [20]	2001.10	Gem 1 g/m^2 × 7/8 weeks → 3/4 weeks	284	25	–	8	3.6	5.9
(JCO 2007)		Gem + Erlotinib (100 mg/day)	285	24	–	9	3.8	6.2

Van Cutsem et al. [21]	2005.07	Gem 1 g/m^2 × 7/8 weeks →3/4 weeks + erlotinib 100 mg/day	301	0	–	9	3.6	6.0
(JCO 2009)		Gem + erlotinib + bev (5 mg/kg q 2 weeks)	306	0	–	14	4.6	7.1
SWOG S0205 [22]	2004.01	Gem 1 g/m^2 × 7/8 weeks → 3/4 weeks	371	22	–	7	3.0	5.9
(JCO 2010)		Gem + cetuximab (250 mg/m^2 q weeks)	372	21	–	8	3.4	6.3
Anti-angiogenic agents								
CALGB 80303 [23]	2004.06	Gem 1 g/m^2 × 3/4 weeks	300	15	–	10	3.8 (3.4–4.0)	5.9 (5.1–6.9)
(JC0 2010)		Gem + Bev (10 mg/kg q 2 weeks)	302	16	–	13	2.9 (2.4–3.7)	5.8 (4.9–6.6)
Rougier et al. [24]	2007.12	Gem 1 g/m^2 × 7/8 weeks → 3/4 weeks	275	10	82	–	3.7 (3.5–4.6)	7.8 (6.8–8.6)
(EJC 2013)		Gem + aflibercept (4 mg/kg q 2 weeks)	271	11	77	–	3.7 (3.5–4.5)	6.5 (5.6–7.9)
Kindler et al. [25]	2007.07	Gem 1 g/m^2 × 3/4 weeks	316	23	77	2	6.9 (3.7–5.2)	8.3 (6.9–10.3)
(Lancet Oncol 2011)		Gem + axitinib (5 mg p.o. BID)	314	25	79	5	7.0 (3.0–5.6)	8.5 (6.9–9.5)
Deplanque et al. [26]	2008	Gem (standard clinical practice)	175	14	–	–	7.6[a]	7.0 (8.2[a])
(Ann Oncol 2015)		Gem + masitinib (4.5 mg/kg BID)	173	13	–	–	–	7.7
GAMMA study [27]	2011.04	Gem 1,000 mg/m^2 × 3/4 weeks	322	0	84	10	3.7 (3.6–4.4)	7.2 (6.3–8.2)
(Ann Oncol 2015)		Gem + ganitumab (12 mg/kg q 2 weeks)	318	0	81	16	3.6 (3.4–3.8)	7.0 (6.2–8.5)
		Gem + ganitumab (20 mg/kg q 2 weeks)	160	0	82	15	3.7 (3.2–5.0)	7.1 (6.4–8.5)

[a]based on supplement in Ann Oncol 2015

cancer [34] and in CONKO-005 and RTOG 8048 adjuvant trials for post-resection pancreatic cancer [35, 36]. All three trials were lunched in 2008–2009. In the former two trials, the LAP07 and CONKO-005 trial, gemcitabine/erlotinib combination therapy was associated with nonsignificant inferior survival as compared to their gemcitabine comparator [34, 35]. Owing to the emergence of more active multi-agent combinations, such as FOLFIRINOX and nab-paclitaxel, the role gemcitabine plus erlotinib in pancreatic cancer management will be vanished.

37.1.3 FOLFIRINOX: The First Active Gemcitabine-Free Regimen for Advanced Pancreatic Cancer

Based on the known efficacies of bolus and infusion 5-FU and high-dose leucovorin plus either irinotecan (FOLFIRI) [37] or oxaliplatin (FOLFOX) in metastatic colorectal cancer [38], and the different action mechanisms and non-overlapping toxicity among the three agents [39], French investigators initiated a phase I trial to investigate the feasibility of combining oxaliplatin, CPT-11, and simplified LV5FU (leucovorin 400 mg/m^2 followed by bolus FU 400 mg/m^2 on day 1, then 5-FU 2,400 mg/m^2 as a 46-h continuous infusion) in patients with refractory solid tumor in April 1998 [40]. In that study, they not only determined the recommended dose of oxaliplatin and CPT-11 as 85 mg/m^2 and 180 mg/m^2, respectively, but also surprisingly noted that two of five patients with advanced pancreatic cancer responded to the triplet regimen. The exciting finding led to a single-arm phase II study to investigate the effect of FOLFIRINOX in advanced pancreatic cancer [41]. A total of 47 patients were enrolled from June 2000 to June 2002, with 26% response rate, 8.2 (95% CI, 5.3–11.6) months of time to progression, and 10.2 (95% CI, 8.1–14.4) months of overall survival. The response rate and median survival of patients with metastatic diseases were 26% and 9.5 months, respectively. So that despite associated with 52% of grade 3–4 neutropenia, a phase II/III trial comparing FOLFIRINOX with gemcitabine monotherapy in patients with chemo-naïve metastatic pancreatic cancer was launched in December 2005, the PRODIGE (Partenariat de Recherche en Oncologie Digestive)/ACCORD (Actions Concertées dans les Cancers Colo-Rectaux et Digestifs) phase III trial [4]. The study completed patient enrollment in October 2009 with data lock in April 2010, which was first presented at the 2010 American Society of Clinical Oncology annual meeting. In a highly selected patient population, median age of 61 years old, ECOG performance status of 0–1 in all but one patient, 38% with pancreatic head cancer, and 14% with biliary stenting, the clinical outcomes of patients receiving FOLFIRINOX were significantly superior to those receiving gemcitabine only, with response rate of 31% versus 9.4% ($p < 0.001$), median overall survival of 11.1 (95% CI, 9.0–13.1) months versus 6.8 (95% CI, 5.5–7.6) months (hazard ratio = 0.57; 95% CI, 0.45–0.73; $P < 0.001$), and median progression-free survival of 6.4 (95% CI, 5.5–7.2) months versus 3.3 (95% CI, 2.2–3.6) months (hazard ratio = 0.47; 95% CI, 0.37–0.59; $P < 0.001$). Not surprisingly, FOLFIRINOX was associated with a significant higher incidence of grade 3 or 4 adverse events, neutropenia (45.7% versus 21.0%, $p < 0.001$), thrombocytopenia (9.1% versus 3.6%, $p = 0.04$), febrile neutropenia (5.4% versus 1.2%, $p = 0.03$), diarrhea (12.7% versus 1.8%, $p < 0.001$), and sensory neuropathy (9.0% versus 0%, $p < 0.001$), but less elevation of alanine aminotransferase (7.3% versus 20.8%, $p < 0.001$). In a follow-up study, the investigators showed that in addition to higher incidence of significant adverse events, FOLFIRINOX treatment was associated with significant reduction of quality of life (QoL) impairment compared with gemcitabine in patients with metastatic pancreatic cancer [42].

The full-dose FOLFIRINOX regimen has also been evaluated in Asian population with metastatic pancreatic cancer. In a Japanese phase II study with more stringent patient selection criteria, which included neutrophil count ≥2,000/mm^3, a normal total bilirubin level, but excluded

patients with UGT1A1*6/*6,*28/*28,*6/*28 genotypes, full-dose FLOFIRINOX could achieve 38.9% (95% CI, 23.1–56.5%) response rate, 10.7 (95% CI, 6.9–13.2) months of median overall survival, and 5.6 (95% CI, 3.0–7.8) months of median progression-free survival. The incidence of grade 3 or 4 toxicities was higher than those observed in the original PRODIGE 4/ACCORD 11 study, including 77.8% neutropenia, 22.2% febrile neutropenia, and 8.3% diarrhea [43]. Based on the results, Japan's Ministry of Health, Labour and Welfare (MHLW) approved FOLFIRINOX as a standard regimen for Japanese patients in December 2013. To reduce the toxicities, Ueno et al. conducted a multicenter phase II study to evaluate the effect and safety profile of a modified FOLFIRINOX regimen consisting of intravenous oxaliplatin 85 mg/m^2, irinotecan 150 mg/m^2, and 5-FU infusion 2,400 mg/m^2 over 46 h and omitted bolus 5-FU [44]. Of 69 accruals, the response rate, median overall survival, and median progression-free survival were 37.7% (95% CI, 26.3–50.2%), 11.2 (95% CI, 9.0 to) months, and 5.5 (95% CI, 4.1–6.7) months, respectively. The grade 3 or 4 neutropenia (47.8%) and febrile neutropenia (8.7%) were significantly reduced but not diarrhea (10.1%). It suggested the approach is feasible in the Asian population and should be further validated in a larger study.

37.1.4 Nab-Paclitaxel Plus Gemcitabine: The First Active Gemcitabine-Containing Chemotherapy Doublet for Advanced Pancreatic Cancer

Based on an earlier molecular profiling study by immunohistochemistry and DNA microarray showing a high expression level of secreted protein acidic and rich in cysteine (SPARC), a known albumin-binding protein, in pancreatic cancer tissue [45], Van Hoff et al. initiated a phase I/II study with a companion translational research program to evaluate the potential application of gemcitabine and nab-paclitaxel combination in patients with advanced pancreatic cancer [46]. With a weekly intravenous administration of nab-paclitaxel following gemcitabine 1,000 mg/m^2 for 3 weeks every 4 weeks, the maximum tolerated dose (MTD) of nab-paclitaxel was determined to be 125 mg/m^2. Of the 44 patients at MTD level, the nab-paclitaxel/gemcitabine combination could achieve 48% response rate, 7.9 (95% CI, 5.8–11.0) months median progression-free survival, and 12.2 (95% CI, 8.9–17.9) months of median overall survival that was associated with significant grade 3–4 neutropenia (71%) and thrombocytopenia (28%) [46]. In vivo patient-derived xenograft model study demonstrated the nab-paclitaxel/gemcitabine combination regimen could result in higher tumor regression rate as compared to either agent treatment alone. In addition, nab-paclitaxel treatment was associated with the reduction of tumor stroma and the increase of tumor vascularization [46]. With such exciting findings, a global phase III trial comparing gemcitabine with and without nab-paclitaxel, the MPACT study, was launched [16]. Between May 2009 and April 2012, a total of 861 patients were included aiming to have a 90% power to detect a 23% reduction in risk of death at a two-sided alpha level of 0.049. Patients received nab-paclitaxel/gemcitabine had significant better median overall survival (8.5 [95% CI, 7.9–9.5] months versus 6.7 [6.0–7.2] months, hazard ratio = 0.72; 95% CI, 0.62–0.83; $P < 0.001$), median progression-free survival (5.5 [4.5–5.9] months versus 3.7 [95% CI, 3.6–4.0] months, hazard ratio = 0.69; 95% CI, 0.58–0.82; $P < 0.001$), and response rate (23% [95% CI, 19–27%] vs. 7% [95% CI, 5–10%]; $P < 0.001$) than those with gemcitabine treatment. As expected, nab-paclitaxel plus gemcitabine treatment was associated with higher incidence of grade 3–4 adverse events than gemcitabine alone, notably neutropenia (38% versus 27%) and sensory neuropathy (17% versus 1%) [16]; however, the results led to rapid approval of the nab-paclitaxel plus gemcitabine for advanced pancreatic cancer by US FDA in September 2013 and EMEA in December 2013. One of the most

surprising translational research findings from MPACT study was that neither tumor epithelial SPARC expression level nor plasma SPARC level served as a predictive factor for overall survival [47]. However, recent preclinical studies seemed to support the synergism between nab-paclitaxel and gemcitabine through the modulation of intracellular level of cytidine deaminase, a catabolic enzyme of gemcitabine, rather than the interaction between nab-paclitaxel and the stroma or SPARC within tumor microenvironment [48–50].

Since the MPACT study only included patients from Europe, America, and Australia, a prospective phase I/II study to evaluate the efficacies and safety profile of the nab-paclitaxel plus gemcitabine combination in Japanese population was performed. With an identical dosing schedule, the nab-paclitaxel plus gemcitabine combination achieved 58.8% (95% CI, 40.7–75.4%) of tumor response rate, 6.5 (95% CI, 5.1–8.3) months of median progression-free survival, and 13.5 (95% CI, 10.6 to not reached) months of median overall survival in 34 Japanese patients with metastatic diseases [51]. Despite no obvious pharmacokinetic variation as compared with monotherapy data, the treatment was associated with grade 3–4 neutropenia and sensory neuropathy in 71% and 12% of patients, respectively. Based on the results of the bridging study, the Japan's MHLW approved the regimen for advanced pancreatic cancer in December 2014.

37.1.5 S-1: The Only Approved Fluoropyrimidine with Documented Activity

In Asia, S-1 is a designed third-generation oral fluoropyrimidine composed of tegafur (pro-drug of 5-FU) and two modulators of 5-FU metabolism-related enzymes, 5-chloro-2,4-dihydroxypyridine (CDHP, a competitive antagonist of dihydropyrimidine dehydrogenase) and potassium oxonate (Oxo, a modulator of pyrimidine phosphoribosyl transferase), in a 1:0.4:1 molar ratio. In an international randomized phase III trial, investigators from Japan and Taiwan compared the first-line activity of gemcitabine and S-1 or in combination in patients with advanced pancreatic cancer, the GEST study [13]. This three-arm study was launched in July 2007, and patients were randomly assigned to have gemcitabine monotherapy (1,000 mg/m^2, weekly for 3 weeks, every 4 weeks), S-1 (fixed twice daily dose of 40/50/60 mg based on body surface, day 1–14 every 3 weeks), and gemcitabine/S-1 combination (weekly gemcitabine 1,000 mg/m2, plus S-1 30/40/50 mg twice daily, for 2 weeks every 3 weeks). The study aimed to demonstrate the non-inferiority of S-1 to gemcitabine monotherapy and the superiority of gemcitabine/S-1 combination over gemcitabine alone. A total of 832 patients were included, 277 in the gemcitabine alone arm, 280 in S-1 arm, and 275 in combination arm. After a median follow-up of 18.4 months for all survivors, the median overall survival in the gemcitabine, S-1, and combination arms was 8.8 (95% CI, 8.0–9.7) months, 9.7 (95% CI, 7.6–10.8) months, and 10.1 (95% CI, 9.0–11.2) months, respectively; while the median progression-free survivals were 4.1 (95% CI, 3.0–4.4) months, 3.8 (95% CI, 2.9–4.2) months, and 5.7 (95% CI, 5.4–6.7) months, respectively. The objective response rate in corresponding group was 13.3% (95% CI, 9.3–18.2), 21.0% (95% CI, 16.1–26.6), and 29.3% (95% CI, 23.7–35.5), respectively. In summary, S-1 was shown to have a significant better objective response rate and non-inferior overall survival and progression-free survival as compared to gemcitabine alone in patients with chemo-naïve advanced pancreatic cancer. On the other hand, gemcitabine/S-1 combination had a significant better tumor response rate and median progression-free than gemcitabine alone, but not overall survival [13]. Of note, since both gemcitabine and S-1 were approved agents for advanced pancreatic cancer in Japan, crossover after disease progression was allowed in current study. In addition, S-1 had significant better safety profile as compared to gemcitabine and combination arm. The incidence of grade 3–4 neutropenia was 8.8% in the S-1 arm, 41.0% in gemcitabine arm, and 62,2% in the

combination arm. Based on this study, Taiwan regulatory authority approved the use of S-1 in advanced pancreatic cancer in September 2013.

37.1.6 Summary

After two decades of intensive investigation and struggle, the introduction and approval of new agents and multi-agent regimens have led to an increase of overall survival time from 6 months with gemcitabine monotherapy up to 9–12 months with nab-paclitaxel plus gemcitabine or FOLFIRINOX or Asia-restricted S-1 in patients with advanced pancreatic cancer, notably for those with metastatic diseases. Metastatic pancreatic cancer should be recognized as a treatable disease nowadays. On the other hand, facing so much failure on trials involving in developing molecular targeted agents for pancreatic cancer, it should be strongly urged to request more comprehensive and dedicated preclinical research before scientists push any new compound into clinical investigation.

37.2 Chemotherapy in Locally Advanced Pancreatic Cancer

Pancreatic cancer is an aggressive malignancy with 15–20% or less of patients presenting with localized tumors that are amenable for curative-intent surgery [1]. Among the other 80–85% of patients who presented with incurable advanced diseases, 40% of them exhibit locally advanced diseases with one or more of the following radiological findings, the aorta encasement, the superior mesenteric vein obliteration, or more than 180° of the superior mesenteric artery or celiac vessels involvement, to preclude a grossly negative tumor margins resection. In such circumstance, surgical resection is not considered to serve as the primary therapy due to its morbidities and unlikely to be curative even after extensive surgical procedure [2]. An optimal therapy for patients with locally advanced pancreatic cancer remains controversial [2].

37.2.1 5-FU and Gemcitabine-Based Concurrent Chemoradiation Therapy

Based on the results of three randomized trials before the 1980s, 5-fluorouracil (5-FU)-based concurrent chemoradiotherapy (5-FU-CCRT) has been a favorable approach for patients with locally advanced pancreatic cancer [52–55]. However, the median overall survival of patients who received frontline 5-FU-CCRT was limited between 8.0 and 11.4 months [52–54]. The result has recently been confirmed by three randomized studies conducted in the early 2000s comparing 5-FU-CCRT with either gemcitabine alone [56], gemcitabine/cisplatin-based CCRT (GC-CCRT), or 5-FU-CCRT plus TNFerade biologic (GenVec, Gaithersburg, MD), a novel means of selectively delivering TNF-α to tumor cells by gene transfer through intratumoral vector injection [57, 58]. In the former two studies, the median overall survival of patients with frontline 5-FU-CCRT was 8.6 and 9.6 months, respectively [56, 57]. The large-scale randomized trial of 5-FU-CCRT with or without TNFerade with a total 304 enrolled patients showed that the median overall survival were 10 months in both two study arms [58].

With the introduction of gemcitabine as a standard of care for advanced pancreatic cancer and a well-known potent radiosensitizer [59, 60], gemcitabine-based concurrent chemoradiation therapy has been evaluated as a frontline therapy in patient with LAPDAC comparing to either 5-FU-based CCRT or gemcitabine monotherapy alone. In a three-arm randomized study, Wilkowski et al. compared conventionally fractionated 50 cGy radiotherapy in combination with concurrent 5-FU (350 mg/m^2/day on each day of radiotherapy, 5-FU-CCRT), concurrent gemcitabine and cisplatin (300 mg/m^2 and 30 mg/m^2, respectively, on days 1, 8, 22, and 29, GC-CCRT), or the latter followed by sequential gemcitabine 1,000 mg/m^2 and cisplatin 50 mg/m^2 every 2 weeks (GC-CCRT+GC) [57]. The 9-month survival rates in patients of the 5-FU-based CCRT, GC-CCRT and GC-CCRT+GC arms were 52%, 58%, and 45%, respectively. The outcomes from

these three arms all failed to meet the 60% of assumption of a 9-month survival rate which was originally designed for the control arm with 5-FU-CCRT. The median overall survival in corresponding study arm was 9.3 months, 9.6 months, and 7.3 months, respectively [57]. In a small Eastern Cooperative Oncology Group trial, Loehrer Sr. et al. compared gemcitabine alone versus gemcitabine (600 mg/m^2/week for weeks 1–5)-based CCRT followed by maintenance gemcitabine (G-CCRT+G) [61]. The trial was early terminated after a total 74 patients were randomized due to poor accrual. However, the median overall survival in locally advanced pancreatic cancer patients with frontline G-CCRT+G was significantly longer than those with gemcitabine treatment alone, 11.1 months versus 9.2 months, $p = 0.017$. The results indicated the median overall survival that could be achieved with frontline concurrent 5-FU or gemcitabine with conventional radiation technology for locally advanced pancreatic cancer would be limited below 12 months.

37.2.2 Primary, Palliative Chemotherapy in Locally Advanced Pancreatic Cancer

In the era of gemcitabine, patients with unresectable, locally advanced pancreatic cancer are frequently included into clinical trials to evaluate the efficacies of primary chemotherapy for advanced pancreatic cancer, as did patients with metastatic diseases. Available subgroup analyses from phase II or III trials evaluating new drugs or new combinations for patients with advanced pancreatic cancers showed that the median survival of patients with locally advanced pancreatic cancer receiving gemcitabine monotherapy ranged from 9.2 to 13.8 months versus the 5.4–8.3 months of patients with metastatic diseases, Table 37.2 [5, 7, 13, 14, 18, 23, 26, 56, 61]. Of note, the median overall survival of the locally advanced disease subgroups was comparable between the controlled arm with gemcitabine alone and the gemcitabine-doublet combination arm, as what was observed in the analysis of intent-to-treat population. The approximate range from 9 to 14 months of overall survival in gemcitabine monotherapy-treated patients with locally advanced pancreatic cancer has recently been confirmed by two small randomization studies, which compared gemcitabine monotherapy with frontline gemcitabine- or 5-FU/cisplatin-based concurrent chemoradiation therapy. The median overall survival after gemcitabine monotherapy was 9.2 months for the 37 patients in the Eastern Cooperative Oncology Group (ECOG 4201) study [61], and 13.0 months for the 60 patients in the Federation Francophone de Cancerologie Digestive (FFCD) and the Societe Francophone de Radiotherapie Oncologique (SFRO) study [56]. The results of large-scale, prospective randomization studies evaluating the effect of modern multi-agent chemotherapy regimens, such as nab-paclitaxel plus gemcitabine and FOLFIRINOX, in patients with locally advanced pancreatic cancer are still pending [62].

37.2.3 Induction Chemotherapy Followed by Consolidation Concurrent Chemoradiotherapy

In 2007, two retrospective studies from MD Anderson Comprehensive Cancer Center and GERCOR showed that induction chemotherapy followed by consolidation CCRT could achieve significant longer survival than those with either CCRT alone or continuous gemcitabine-based chemotherapy in patients with locally advanced pancreatic cancer, respectively [63, 64]. In the former study, 323 consecutive patients with locally advanced pancreatic cancer who had gemcitabine- or fluoropyrimidine-based CCRT in MD Anderson hospital between December 1999 and July 2005 were included. Among them, 247 patients had frontline CCRT; while 76 patients had a median of 2.5 months of induction gemcitabine-based chemotherapy before CCRT. The median overall survival of patient with and without induction chemotherapy was 11.9 and 8.5 months, respectively, $P < 0.001$ [63]. In the latter study, Huguet et al. retrospectively analyzed the

Table 37.2 Overall survival of locally advanced pancreatic cancer patients in multicenter randomized trials with gemcitabine-based therapy for advanced pancreatic cancer

Study/author publication year	Launched date	Study design	N	% LAPDAC	Objective response rate			Median overall survival (months)		
					IIT	mPDAC	LAPDAC	IIT	mPDAC	LAPDAC
I. *Gemcitabine vs. gemcitabine-based doublet therapy for advanced PDAC*										
Van Cutsem et al. [18]	1999.11	Gem	347	23%	8%	–	–	182 days	170 days	264 days
(JCO 2004)		Gem + tipifarnib	341		6%	–	–	193 days		318 days
Rocha Lima et al. [14]	2000.02	Gem	180	13%	4%	4%	4%	6.6	5.9	11.7
(JCO 2004)		Gem + irinotecan	180	15%	16%	15%	26%	6.3	5.4	9.8
GERCOR/GISCAD [7]	2001.03	Gem	156	30%	17%	18%	15%	7.1	6.7	10.3
(JCO 2005)		Gem + oxaliplatin	157	32%	27%	26%	27%	9.0	8.5	10.3
Heinemann et al. [5]	1997.12	Gem	98	21%	8%	–	–	6.0	4.7	10.4
(JCO 2006)		Gem + cisplatin	97	20%	10%	–	–	7.5	7.2	10.3
CALGB 80303 [23]	2004.06	Gem	300	15%	10%	–	–	5.9	5.7	9.9
(JC0 2010)		Gem + bevacizumab	302	16%	13%	–	–	5.8		
GEST study [13]	2007.07	Gem S-1 alone	277	24%	1	–	–	8.8	8.3	12.7
(JCO 2013)		Gem + S-1	280	24%	3%	–	–	9.7	7.4	13.8
			275	5%	21%	–	–	10.1	9.4	15.9
					29%					
Kindler et al. [25]	2007.07	Gem	316	23%	2%	–	–	8.3	6.9	10.6
(Lancet Oncol 2011)		Gem + axitinib	314	25%	5%	–	–	8.5	7.0	9.5
Deplanque et al. [26]	2008	Gem	175	14%	–	–	–	7.0 (8.2[a])	7.6[a]	13.8[a]
(Ann Oncol 2015)		Gem + masitinib	173	13%	–	–	–	7.7	–	–
II. *Gemcitabine vs. frontline CCRT for LAPDAC*										
ECOG 4201 [61]	2003.04	Gem	37	100%	–	–	3%	–	–	9.2
(JCO 2011)		Gem-CCRT + Gem	34	100%	–	–	6%	–	–	11.1
FFCD/SFRO [56]	2000.03	Gem	60	100%	–	–	–	–	–	13.0
(Ann Oncol 2008)		5-FU/Cis-CCRT + Gem	59	100%	–	–	–	–	–	8.6

[a]Based on supplement in Ann Oncol 2015

outcome of 181 patients with locally advanced pancreatic cancer who participated onto prospective phase II and III GERCOR gemcitabine-based chemotherapy studies for advanced or metastatic pancreatic cancer. Excluding the 53 (29.3%) patients who had systemic dissemination during the first 3 months of assigned chemotherapy, of the rest 128 non-progressed patients, 72 (56%) received consolidation CCRT, while 56 (44%) continued their chemotherapy. The median overall survival of patients with and without consolidation CCRT was 15.0 and 11.7 months, respectively, $P = 0.0009$ [64]. This novel, multidisciplinary approach is attractive because of the unsatisfactory therapeutic effect of frontline chemoradiation therapy and the recognition of locally advanced pancreatic cancer as a systemic disease with frequent occult metastases. Induction chemotherapy can not only provide systemic control for micrometastases but also help to identify patients who are likely to benefit from aggressive local therapy so as to avoid unnecessary radiotherapy for those with rapid systemic progression even during chemotherapy. It soon became a favorable investigational treatment option for patients with locally advanced pancreatic cancer. In the past decade, several single-arm phase II studies prospectively evaluated the therapeutic effect of this multidisciplinary approach in patients with unresectable locally advanced diseases with various induction chemotherapy regimens and duration of treatment and also different radiosensitizing agents and the administration of maintenance chemotherapy [65–72]. In general, the multidisciplinary approach could achieve encouraging 12.2–18.3 months of overall survival in per protocol patients who were progression-free after induction chemotherapy and received consolidation CCRT. However, in those studies, only 50–85% of intent-to-treat patients would receive the assigned consolidation CCRT, and median overall survival of intent-to-treat population including those who failed induction chemotherapy were 12–14.5 months (Table 37.3). The results seem not so different from that of the 13.0 months in the gemcitabine alone control arm in the FFCD/SFRO randomization study [56]. The therapeutic efficacies and potential superiority of incorporating CCRT after induction chemotherapy versus chemotherapy alone for locally advanced pancreatic cancer can only be defined by large-scale prospective randomization trials. In 2 × 2 designed, LAP07 randomized phase III trials, the largest prospective study for locally advanced pancreatic cancer investigated the effect of chemoradiotherapy versus chemotherapy on survival of patients with locally advanced pancreatic cancer following gemcitabine-based induction chemotherapy [34]. The primary endpoint of the trial was overall survival with an assumption that chemoradiotherapy could improve median overall survival from 9 to 12 months. A total of 442 patients were included between February 2008 and December 2011, with 223 randomized to receive 4 months of weekly gemcitabine 1,000 mg/m^2 for 3 weeks every 4 weeks alone and 219 to have the same gemcitabine dose schedule plus erlotinib 100 mg daily. Tumor assessments were performed every 8 weeks by spiral computed tomography scan or magnetic resonance imaging. After the second tumor assessment, 269 (61%) without disease progression, unacceptable toxicity, or consent withdraw underwent the second randomization with 136 to continue the assigned chemotherapy for 2 months and 133 to have capecitabine (800 mg/m^2 twice daily on the days of radiotherapy)-based CCRT. Maintenance erlotinib 150 mg daily was given only to patients who were initially allocated to the gemcitabine plus erlotinib arm. After a median follow-up of 34.3 (95% CI, 27.6–43.8) months with 379 deaths, the median survival was 13.6 (95% CI, 12.3–15.3) months and 11.9 (95% CI, 10.4–13.5) months for patients who were initially assigned to gemcitabine alone and gemcitabine plus erlotinib arms, respectively (hazard ratio, 1.19 [95% CI, 0.97–1.45], $P = 0.09$); while the median survival of a patient who underwent second randomization was 15.2 (95% CI, 13.9–17.3) months and 16.5 (95% CI, 14.5–18.5) months in the chemoradiotherapy and chemotherapy arms, respectively (hazard ratio, 1.03 [95% CI, 0.79–1.34], P = 0.83). The median overall survival of the 173 patients who failed to the induction chemotherapy was 7.7 (95% CI, 6.6–8.7) months.

The LAP07 was the first large-scale randomized study not only to confirm that gemcitabine monotherapy could achieve 13 months or more of

Table 37.3 Clinical outcomes of patients with locally advanced pancreatic cancer received induction chemotherapy (ICT) followed by CCRT

Organization/ author	Launched date	Study design ICT regimen	ICT duration (months)	N	Intent-to-treat population			Per-protocol cohort		
					ORR (%)	Median PFS (months)	Median OS (months)	*N*	Median PFS (months)	Median OS (months)
I. *Single-arm phase II studies*										
Marti et al. [65]	1997.11	Gem/cisplatin + GC-CCRT	2	26	–	7.0	13.0	18	–	–
GERCOR [66]	2001.03	GEMOX + ciFOxal-CCRT	2	59	15.2%	7.6	12.2	50	9.4	12.6
Ko et al. [67]	2002.05	Gem/Cisplatin + Cap-CCRT	6	25	–	10.5	13.5	12	12.5	17.0
Nakachi et al. [68]	–	Gem + S-1	4	20	–	8.1	14.4	16	–	–
TCOG [69]	2004.12	Gem + FOLFOX + Gem-CCRT	3	50	28%	9.3	14.5	30	14.7	18.3
AGITG [70]	2005.07	GEMOX + 5-FU CCRT	1	47	35%	11.0	15.7	45	–	–
Crane et al. [71]	2005.10	C-GEMOX	2	69	18%	12.5	19.2	60	–	–
Esnaola et al. [72]	2006.03	C-GEMOX + Cap-CCRT	3	37	18%	10.4	11.8	26	–	–
II. *Randomized phase II/III studies*										
LAP07 [34] (IIT)	2008.02	Gem ± Cap-CCRT	4	233	–	7.8	13.6	135	–	17.1
		Gem/erlotinib ± Cap-CCRT	4	219	–	6.5	11.9	134	–	14.5
LAP07 [34] (PP cohort)	2008.02	Gem ± erlotinib	4	269	–	–	–	136	8.4	16.5
		Gem ± erlotinib + Cap-CCRT						133	9.9	15.2
SCALOP [73]	2009.12	Gem/Cap + Gem-CCRT	3 + 1	114	–	–	12.7	38	10.4	13.4
		Gem/Cap + Cap-CCRT						36	12.0	15.2

median overall survival in intent-to-treat population but also to question the effect of consolidation CCRT and add-on erlotinib in the management of patients with locally advanced pancreatic cancer receiving gemcitabine-based therapy. However, the survival outcomes of the IIT population (all initially randomized patients) and per-protocol patients (second randomized patient) in the LAP07 were largely confirmed by a UK study, the SCALOP (Selective Chemoradiation in Advanced Localised Pancreatic Cancer) trial, which was a non-comparative randomized phase II study with a Fleming's single-stage design and 9-month progression-free survival rate as a primary endpoint [73]. A total of 114 patients were included between December 2009 and October 2011 to have three cycles of induction chemotherapy with weekly gemcitabine (1,000 mg/m^2) plus twice daily capecitabine, (830 mg/m^2) for 3 weeks, every 4 weeks as one cycle. Of them, 74 (64.9%) patients with controlled diseases and good performance were randomly assigned to have another one cycle of gemcitabine/capecitabine chemotherapy then either gemcitabine (300 mg/m^2, weekly)-based or capecitabine (830 mg/m^2, twice daily on the days of radiotherapy)-based CCRT. The median survival was 12.7 (95% CI 11.0–14.5) months for the 114 registered patients and 14.6 (95% CI 13.0–15.8) months and 8.1 (95% CI 4.1–10.5) months for the 74 further randomized and 40 patients who did not proceed to randomization, respectively.

37.2.4 Summary

The standard of care for patients with locally advanced pancreatic cancer remains controversial. However, with the unsatisfactory clinical outcomes of locally advanced pancreatic cancer patients who received frontline 5-FU or gemcitabine-based CRRT, locally advanced pancreatic cancer is currently recognized as a systemic disease that should have chemotherapy as frontline treatment with or without consolidation CCRT. Such speculation was further supported by subgroup analyses in the previous phase II/III gemcitabine-based chemotherapy trial for advanced pancreatic cancer, in which the median overall survival for patients with locally advanced diseases ranged from 10 to 16 months after either gemcitabine monotherapy or gemcitabine-containing doublets [5, 7, 13, 14, 18, 23, 26, 56, 61]. Recent FFCD/SFRO and LAP07 trials provided further evidence to support the survival results of frontline gemcitabine-based chemotherapy in this disease category [34, 56]. In addition, with the negative results of LAP07 questioned the requirement of consolidation CCRT in patients with unresectable, locally advanced pancreatic cancer receiving frontline gemcitabine or gemcitabine plus erlotinib chemotherapy. However, there are ongoing randomized trials to reassess the role of CCRT after induction chemotherapy with modern combination regimens in patients with locally advanced pancreatic cancer, such as CONKO-007 (NCT01827553) and SCALOP-2 (NCT02024009) studies. The CONKO-007, a phase III study examined the effectiveness of 3 months of induction chemotherapy with gemcitabine or FOLFIRINOX followed by consolidation gemcitabine-based chemoradiotherapy versus chemotherapy only for 6 months, with a targeted patient number of 830; the SCALOP-2 is a five-arm phase II study to determine the effectiveness of induction nab-paclitaxel plus gemcitabine followed by capecitabine (± nelfinavir, an anti-retroviral agent with radiosensitizer activity) with high- or standard-dose radiotherapy versus six cycles of chemotherapy alone. These two trials will not only determine whether the progress of modern chemotherapy for metastatic pancreatic cancer can also lead to further survival improvement but also redefine the role of consolidation CCRT in patients with locally advanced diseases.

37.3 Adjuvant Chemotherapy in Pancreatic Cancer After Curative Intent Resection

Pancreatic cancer has a dismal outcome with an overall 5-year survival rate approximately 7% according to the 2016 Stat Fact Sheet of Surveillance, Epidemiology and Results (SEER)

Program, National Cancer Institute (NCI) [1]. Although a delay diagnosis with majority of cases being diagnosed at advanced stage to preclude curative intent treatment is a main cause, however, the surgical outcomes of patients with resectable pancreatic cancer are also largely unsatisfactory [2]. Despite the improvement of surgical technique and postoperative care, the median recurrence-free survival after curative intent surgery was 6.7 and 5.0 months in the observation arms of the modern CONKO-001 and JSAP-02 adjuvant trials [74, 75], respectively. Of note, 66% of first recurrences were manifested as systemic dissemination in the latter study. These findings emphasize that resectable, early-stage pancreatic cancer should be considered as a systemic disease and require multidisciplinary approach to maximize its therapeutic outcome.

37.3.1 Earlier Trials Defining the Role of Adjuvant Chemotherapy in Pancreatic Cancer

The European Study Group for Pancreatic Cancer (ESPAC)-1 trial, the first large-scale, multicenter, randomized trial to evaluate the role of adjuvant chemotherapy in postoperative pancreatic cancer, was started in February 1994, more than 2 years before the approval of gemcitabine for advanced pancreatic cancer [76]. It was a 2 × 2 designed study composed of observation alone, 5-FU/LV chemotherapy alone (leucovorin 20 mg/m^2 bolus injection followed by 5-FU 425 mg/m^2 bolus injection, days 1–5, every 28 days, for six cycles, the Mayo Clinic bolus 5-FU/LV regimen), chemoradiation therapy (a total of 40-Gy in 20 fractions over days 1–14 and days 29–42 to tumor bed plus bolus 5-FU 500 mg/m^2 on each first 3 days of radiation therapy), or chemoradiation therapy followed by 5-FU/LV chemotherapy. The study completed 289 patients accrual by June 2000. Of them, 147 patients were randomized to receive chemotherapy (alone in 73 or following chemoradiation therapy in 72), and 144 were randomized not to receive chemotherapy (observation alone in 69 and chemoradiation therapy group in 75), while 145 had chemoradiation therapy and 142 did not. Treatment detail was only available in 122 patients with chemotherapy and 128 patients with chemoradiation therapy. Of them, 21 (17%) in the former and 11 (9%) in the latter group did not receive their assigned chemotherapy and chemoradiation therapy, respectively. Despite such a poor adherence to study protocol, after a median of 47 months follow-up for the 52 survivors, patients assigned to have chemotherapy achieved significant better median time to recurrence (15.3 [95% CI, 10.5–19.2 months] vs. 9.4 [95% CI, 8.4–15.2] months, p = 0.02), median overall survival (20.1 [95% CI, 16.5–22.7] months vs. 15.5 [95% CI, 13.0–17.7 months], p = 0.009), and 5-year survival rate (21% vs. 8%) than those without chemotherapy. On the other hand, patients assigned to have chemoradiation therapy had significant inferior median time to recurrence (10.7 [95% CI, 8.8–15.5 months] vs. 15.2 [95% CI, 9.8–22.2] months, p = 0.04), median overall survival (15.9 [95% CI, 13.7–19.9] months vs. 17.9 [95% CI, 14.8–23.6 months], p = 0.05), and 5-year survival rate (10% vs. 20%) as compared to those assigned not to have chemoradiation therapy. In current study, patients in the observation arm had a median overall survival of 16.9 (95% CI, 12.3–24.8) months and 5-year survival rate of 11%, and those for patients received 5-FU/LV-alone adjuvant therapy was 21.6 (95% CI, 13.5–27.3) months and 19%, respectively.

The survival outcomes of post-resection pancreatic cancer without adjuvant therapy have been further explored in the Charité Onkologie (CONKO)-001 and JSAP-02 studies. In both studies, observation alone served as the control arm to evaluate the effect of adjuvant gemcitabine alone, weekly gemcitabine 1,000 mg/m^2 for succeeding 3 weeks, 4 weeks per cycle, in post-resection pancreatic cancer. The CONKO-001 study was launched in July 1998, 2 years after the approval of gemcitabine application in advanced pancreatic cancer [74]. With the assumption of 20% dropout rate, a total of 368 patients were recruited aiming to detect an improvement in disease-free survival from 12 to 18 months after

gemcitabine therapy with 90% power at a two-sided 0.05 significance level. Excluding those ineligible or consent-withdrawn accruals, 354 patients were included in the final survival analysis, 179 in the gemcitabine arm, and 175 in the observation arm. In primary efficacy analyses after a median follow-up of 53 (ranged 9–96) months with 259 (73.1%) death events, adjuvant gemcitabine therapy resulted in a significant improvement in median disease-free survival, 13.4 (95% CI, 11.4–15.3) months versus 6.9 (95% CI, 6.1–7.8) months in the observation arm, $p < 0.001$, and a marginal prolongation of overall survival, median 22.1 (95% CI, 18.4–25.8) months versus 20.2 (95% CI, 17–23.4) months in the observation arm, $p = 0.06$ [74]. However, in a follow-up analysis with a cutoff date of 2012 September and 316 (89.3%) deaths, the survival benefit of gemcitabine became statistically significant, 22.8 (95% CI, 18.5–27.2) months versus 20.2 (95% CI, 17.7–22.8) months in the observation arm, hazard ratio = 0.76 (95% CI, 0.61–0.95), $p = 0.01$ [77]. In the Japanese JSAP-02 study, 118 eligible patients were enrolled between April 2002 and March 2005 [75]. The sample size was calculated based on the assumption that adjuvant gemcitabine could result in a 45% improvement in overall survival with 80% power at a two-sided 0.05 significance level. The final analysis was made with a cutoff date of 2009 March 31 with 98 (83%) deaths and a median follow-up period of 60.4 months for survivors. The survival benefit of gemcitabine was not statistically significant, 22.3 (95% CI, 16.1–30.7) months versus 18.4 (95% CI, 16.1–30.7) months in the observation arm, $p = 0.19$. However, the hazard ratio for risk of death was 0.77 (95% CI, 0.51–1.14), compatible with that of the CONKO-001 study. On the other hand, gemcitabine significantly improved the disease-free survival as compared to observation alone, with median disease-free survival of 11.4 (95% CI, 8.0–14.5) months and 5.0 (95% CI, 3.7–8.9) months, respectively, hazard ratio = 0.60 (95% CI, 0.40–0.89), $P = 0.01$ [75]. Both studies demonstrated that adjuvant gemcitabine therapy could double the disease-free survival of patients with resected pancreatic cancer and a 23–24% reduction in risk of death as compared to those with surgery alone.

Soon after the completion of enrollment in adjuvant gemcitabine versus observation of the CONKO-001 trial, a large-scale, global, randomized trial to compare the efficacies of adjuvant gemcitabine versus Mayo Clinic 5-FU/LV regimen in postoperative pancreatic cancer, the ESPAC-3 trial, was launched in July 2000 [78]. A total of 1,088 patients were included to receive six cycles of adjuvant chemotherapy with 551 patients in the Mayo Clinic 5-FU/LV arm and 537 in the gemcitabine arm. The median recurrence-free survival and median overall survival of patients who received adjuvant 5-FU/LV were 14.1 (95% CI, 12.5–15.3) months and 23.0 (95% CI, 21.1–25.0) months, respectively, which were compatible to that of 14.3 (95% CI, 13.5–15.6) months and 23.6 (95% CI, 21.4–26.4) months, respectively, in patients with adjuvant gemcitabine. The ESPAC-3 study has actually set up 6 months of adjuvant bolus 5-FU/LV or weekly gemcitabine as standard of care for post-resection pancreatic cancer.

The therapeutic effects of adjuvant bolus 5-FU/LV has been further confirmed in a randomized trial comparing bolus 5-FU/LV with 5-FU/cisplatin and interferon α-2b-based plus radiation therapy, the CapRI study [79, 80]. The study was launched in August 2004, and a total of 132 patients were enrolled. After a median follow-up of 42.7 months, the median overall survival was 28.5 (95% CI, 21.6–39.5) months in 64 eligible patients who were assigned to receive the Mayo Clinic bolus 5-FU/LV regimen [80]. The authors attributed the excellent survival to the early detection of recurrence with the improvement of imaging study and the administration of salvage chemotherapy to a high proportion (72%) of recurrence patients.

Besides the above adjuvant chemotherapy-based studies, there was a Radiation Therapy Oncology Group leading a US intergroup trial, the RTOG-97 04 trial, which compared 3 weeks of weekly gemcitabine 1,000 mg/m^2 versus continuous infusion of 5-FU 250 mg/m^2/day followed by 5-FU-based chemoradiation therapy then another three cycles of 3 weeks-on/1

week-off gemcitabine therapy or two cycles of 4 weeks-on/2 weeks-off continuous infusion of 5-FU [81]. The study was launched in July 1998 with targeted recruitment of 470 analyzable patients aiming to detect an increase of overall survival from 18 to 25 months by gemcitabine-containing treatment in intent-to-treat population as well as pancreatic head tumor cohort. A total of 538 patients were randomized, but only 451 eligible were included in primary analysis, 230 in 5-FU arm and 221 in gemcitabine arm. The final analysis was made upon 368 (80%) deaths and 6.98 years of minimum follow-up in all survivors. On intent-to-treat analysis, the estimated median overall survival of patients in the gemcitabine and 5-FU arms were approximately 18.5 months and 17.1 months, respectively (hazard ratio = 0.93 [95% CI, 0.76–1.14]; $P = 0.51$), while the reported corresponding median survival in pancreatic head cohort was 20.5 months and 17.1 months, respectively (hazard ratio = 0.84 [95% CI, 0.67–1.04]; $P = 0.12$). Interestingly, the disease-free survival was never reported even in the follow-up publication [82]. As exploratory, parallel trials comparison between RTOG-97 04 and other adjuvant gemcitabine trials without radiation component, such as CONKO-001, ESPAC-3, and JSAP-02 trials [74, 75, 78], suggested incorporation of conventional CCRT is unlikely to improve the recurrence-reducing effect of adjuvant gemcitabine in post-resection pancreatic cancer, as shown in a small French-initiated EORTC/FFCD/GERCOR study [83].

Therefore, with the convenience of administration and consistency in the median overall survival of patients who received adjuvant gemcitabine monotherapy, 22.8 (95% CI, 18.5–27.2) months in CONKO-001 study [77], 23.6 (95% CI, 21.4–26.4) months in the ESPAC-3 study [78], 22.3 (95% CI, 16.1–30.7) months in the JSAP-02 study [75], and 24.4 (21.5 to ∞) months in the EORTC/FFCD/GERCOR study [83], gemcitabine alone has thus become a favorable control to evaluate the efficacies of gemcitabine-containing doublets or S-1 in adjuvant setting for post-resection pancreatic cancer afterward.

37.3.2 Recent Trials Evaluating Borderline Effective Combinations and S-1 in Adjuvant Setting

After 2005, four newly adjuvant studies were launched to investigating whether borderline active gemcitabine-based doublets or other active single agent for advanced pancreatic cancer, including gemcitabine plus erlotinib, gemcitabine plus capecitabine, and S-1, could more effectively improve the survival of patients with pancreatic cancer after curative-intent resection than adjuvant gemcitabine.

With the known activity of S-1 and the demonstration of superior benefit/risk (objective tumor response rate/incidence of grade 3–4 neutropenia) ratio and non-inferiority overall survival of S-1 versus standard gemcitabine monotherapy in patients with advanced pancreatic cancer in previous GEST study from Japan and Taiwan [13], it is reasonable to evaluate the effects of oral S-1 in postoperative adjuvant setting. The JASPAC-01, a randomized, multicenter, non-inferiority phase III trial conducted solely in Japan, was launched in April 2007, given its first presentation in 2013 ASCO GI meeting, and published in May 2016 [84]. A total of 385 patients were randomly assigned, 193 to the gemcitabine group (1,000 mg/m^2 on days 1, 8, and 15 every 28 days per cycle for six cycles) and 192 to the S-1 group (standard 4 weeks-on/2 weeks-off schedule with a fixed dose of 40–60 mg/m^2 by body surface for four cycles). The study was designed with an expected hazard ratio (HR) for death of 0.87 with a non-inferiority margin of 1.25 (power 80%; one-sided type I error 2.5%); however, it was prespecified to evaluate the superiority of S-1 on overall survival by log-rank test, if the non-inferiority of S-1 was verified. The study was early discontinued at September 15, 2012, because interim analysis results showing prespecified criteria for efficacy were met. After an approximately 40 months of median follow-up in both arms, the median overall survival and 5-year survival rate was 46.5 (37.8–63.7) months and 44.1 (36.9–51.1)%, respectively, in the S-1 arm and 25.5 (22.5–29.6) months and 24·4

(18.6–30.8)%, respectively, in the gemcitabine arm with a HR of 0·57 (95% CI, 0.44–0.72, $p < 0.0001$ for superiority). In addition, S-1 seems to be more tolerable, with 59% and 35% of patients in the S-1 and gemcitabine arm who could complete their assigned treatment without dose reduction, $p < 0.0001$. The authors gave a fair conclusion that S-1 can be a new standard care for adjuvant chemotherapy in Japanese patients with resected pancreatic cancer, and these results should be further validated in non-Asian patients.

Based on previous ESPAC-3 trial showing adjuvant 5-FU/LV had similar effect as gemcitabine for resected pancreatic cancer [78], and the tolerability and the marginal superiority of gemcitabine plus capecitabine doublet compared to gemcitabine alone in advanced pancreatic cancer, the European investigators conducted another trial, the ESPAC-4 study, to evaluate the role of gemcitabine/capecitabine combination in adjuvant setting. The ESPAC-4 study was launched in November 2008, and eligible patients were included within 12 weeks after surgery, stratified for R0/R1 resection and country and then randomly assigned to have either six cycles of gemcitabine (weekly 1,000 mg/m^2, 3 weeks on/1 week off per cycle) or six cycles of same gemcitabine schedule plus oral capecitabine (1,660 mg/m^2/day, 3 weeks on/1 week off per cycle) [85]. Of 730 evaluable patients for final analysis, their clinic-pathological characteristics were in general agreement with those in other phase III trials, such as age, performance status distribution and R1 resection rate, and incidence of poorly differentiated tumor and node involvement. The study completed its patient recruitment in September 2014, and data was locked on March 2016. The results of primary final analysis were presented at the 2016 ASCO meeting [85]. Despite the dose intensity of gemcitabine which was 93% in gemcitabine alone arm and 83% in gemcitabine/capecitabine arm, the median survival patients treated with gemcitabine/capecitabine were significantly superior to gemcitabine alone, 28.0 (95% CI, 23.5–31.5) months versus 25.5 (22.7–27.9) months, respectively, with a stratified HR of 0.82 (95% CI, 0.68–0.98), $P = 0.032$. Gemcitabine/capecitabine was associated with a more significant, but manageable, grade 3–4 neutropenia (38% vs. 24%), hand-and-foot syndrome (7% versus 0%), and diarrhea (5% versus 2%) as compared to gemcitabine alone.

Similar to the rationale of incorporation of oral fluoropyrimidine into the adjuvant therapy in pancreatic cancer after resection, there were also interests in investigating the gemcitabine and erlotinib combination, a FDA-approved regimen for the treatment of advanced pancreatic cancer based on the results of the NCIC CTG PA.3 trial [20], in adjuvant setting. Two large phase III studies were started soon after the publication of NCIC CTG PA.3 trial results to investigating whether the addition of erlotinib can further improve the effect of adjuvant gemcitabine in resectable pancreatic cancer.

The first one is the CONKO-005 study, which was launched in April 2008 to evaluate if the combination of erlotinib (100 mg daily) with standard 3 weeks-on/1 week-off gemcitabine could improve overall survival in pancreatic cancer patients with R0 resection as compared to gemcitabine alone [35]. The study completed the 436 patients enrollment by July 2013 with similar patients' demographic characteristics to those in the ESPAC-4 study except CONKO-005, which only included R0 resection patients with a lower LN involvement rate (65% versus 80% in ESPAC-4). After 41 months of median follow-up, the median overall survival was 24.6 (20.9–28.4) months in the gemcitabine plus erlotinib arm and 26.5 (22.2–30.8) months in the gemcitabine alone arm, HR = 0.90 (95% CI, 0.71–1.15), $p = 0.406$. However, a split of survival curves after 3 years of follow-up favoring the improvement of long-term survival in gemcitabine plus erlotinib arm was observed, which is interesting and deserves further investigation. Median recurrence-free survival was 11.6 months in both arms. Of interesting to note, the median overall survival of gemcitabine alone arm of the three recently reported European and Japanese trials, the JASPAC-01, the ESPAC-4, and the current study, was consistently ranging from 25.5 to 26.5 months [35, 84, 85]. On the contrary to the finding in the NCIC CTG PA.3 study, the severity of skin rash was not correlated with progression-free survival in the current study.

The results of the LAP07 and current CONKO-005 studies suggested that erlotinib has a little role in the treatment of locally advanced and resectable pancreatic cancer [34, 35].

The other study involving adjuvant erlotinib, RTOG 8048 (ClinicalTrials.gov Identifier: NCT01013649), is an NCI-sponsored intergroup trial with a two-step randomization design [86], similar to the French LAP07 for locally advanced pancreatic cancer [36]. Following the experience of RTOG 97-04, which showed gemcitabine plus 5-FU-based CCRT marginally improved the overall survival of pancreatic head cancer patient but not the intent-to-treat population as compared to 5-FU plus 5-FU-based CCRT [81], only patients with pancreatic head cancer after surgery are eligible. Enrolled patients will be firstly randomized to receive adjuvant gemcitabine or gemcitabine plus erlotinib for five cycles. Patients who can tolerate the treatment and have no disease progression will be further randomized to receive another one cycle of chemotherapy alone or one cycle of chemotherapy followed by 5-FU or capecitabine-based CCRT. The study aims to determine whether the addition of erlotinib can improve the overall survival of patients with adjuvant gemcitabine after R0 or R1 resection of pancreatic head cancer and to determine whether consolidation fluoropyrimidine-based CCRT can further enhance survival for such patients. The study was launched in November 2009 with a targeted recruitment of 846 patients, and the estimated final data collection date for the primary outcome measure will be on August 2020 [36]. However, the recently published negative results of CONKO-005 and LAP07 trials may challenge the benefits of add-on erlotinib to adjuvant gemcitabine and jeopardize the patient enrollment in the current study.

37.3.3 Current Ongoing Trials Evaluating Active Combinations in Adjuvant Setting

Nowadays, nab-paclitaxel plus gemcitabine doublet and the gemcitabine-free FOLFIRINOX are the only two regimens that showed to provide clinically relevant, significant survival benefits in patients with metastatic pancreatic cancer as compared to gemcitabine monotherapy. Perhaps considering their safety profiles, the two regimens are not investigated for their role in adjuvant setting until very recently. APACT (ClinicalTrials.gov Identifier: NCT01964430), also known as ABI-007-PANC-003, is an industry-sponsored international, randomized, phase III trial comparing to the efficacy of adjuvant nab-paclitaxel plus gemcitabine versus gemcitabine alone in patients with surgically resected pancreatic cancer. The treatment regimens consisted of standard weekly gemcitabine (1,000 mg/m^2) ± nab-paclitaxel (125 mg/m^2) on days 1, 8, and 15 every 28 days as a cycle for a total of six cycles. Interestingly, APACT is the first randomized phase III trial using disease-free survival as the primary endpoint [86]. The study was launched on October 2013 and has completed the recruitment of targeted 846 patients in the first half year of 2016. The estimated final data collection date for the primary outcome measure will be on April 2019.

In an ongoing Germany investigator-initiated, randomized, phase II/III multicenter study (ClinicalTrials.gov Identifier: NCT02172976), patients with resectable pancreatic cancer will be evaluated before surgery. Eligible patients will be randomized to receive either perioperative FOLFIRINOX plus surgery or adjuvant gemcitabine following surgery. Chemotherapy consisted of a full dose of biweekly FOLFIRINOX (oxaliplatin 85 mg/m^2, irinotecan 180 mg/m^2 followed by bolus 5-FU 400 mg/m^2, and 46-h infusion of 5-FU 2,400 mg/m^2 and folic acid 400 mg/m^2) in each six cycles before and after surgery or six cycles of gemcitabine (1,000 mg/m^2 on days 1, 8, and 15 every 28 days) after surgery [87]. Overall survival is the primary endpoint, while perioperative morbidity and mortality, R0 resection rate, and pathological complete remission rate are part of secondary endpoints. The study was launched on November 2014 with a targeted recruitment of 126 patients, and the estimated final data collection date for primary outcome measure will be on June 2019. Although patients with resectable pancreatic cancer may

tolerate aggressive chemotherapy more before surgery, however, the compliance of patients to the full-dose FOLFIRINOX especially after Whipple's operation will be challenging.

37.3.4 Summary

ESPAC-1 has established the role of adjuvant systemic chemotherapy in patients with pancreatic cancer after curative-intent resection [76]. Two observation-controlled studies further demonstrated that 6 months of gemcitabine monotherapy could double the recurrence-free survival, from 5.0–6.7 to 11.4–13.4 months, and reduced risk of death by 23–24% as compared to observation alone [74, 75]. Of interesting to note, the recurrence-free survival of patients receiving gemcitabine monotherapy decreased from 13.4–14.3 months in the CONKO-001 and ESPAC-3 to 10.9–11.6 months in the five recent randomized trials launched between 2002 and 2008. However, the median overall survival of those patients improved from 22.8 months in the 1998 launched CONKO-001 study to 26.5 months in the 2008 launched CONKO-005 study [74, 85]. The difference in median overall survival and median recurrence-free survival (Δ mOS – mPFS) increased from 9.4 to 15.0 months during the 10-year period of time. The observation suggests the recent improvement in overall survival of patients with pancreatic cancer after the R0/R1 resection could largely result from the improvement in earlier detection of recurrence and the emergence of more effective primary chemotherapy for patients with recurrent or metastatic diseases, such as FOLFIRINOX and nab-paclitaxel plus gemcitabine in 2010 and 2013, respectively [4, 16]. In such case, how the application of modern combination chemotherapy in adjuvant setting will impact the overall survival and/or recurrence-free survival of patients with postoperative pancreatic cancer will be answered by the APCAT trial in the near future [87]. Table 37.4 summarizes the results of recent prospective randomized phase III adjuvant trials.

37.4 Second-Line Chemotherapy in Metastatic Pancreatic Cancer

Perhaps due to the modest activity of frontline 5-FU and gemcitabine monotherapy in improving the clinical outcomes, and the advanced age and poor general condition of patients, recent reports from Boyd CA et al. and Enewold L et al. suggested that only 50% or less of patients with advanced PDAC received chemotherapy treatment in the US before 2010 [88, 89]. Although there is little, if any, population data on the administration of second-line chemotherapy in patients with advanced PDAC after the failure of frontline chemotherapy, however, it can be expected that the percentage of patients with second-line therapy would be even lower. According to the report of the three recent pivotal, frontline chemotherapy trials of ACCORD 11 (FOLFIRINOX versus gemcitabine), GEST (gemcitabine versus S-1 versus gemcitabine/S-1), and MAPCT (gemcitabine versus nab-paclitaxel/gemcitabine), there were only 40–65% of patients receiving second-line therapy after frontline therapy failure [4, 13, 16]. However, the requirement for second-line treatment can be anticipated to further increase after the emergence of more effective frontline and second-line treatments.

37.4.1 Second-Line Therapy After Gemcitabine-Based Treatment: Global Perspective

Previously, a series of prospective single-arm or small randomized phase II studies that evaluated both cytotoxic and/or targeted agents in patients with gemcitabine-refractory diseases generally delivered inconclusive results because of the lack of efficacies or the lack of adequate control arm. CONKO-003, an investigator-initiated randomized phase III trial, was initially designed as a best supportive care (BSC) plus placebo-controlled study to evaluate the efficacies of weekly folinic acid 200 mg/m^2 followed by 24-h infusion of 5-FU 2 g/m^2 for consequently 4 weeks

Table 37.4 Clinical outcomes in selected randomized phase II/III studies of adjuvant chemotherapy in post-curative intent resection pancreatic cancer

Study/author publication year	Launched date	Regimens	Case no.	Median age (years/old)	T3–4 (%)	N+ (%)	R1 (%)	Median RFS (months)	Median OS (months)	HR (95% CI)	*P* value
ESPAC-1 [78]	1994.02	5-FU/LV ± CRT	14	61	NA	50	19	15.3 (10.5–19.2)	20.1 (16.5–22.7)	0.71 (0.55–0.92)	0.009
(NEJM 2004)		Observation ± CRT	7	61	NA	58	16	9.4 (8.4–15.2)	15.5 (13.0–17.7)	1.28 (0.99–1.66)	0.05
		CRT ± 5-FU/LV	142	62	N A	5	1	10.7 (8.8–15.5)	15.9 (13.7–19.9)		
		Observation ± 5-FU/LV	14	61	NA	3	9	15.2 (9.8–22.2)	17.9 (14.8–23.6)		
			5			54	16				
			14								
			4								
CONKO-001 [74, 77]	1998.07	Gem alone	179	62	86	71	19	13.4 (11.6–15.3)	22.8 (18.5–27.2)	0.76 (0.61–0.95)	0.01
(JAMA 2013)		Observation	175	62	86	73	15	6.7 (6.0–7.5)	20.5 (17.7–22.8)		
RTOG 9704 [81]	1998.07	Gem – CRT – Gem	221	61	81	68	35	NA	18.5[a]/20.5[b] (NA)	0.93 (0.76–1.14)[a]	0.51[a]
(ASO 2011)		5-FUci – CRT – 5-FUci	230	62	70	65	33	NA	17.1[a]/17.1[b] (NA)	0.84 (0.67–1.04)[b]	0.12[b]
ESPAC-3 [78]	2000.07	Gem alone	537	63	NA	73	35	14.3 (13.5–15.6)	23.6 (21.4–26.4)	0.94 (0.81–1.08)	0.39
(JAMA 2010)		5-FU + FA	551	63	NA	70	35	14.1 (12.5–15.3)	23.0 (21.1–25.0)		
JAPS-02 [75]	2002.04	Gem alone	58	65	88	6	1	11.4 (8.0–14.5)	22.3 (16.1–30.7)	0.77 (0.51–1.14)	0.19
(BJC 2009)		Observation	60	64	84	7	9	5.0 (3.7–8.9)	18.4 (15.1–25.3)		
						70	13				
CapRI study [80]	2004.08	FP-IFN-CRT + 5-FUci	53	60	94	79	45	15.2 (10.3–24.8)	26.5 (21.6–39.5)	1.04 (0.66–1.53)	0.99
(JCO 2012)		5-FU + LV	57	60	98	79	34	11.5 (9.8–17.6)	28.5 (20.4–38.6)		
EORTC/FFCD [83]	2004.09	Gem + Gem-CR T	45	61	71	71	4	11.8 (10.1–19.3)	24.3 (20.5 to ∞)	NA	NA
(JCO 2010)		Gem alone	45	58	76	70	2	10.9 (8.3–16.0)	24.4 (21.5 to ∞)		
JASPCA-01 [84]	2007.04	S-1 alone	187	66	88	64	12	22.9 (17.4–30.6)	46.5 (37.8–63.7)	0.57 (0.44–0.72)	<0.0001[c]
(Lancet 2016)		Gem alone	190	66	86	62	14	11.3 (9.7–13.6)	25.5 (22.5–29.6)		
CONKO-005 [35]	2008.04	Gem + Erlotinib	219	63	88	64	0	11.6 (9.5–13.7)	24.6 (20.9–28.4)	0.90 (0.71–1.15)	0.406
(ASCO 2015)		Gem alone	217	65	86	66	0	11.6 (9.1–12.4)	26.5 (22.2–30.8)		
ESPAC-4 [85]	2008.11	Gem + Cap	364	65	NA	79	61	13.9 (12.1–16.6)	28.0 (23.5–31.5)	0.82 (0.68–0.98)	0.032
(ASCO 2016)		Gem alone	366	65	NA	82	60	13.1 (11.6–13.3)	25.5 (22.7–31.5)		
RTOG 8048 [36] (ongoing)	2009.11	Gem ± CRT	950								
		Gem + erlotinib ± CRT									
APACT [86] (ongoing)	2013.10	Gem + nab-paclitaxel	846								
		Gem alone									
NCT02172976 [87] (ongoing)	2014.11	FOLFIRINOX (peri-OP)	126								
		Gem alone									

[a]Estimated median overall survival from figure and reported HR of intent-to-treat population in Ann Surg Oncol 2011; 18:1319–26
[b]Reported median overall survival and its HR of pancreatic head cancer subpopulation in Ann Surg Oncol 2011; 18:1319–26
[c]$p < 0.0001$ for both non-inferiority and superiority

plus oxaliplatin 85 mg/m^2 on days 8 and 22, every 6 weeks (OFF regimen) as the second-line treatment in patients with advanced pancreatic cancer progressed during gemcitabine treatment. The study was early terminated after the inclusion of the first 46 patients between December 2002 and December 2003 because of insufficient patient accrual owing to poor acceptance of BSC plus placebo control by patients and investigators. However, even with such a small number of patients, OFF provided significant survival benefit over placebo in gemcitabine-refractory advanced PDAC patients. The median second-line survival in OFF and placebo arms was 4.82 (95% CI, 4.29–5.35) and 2.30 (95% CI, 1.76–2.83) months, respectively, with a hazard ratio of 0.45 (95% CI, 0.24–0.83), p = 0.008 [90]. The study was adapted to include an active control arm, weekly folinic acid 200 mg/m^2 followed by 24-h infusion of 5-FU 2,000 mg/m^2 for consequently 4 weeks (FF regimen) [29]. A total of 160 patients were included between January 2004 and May 2007. After a median follow-up of 54.1 months, patients receiving OFF had significantly better time-to-progression and overall survival as compared to those receiving FF. The median time-to-progression was 2.9 (95% CI, 2.4–3.2) versus 2.0 (95% CI, 1.6–2.3) months with a HR of 0.68 (95% CI, 0.50–0.94, log-rank P = 0.019), while the median overall survival was 5.9 (95% CI, 4.1–7.4) versus 3.3 (95% CI, 2.7–4.0) months with a HR of 0.66 (95% CI, 0.48–0.91, log-rank P = 0.010). OFF was generally well tolerated except the occurrence of grade 1–2 peripheral sensory neuropathy in 38.2% of patients, which is one of the disadvantages for its usage in the era of gemcitabine/nab-paclitaxel [91, 92].

Almost at the same period of time, an international phase III trial was conducted to evaluate the efficacies of glufosfamide plus BSC versus BSC alone in gemcitabine-refractory advanced PDAC. Glufosfamide is a β-D-glucose-linked isophosphoramide mustard (IPM), an active metabolite of ifosfamide, which was designed to enhance the uptake of glucose-linked cytotoxic agent by high glucose-consuming cancer cells. Between September 2004 and August 2006, a total of 303 patients were enrolled. The median survival was 105 (range 5–875) days for glufosfamide and 84 (range 2–761) days for BSC, with a HR of 0.85 (95% CI, 0.66–1.08, p = 0.19) [93]. Although this is a negative study, the median overall survival of 2.8 months in patients who received BSC alone was comparable to that of 2.3 months in the first CONKO-003 study [92]. On the other hand, based on the promising results of the first COKO-003 study and previously reported single-arm study of FOLFIRI.3, a regimen with split irinotecan infusion on days 1 and 3 plus leucovorin-modulated 46-h infusion of 5-FU, in patients with chemo-naive and prior gemcitabine-treated advanced pancreatic cancer [94], Korean investigators conducted a randomized phase II study to compare the therapeutic efficacies of modified FOLFORI.3 and modified FOLFOX6 as second-line therapy for patients with advanced PDAC refractory to gemcitabine-based therapy. Modified FOLFIRI.3 consisted of a 1-h infusion of irinotecan 70 mg/m^2 on day 1 and day 3, which was given immediately before and after a 2-h infusion of leucovorin 400 mg/m^2 followed by a 46-h infusion of 5-FU 2,000 mg/m^2, respectively. Modified FLOFOX6 consisted of a 2-h infusion of oxaliplatin 85 mg/m^2 followed by an identical 5-FU and leucovorin dosing schedule. Both treatments were every 2 weeks. Between January 2007 and December 2008, a total of 61 patients were recruited. The median overall survival of patients who received modified FOLFIRI.3 and modified FOLFOX6 were 16.6 weeks and 14.9 weeks, respectively, while the 6-month survival rates were 27% and 30%, respectively. Both regimens were associated with 38% of grade 3–4 adverse events, including 20–24% of grade 3–4 neutropenia in this fragile patient population [95]. These results suggested that while in combination with infusion 5-FU and leucovorin, irinotecan might have compatible therapeutic effects as compared to oxaliplatin in advanced pancreatic cancer after previously gemcitabine-based treatment. Of note, only 10% of patients in the study had prior gemcitabine monotherapy, while frontline therapy comprised of gemcitabine plus capecitabine in 75%, gemcitabine plus erlotinib in 10%, and gemcitabine plus cisplatin in 5%. Whether

previous treatment of gemcitabine monotherapy versus gemcitabine-based combination therapy will affect the clinical outcomes of second-line therapy in patients with advanced pancreatic cancer deserves further investigation. One recent Canadian phase III PANCREOX study compared the effect of infusion 5-FU/LV (LV 400 mg/m^2 2-h infusion followed by bolus and then a 46-h infusion of 5-FU at a dose of 400 mg/m^2 and 2,400 mg/m^2, respectively, every 2 weeks) vs. modified FOLFOX6 (2-h infusion of oxaliplatin 85 mg/m^2 followed by same infusion 5-FU/LV schedule, every 2 weeks) in patients with previous first-line gemcitabine-based chemotherapy, but excluding those with previous oxaliplatin and 5-FU exposure [96]. The study was launched in May 2010, with a total of 108 patients included, 54 in the ear study arm. The primary endpoint was progression-free survival. After a median of an 8.8-month follow-up, modified FOLFOX6 achieved similar progression-free survival (median 3.1 months versus 2.9 months, hazard ratio = 1.00 [95%CI, 0.66–1.53], $P = 0.989$) and objective response rate (13.2% versus 8.5%, $P = 0.361$), but significant inferior overall survival (median, 6.1 months versus 9.9 months, hazard ratio = 1.78 [95% CI, 1.08–2.93], $P = 0.024$) as compared to the 5-FU/LV control arm. The median overall survival of 6.1 months in patients with modified FOLFOX in current PANCREOX study was compatible with those in the CONKO-003 and Korean randomized phase II study. But the 9.9 months of median overall survival in the current 5-FU/LV arm was surprisingly good as compared to that of 3.3 months and 4.2 months in CONKO-003 and NAPOLI-1 studies, respectively [28, 29]. Although Gill et al. attributed the difference in overall survival between their two study arms to higher proportion of patients who received post-progression chemotherapy, 23% versus 7% ($P = 0.015$) [96], however, 20% and 38% of patients with 5-FU/LV (FF) in CONKO-003 and NAPOLI-1 studies, respectively, also had post-progression therapy [28, 29]. Therefore, a small sample-size related selection bias can be a more reasonable etiology for the extremely good survival of the 5-FU/LV control arm in PANCREOX.

Nal-IRI is a new formulation of irinotecan encapsulated in liposomes (80–120 nm in size) that was designed to protect the rapid hydrolysis and activation of encapsulated irinotecan in circulation and to preferentially localize within the tumor microenvironment through a process called “passive diffusion” so as to increase and prolong the levels of irinotecan and its active metabolite (SN-38) within the tumor tissue as compared with conventional irinotecan [97]. The favorable pharmacokinetic characteristics of nal-IRI, notably lower Cmax, longer half-life, and higher AUC of SN-38 than conventional irinotecan, were demonstrated in both preclinical models and human studies. With the observations of a partial responder and four disease stabilizers among a total of seven previously heavily treated metastatic pancreatic cancer patients in the first-in-human and subsequent combination phase I trials [98, 99], an international, single-arm phase II trial to evaluate the efficacies of nal-IRI monotherapy at 120 mg/m^2 (the maximum tolerated dose defined in phase I study) intravenous injection, once every 3 weeks in patients with gemcitabine-refractory advanced pancreatic cancer was launched in March 2009 [100]. Of the 40 participants whose previous treatment consisted of gemcitabine monotherapy in 9 (22.5%) and gemcitabine-based combination in 31 (77.5%), the disease-control rate, median progression-free survival, and overall survival were 50%, 2.4 months, and 5.2 months, respectively.

Based on such an exciting results, a global randomized phase III trial, the NAPOLI-1 study, was launched in May 2011 to evaluate nal-IRI alone or in combination with 5-FU/LV (nal-IRI+5-FU/LV) versus a common control (5-FU/LV) in patients with metastatic pancreatic cancer previously treated with gemcitabine-based therapies [28]. Patients were initially randomized with 1:1 ratio to receive nal-IRI 120 mg/m^2 every 3 weeks or a weekly 30-min infusion of leucovorin 200 mg/m^2 followed by a 24-h infusion of 5-FU/LV 2,000 mg/m^2 for 4 weeks every 6 weeks (5-FU/LV, identical to the FF control arm in CONKO-003 study). After the first 63 patients were enrolled, the protocol was amended to include a third arm of biweekly nal-IRI+5-FU/

LV (nal-IRI 80 mg/m^2 and LV 400 mg/m^2 followed by 46-h infusion of 5-FU 2,400 mg/m^2), of which the feasibility has been evaluated in a French GERCOR phase 2 PEPCOL trial in metastatic colorectal cancer [101]. The accrual of 417 patients was completed in September 2013. Of them, 45% had prior gemcitabine monotherapy, and 55% had gemcitabine combination therapy, including fluorouracil-based in 43%, irinotecan-based in 10%, and/or platinum-based in 32%. The primary final analysis showed nal-IRI+5-FU/LV significantly improved the OS of intent-to-treat population with a median overall survival of 6.1 (95% CI, 4.8–8.9) versus 4.2 (95% CI, 3.6–4.9) months in 5-FU/LV comparator arm and a HR of 0.67 (95% CI, 0.49–0.92, p = 0.012). Nal-IRI+5-FU/LV treatment also significantly improved the objective response rate (16% vs. 1%), median progression-free survival (3.1 months versus 1.5 months, HR = 0.56, 95% CI, 0.41–0.75, $p < 0.001$), and tumor marker response rate, which was defined as the proportion of patients with a 50% or more reduction of abnormal baseline CA 19.9 (29% versus 9%, $p <$ 0.001). Although nal-IRI only was associated with significant improvement in an objective response rate (6% versus 1%, $p = 0.02$) and tumor marker response rate (24% versus 11%, p = 0.024), it only marginally improved the progression-free survival (2.7 months versus 1.6 months, p = 0.1) but not overall survival (4.9 months versus 4.2 months, HR = 0.99, 95% CI, 0.77–1.28, $p = 0.97$) as compared to the comparator 5-FU/LV arm. Most common grade 3–4 adverse events associated with nal-IRI+5-FU/LV treatment were neutropenia 27%, fatigue 14%, diarrhea 13%, and vomiting 11%. Of note, patients with homozygous *UGT1A1*28(TA)$_7$* genotype had reduced initial dose of nal-IRI by 20 mg/m^2, which was allowed to be reescalated to the standard dose in the absence of treatment-related adverse events during the first treatment cycle. Based on the results, nal-IRI+5-FU/LV have become the first US FDA-approved regimen for the treatment of patients with metastatic pancreatic cancer after previous gemcitabine-based therapy on October 2015. On the other hand, despite similar scheduled dose intensity of 5-FU and leucovorin in the nal-IRI+5-FU/LV and 5-FU/LV arms, the study was frequently questioned for the use of different 5-FU/LV schedules in the experimental and control arms. However, the issue will be addressed in a bridging randomized phase II study in Japan (ClinicalTrials.gov Identifier: NCT02697058, launched in March 2016) [102].

Based on the known frequent occurrence of *KRAS* mutation, which can lead to activation of PI3K/Akt/mTOR and RAS/RAF/MEK/ERK signaling pathways in pancreatic cancer, a randomized phase II SWOG-S1115 trial comparing the combination of MEK 1/2 inhibitor (selumetinib 100 mg once daily) and an allosteric Akt inhibitor (MK-2206, 135 mg weekly) versus modified FOLFOX6 was launched in August 2008 [103]. A total of 113 patients were included and overall survival was the primary endpoint of the study. In the primary report presented in the 2015 ASCO meeting, the median overall survival of 4.0 months in the selumetinib/MK-2206 combination arm was marginally inferior to that of 6.9 months in the mFOLFOX6 arm, HR = 1.33 (95% CI, 0.86–2.07), p = 0.20. In a randomized phase II study with 127 participants, Hurwitz et al. showed that add-on 15 mg twice daily of ruxolitinib, a Janus kinase (JAK) 1/2 inhibitor, did not significantly improve the overall survival of patients with previous gemcitabine-based, therapy-treated metastatic pancreatic cancer receiving capecitabine (1,000 mg/m^2 twice daily, days 1–14, every 3 weeks) on intent-to-treat analysis. The median overall survival was 4.5 months (95% CI, 3.1–6.4) in the ruxolitinib arm and 4.3 months (95% CI, 2.3–5.9) in the placebo-controlled arm, with a HR of 0.79 (95% CI, 0.53–1.18), p = 0.25 [104]. However, the ruxolitinib arm achieved significant longer survival in patients with high baseline C-reactive protein (CRP >13 mg/L) in prespecified subgroup analysis, with a median overall survival of 2.7 months (95% CI, 1.8–72) versus 1.8 months (95% CI, 1.3–2.3) in the placebo arm, HR = 0.47 (95% CI, 0.26–.085), p = 0.011. Two randomized, phase III studies, the JANUS-1 and JANUS-2, were launched in Europe, March 2014, and the USA, April 2014, respectively, to investigate ruxolitinib or placebo

in combination with capecitabine for the second-line treatment of patients with advanced or metastatic PDAC [105, 106]. Unfortunately, both studies were discontinued early because of unsatisfactory efficacy after an interim analysis on survival data of JANUS-1 in February, 2016. The other phase III, the PANCRIT-1 study of ^{90}Y-clivatuzumab tetraxetan, targeting on MUC1, or the best supportive care in combination with low-dose gemcitabine in patients with metastatic PDAC who have received at least two prior therapies (ClinicalTrials.gov Identifier: NCT01956812) was launched in September 2013 [107].

However, it was early terminated in March 2016 following the recommendation of the independent Data and Safety Monitoring Board (DSMB) after the planned interim analysis on overall survival data.

37.4.2 S-1-Based Second-Line Therapy After Gemcitabine-Based Treatment: Asian Perspective

In the GEST study, S-1 has been shown its activity in patients with chemo-naïve advanced pancreatic cancer [13]. The role of second-line S-1, either alone or in combination with leucovorin, oxaliplatin, or irinotecan, for gemcitabine monotherapy-refractory advanced pancreatic cancer has also been evaluated in randomized phase II trials. Between January 2009 and July 2010, a total of 271 patients were enrolled and 1:1 randomized to receive S-1 alone (standard 4 weeks-of/2 weeks-off schedule with fixed dose of 40, 50, and 60 mg twice daily for patients with body surface <1.25 m^2, ≥1.25 to <1.50 m^2, and ≥1.50 m^2, days 1–28 every 6 weeks) or SOX (oxaliplatin 100 mg/m^2 on day 1 plus S-1 at same dose on days 1–14 every 3 weeks) [108]. Despite SOX which had a superior objective response rate (20.9% versus 11.5% in S-1 alone arm), however, it did not significantly improve the median progression-free survival and overall survival, with 3.0 (95% CI, 2.8–3.7) months versus 2.8 (95% CI, 1.9–3.5) months (HR = 0.84; 95% CI, 0.65–1.08, P = 0.18) and 7.4 (95% CI, 6.2–8.6) months versus 6.9 (95% CI, 5.8–9.0) months (HR = 1.03, 95% CI, 0.79–1.34, P = 0.82), respectively. Both regimens were well tolerated with grade 3 neutropenia and thrombocytopenia below 12%, and grade 3 diarrhea 5–6%. Between November 2008 and March 2011, a total of 127 eligible patients were randomized in 1:1 ratio to receive S-1 alone (standard 4 weeks-of/2 weeks-off schedule) or IRIS (irinotecan 100 mg/m^2 on day 1 and day 8 plus S-1 at same dose on day 1–14 every 4 weeks) [109]. Of note, the IRIS regimen can be consider to be similar to the FOLFIRI.3 using a slit irinotecan dosing in combination with either 1 week of S-1 or a 46-h infusion of 5-FU. Despite IRIS which had a superior objective response rate (18.3% versus 6.0% in S-1 alone arm, p = 0.031), however, it did not significantly improve the median progression-free survival and overall survival, with 107 days versus 58 days (p = 0.175) and 208 days versus 176 days (p = 0.134), respectively. IRIS treatment was associated with a higher incidence of grade 3 neutropenia (15.6% versus 4.3%) but had similar grade 3 diarrhea as compared to S-1 alone, 3.1% versus 2.9%.

With the recent revival of S-1 and leucovorin combination for the treatment of gastrointestinal tract tumors [110], the second-line efficacies of S-1 plus leucovorin (SL) has also been evaluated in a randomized phase II trial. Between August 2011 and August 2012, a total of 142 patients were enrolled and 1:1 randomized to receive S-1 alone (standard 4 weeks-on/2 weeks-off schedule) or SL (S-1 at same dose plus leucovorin 25 mg twice daily on days 1–7 every 2 weeks) [111]. Both regimens were well tolerated with grade 3 neutropenia 6–9% and grade 3 diarrhea 4–6%. Despite SL which had significant superior disease control rate (91% versus 72% in S-1 alone arm, p = 0.004) and median progression-free survival 3.8 (95% CI, 3.7–6.0) months versus 2.7 (95% CI, 1.9–3.7) months in the S-1 arm with a HR of 0.56 (95% CI, 0.37–0.85, P = 0.003), however, it did not significantly improve the overall survival, 6.3 (95% CI, 5.3–8.4) months versus 6.1 (95% CI, 5.3–7.8) months in the S-1 arm (HR = 0.82, 95% CI, 0.54–1.22, P = 0.463). Roughly 40% of patients in each study arm

received post-protocol therapy which mainly consisted of S-1 with or without gemcitabine. In multivariate analysis after being adjusted for other prognostic factors, SL showed trend to improve overall survival as compared to S-1, HR = 0.71 (95% CI, 0.47–1.07, $P = 0.099$). Based on the observation, a phase III trial comparing the overall survival of TAS-118 (a combo of S-1 and leucovorin) and S-1 in 600 patients with gemcitabine-only-refractory advanced pancreatic cancer was launched in July 2013 in Japan and Korea (registered number: JapicCTI-132172). The study has completed patient recruitment and pending for the disclosure of final results [112].

37.4.3 Second-Line Therapy After FOLFIRINOX

Currently, there was no randomized study to evaluate the therapeutic effect of any regimen on patients with advanced pancreatic cancer after previous FOLFIRINOX treatment. However, the median overall survival of 80 patients who had second-line therapy (82.5% with gemcitabine alone and 12.5% with gemcitabine-based combination) after FOLFIRINOX failure was 4.4 months in the original report of the ACCORD study [4]. In addition, there was a prospective cohort study, in which Association des Gastro-Entérologues Oncologues (AGEO) prospectively collected the data of consecutive advanced pancreatic cancer patients who failed to FOLFIRINOX from 12 AGEO centers to evaluate the effects of second-line nab-paclitaxel plus gemcitabine after FOLFIRINOX failure between February 2013 and July 2014 [113]. Of the 110 patients with advanced pancreatic cancer who failed to FOLFIRINOX during that period of time, 77 patients (70%) had nab-paclitaxel plus gemcitabine as second-line treatment. After excluding the 20 patients with non-metastatic diseases and/or poor performance, 57 patients were included into the study. In this highly selected patient population, median age of 60 years-old, ECOG performance 0–1 in 79%, median 12 cycles of previous FOLFIRINOX treatment and with solitary metastatic site involvement in 63%, 38% of patients experienced grade 3–4 adverse events including neutropenia in 12.5% and peripheral sensory neuropathy in 12.5% after nab-paclitaxel and gemcitabine. Dose reduction and treatment discontinuation occurred due to adverse events occurred in 67% and 12.5% of patients, respectively. The best tumor response was partial response in 17.5% and stable disease in 40.5%. Median progression-free survival and overall survival after nab-paclitaxel and gemcitabine were 5.1 months (95% CI, 3.2–6.2) and 8.8 months (95% CI, 6.2–9.7), respectively. Although the data has been challenged [114], however, biomarker findings to identify appropriate patient population for such aggressive treatment as well as prospective study to validate the results will be mandatory before it can be used in clinical practice.

37.5 Summary

In conclusion, CONKO-003 and NAPOLI-1 were the only two randomized phase 3 trials that demonstrated the survival benefit of second-line therapy with either OFF in the CONKO-003 study or nal-IRI+5-FU/LV in the NAPOLI-1 study against a same 5-FU/LV control arm in patients with advanced pancreatic cancer previously treated with gemcitabine-based therapy [28, 29], as shown in Table 37.5. Both OFF and nal-IRI+5-FU/LV were well tolerated and had comparable median PFS and OS; however, the less neurotoxic nal-IRI+5-FU/LV regimen will be a favorable second-line treatment after gemcitabine/nab-paclitaxel frontline treatment, as suggested by Oettle and Lehmann [91]. On the other hand, the role of S-1 either alone or in combination with other agents as a second-line setting for advanced pancreatic cancer with refractory to gemictabine-based therapy requires further investigation in large-scale randomization studies; while the role of gemcitabine-based therapy, such as gemcitabine plus nab-paclitaxel in the second-line setting should also be prospectively evaluated to determine the efficacy after FOLFIRINOX.

Table 37.5 Selected randomized phase II/III studies of second-line chemotherapy ± targeted agents in metastatic pancreatic cancer

Study/author publication year	Launched date	Regimens	Case no.	Median age (years/old)	ORR (%)	Median PFS (months)	Median OS (months)	HR (95% CI)	*P* value
Post-gemcitabine alone									
CONKO-003 [90]	2002.01	OFF + BSC	23	60	NA	NA	4.8 (4.3–5.4)	0.45 (0.24–0.83)	0.008
		BSC	23	61	NA	NA	2.3 (1.8–2.8)		
CONKO-003 [29]	2004.01	OFF + BSC	76	62	NA	2.9 (2.4–3.2)	5.9 (4.1–7.4)	0.66 (0.48–0.91)	0.010
(JCO 2014)		FF + BSC	84	61	NA	2.0 (1.6–2.3)	3.3 (2.7–4.0)		
Ciuleanu et al. [93]	2004.09	Glucosamine + BSC	148	58	NA	NA	3.5 (NA)	0.85 (0.66–1.08)	0.19
(EJC 2009)		BSC	155	57	NA	NA	2.8 (NA)		
Ohkawa et al. [108]	2009.01	SOX (oxaliplatin + S-1)	134	65	20.9	3.0 (2.8–3.7)	7.4 (6.2–8.6)	1.03 (0.79–1.34)	0.82
(BJC 2015)		S-1 alone	130	64	11.5	2.8 (1.9–3.5)	6.9 (5.8–9.0)		
Mizuno et al. [109]	2008.11	IRIS (irinotecan + S-1)	60	NA	18.3	107 days	208 days	0.75 (0.51–1.09)	0.134
(ASCO GI 2013)		S-1 alone	67	NA	6.0	58 days	176 days		
Ueno et al. [111]	2011.08	SL (S-1 + leucovorin)	69	65	27.5	3.8 (3.7–6.0)	6.3 (5.3–8.4)	0.82 (0.54–1.22)	0.436
(Ann Oncol 2016)		S-1 alone	71	64	19.7	2.7 (1.9–3.7)	6.1 (5.3–7.8)		
Post-gemcitabine-based therapy									
Yoo et al. [95]	2007.01	mFOLFIRI.3	31	55	0.0	2.1 (1.7–2.4)	4.2 (3.1–7.2)	NA	NA
(BJC 2009)		mFOLFOX6	30	55	6.7	1.5 (1.3–1.7)	3.7 (2.0–5.4)		
PANCREOX [96]	2010.05	5-FU/LV	54	67	8.5	2.9 (1.9–7.2)	9.9 (6.7–16.9)	1.78 (1.08–2.93)[a]	0.024[a]
(JCO 2016)		mFOFOX6	54	65	13.2	3.1 (1.7–5.1)	6.1 (3.2–8.0)		
NAPOLI-1 [28]	2011.05	Nal-IRI+5-FU/LV	117	63	16.2	3.1 (2.7–4.2)	6.1 (4.8–8.9)	0.67 (0.49–0.92)	0.012
(Lancet 2016)		5-FU/LV[a]	119[a]	62	0.8	1.5 (1.4–1.8)	4.2 (3.6–4.9)	0.99 (0.77–1.28)	0.99
		Nal-IRI alone	151	65	6.0	2.7 (2.1–2.9)	4.9 (4.2–5.6)		
		5-FU/LV	149	63	0.7	1.6 (1.4–1.8)	4.2 (3.6–4.9)		
SWOG S1115 [103]	2012.08	Selumetinib + MK2206	55	69	0.0	1.9 (NA)	4.0 (NA)	1.33 (0.86–2.07)	0.20
(ASCO 2015)		mFOLFOX6	60	66	6.7	2.0 (NA)	6.9 (NA)		
Hurwitz et al. [104]	2011.11	Ruxolitinib + Cap	64	66	7.8	2.7 (1.8–7.2)	4.5 (3.1–6.4)	0.79 (0.53–1.18)	0.25
(JCO 2015)		Placebo + Cap	63	68	1.6	1.8 (1.3–2.3)	4.3 (2.3–5.9)		
JANUS-1/2 [105, 106]	2014.03	Ruxolitinib + Cap	310/270	NA	NA	NA	NA	Early terminated after interim analysis at 2016.02	
(Early terminated)		Placebo + Cap		NA	NA	NA	NA		
PANCRIT-1 [107]	2013.09	^{90}Y-clivatuzumab + *ld*-Gem	334	NA	NA	NA	NA	Early terminated after interim analysis at 2016.03	
(Early terminated)		Placebo + *ld*-Gem		NA	NA	NA	NA		

BSC best supportive care, *Cap* capecitabine, *FF* 5-FU/folinic acid, *Gem* gemcitabine, *ld-Gem* low-dose gemcitabine, *OFF* oxaliplatin plus 5-FU/folinic acid

[a]Primary endpoint of the study was progression-free survival; however, the hazard ratio was for overall survival difference

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Radiation Therapy

38

Jinhyun Choi and Jinsil Seong

38.1 Adjuvant Radiotherapy

Despite recent advances in the management of patients with pancreatic cancer, the 5-year survival of patients that underwent curative resection of pancreatic cancer is only 10–20% [1]. In addition, local recurrence rates range from 50 to 86% and distant recurrence rates from 40 to 90% [2–7]. These indicate the need for effective adjuvant treatment. High rates of distant metastases cause an arguing point in favor of chemotherapy and high rates of local recurrence of radiotherapy [8]. To date, multiple randomized trials (Table 38.1) showed the conflicting results; therefore the definitive role of adjuvant radiotherapy has not been established in resectable pancreas cancer.

38.1.1 Randomized Trials

As an initial randomized trial, the Gastrointestinal Tumor Study Group (GITSG) showed a survival benefit with the addition of chemoradiation to surgical resection on interim analysis. Forty-three patients with R0 resection were randomized to chemoradiotherapy versus observation. Twenty-two patients randomized to no adjuvant treatment and 21 to combined therapy were analyzed. Radiotherapy was delivered to 40 Gy in 20 fractions via split course, with a 2-week break after 20 Gy. Bolus 5-fluorouracil (FU) (500 mg/m^2) was administered during radiotherapy and then once weekly for 2 years after radiotherapy. Median survival for chemoradiation group with 20 months was significantly longer than that observed for the control group with 11 months. Two-year and 5-year overall survival (OS) were 42% and 14% versus 15% and 4%, respectively [9]. After survival benefit on interim analysis, the results of an additional 30 patients treated with identical chemoradiation regimen showed a similar survival, with median survival of 18 months and a 2-year survival of 46% [10]. Because of this significant improvement in survival, the adjuvant chemoradiotherapy became a standard treatment, particularly in North America. However, the GITSG trial has been criticized for several limitations. The trial was terminated prematurely because of an unacceptably low rate of accrual combined with the observation of increasingly large survival differences between the study groups. The trial accrued only 43 patients over 8 years. Since this trial used the split-course technique with low radiation dose (40 Gy) and used two-dimensional therapy with AP-PA (anteroposterior-posteroanterior) fields, which encompassed the entire pancreas or pancreatic bed and the celiac, pancreaticosplenic, peripancreatic, and retroperitoneal regional lymph nodes, the results may not be applicable to modern radiotherapy practice. Additionally, this trial

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Table 38.1 Randomized trials for adjuvant radiation therapy in pancreatic cancer

Trial	Treatment	*n*	Median survival month)	Overall survival (%)
GITSG [9, 10]	Chemoradiation	21	21	14 (5 years)
	Observation	22	10.9	4 (5 years)
	Chemoradiation (additional study)	30	18	46 (2 years)
EORTC [2]	Chemoradiation	110	24.5	51 (2 years)
	Observation	108	19	41 (2 years)
ESPAC-1 (pooled data) [12]	Chemoradiation	175	15.5	NA
	No chemoradiation	178	16.1	NA
	Chemotherapy	238	19.7	NA
	No chemotherapy	235	14	NA
ESPAC-1 (2 × 2 design) [14]	Observation	69	16.9	11 (5 years)
	Chemotherapy	75	21.6	29 (5 years)
	Chemoradiation	73	13.9	7 (5 years)
	Chemoradiation plus chemotherapy	72	19.9	13 (5 years)

evaluated the use of adjuvant chemoradiotherapy, but did not address the effect of adding radiation to chemotherapy.

On the other hand, the addition of chemoradiation to surgical resection did not show an overall survival benefit in the European Organization of Research and Treatment of Cancer (EORTC) study. Two hundred eighteen patients with pancreatic head or periampullary cancer were randomized to chemoradiotherapy or observation after surgical resection. The radiation dose of 40 Gy was delivered with split course as in the GITSG trial. Unlike the GITSG trial, concurrent continuous infusional 5-FU (25 mg/kg) with no maintenance chemotherapy was administered. A trend toward improved survival was identified in an analysis including only pancreatic head cancer patients ($p = 0.099$). The median survival for 81 patients with pancreatic head cancer was 17.1 months in the chemoradiation group versus 12.6 months in the observation group, but this study confirmed the absence of a statistical significant advantage for adjuvant chemoradiotherapy. The median survival was 19.0 months for the observation group and 24.5 months for the chemoradiation group ($p = 0.208$), and the 2-year survival were 41% and 51%, respectively [2]. With long-term follow-up of median 11.7 years, EORTC trial further confirmed no statistical advantage for adjuvant chemoradiotherapy over observation [11]. However, there are several contributing factors for a lack of survival benefit of adjuvant chemoradiotherapy in this trial. One potential explanation is its heterogeneity of patient population. This trial included patients with both pancreatic and periampullary cancer; it is known that periampullary cancer has a significantly better prognosis compared with pancreatic cancer. In an analysis including only patients with pancreatic cancer, improved survival of adjuvant chemoradiotherapy was shown in this study. And more than 20% of patients in the chemoradiation group did not apply the planned protocol due to postoperative complications or patient refusal. Also, this trial allowed 25% of patients with positive surgical margins and 47% of patients with node positive which carries a worse prognosis. With respect to the radiotherapy, it employed suboptimal therapy with a low dose delivered in a split course similar to the GITSG study. In addition, this study omitted a maintained chemotherapy and included small sample size. The result for discordant survival benefit observed in the EORTC trial as opposed to the GITSG trial was considered as the absence of maintenance of chemotherapy rather than administration of radiotherapy. Therefore, the adjuvant

chemotherapy is considered as the standard treatment for patients with resected pancreatic cancer in Europe [12, 13].

The European Study Group for Pancreatic Cancer-1 (ESPAC-1) was a randomized controlled trial, which evaluated the roles of chemoradiotherapy and chemotherapy consisting of four arms. After resection, 285 patients enrolled (1) observation (n = 69), (2) adjuvant chemotherapy alone (n = 74), (3) adjuvant radiation with concurrent chemotherapy (n = 70), or (4) adjuvant radiation with concurrent chemotherapy followed by maintenance chemotherapy (n = 72). In addition, clinicians could choose to randomize the patients either (1) observation versus chemoradiotherapy (n = 68), consisting of 20 Gy over 2 weeks with 5-FU (500 mg/m^2) and then repeated after 2-week break, or (2) observation versus chemotherapy (n = 188). The data from the treatment groups of the two-by-two factorial design plus two optioning trials were pooled for analysis. Chemoradiation regimen was similar to those of the GITSG and EORTC trials, but the total radiation dose was either 40 Gy or 60 Gy. Positive margins were allowed, and this trial included 18% of patients with positive margins. Overall results showed no benefit for adjuvant chemoradiotherapy. Median survival was 15.5 months in 175 patients with chemoradiotherapy versus 16.1 months in 178 patients without chemoradiotherapy. There was evidence of a survival benefit for adjuvant chemotherapy [12]. In update of the interim results reporting only 289 patients who underwent randomization using a two-by-two factorial design, median survival of observation, chemotherapy alone, chemoradiation, and chemoradiation followed by chemotherapy was 16.9 months, 21.6 months, 13.9 months, and 19.9 months, respectively. On analysis performed grouping patients who received chemotherapy versus patients who received no chemotherapy, the 5-year survival rate was 21% among patients who received chemotherapy and 8% among patients who did not receive chemotherapy (P = 0.009). On another analysis performed grouping patients who received radiotherapy versus patients who received no radiotherapy, patients who received radiotherapy had a survival detriment compared to those who did not (p = 0.05). The authors concluded that adjuvant chemotherapy had a beneficial effect on survival, but adjuvant chemoradiotherapy had a deleterious effect on survival based on these results [14]. However, the ESPAC-1 trial has been strongly criticized for several problems. Regarding that physicians could choose the randomization arm, the trial design has the potential for selection bias in the enrollment process [15]. Similar to the GITSG and EORTC study, this trial employed suboptimal radiotherapy including outdated radiotherapy regimen using split-course and low radiation dose. Also, there was absence of quality assurance of radiotherapy plans, and radiotherapy field size and technique were not specified. In addition, this trial included patients with uncontrolled and previous therapy substantially as well as a high proportion of noncompliance to the treatment regimens. Only 62% of patients received full course of chemoradiation treatment, and 42% of patients in the chemotherapy arms completed the scheduled regimen, which questions the validity of any analysis and therefore its conclusions. All of these factors could have adversely impacted the outcomes against the chemoradiotherapy arm.

The development of gemcitabine may be considered a major advance in the treatment of pancreatic cancer. Based on the data showing potential benefit to adjuvant chemotherapy, the Charite Onkologie (CONKO)-1 trial was initiated, which evaluated surgery alone versus surgery plus six cycles of gemcitabine-based chemotherapy (1,000 mg/m^2). Three hundred sixty-eight patients were enrolled, and patients treated with gemcitabine achieved a statistically significantly lower disease-free survival (DFS) than those observed after surgical resection (13.4 vs. 6.9 months) [16]. To address the role of radiotherapy, the results of the gemcitabine arm of the CONKO-1 trial have been compared to the gemcitabine arm of Radiation Therapy Oncology Group (RTOG) 97-04 including radiotherapy. Given differences in the two trials, such comparisons are statistically invalid, which cannot draw conclusions regarding the benefit of RT in addition to chemotherapy [8]. The most difference between two studies is that the

CONKO-1 trial included only patients with carbohydrate antigen (CA) 19-9 serum values of less than 2.5 times normal, whereas RTOG 97-04 did not define an upper limit. When 385 patients were stratified based on CA 19-9 levels (<180 IU/mL vs. ≥180 IU/mL, ≤90 IU/mL vs. >90 IU/mL), there was a significant survival difference favoring patients with CA 19-9 levels of <180 IU/mL [17]. In an analysis of 200 patients with CA 19-9 levels of ≤90 IU/mL, median survival was similar to that observed in the gemcitabine arm of the CONKO-1 trial. Despite the use of radiotherapy and including a higher percentage of patients with positive margins in the RTOG 97-04 trial compared to CONKO-1 trial, local recurrence rates were similar in the gemcitabine arm of both trials.

To determine whether gemcitabine is superior to 5-FU in terms of overall survival as adjuvant treatment, ESPAC-3, phase III randomized controlled trial enrolled 1,088 patients between 2000 and 2007 and underwent at least 2 years of follow-up. Patients received either six cycles of 5-FU (425 mg/m^2) plus folinic acid (20 mg/m^2) ($n = 551$) or gemcitabine (1,000 mg/m^2) ($n = 537$). After a median 34.2 months of follow-up, there were no significant differences in either progression-free survival (PFS) or global quality-of-life scores between the treatment groups. However, 14% of patients receiving 5-FU had 97 treatment-related serious adverse events, compared with 7.5% of patients receiving gemcitabine, who had 52 events ($P < 0.001$). Given its favorable toxicity profile, gemcitabine is considered the standard adjuvant treatment in many parts of Europe [18].

Unlike Europe, the focus of future adjuvant therapy for resectable pancreatic cancer has been chemoradiation in the United States. The RTOG 97-04 evaluated the efficacy of gemcitabine in the adjuvant setting compared to 5-FU, with both regimens followed by chemoradiotherapy. Chemoradiation was provided with 50.4 Gy and continuous 5-FU. Univariate analysis showed no difference in OS between two groups. On analysis of pancreatic head tumor patients ($n = 388$), a median survival and 5-year OS were 20.5 months and 22% with gemcitabine versus 17.1 months and 18% with 5-FU. Also, patients on the gemcitabine arm with pancreatic head tumors showed a trend toward improved OS on multivariate analysis ($P = 0.08$). The distant relapse rate was still remained higher over 70% of patients although the local recurrence was half of that reported in previous trials [19, 20].

Currently, EORTC/RTOG 0848 phase III trial evaluates the impact of the small-molecule epidermal growth factor receptor (EGFR), erlotinib, and chemoradiation on OS after completion of a full course of gemcitabine. Patients with resected pancreatic head tumor are randomized to receive treatment with either gemcitabine alone or gemcitabine combined with erlotinib for five cycles. If no progression is seen following the completion of systemic therapy, patients are further randomized either to receive an additional cycle of the previously administered chemotherapy and no further treatment or to receive 50.4 Gy radiation with concurrent capecitabine or 5-FU. This trial was designed to address the issue of high rate of distant metastasis as well as to further define the role of chemoradiotherapy in adjuvant setting.

38.1.2 Nonrandomized Trials

Two nonrandomized trials from Johns Hopkins Hospital and Mayo Clinic also suggested a survival benefit with adjuvant chemoradiotherapy in pancreatic cancer. In a prospective review from Johns Hopkins Hospital, 616 patients receiving 5-FU-based chemoradiotherapy after resection experienced an improved median survival with 21.2 months versus 14.4 months ($P < 0.001$). Both 2-year (43.9% vs. 31.9%) and 5-year (20.1% vs. 15.4%) survival were better compared with no adjuvant therapy [21]. Similarly, the Mayo Clinic experience reported the outcomes of 472 patients who underwent complete surgical resection with negative margins between 1975 and 2005. For the

466 surviving patients, median OS after adjuvant chemoradiotherapy was 25.2 versus 19.2 months after no adjuvant therapy ($P = 0.001$). A 2-year OS was 50% versus 39%, and a 5-year OS was 28% versus 17%. Despite patients receiving adjuvant therapy had more adverse prognostic factors such as higher frequency of positive lymph nodes and histologic grade than those not receiving adjuvant therapy ($P = 0.001$), adjuvant chemoradiotherapy improved median, 2-year, and 5-year survival significantly compared to surgery alone [22]. Both studies applied 50.4 Gy in 28 fractions of radiation dose. A subsequent pooled analysis of approximately 1,300 patients from both institutions showed that OS was longer for those who received chemoradiotherapy compared to surgery alone. Median survival was 21.1 versus 15.5 months, and 2- and 5-year OS were 44.7% versus 34.6% and 22.3% versus 16.1%, respectively ($P < 0.001$) [23].

Unlike randomized trials, reports of single-institution experiences have provided evidence to the benefit of adjuvant therapy for resected pancreatic cancer. Given that 11–26% of patients experience distant progression during radiotherapy [24, 25], multimodality therapy seems necessary in adjuvant setting; therefore, a reasonable consideration is to begin with adjuvant chemotherapy, followed by radiotherapy in patients who do not progress.

38.2 Neoadjuvant Radiotherapy

The use of neoadjuvant treatment in pancreatic cancer offers several theoretical advantages compared to adjuvant treatment: (1) Pancreatic cancer overall has the poor prognosis because it has a low rate of resectability. Neoadjuvant therapy may downstage the local, borderline, and unresectable disease, which potentially facilitates resectability with clear margins (R0 resection) and decreases lymphatic spread [26]. (2) Pancreatic cancer is more likely a systemic disease with high incidence of recurrence, and 80–85% of patients experienced recurrence even after undergoing curative resection [13, 14]. To start, early chemoradiation therapy may reduce the incidence of distal metastasis and contribute to improved survival. (3) A proportion of patients will develop distant metastatic disease during neoadjuvant therapy, in whom a major unnecessary surgical procedure can be avoided [8]. (4) In naïve tumor bed, radiotherapy can be more effective due to rich oxygenated tissue compared to postoperative status. In addition, by avoiding bowel displacement due to surgery, radiotherapy can be well tolerated without higher gastrointestinal toxicity [27, 28]. However, there have been no large randomized trials of neoadjuvant therapy in resectable pancreatic cancer, and several institutions have used this strategy to improve the survival rates of patients with pancreatic cancer (Table 38.2).

Table 38.2 Results from studies of neoadjuvant chemoradiation in pancreatic cancer

Trial	*n*	Chemotherapy	Radiotherapy	Resection rate (%)	Median survival (month)
MD Anderson Cancer Center [29]	132	5-FU, paclitaxel, gemcitabine	45–50.4 Gy or 30 Gy	100	21
Mount Sinai Hospital [30]	68	5-FU, streptozotocin, cisplatin	Split course	29.4	23.6
Duke University Medical Center [27]	180	5-FU	50.4 Gy	20	23 (resection)
MD Anderson Cancer Center [31, 32]					
CRT	86	Gemcitabine	30 Gy	85	34 (resection)
CTx-CRT	90	Cisplatin/ gemcitabine-gemcitabine	30 Gy	69	31 (resection)
Meta-analysis [35]	4,394	Gemcitabine, 5-FU, MMC, platinum compounds	24–63 Gy	33	20.5 (resection)

CRT chemoradiotherapy, *CTx* chemotherapy, *5-FU* 5-fluorouracil, *MMC* mitomycin-C

38.2.1 Selected Studies of Neoadjuvant Chemoradiation Therapy

According to reports from the MD Anderson Cancer Center on 132 patients who have been treated between 1990 and 1999, patients received either 45 or 50.4 Gy radiation at 1.8 Gy per fraction in 28 fractions or 30.0 Gy at 3.0 Gy per fraction in 10 fractions with concomitant chemotherapy (5-FU, paclitaxel, or gemcitabine). Median OS time of 21 months is excellent and supports prior studies which suggested that the survival duration of patients with potentially resectable pancreatic cancer was maximized by the combination of chemoradiation and pancreaticoduodenectomy [29].

Mount Sinai Hospital reported the prospective clinical trial results comparing neoadjuvant therapy to up-front surgery [30]. Ninety-one patients with resectable tumors initially underwent immediate surgery without preoperative chemoradiotherapy, with or without postoperative chemoradiotherapy. Sixty-eight patients with locally invasive and unresectable pancreatic tumor were treated with simultaneous split-course radiotherapy plus 5-FU, streptozotocin, and cisplatin followed by subsequent surgery if resection was amendable. Among them, 30 patients (29.4%) underwent surgery and tumors were downstaged in 20 patients. The median survival and 3-year OS of all patients receiving neoadjuvant treatment were 23.6 months and 21% compared to 14 months and 14%, respectively, for patients who had up-front surgery ($p = 0.006$).

Since 1994, Duke University Medical Center has treated over 180 patients with localized pancreatic cancer using neoadjuvant chemoradiation therapy [27]. Patients received fractionated radiotherapy to a total dose of 50.4 Gy with 5-FU-based chemotherapy concurrently. Patients underwent surgical resection if there was no evidence of metastatic disease. Approximately 20% of patients demonstrated distant disease progression during chemoradiation therapy therefore subsequently avoided the morbidity from unnecessary laparotomy. Almost 20% of locally advanced tumors on initial staging CT could be resected following chemoradiation therapy. Patients who had successfully undergone resection showed favorable survival with an estimated 5-year survival rate of 36%, and a median survival was 23 months.

At MD Anderson Cancer Center, two different strategies were tested to evaluate the use of gemcitabine as part of neoadjuvant regimen. In the first trial, patients received daily fractionated radiotherapy to a total dose of 30 Gy in ten fractions over 2 weeks concurrent with seven cycles of gemcitabine (400 mg/m^2). Of the 86 enrolled patients treated with chemoradiation, 73 patients (85%) underwent surgery. An R0 resection was achieved in 89% of patients. The 5-year OS for resected patients was 36% compared 27% for all patients. Median survival was 34 months for resected patients and 7 months for unresected patients ($p < 0.001$) [31].

Given the high incidence of distant disease in pancreatic cancer, neoadjuvant chemotherapy prior to chemoradiation was attempted in the second trial. Ninety patients received two cycles of cisplatin (30 mg/m^2) and gemcitabine (400 mg/m^2) followed by concurrent chemoradiation therapy consisted of four weekly infusions of gemcitabine (400 mg/m^2) combined with radiation (30 Gy in ten fractions over 2 weeks). Seventy-nine patients (88%) completed chemo-chemoradiation. Sixty-two (78%) of 79 patients who completed chemo-chemoradiation were taken to surgery, and 52 (66%) underwent successful resection. Subsequently, 66% of patients underwent R0 resection. The median survival of all patients was 17.4 months. Patients who underwent a resection did better with median survival of 31 months compared to 10.5 months for patients who did not ($p < 0.001$). However, the addition of induction chemotherapy prior to chemoradiation therapy did not improve OS [32].

An earlier phase II trial of 53 patients with resectable pancreatic cancer used 50.4 Gy of radiotherapy with mitomycin and 5-FU for neoadjuvant treatment [33]. Twelve patients (23%) did not proceed to surgery, mainly due to distant progression. Median survival for all patients and for the 24 patients with resection was 9.7 and 15.7 months, respectively. The lower survival

Table 38.3 Selected studies for neoadjuvant therapy in borderline resectable pancreatic cancer

Author	*n*	Chemotherapy	Radiotherapy	% R0/total no. of resected (n)
Kang CM et al. [36]	32	Gemcitabine	50.4 Gy	87.5 (28/32)
Christians KK et al. [37]	18	FOLFIRINOX	50.4 Gy	100 (12/12)
Boone BA et al. [38]	12	FOLFIRINOX		85.7 (6/7)
Paniccia A et al. [39]	18	FOLFIRINOX	30 Gy	100 (17/17)
Rose JB et al. [40]	64	Gemcitabine + docetaxel		87 (27/31)
Lee JL et al. [41]	18	Gemcitabine	60 Gy	81.8 (9/11)

FOLFIRINOX 5-fluorouracil, oxaliplatin, irinotecan, and leucovorin

rate than that of MD Anderson Cancer Center is likely due to the use of 5-FU-based, rather than gemcitabine-based, chemotherapy.

Retrospective analysis based on the Surveillance, Epidemiology, and End Results (SEER) registry database showed a survival benefit for the use of neoadjuvant radiotherapy over surgery alone or surgery with adjuvant radiotherapy in treating pancreatic cancer. This analysis included 3,885 cases. Of these, 70 patients (2%) had received neoadjuvant radiotherapy, 1,478 (38%) had received adjuvant radiotherapy, and 2,337 (60%) had been treated with surgery alone. The median OS of patients received neoadjuvant radiotherapy was 23 months versus 12 months with no radiotherapy and 17 months with adjuvant radiotherapy. This analysis did not address the role of chemotherapy [34].

A recent review and meta-analysis including 111 trials with total of 4,394 patients was conducted to show the neoadjuvant treatment results. In these studies, a total radiation dose ranging from 24 to 63 Gy was used, and chemotherapy was administered with the regimens consisting of gemcitabine, 5-FU, mitomycin C, and platinum compounds. Following neoadjuvant treatment, one third of the unresectable tumors were resected, and those patients with initially unresectable but converted to resectable tumor had comparable survival to patients with initially resectable tumors. The median survival of patients receiving neoadjuvant followed by surgery was 20.5 months compared 23.3 months for patients who had initial tumor resection [35].

Despite these encouraging results using a neoadjuvant treatment, there is no prospective randomized phase III trial to support its routine use in resectable pancreatic cancer.

38.2.2 Borderline Resectable Disease

Regarding that patients with borderline resectable disease are likely to ultimately undergo surgical resection, neoadjuvant therapy has a strong rationale due to its ability for converting locally unresectable to resectable disease. According to results from previous series, approximately 30% of patients were converted to a resectable state after neoadjuvant therapy [35]. Although the definition of borderline resectable disease is still under debate, chemoradiotherapy rather than chemotherapy alone should be strongly considered in these patients (Table 38.3) [36–41]. In a retrospective study from the MD Anderson Cancer Center evaluating borderline resectable patients, 41% of 160 patients receiving chemoradiation underwent pancreatectomy with margin-negative resection in 94% [42]. This study provides that neoadjuvant therapy can provide a higher rate of local control as well as R0 resection and N0 disease.

38.3 Definitive Radiotherapy

Surgical resection offers the only potentially curative treatment in pancreatic cancer, and subset of patients with borderline resectable disease who do not develop progressive disease will benefit from surgery after neoadjuvant approach [43]. On the other hand, pancreatic tumors are usually considered unresectable/locally advanced if it has the following features: (1) involvement of nodes outside resection field, (2) encasement of more than half circumference of the superior mesenteric artery, (3) abutting or encasement of

Table 38.4 Randomized trials for definitive treatment in unresectable pancreatic cancer

Trial	*n*	Treatment	Median survival (month)	1-year survival (%)
Chemoradiation versus radiotherapy alone				
GITSG [45]	194	60 Gy +5-FU	10.1	40
		40 Gy + 5-FU	10.6	40
		60 Gy	5.7	10
ECOG [46]	114	59.4 Gy + 5-FU/MMC	8.4	NA
		59.4 Gy	7.1	NA
Chemoradiation versus chemotherapy alone				
GITSG [48]	43	54 Gy + 5-FU→SMF	10.5	41
		SMF	8	19
ECOG [49]	91	40 Gy + 5-FU	8.3	28
		5-FU	8.2	28
FFCD/SFRO [50]	119	60 Gy + 5-FU/ Cisplatin→gemcitabine	8.6	32
		Gemcitabine	13	53
ECOG [52]	71	50.4Gy + gemcitabine	11	50
		Gemcitabine	9.2	32

5-FU 5-fluorouracil, *MMC* mitomycin-C, *SMF* streptozotocin, mitomycin-C, 5-fluorouracil

more than half circumference of celiac axis, (4) superior mesenteric vein or portal vein occlusion of without suitable vessel for reconstruction, and (5) invasion or encasement of the aorta. These patients have poor prognosis with median survival that ranges from 8 to 12 months [44]. Treatment options in patients with locally advanced/unresectable cancer are chemotherapy alone, chemotherapy and radiation including intensity-modulated radiotherapy (IMRT), and stereotactic radiation therapy (SBRT) which can also give chemotherapy followed by radiotherapy. With conflicting results, there is little consensus as to the appropriate management of locally advanced patients (Table 38.4). In addition, the role of radiotherapy in unresectable, locoregionally advanced pancreatic cancer remains unclear. The addition of radiation may slow the local progression and offer palliation of symptoms such as pain, biliary, or bowel obstruction. On the other hand, the likelihood of micrometastatic distant disease is high, so that locally advanced cancer is quite often treated with chemotherapy, which improves quality of life and survival when compared with supported care. Also, when chemotherapy and radiotherapy are combined, long-term survival has been reported. However, several issues remain to be defined about the optimal treatment of locally advanced pancreatic cancer: (1) defining the optimal systemic regimen which administers with or without radiation, (2) determining whether radiation should be added to chemotherapy, and (3) determining when radiation and how radiation should be delivered.

38.3.1 Trials Comparing Chemoradiation to Radiotherapy Alone

Early randomized trial by GITSG demonstrated the addition of 5-FU to radiation improved overall survival. One hundred and ninety-four eligible and evaluable patients with histologically confirmed locally unresectable adenocarcinoma of the pancreas were randomized to therapy with 60 Gy radiation therapy alone, to 40 Gy radiation plus 5-FU, and to 60 Gy plus 5-FU. Combined chemoradiation was superior to radiotherapy alone with median survival of 10.4 months versus 6.3 months although higher-dose (60 Gy) radiotherapy did not improve survival [45]. The 1-year survival rate in the two combined therapy arms was 40% versus 10% in the radiotherapy alone arm. This study established a general consensus that radiotherapy should be given with chemotherapy concurrently

in patients with locally advanced pancreatic cancer. The radiotherapy alone arm was closed early as a result of an inferior survival rate, but this trial used a split course of radiotherapy with an old radiotherapy technique.

In contrast to these encouraging results for chemoradiation therapy, the ECOG E8282 study did not show a survival benefit for chemoradiation. One hundred fourteen patients were randomly assigned to receive 59.4 Gy radiation in 1.8 Gy fractions alone or in combination with 5-FU (1,000 mg/m^2) and mitomycin-C (10 mg/m^2). There were no differences either in median DFS or in OS between the combination therapy and radiation alone group. Median OS was 8.4 months in chemoradiation group compared 7.1 months in radiotherapy alone group. Higher rates of toxicity, primarily hematologic, were noted in the chemoradiation group [46]. The authors concluded that the combination of chemotherapy and radiotherapy increased toxicity without improving survival. However, several factors contributable to the lack of survival benefit were seen in this study. It required the laparotomy to prove locally advanced disease, and the administered chemotherapy showed the relative ineffectiveness. This study offered conflicting evidence as to whether chemotherapy or radiation therapy is superior to either alone for all patients, but given the superiority of gemcitabine over 5-FU, the addition of radiation may not improve outcome further in some patients with locally advanced cancers without increasing side effects. A meta-analysis that included 11 trials involving 794 patients demonstrated a survival benefit for chemoradiation compared with radiotherapy alone, but chemoradiation followed by chemotherapy did not lead to a survival benefit over chemotherapy alone [47].

38.3.2 Trials Comparing Chemoradiation to Chemotherapy Alone

Four randomized trials have compared chemoradiotherapy to chemotherapy alone. All of these trials delivered chemotherapy during radiotherapy, as well as maintenance chemotherapy following chemoradiotherapy.

In 1988, the GITSG compared the survival of patients treated combination streptozotocin, mitomycin-C, and 5-FU (SMF) chemotherapy versus chemoradiation with 5-FU. In 43 patients randomly assigned between these two arms, an improved median survival for the chemoradiation compared with chemotherapy alone was demonstrated (10 vs. 8 months, $p < 0.02$) [48].

In contrast to the GITSG trial, ECOG study comparing 40 Gy radiation plus 5-FU (600 mg/m^2) versus 5-FU (600 mg/m^2) alone showed no difference in median survival (8.3 vs. 8.2 months) [49]. Actually, the ECOG study allowed worse prognostic factors including patients with residual disease after resection or recurrent disease for enrollment. Also, ECOG study used 5-FU chemotherapy which is less effective than gemcitabine in current view and used split course of radiotherapy consisting of 20 Gy with a 2-week break. It seems inadequate to produce a substantial antitumor effect. Therefore, a definite conclusion about the benefit of adding radiation to chemotherapy cannot be drawn from these studies due to their small number of patients and outdated techniques employed.

Several subsequent randomized trials have compared chemoradiotherapy to chemotherapy alone in locally advanced pancreatic cancer. Early ECOG trial, mentioned above, and Federation Francophone de Cancerologie Digestive and Societe Francaise de Radiotherapie Oncologique (FFCD/SFRO) showed no survival benefit to chemoradiotherapy. The FFCD/SFRO trial randomized 119 patients to chemoradiation consisting 60 Gy of radiation with 5-FU and cisplatin with maintenance gemcitabine versus gemcitabine alone. In fact, accrual was terminated early when an interim analysis indicated that patients receiving radiotherapy did worse. Survival was inferior with 8.6 months in the chemoradiation arm compared with 13 months with gemcitabine alone [50]. It should be interpreted with caution because radiotherapy used in ECOG trial was suboptimal with split-course radiotherapy technique. FFCD/SFRO trial used unusually high dose of radiation (60 Gy) given concurrent with aggressive and nonstandard chemotherapy such as 5-FU and cisplatin, causing high toxicity and masking the benefit of

radiotherapy. Given that the standard treatment is single agent of 5-FU chemotherapy during 50.4 Gy according to the National Cancer Care Network (NCCN) guideline [51], these factors could have adversely affected the outcome.

The ECOG E4201 phase III trial used gemcitabine-based chemotherapy and modern radiotherapy techniques. Thirty-seven patients were treated with gemcitabine alone (1,000 mg/m^2) and 34 patients with gemcitabine (600 mg/m^2) and concurrent 50.4 Gy of radiotherapy, using an involved field approach. In summary, addition of radiation therapy to gemcitabine-based chemotherapy significantly improved OS with 11 months versus 9.2 months (p = 0.034) and a 2-year survival rate with 12% versus 4% for patients with locally advanced pancreatic cancer. Patients in chemoradiation arm had greater incidence of Grades 4 and 5 toxicities, but no statistical differences were seen in quality of life measurements [52]. Although this study was closed early because of slow accrual, the results support that there can be a role for radiotherapy in patients with locally advanced disease in combined with gemcitabine-based chemotherapy.

38.3.3 Induction Chemotherapy Followed by Concurrent Chemoradiation

Because of high incidence of micrometastatic distant disease in those patients with locally advanced pancreatic cancer, the use of induction chemotherapy was proposed to identify the patients who will progress to metastasis. In a retrospective analysis of 181 patients with locally advanced pancreatic cancer by the Groupe Cooperateur Multidisciplinaire en Oncologie (GERCOR), patients received at least three cycles of gemcitabine-based induction chemotherapy followed by either chemoradiotherapy or continued chemotherapy [53]. Fifty-three patients (29.3%) had metastatic disease after 3 months of induction chemotherapy and were not eligible for chemoradiation. Among the remaining patients who had no metastatic disease, 56% received chemotherapy combined with 55 Gy dose of radiation, whereas 44% maintained with chemotherapy. Combined chemoradiation after induction chemotherapy improved median progression-free survival (PFS) with 10.8 months versus 7.4 months (p = 0.005) and median OS times with 15 months versus 11.7 months (p = 0.0009). These results suggest that chemoradiation could significantly improve survival in patients with locally advanced disease after induction chemotherapy as well as select the 30% of patients with occult metastatic disease.

MD Anderson Cancer Center retrospectively evaluated on whether there were differences in outcome for 323 patients with unresectable locally advanced pancreatic cancer between chemoradiation therapy and induction chemotherapy prior to chemoradiation [54]. Most patients received a radiation dose of 30 Gy in ten fractions with gemcitabine or 5-FU chemotherapy concurrently. Two hundred forty-seven patients received chemoradiation as an initial treatment, whereas 76 patients received a median 2.5 months of gemcitabine-based induction chemotherapy followed by chemoradiation. The median OS and PFS were 8.5 months and 4.2 months in the chemoradiation group and 11.9 months and 6.4 months in the induction chemotherapy followed by chemoradiation group, respectively (P < 0.001). The median times to local and distant progress were improved in those patients who received induction chemotherapy. There was no significant difference in the patterns of failure between two groups, with locoregional recurrence as the initial site of failure in approximately 25% of patients and distant metastasis as the initial site of failure in approximately one third of patients. These results indicate that induction chemotherapy could select patients with locally advanced pancreatic cancer for optimal benefit from chemoradiation by excluding patients with rapid distant progression.

Several phase II trials also have shown the improved survival outcomes of induction chemotherapy followed by concurrent chemoradiation [55–58]. These results suggest that a period of

induction chemotherapy is beneficial in selecting a subgroup of patients who are likely to benefit from locoregional control with chemoradiation and translates into the most promising outcomes for these patients.

38.4 Advances in Radiotherapy

Majority of the trials published have used conventional radiotherapy with anterior-posterior techniques including larger field of radiation encompassing the pancreas or pancreatic bed and regional nodes with margin. The use of large volume of radiation fields contributes to high incidence of GI toxicity, especially when chemotherapy is administered concurrently. Currently, three-dimensional computed tomography (CT)-based treatment planning is used worldwide. Three-dimensional conformal radiotherapy (3D-CRT) allows the use of multiple custom-shaped radiation fields, with optimum coverage of the target and maximal sparing of critical normal organs. Intensity-modulated radiation therapy (IMRT), which is more advanced in the delivery of radiation, generates more conformal coverage on target and minimal dose to normal critical structures than 3D-CRT (Fig. 38.1). With IMRT, it is possible to achieve a dose escalation which can enhance local tumor control.

38.4.1 Dose Escalation with IMRT

Although systemic therapy is emphasized, local tumor control is very important. Dose distribution within each radiation filed is nonuniform on IMRT, which is designed to minimize the radiation dose to normal tissues. As a result, it is possible to deliver doses of 45–50 Gy to the larger fields while escalating the dose to the focal tumor site to 54–60 Gy, which may be needed to improve both local control and overall outcome (Fig. 38.2). The rationale for radiation dose escalation using a high radiation dose and a high daily dose is based on the feasibility of a small radiation volume by omitting prophylactic nodal irradiation and previous reports of IMRT to the upper abdomen. Murphy et al. [59] limited the planning target volume (PTV) as the gross tumor volume (GTV) plus 1 cm margin. In conjunction with full-dose gemcitabine, the use of conformal fields encompassing only the GTV helps reduce toxicity and does not result in marginal failures. In a report from retrospective analysis, 46 patients received chemoradiotherapy based on 5-FU similar to RTOG 97-04. Rates of acute GI toxicity from this study of IMRT-treated patients were compared with those from RTOG 97-04, where all patients were treated with 3D conformal techniques. IMRT is associated with a significant decrease in acute Grade 3–4 toxicities

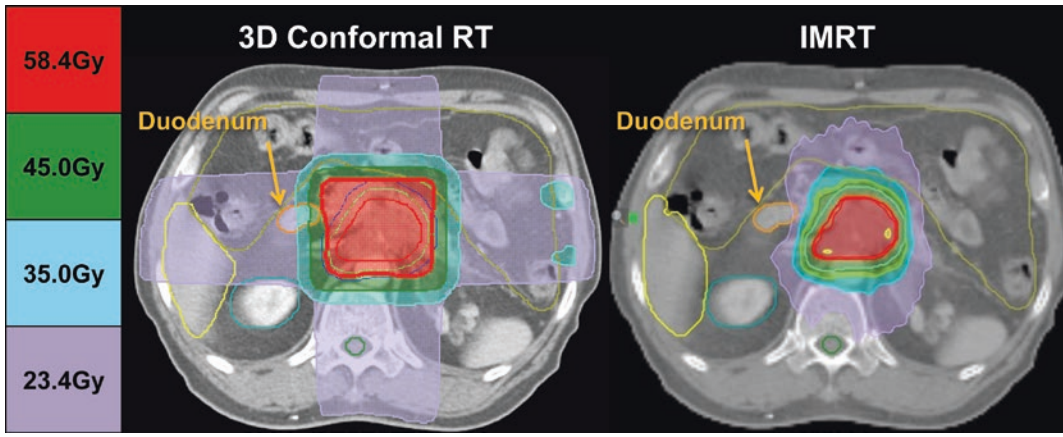

Fig. 38.1 The comparison of a radiation dose coverage. Intensity-modulated radiation therapy (IMRT) generates more conformal coverage of RT on target and maximizes the sparing normal tissue, especially the duodenum, than three-dimensional conformal radiotherapy (3D-CRT)

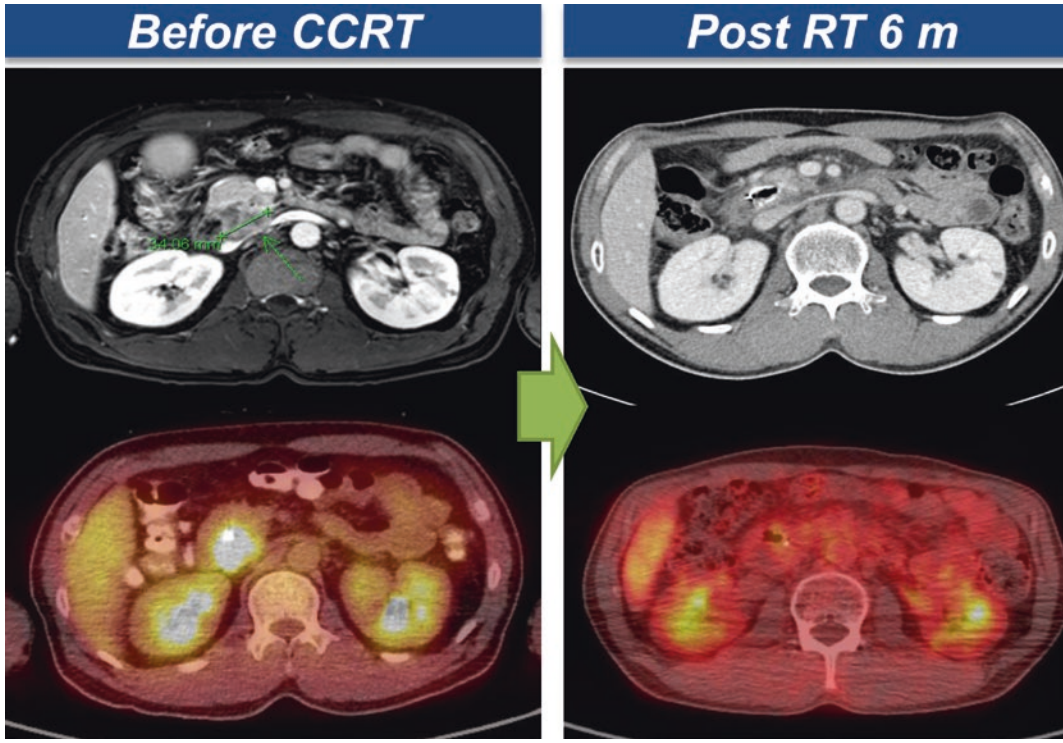

Fig. 38.2 Case illustration of a 42-year-old patient with an unresectable pancreatic cancer. About 4 cm-sized mass with direct invasion of the Lt. renal vein and 3rd portion of the duodenum showed an intense FDG uptake in the pancreatic head, consistent with malignancy. After definitive gemcitabine-based concurrent chemoradiotherpy with total 45.72 Gy (2.54 Gy/fx) radiation using IMRT, tumor response, both imaging and metabolic, was complete remission on follow-up 6 months

among patients treated with chemoradiation for pancreatic cancers. The improved tolerability of treatment cannot only improve patients' quality of life but also allow for radiation dose escalation and intensification of chemotherapy regimens to improve the cure rates [60]. A phase I/II study by Ben-Josef et al. demonstrated that high-dose radiation therapy ranged from 50 to 60 Gy in 25 fractions can be delivered safely. Median and 2-year OS are also encouraging with 14.8 months and 30%, respectively [61]. A review of the Yonsei University experience reported the outcomes of 39 patients who treated with high-dose radiotherapy using IMRT (median, 58.4 Gy; range, 50.8–59.9 Gy) combined with concurrent full-dose chemotherapy. Patients showed significant improvement in local progression-free survival with 1- and 2-year actuarial rates of 82.1% and 77.3%, respectively. The overall in-field tumor response rate was 36% a month after and 52% 3 months after radiotherapy. The conversion rate of locally advanced pancreatic cancer to resectable disease was 20% [62]. However, the small bowel especially the duodenum, which cannot be completely excluded from the radiation field given the proximity to the pancreas, remains a dose-limiting structure despite advances in radiation technique. The rate of Grade 3 or higher late GI toxicity was significant (26%), including one patient with Grade 5 GI bleeding [62].

38.4.2 SBRT as a Precise Targeting Technology

Another radiation technique for precise targeting and dose escalation in pancreatic cancer is stereotactic body radiation therapy (SBRT), which delivers one to five of high dose per fraction to small field size only including gross tumor with margin. SBRT with dose escalation may offer an improved survival benefit if tolerated. Several

institutions have reported their experience using SBRT for locally advanced pancreatic cancer [63–68] but failed so far to show a meaningful survival benefit; even some series have shown significant toxicity. Stanford University reported outcomes for 77 patients treated using single fraction of 25 Gy with various gemcitabine-based chemotherapy regimens [67]. Local control was excellent with the local progression-free rates at 6 months and 12 months of 91% and 84%, respectively. Seven patients (9%) experienced Grade 3 or higher late toxicity. Authors concluded that SBRT for pancreatic cancer was effective for local control with associated risk of toxicity. Similarly, a single institution reported results of series of 36 patients treated with SBRT to total dose 24–36 Gy in three fractions followed by gemcitabine for 6 months. Radiation dose was dependent to the tumor location in relation to the stomach and duodenum. Treatment outcome was promising with the local control rate of 78%, the median overall survival time of 14.3 months [68]. However, nine Grade 2 (25%) and five Grade 3 (14%) toxicities occurred from SBRT. To determine the role of SBRT as a boost, Stanford University enrolled 19 patients onto the prospective study in which protocol consisted of 45 Gy IMRT with concurrent 5-FU followed by a 25 Gy single fraction SBRT boost to the primary tumor. It showed an excellent rate of local control with 94% without improving overall survival due to rapid progression of systemic metastases. There was 12.5% Grade 3 toxicity [64]. Overall, results of these studies indicate that further efforts to reduce complications are warranted, and prospective trials are needed to determine the optimal dose fractionation.

38.4.3 Prediction of Clinical Outcomes

CA 19-9 level has been proven to be useful in the assessment of prognosis and monitoring treatment outcome, and several studies showed that decrease in serum CA 19-9 levels has correlated with radiologic response [69, 70]. Recently, ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) is getting attention for prediction the response to radiation as well as detecting radiographically occult distant metastases [71, 72]. A report from single institution analyzed 388 patients who were planned to undergo chemoradiation therapy. It showed that patients with a baseline standardized uptake value (SUV) <3.5 and/or SUV decline ≥60% had significantly better OS and PFS than those having none [73]. Results from these studies provide the role of metabolic response to radiation as a predictive markers; however, further trials are needed to evaluate the benefits of incorporating FDG-PET in RT planning.

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Endoscopic Intervention

39

Sung-Hoon Moon and Myung-Hwan Kim

39.1 Introduction

Approximately eight cases of pancreatic cancer are newly diagnosed per 100,000 person-years around the globe [1, 2]. Only 10–20% of these patients with pancreatic cancer are candidates for curative surgery, because most are asymptomatic until the disease develops to an advanced stage [3, 4]. Moreover, even after potentially curative surgery, most patients will eventually relapse due to the biologically aggressive nature of the disease, so the 5-year survival of completely resected patients is less than 25% [3]. Patients with locally advanced pancreatic cancer have a median survival time of 8–12 months, while patients with metastatic pancreatic cancer have a median survival time of 3–6 months. Aggressive chemotherapy/radiotherapy can prolong the life of these patients by only several weeks or months [5]. Accordingly, the literature states that the incidence of pancreatic cancer nearly equals its mortality [3, 4].

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Table 39.1 Endoscopic intervention for pancreatic cancer

Biliary intervention
Preoperative biliary drainage
Palliation of obstructive jaundice
Duodenal intervention
Palliation of duodenal and gastric outlet obstruction
Palliation of pain
Pancreatic duct stent placement
Endoscopic ultrasound-guided celiac plexus/ganglia neurolysis

Treatment planning for patients with advanced pancreatic cancer should include both tumor control and symptom management. However, any attempt to treat this cancer aggressively usually creates a frustrating and difficult situation for clinicians, as their patients with advanced pancreatic cancer can suffer from pain, biliary obstruction, and intestinal obstruction. Adequate palliation of the later manifestations of pancreatic cancer therefore becomes a major concern for clinicians. Table 39.1 summarizes the role of endoscopic intervention in patients with pancreatic cancer.

39.2 Biliary Intervention

Endoscopic biliary intervention in pancreatic cancer includes palliation of biliary obstructions for locally advanced or metastatic disease and preoperative biliary drainage for potentially resectable disease.

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39.2.1 Palliation of Biliary Obstruction

Malignant biliary obstruction by pancreatic cancer can present with jaundice and requires palliative drainage if it is unresectable. The mechanisms of biliary obstruction by pancreatic tumor are extrinsic compression, direct tumor infiltration, adjacent inflammation, desmoplastic reaction, or a combination of these factors [6]. Biliary obstruction can develop in as many as 80% during the course of pancreatic cancer if not intervened [7, 8]. Restoration of biliary flow, together with relief of jaundice and pruritus, is the primary goal in the palliation of malignant biliary obstruction, and it also prevents biliary obstruction-related complications such as cholangitis, coagulopathy, malabsorption, and hepatocellular dysfunction [9, 10]. Drainage can be approached in three ways, including surgical bypass (e.g., hepaticojejunostomy or choledochojejunostomy), percutaneous transhepatic biliary drainage, and endoscopic stenting.

A meta-analysis of endoscopic and surgical bypass outcomes in malignant distal biliary obstruction demonstrated the same technical and therapeutic success for endoscopic stenting as for surgical drainage procedures, with similar quality of life and overall survival, but with reduced risk of complications, albeit with an increased risk of recurrent biliary obstruction for endoscopic stenting [11–13]. More treatment sessions are needed after endoscopic stenting than after surgical bypass, but endoscopic stenting still continues to be the most cost-effective approach [14]. Percutaneous transhepatic biliary drainage is associated with considerable morbidity, patient discomfort, and the need for repeated intervention [12].

Endoscopic biliary stenting via endoscopic retrograde cholangiopancreatography (ERCP) is presently the standard of care for the palliation of distal malignant biliary obstruction caused by pancreatic cancer (Fig. 39.1) [11, 12, 15]. It provides effective palliation and may offer lower morbidity and mortality, shorter hospital stay, and diminished overall cost when compared with surgical or radiological approaches [15].

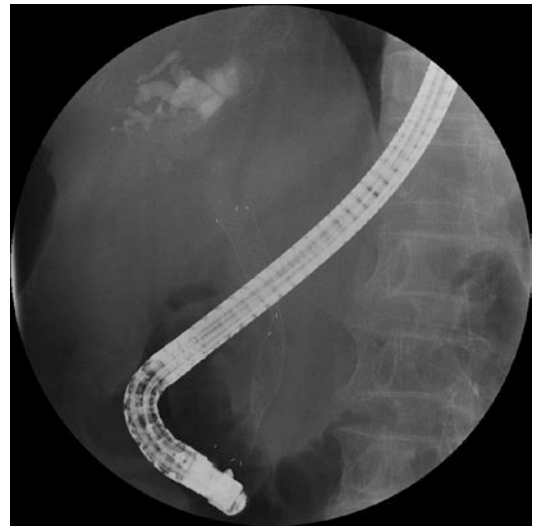

Fig. 39.1 Fluoroscopic image of endoscopically inserted biliary metal stent for a patient with pancreatic head cancer

Percutaneous transhepatic biliary drainage is most often used when endoscopic biliary stenting has failed. Endoscopic ultrasound (EUS)-guided biliary drainage can be an effective alternative for percutaneous transhepatic biliary drainage after failed ERCP [16]. Surgical bypass is usually reserved for unsuccessful or unfeasible endoscopic/percutaneous drainage [11].

Various types of stent can be used for endoscopic biliary stenting via ERCP. The biliary stents used for endoscopic palliation include plastic stents and self-expandable metal stents (SEMSs). The SEMSs are classified into uncovered SEMSs and covered SEMSs; the latter are further subclassified into partially covered SEMSs and fully covered SEMSs.

A group of studies comparing between the use of plastic and metal stents in distal malignant biliary obstruction concluded that the patency periods of metal stents are approximately twice those of plastic stents, with a time to first obstruction of 6–10 months vs 3–5 months, respectively [12, 15, 17–19]. SEMS placement is also associated with a lower therapeutic failure, less need for reintervention, lower cholangitis incidence, and decreased hospital readmission but shows no difference in patient survival [20, 21]. Initial insertion of a

SEMS (preferably 10 mm of diameter) is preferable as it is more cost-effective if patient life expectancy is longer than 4 months [20]. Initial insertion of a plastic stent (preferably 10 F) is recommended if patient life expectancy is shorter than 4 months or the diagnosis of malignancy is not established.

39.2.2 Preoperative Biliary Drainage

Preoperative biliary drainage has been used for patients with obstructive jaundice by pancreatic head cancer if it is resectable. The theoretical basis of this practice is that surgery in patients with jaundice may increase the risk of postoperative complications [22]. However, as a means of reducing postoperative morbidity and mortality, preoperative biliary drainage has shown conflicting efficacy [22–25]. A recent well-designed randomized trial tested 202 patients with pancreatic head cancer, who were assigned to one of two treatments: (1) surgery alone within 1 week after diagnosis or (2) preoperative biliary drainage with a plastic stent for 4–6 weeks, followed by surgery [26]. The primary outcome was the occurrence of serious complications within 120 days after randomization; these occurred in 39% of patients who underwent early surgery alone and in 74% of patients who underwent preoperative biliary drainage followed by surgery. The rate of occlusion or need for exchange (30%) within a short period in this study was far in excess of routine practice, even then risk of complications associated with routine preoperative biliary decompression in patients with malignant obstructive jaundice and potentially curable cancer of the pancreatic head appeared to outweigh the theoretical benefits of jaundice resolution [27]. Selected patients with suppurative cholangitis or deep obstructive jaundice, or those who awaiting preoperative adjuvant chemotherapy/radiotherapy, may benefit from short-term preoperative biliary drainage. SEMSs are preferred over plastic stents when preoperative biliary drainage is indicated because of their longer patency and better outcome [27, 28].

39.3 Duodenal Intervention

Pancreatic head cancer can invade the duodenum, leading to duodenal and gastric outlet obstruction. This obstruction usually causes nausea and vomiting that becomes intractable, and oral intake eventually becomes markedly reduced or impossible in these patients [8]. Duodenal and gastric outlet obstruction occurs during the course of disease in 10–25% of patients with unresectable pancreatic cancer [8, 29]. Symptoms related to duodenal and gastric outlet obstruction also occur in 10–25% of patients who undergo surgical biliary bypass without gastrojejunostomy during the initial procedure [8]. As a consequence, many surgeons have routinely added gastrojejunostomy at the time of palliative surgical biliary bypass or during exploration of unresectable disease. However, routine gastrojejunostomy is largely being supplanted by an endoscopic placement of duodenal stent.

Duodenal stents used for endoscopic palliation are mostly SEMSs (covered or uncovered) that are 18–22 mm in diameter when fully expanded. Endoscopic insertion of duodenal stents has demonstrated adequate safety and high technical success (approximately 95%), and substantially improves the time to oral intake, which can be as rapid as within 24 h of the procedure [8, 30]. Endoscopic duodenal stenting also resulted in an earlier discharge from hospital and possibly improved survival, when compared with surgical gastrojejunostomy [29].

39.3.1 Palliation of Simultaneous Biliary and Duodenal Obstruction

Surgical diversion of the bile duct and stomach as a one-stage operation has traditionally been performed in cases with dual obstructions of the duodenum and bile duct. Endoscopic palliation of biliary and duodenal obstruction can also be achieved, although this can sometimes be technically difficult [31]. Currently, three types of procedures are recommended in this situation:

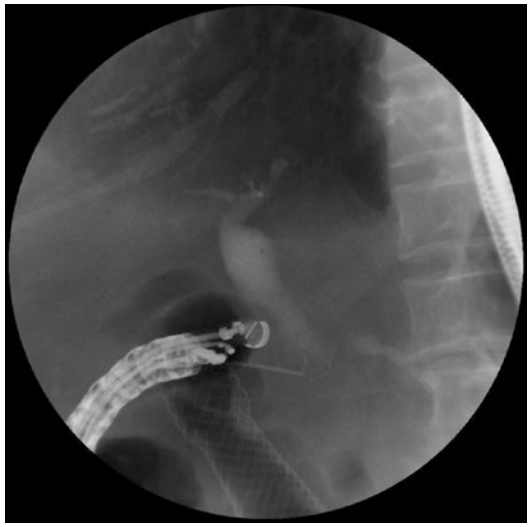

Fig. 39.2 Endoscopic ultrasound-guided cholangiogram was performed after the placement of duodenal stent in a pancreatic cancer patient with duodenal and biliary obstruction. After obtaining cholangiogram, endoscopic choledochoduodenostomy was performed

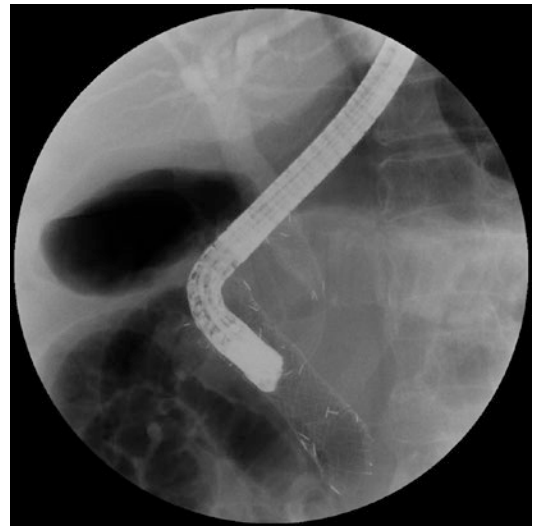

Fig. 39.3 In a pancreatic cancer with duodenal and biliary obstruction, combined endoscopic stenting with duodenal and biliary stents in a stent-in-stent method was performed

(1) endoscopic duodenal stenting and EUS-guided biliary drainage (Fig. 39.2), (2) combined endoscopic stenting with duodenal and biliary stents, and (3) endoscopic duodenal stenting and percutaneous biliary drainage. The choice of technique depends on the level of duodenal obstruction, as well as on the local expertise, facilities, and clinical experience.

The location of the duodenal obstruction in relation to the major duodenal papilla may be the major determinant of the success of endoscopic palliation, since a duodenal obstruction can limit access to the biliary orifice [31]. Three duodenal stenosis types are recognized in relation to the major duodenal papilla: (1) at the level of the duodenum proximal to and without involvement of the papilla, (2) affecting the second part of the duodenum with involvement of the major papilla, and (3) involving the third part of the duodenum, distal to and without involvement of the major papilla. Endoscopic dual stenting using a stent-in-stent method can be conducted using a dedicated duodenal stent with a central portion designed to facilitate passage of a biliary stent through the mesh of the duodenal stent (Fig. 39.3) [32]. Nevertheless, the overall survival from the time of combined biliary and duodenal stent placement is relatively short due to disease progression [31, 32].

39.4 Palliation of Pain

The pain associated with pancreatic cancer can arise due to multiple factors, including perineural encasement by the tumor, invasion of peripancreatic tissues/organs, and obstruction of the main pancreatic duct [33]. Pain due to neoplastic infiltration of the nerve endings in pancreatic and peripancreatic tissues is characterized by chronic, continuous pain of a dull nature, unrelated to meals, located in the upper abdominal quadrants and often radiates to the back [33]. This type of pain is present in the vast majority of advanced pancreatic cancer patients. Pain of obstructive quality may occur in 15% of patients with inoperable advanced pancreatic cancer. This type of pain is characterized by postprandial occurrence, located at the epigastrium and left hypochondrium and radiates to the left back, starting a few minutes after the end of the meal and lasting for 1–2 h; it is associated with a dilated pancreatic duct upstream from the malignant stricture [33, 34].

39.4.1 Pancreatic Duct Intervention

Pain of obstructive quality may be relieved by pancreatic stent placement across the obstructing tumor [34]. The technique used for endoscopic pancreatic stent placement does not differ from that used for the biliary drainage [33]. Large-diameter plastic stents (7–10 F) are preferred for palliation. Steatorrhea associated with ductal obstruction can also be treated by pancreatic stent placement instead of pancreatic enzyme replacement.

39.4.2 EUS-Guided Celiac Plexus/ Ganglia Neurolysis

Celiac plexus/ganglia neurolysis has been established as an optional method for providing pain relief and reducing opioid use, because the use of opioid agents is commonly associated with dry mouth, constipation, nausea, vomiting, drowsiness, and delirium [35, 36]. The celiac plexus is located caudal to the diaphragm, surrounds the origin of the celiac trunk, and comprises a dense network of ganglia and interconnecting fibers [36]. The celiac ganglia are predominantly oval or almond shaped with irregular margins, and they vary in number [1–5], diameter (0.5–4.5 cm), and location [36, 37]. The celiac plexus transmits pain sensations from most of intra-abdominal viscera, except the left colon, rectum, and pelvic organs [36, 38]. Advanced pancreatic cancer often infiltrates the retroperitoneal nerves of the upper abdomen, so celiac plexus neurolysis should be considered for pain relief. The celiac plexus can be approached in three ways, for surgical, percutaneous (under fluoroscopic or CT guidance), or EUS-guided neurolysis.

The efficacy of celiac plexus neurolysis is difficult to analyze, due to the mostly retrospective and uncontrolled nature of the studies. A meta-analysis concluded that percutaneous celiac plexus neurolysis leads to successful relief of pancreatic cancer pain [39], whereas another meta-analysis found the data insufficient to judge the efficacy, long-term morbidity, or cost-effectiveness [40]. Eisenberg et al. reviewed 24 studies on percutaneous celiac plexus neurolysis and concluded that (1) celiac plexus neurolysis has a long-lasting benefit for 70–90% of patients with pancreatic and other intra-abdominal cancers; (2) adverse effects are common, but they are transient and mild; and (3) severe adverse effects are uncommon [41]. The limitations of the percutaneous-guided neurolysis are the lack of direct visualization of the celiac trunk, with only approximate accuracy of needle placement, and the risk of vascular puncture and neurologic damage with a posterior approach [42]. A surgical approach termed the intraoperative chemical splanchnicectomy with alcohol also provides pain relief in patients with unresectable pancreatic cancer [43]. Laparoscopic, thoracoscopic, and open surgical approaches can be used, although a surgical approach is rarely undertaken solely for this purpose at present [42].

EUS-guided celiac neurolysis is largely supplanting percutaneous celiac plexus neurolysis because of several potential advantages [37, 44]. First, the location of the celiac plexus, and even the celiac ganglia per se, can be more easily visualized by a transgastric anterior approach of endoscopic ultrasound (Fig. 39.4). Second, EUS can provide a continuous real-time visualization of the target area, and the availability of Doppler

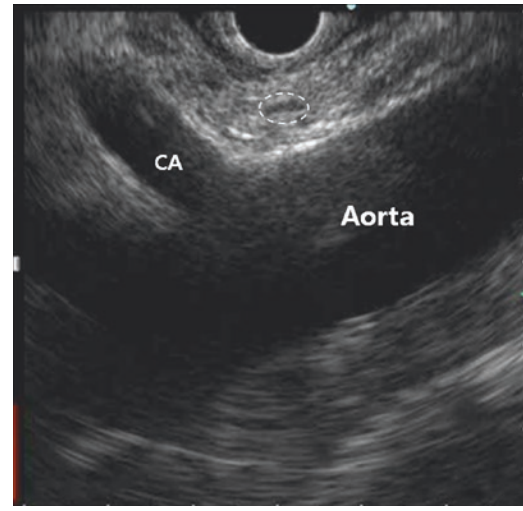

Fig. 39.4 Endosonographic view of the location of the celiac plexus. Celiac ganglia (*dotted circle*) is suspected between celiac artery and aorta. *CA* celiac artery

allows assessment of the vasculature, which facilitates accurate needle placement, thereby potentially improving pain relief and reducing complications (such as paraplegia) [36]. The NCCN guidelines, version 2.2015, for pancreatic adenocarcinoma also recommend EUS-guided celiac plexus neurolysis for severe tumor-associated abdominal pain. EUS-guided celiac neurolysis techniques include celiac plexus neurolysis (unilateral or bilateral), celiac ganglia neurolysis, and broad plexus neurolysis [36].

Several randomized controlled trials have demonstrated that celiac plexus neurolysis significantly improves pain relief in patients with advanced pancreatic cancer [43, 45, 46]. Several studies also reported that EUS-guided celiac neurolysis may improve the quality of life, such as functional status, work capability, sleep, and enjoyment of leisure activities [47, 48]. A recent meta-analysis suggested the duration of pain relief provided by celiac plexus neurolysis, as it significantly decreased the patients' pain scores at 4 weeks, but the significance was not maintained at 8 weeks. Celiac plexus neurolysis has currently been used as a salvage therapy for opioid-resistant pancreatic cancer pain. However, one study suggested that "early" EUS-guided celiac plexus neurolysis reduced pain and could moderate morphine consumption in patients with painful, inoperable pancreatic cancer [49]. A study that evaluated the benefit of repeated EUS-guided celiac plexus neurolysis was disappointing, because the rate of successful pain relief was much lower than for the first procedure, and disease progression was determined as a potential factor that limited the response [50].

Conclusion

Endoscopic intervention is widely used for the management of pancreatic cancer, particularly for palliation. Patients with unresectable pancreatic cancer frequently require palliation for biliary obstruction, duodenal obstruction, pancreatic duct obstruction, and cancer-associated pain. The expected survival is mostly short in these patients. Endoscopic intervention is now accepted as a primary option for palliation, with the advent and development of various endoscopic procedures. However, percutaneous intervention or surgery remains an effective method for palliation because endoscopic palliation in pancreatic cancer is imperfect and sometimes not feasible.

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Personalized Peptide Vaccine for Advanced Pancreatic Cancer

40

Shigeru Yutani and Kyogo Itoh

40.1 Introduction

Pancreatic cancer, the fourth largest cause of cancer death in the world, is one of the most aggressive cancers [1, 2]. Although there have been advances in the therapeutic modalities for pancreatic cancer, including systemic chemotherapies, the prognosis of aPC patients still remains dismal [1, 2]. Therefore, development of new therapeutic approaches, including immunotherapy, is needed.

New types of peptide-based cancer vaccine are currently undergoing clinical trial, although none of them have been approved at the present time (Fig. 40.1) [3]. We have developed a novel immunotherapeutic approach, the personalized peptide vaccination (PPV), in which HLA-matched peptides are selected and administered based on the pre-existing host immunity before vaccination [3–5]. Randomized clinical trials of PPV for chemotherapy-naïve prostatic cancer [6] or chemotherapy-resistant bladder cancer [7] showed clear clinical benefits of this novel vaccine. In this review, we consider how to provide clinical benefits for advanced pancreatic cancer patients utilizing PPV, with a primary focus on combination treatments using PPV plus chemotherapy or traditional Japanese Kampo medicine.

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40.2 No Impact of Recent Advances of Cancer Immunotherapy for aPC

Remarkable advances have been made in the field of cancer immunotherapy in the past 5 years. Immune checkpoint blockers (ICB) (e.g., anti-CTLA-4, anti-PD-1, and anti-PDL-1 antibodies) can achieve durable clinical responses in at least one-fifth of patients with several types of advanced cancer [8–10]. However, these ICB have exhibited very limited clinical benefit for the other cancers, including pancreatic cancer, which displayed no or few tumor-infiltrating lymphocytes [11–13]. Cancer vaccines tested in the past two decades also failed to show clinical benefits for pancreatic cancers [14–16]. In addition to the dearth of tumor-infiltrating lymphocytes, the large heterogeneity of tumor-associated antigens and the diversity in both HLA and T-cell subsets may hamper the successful development of a cancer vaccine for aPC [3–5].

40.3 Rationale for Personalized Selections of Vaccine Peptides

Cancer patients possess antitumor immunity, which may depend strongly on both the tumor cell characteristics and the immunological status of the host [17–20]. The antitumor immunity differs widely among individuals, since the tumor cell characteristics and the host immune cell repertoires are quite diverse and heterogeneous among patients, even among

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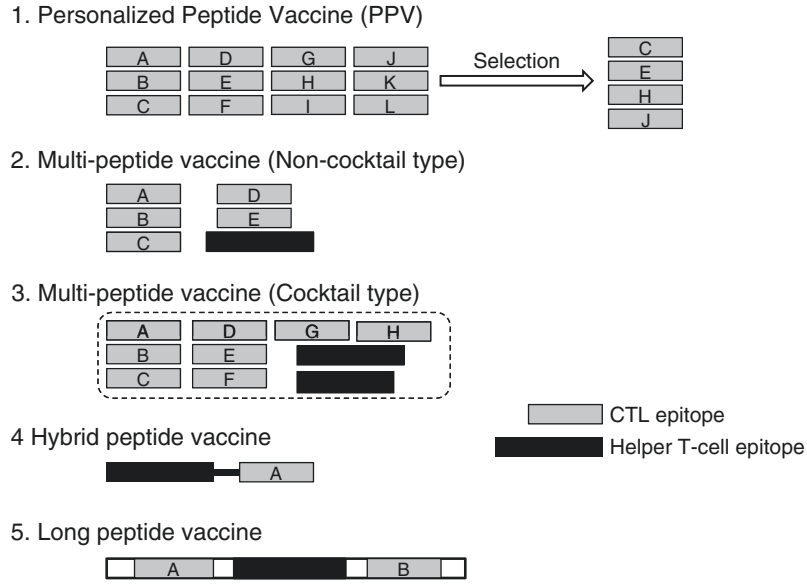

Fig. 40.1 New types of peptide-based vaccines: Examples of new types of peptide-based vaccines are shown. *Gray* and *black boxes* indicate CTL and helper T-cell epitopes, respectively

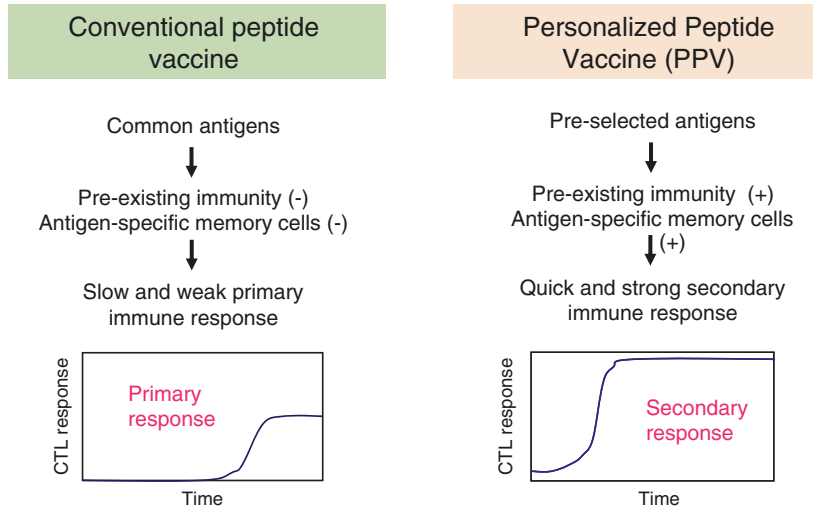

Fig. 40.2 Rationale of personalized peptide vaccine: In conventional peptide vaccines without measuring pre-existing immunity, patients without immunological memory to vaccine antigens would be expected to take more time to develop effective antitumor immune responses, since several rounds of repeated vaccinations might be required to prime antigen-specific naïve T cells to functional effector cells. In personalized peptide vaccines based on pre-existing immunity, patients with antigen-specific immunological memory are expected to show quick and strong secondary immune responses to the selected peptides (This figure is reproduced from reference Sasada et al. [3])

those with identical HLA types and the same pathological types of cancer. Considering the complexity and diversity of the host immune cell repertoires, it is likely that vaccine antigens that are selected and administered without considering the host immunological status would not efficiently induce beneficial antitumor immune responses [20]. To evaluate the host immune cell repertoires, we examined patients' pre-existing immunity to a panel of vaccine candidates before vaccination and selected appropriate vaccine antigens for which the individual patients exhibited immunological memory [3–5]. Vaccine antigens to which patients already possess antigen-specific immunological memory are expected to elicit quick and strong secondary immune responses after vaccination (Fig. 40.2) [3–5].

In light of this, it would be quite reasonable to select vaccine antigens on the basis of the pre-existing immune cell repertoires in each patient. These facts suggest that our new concept of "personalized" cancer vaccine formulation may confer several advantages, including the possibility of bypassing both immunological diversity and tumor heterogeneity.

40.4 PPV Procedures

For PPV, a maximum of four peptides are selected based on the results of HLA typing and the pre-existing immune responses specific to each of the 31 HLA class I-restricted cytotoxic T-lymphocyte (CTL) epitope peptides (9-mer or 10-mer short peptides): 12 peptides for HLA-A2, 14 peptides for HLA-A24, 9 peptides for the HLA-A3 supertypes (A3, A11, A31, or A33), and 4 peptides for HLA-A26 (Table 40.1). These peptides were identified mainly through the cDNA expression cloning method with tumor-infiltrating T-lymphocyte lines [3–5, 21–24]. The safety and potential immunological effects of these vaccine candidates have been demonstrated in clinical studies [3–5, 25, 26]. It should be noted that we currently employ these 31 CTL epitopes, which has also been shown to induce antigen-specific

Table 40.1 Peptide candidates for personalized peptide vaccination

Symbol for peptide	HLA type	Origin protein	Position of peptide	Amino acid sequence
CypB-129	A2,A3sup	Cyclophilin B	129–138	KLKHYGPGWV
Lck-246	A2	p56 lck	246–254	KLVERLGAA
Lck-422	A2,A3sup	p56 lck	422–430	DVWSFGILL
MAP-432	A2,A26	ppMAPkkk	432–440	DLLSHAFFA
WHSC2-103	A2,A3sup,A26	WHSC2	103–111	ASLDSDPWV
HNRPL-501	A2,A26	HNRPL	501–510	NVLHFFNAPL
UBE-43	A2	UBE2V	43–51	RLQEWCSVI
UBE-85	A2	UBE2V	85–93	LIADFLSGL
WHSC2-141	A2	WHSC2	141–149	ILGELREKV
HNRPL-140	A2	HNRPL	140–148	ALVEFEDVL
SART3-302	A2	SART3	302–310	LLQAEAPRL
SART3-309	A2	SART3	309–317	RLAEYQAYI
SART2-93	A24	SART2	93–101	DYSARWNEI
SART3-109	A24,A3sup,A26	SART3	109–118	VYDYNCHVDL
Lck-208	A24	p56 lck	208–216	HYTNASDGL
PAP-213	A24	PAP	213–221	LYCESVHNF
PSA-248	A24	PSA	248–257	HYRKWIKDTI
EGFR-800	A24	EGFR	800–809	DYVREHKDNI
MRP3-503	A24	MRP3	503–511	LYAWEPSFL
MRP3-1293	A24	MRP3	1293–1302	NYSVRYRPGL
SART2-161	A24	SART2	161–169	AYDFLYNYL
Lck-486	A24	p56 lck	486–494	TFDYLRSVL
Lck-488	A24	p56 lck	488–497	DYLRSVLEDF
PSMA-624	A24	PSMA	624–632	TYSVSFDSL
EZH2-735	A24	EZH2	735–743	KYVGIEREM
PTHrP-102	A24	PTHrP	102–111	RYLTQETNKV
SART3-511	A3sup	SART3	511–519	WLEYYNLER
SART3-734	A3sup	SART3	734–742	QIRPIFSNR
Lck-90	A3sup	p56 lck	90–99	ILEQSGEWWK
Lck-449	A3sup	p56 lck	449–458	VIQNLERGYR
PAP-248	A3sup	PAP	248–257	GIHKQKEKSR

A3sup HLA-A3 supertype (A3, A11, A31, and A33), *HLA* human leukocyte antigen
The safety and immunological effects of these 31 peptides had been confirmed in previous clinical trials, and all peptides were prepared under conditions of Good Manufacturing Practice using a multiple peptide system (San Diego, CA)

B-cell immune responses, as vaccine antigen candidates for PPV, since it has been suggested that a CTL peptide with the ability to induce antigen-specific B-cell responses could provide more effective immune responses than a CTL peptide without this ability [27, 28].

For the selection of peptides suitable for each patient, in the earlier stage of translational studies of PPV, pre-existing immunity was defined by the frequencies of CTL precursors in pre-vaccination peripheral blood mononuclear cells (PBMCs) [29–33]. However, we are currently evaluating the pre-existing immunity to vaccine candidates by measuring peptide-specific IgG titers in pre-vaccination plasma by the multiplex bead-based Luminex assay rather than CTL precursor frequencies, since the performance characteristics, such as the sensitivity and reproducibility, of the current T-cell assays are sometimes unsatisfactory for detecting low frequencies of antigen-specific CTLs [34, 35].

For PPV, to prevent competition among peptides at the vaccination sites, a maximum of four immunogenic peptides selected from the 31 different vaccine candidates are individually mixed with incomplete Freund's adjuvant (Montanide ISA51; Seppic, Paris, France) and subcutaneously injected at different sites, rather than at a single site as a mixture. Regarding the vaccination schedule, the selected peptides are administered weekly or biweekly for at least the first cycle of six to eight vaccinations [3–5].

40.5 Phase I Study of PPV Monotherapy for aPC Patients

We conducted a phase I trial of PPV in 11 aPC patients with either the HLA-A2$^+$ or HLA-A24$^+$ phenotype [36]. This study was well tolerated with no treatment-related severe adverse events (SAE) except for one grade 3 injection site reaction. Peptide-specific CTL responses or IgG responses were augmented in four of eight or four of ten patients tested. Median progression-free survival (PFS) and median overall survival (MST) were 3.2 and 7.9 months. Notably, two patients survived for more than 2 years. These results indicated that PPV was safe and had the potential to induce peptide-specific immune responses in about half of the aPC patients.

40.6 Phase I Study of PPV Combined with Gemcitabine for aPC Patients

We then conducted a phase I trial of PPV and gemcitabine (GEM) for 13 aPC patients with HLA-A2$^+$ or HLA-A24$^+$ phenotypes, who were treated by PPV at three different doses (1, 2, or 3 mg/peptide) [15]. Nine of 13 patients were previously treated with chemotherapy. This combination therapy was well tolerated with no treatment-related SAE, and 11 of 13 patients (85%) showed reduced tumor sizes and/or reduced levels of tumor markers. Peptide-specific CTL responses were augmented at each dose level in the vast majority (70%) of patients, and the increment of peptide-specific IgG antibodies was dependent on the peptide dose. PFS was 4.1 months and MST was 7.6 months (range, 3.1–13 months). These findings suggest that GEM did not inhibit the immune responses induced by PPV. PPV combined with GEM might have the potential to prolong the overall survival of aPC patients.

40.7 Phase II Study of PPV Combined with GEM as a First-Line Therapy for Non-resectable aPC Patients

Based on the results of phase I studies, we conducted a phase II trial of PPV in combination with GEM to evaluate the safety, clinical efficacy, and antigen-specific immune responses as the first-line therapy for 21 non-resectable aPC patients with HLA-A2$^+$ or HLA-A24$^+$ phenotype [16]. This combination therapy was also well tolerated, and the best clinical responses were seven partial responses, nine stable diseases, and five progressive diseases. The MST of all 21 patients

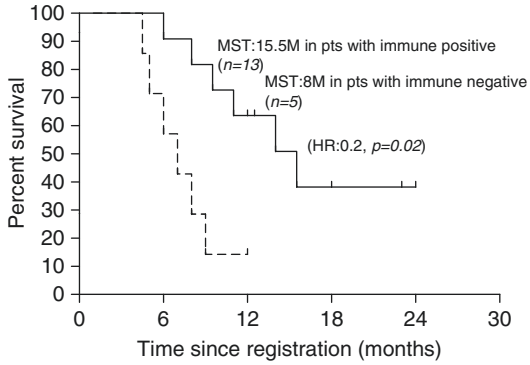

Fig. 40.3 Overall survival of aPC patients under PPV and GEM as a first-line therapy: The MST of all 21 patients was 9 months. The MSTs of the patients showing positive (n = 13) or negative (n = 5) immune responses were 15.5 and 8 months, respectively (HR, 0.2; 95% CI, 0.06–0.73; p = 0.024) as reported previously [16] (This figure is reproduced from reference Sasada et al. [3])

was 9 months with a 1-year survival rate of 38%. Importantly, the MST was 15 months in patients who showed both CTL and IgG responses to vaccine peptides (Fig. 40.3).

40.8 A Phase II Study of PPV for Chemotherapy-Resistant aPC Patients

We then conducted a phase II trial of PPV for 41 chemotherapy-resistant aPC patients [37].

No vaccine-related SAE was observed. Prior to enrollment, the patients had failed to respond to one (n = 11), two (n = 24), three (n = 5), or four (n = 1) regimen(s) of chemotherapies. The median duration of chemotherapy prior to PPV was 8 months with a range from 1 to 36 months. To address whether the combined chemotherapy facilitated clinical benefits, PPV was combined with GEM (n = 11), S-1 (n = 6), GEM and S-1 (n = 8), or other combinations of chemotherapeutic agents including CDDP-based regimens (n = 8) in a personalized manner. PPV alone was administered to eight patients, either because chemotherapy could not be tolerated (n = 4) or due to patient refusal (n = 4). IgG responses specific to at least one of the vaccine peptides were augmented in 14 of 36 patients (39%) and in 18 of 19 patients (95%) tested after the 5th and 11th vaccination, respectively. The MST from the first vaccination was 7.9 months with a 1-year survival rate of 26.8%. Among them, MST in patients treated with PPV in combination with (n = 33) or without (n = 8) chemotherapies was 9.6 or 3.1 months, respectively (P = 0.0013). When calculated from the initiation of the first-line chemotherapy, MST of all 41 cases was 19.0 months [95% confidence interval (CI), 15.0–25.0 months]. Higher serum amyloid A (SAA) and C-reactive protein (CRP) levels in pre-vaccination plasma were unfavorable factors for OS. Collectively, PPV could have the potential to prolong OS of chemotherapy-resistant aPC patients when used together with different chemotherapy regimens.

40.9 A Randomized Phase II Study of PPV Combined with Kampo Medicine

We recently conducted an open-labeled randomized clinical study of PPV with Juzen-taiho-to (JTT) to investigate whether JTT could increase PPV-induced immune responses [38]. JTT is a well-known Kampo medicine that has been reported to modulate immune responses and enhance antitumor immunity in animal models. Fifty-seven patients refractory to all the conventional treatment modalities were randomly assigned to receive PPV with (n = 28) or without (n = 29) JTT. The results showed that JTT did not significantly affect either cellular or humoral immune responses specific to the vaccine antigens. JTT also did not significantly prolong overall survival. Nevertheless, JTT prevented deterioration of the patients' conditions, such as anemia, lymphopenia, hypoalbuminemia, plasma IL-6 elevation, and reduction of performance status. These results suggest that the combination of PPV plus Kampo medicine has potential to prevent deterioration of the conditions of aPC patients refractory to the conventional treatment modality. Kampo regimens are generally selected in a personalized manner depending on the symptoms and laboratory data of each patient, in order

to control various symptoms and normalize abnormal laboratory data. Therefore, we are currently conducting a phase II study of PPV combined with Kampo medicine with a focus on the personalized prescription of Kampo medicine.

Conclusion

There are few tumor-infiltrating lymphocytes in pancreatic adenocarcinoma tissues, which is one of the hurdles in cancer immunotherapy including ICB [11–13]. Such tumor microenvironment of pancreatic cancers makes it possible to exclude T-cell infiltration as an immune privilege site, which is usually observed in normal endocrine organs or testis. Notably, we previously reported that PPV rapidly induced the infiltration of $CD45RO^{+}$ memory/activated lymphocytes into cancer tissues [39, 40]. We also reported in this review article that PPV was safe and induced both CTL and IgG boosting for the majority (>60%) of aPC patients, although their levels were modest. PPV combined with chemotherapy for chemotherapy-naïve aPC patients could provide longer overall survival if the patients showed increased CTL and IgG responses. Furthermore, the MST of chemotherapy-resistant aPC patients was 7.5 months or 19 month when calculated from the initiation of the first-line chemotherapy. Kampo medicine has potential to prevent the deterioration of aPC patients refractory to conventional treatment modalities. Predictive unfavorable biomarkers were higher serum amyloid A and C-reactive protein levels in pre-vaccination plasma, while favorable biomarkers were peptide-specific immune responses after PPV.

Collectively, the above results indicate that PPV has potential as a clinically effective cancer vaccine for aPC patients. Further development of a new regimen of PPV capable of inducing more potent CTL boosting may be required to provide clinical benefits for the vast majority of aPC patients. One such approach could be to develop combination therapies using PPV, chemotherapy, and Kampo medicine in a personalized manner.

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41 Emerging New Treatment Modalities: Irreversible Electroporation

Robert C.G. Martin II

41.1 Introduction

Pancreatic ductal adenocarcinoma is still one of the most aggressive cancers and is the fourth most frequent tumor-related cause of death in the Western world [1]. Locally advanced disease is difficult to control, and limited improvement in outcomes has been achieved in the last 30 years despite the advances of diagnostic modalities and therapeutic options. For all stages combined, the 1-year survival rate is 20%, and the overall 5-year survival rate has remained dismally poor at 5% [2]. Complete surgical resection remains the only curative treatment for pancreatic cancer. The advanced T-stage of pancreatic adenocarcinoma is defined according to the involvement of the superior mesenteric artery, the celiac axis, long-segment portal vein occlusion, or their combination on cross-sectional imaging [3, 4].

Pancreatic tumors become symptomatic at a very advanced stage; therefore, a small percentage (15–20%) of patients may undergo therapeutic resection. In the rest of the patients, there might be either advanced locoregional disease without distant metastases (expected survival of 6–12 months) or locoregional disease with distal metastases (expected survival of 3–6 months) [5]. Chemoradiation therapy (CRT) provides short-term disease control. The majority of the chemotherapeutic schemes fail completely to prolong survival, and only recently did gemcitabine-associated CRT appear to offer a modest survival benefit of 3 months [6, 7]. The recent combination of 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin – FOLFIRINOX combination – demonstrated better response and survival rates in this specific subgroup (stage III) patients; however, long-term results from ongoing trials are not yet available [8]. The usefulness of radiation therapy was also tested; however, the results were not significant [7, 9].

Considering the limited duration of effect of CRT, there is a clear need for an adjunctive or consolidative local treatment to provide greater durable local control to provide pain control, which could possibly improve overall survival in patients with LAPC. Image-guided ablation techniques, such as radiofrequency ablation (RFA), microwave ablation (MWA), high-intensity focused ultrasound (HIFU), and irreversible electroporation (IRE), have been proposed as new treatment options in such cases.

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Table 41.1 Use of chemical ablative therapies to treat cystic and solid premalignant lesions of the pancreas

Author	Premalignant lesion	*n*	Treatment	Median area of ablation, mm (range)	Outcome	Complications
Gan et al.	Cystic tumors of the pancreas	25	EUS-guided ethanol lavage	19.4 (6–30)	Complete resolution in 35%	None
Oh et al.	Cystic tumors of the pancreas	14	EUS-guided ethanol lavage + paclitaxel	25.5 (17–52)	Complete resolution in 79%	Acute pancreatitis ($n = 1$) Hyperamylasemia ($n = 6$) abdominal pain ($n + 1$)
Oh et al.	Cystic tumors of the pancreas	10	EUS-guided ethanol lavage + paclitaxel	29.5 (17–52)	Complete resolution in 60%	Mild pancreatitis ($n = 1$)
DeWitt et al.	Cystic tumors of the pancreas	42	Randomized double-blind study: saline vs ethanol	22.4 (20–68)	Complete resolution in 33%	Abdominal pain at 7 days ($n = 5$) pancreatitis ($n = 1$) Acystic bleeding ($n = 1$)
Oh et al.	Cystic tumors of the pancreas	52	EUS-guided ethanol lavage + paclitaxel	31.8 (17–68)	Complete resolution in 62%	Fever (1.52)
						Mild pancreatitis (1/52) Splenic vein obliteration (1/52)
Levy et al.	PNET	8	EUS-guided ethanol lavage (5 patients) and intraoperative ultrasound-guided (IOUS) ethanol lavage (3 patients)	16.6 (8–21)	Hypoglycemia symptoms disappeared 5/8 and significantly improved 3/8	EUS guided: no complications IOUS-guided ethanol injection: minor peritumoral bleeding (1/3), pseudocyst (1/3)
Pai et al.	Cystic tumors of the pancreas + neuroendocrine tumors	8	EUS-guided RFA	Mean size pre-RFA, 38.8 mm vs mean size post-RFA, 20 mm	Complete resolution in 25% (2/8)	2/8 patients had mild abdominal pain that resolved in 3 days

RFA radiofrequency ablation, *EUS* endoscopic ultrasound, *PNET* pancreatic neuroendocrine tumor

41.2 Local Ablative Therapies

When local ablative therapies are applied, chemical, thermal, or electrical energy is transferred to a specific area of soft tissue with the intent of complete tissue destruction or ablation.

Chemical ablation includes the use of ethanol or acetic acid, which induces coagulation necrosis of the tumor mass after direct injection/contact with these agents (Tables 41.1, 41.2, 41.3, 41.4, 41.5, and 41.6). With chemical ablation, there is always the risk of migration/injection into the arterial system with fatal consequences, and its application in the treatment of pancreatic tumor is limited [10].

Thermal ablation is based on the increase or the decrease of tumor temperature. When heat is applied, a target temperature [50 °C (particularly temperatures ranging from 60 to 100 °C or more)] results in tissue thermal injury ablation. The method of cell death results from apoptosis and eventually coagulative necrosis, which occurs at temperatures 50 °C after 2 min. When cold is applied (cryoablation), temperatures lower than the tissue-freezing edge are achieved; the target temperature is lower than −40 °C, which in most is necessary to cause necrosis of target cells [11, 12]. There are several thermal ablation studies on the treatment of pancreatic cancer, mainly with the use of applied heat, and very limited studies on cryoablation in the literature.

Table 41.2 Endoscopic ultrasound administered non-ablative and antitumor therapies for pancreatic ductal adenocarcinoma

Author	Therapy	Patients	*n*	Outcome and survival	Complications
Chang et al.	Cytoimplant (mixed lymphocyte culture)	Unresectable PDAC	8	Median survival: 13.2 months, 2 partial responders and 1 minor response	7/8 developed low-grade fever 3/8 required biliary stent placement
Hecht et al.	ONYX-015 (55-kDa gene-deleted adenovirus) + IV gemcitabine	Unresectable PDAC	21	No patient showed tumor regression at day 35. After commencement of gemcitabine, 2/15 had a partial response	Sepsis: 2/15, duodenal perforation: 2/15
Hecht et al. Chang et al.	TNFerade (replication-deficient adenovector containing human tumor necrosis factor (TNF)-a gene)	Locally advanced PDAC	50	Response: one complete response, 3 partial responses. 7 patients eventually went to surgery, 6 had clear margins, and 3 survived >24 months	Dose-limiting toxicities of pancreatitis and cholangitis were observed in 3/50
Herman et al.	Phase III study of standard care plus TNFerade (SOC + TNFerade) vs standard of care alone (SOC)	Locally advanced PDAC	304 (187 SOC + TNFerade)	Median survival: 10.0 months for patients in both the SOC + TNFerade and SOC arms[hazard ration (HR), 0.90, 95% Cl; 0,66–1.22, P – 0.26]	No major complications, patients in the SOC+ TNFerade arm experienced more grade 1–2 fever than those in the SOC alone arm ($P < 0.001$)
Sun et al.	EUS-guided implantation of radioactive seeds (iodine-125)	Unresectable PDAC	15	Tumor response: "partial" in 27% and "minimal" in 205. Pain relief: 30%	Local complications (pancreatitis and pseudocyst formation) 3/15. Grade 3 hematologic toxicity in 3/15
Jin et al.	EUS-guided implantation of radioactive seeds (iodine-125)	Unresectable PDAC	22	Tumor response: "partial" in 3/22 (13.6%)	No complications

PDAC pancreatic ductal adenocarcinoma, *EUS* endoscopic ultrasound

Electrical current ablation is a technology that is based on the irreversible increase of permeability of the cellular membrane with the use of high-voltage (3,000 V), short-pulse (70–90 us) electric currents. IRE is one of the latest technological advances, and recent studies have been performed on its application in the local treatment of pancreatic cancer. Improvements in intraoperative imaging, electrodes, and ultrasound (US) technology have enabled the technology to accurately treat tumors [13–15]. IRE has been applied to patients who are not considered suitable for surgical resection and have received CRT with persistent disease, thus aiming to offer consolidative disease control, with symptom relief, control of pain, and definitive eradication of the lesion.

The inherent limitation for local ablative therapy of the pancreas is the heterogeneity of the tissue and the surrounding structures, which limits

Table 41.3 Studies of cryoablation in pancreatic ductal adenocarcinoma

Study	*n*	Patients	Study	Outcome	Complications
Patiutko et al. (non-English article)	30	Locally advanced PDAC	Combination of cryosurgery and radiation	Pain relief and improvement in performance status 30/30	Not reported
Kovach et al.	9	Unresectable PDAC	Phase I study of intraoperative cryoablation under US guidance; 4 had concurrent gastrojejunostomy	7/9 discharged with non-intravenous analgesia and 1/ discharged with no analgesia	No complications reported
Li et al. (non-English article)	44	Unresectable PDAC	Intraoperative cryoablation under US guidance	Median overall survival: 14 months	40.9% (18/44) had delayed gastric emptying. 6.8% (3/44) had a bile and pancreatic leak
Wu et al. (non-English article)	15	Unresectable PDAC	Intraoperative cryoablation under US guidance	Median overall survival: 13.4 months	1/15 patients developed a bile leak
Yi et al. (non-English article)	8	Unresectable PDAC	Intraoperative cryoablation under US guidance	Not reported	25% (2/8) developed delayed gastric emptying
Xu et al.	38	Locally advanced PDAC, 8 had liver metastases	Intraoperative or percutaneous cryoablation under US or CT guidance + (125) iodine seed implantation	Median overall survival: 12 months 19/38 (50,9%) survived more than 12 months	Acute pancreatitis: 5/38 (one has severe pancreatitis)
Xu et al.	49	Locally advanced PDAC, 12 had liver metastases	Intraoperative or percutaneous cryoablation under US or CT guidance + (125) iodine seed implantation. Some patients also received regional celiac artery chemotherapy	Median survival: 16.2 months 26 patients (53.1%) survived more than 12 months	Acute pancreatitis: 6/49 (one had severe pancreatitis)
Li et al.	68	Unresectable PDAC requiring palliative bypass	Retrospective case series of intraoperative cryoablation under US guidance, followed by palliative bypass	Median overall survival: 30.4 months (range 6–49 months)	Postoperative morbidity: 42.9% Delayed gastric emptying occurred in 35.7%
Xu et al.	59	Unresectable PDAC	Intraoperative or percutaneous cryotherapy	Overall survival at 12 months: 34.5%	Mild abdominal pain: 45/59 (76.3%) Major complications (bleeding, pancreatic leak): 3/59 (5%)
Niu et al.	36 (CT) 31 (CIT)	Metastatic PDAC	Intraoperative cryotherapy (CT) or cryo-immunotherapy (CIT) under US guidance	Median overall survival in CIT: 13 months CT: 7 months	Not reported

Table 41.4 Studies of photodynamic therapy in pancreatic ductal adenocarcinoma

Study	*n*	Study	Photosensitizer	Number of fibers	Number of ablations	Outcome and survival	Complications
Brown et al.	16	CT-guided percutaneous PDT to locally advanced but inoperable PDAC without metastatic disease	mTHPC	1	Single	Tumor necrosis: 16/16 Median survival: 9.5 months 44% (7/16) survived > 1 year	Significant gastrointestinal bleeding: 2/16 (controlled without surgery)
Huggett et al.	13 + 2	CT-guided percutaneous PDT to locally advanced but inoperable PDAC without metastatic disease	Verteporfin	1	Single (13) Multiple (2)	Technically feasible: 15/15. Dose-dependent necrosis occurred	Single fiber: no complications. Multiple fibers: CT evidence of inflammatory change anterior to the pancreas, no clinical sequelae

PDAC pancreatic ductal adenocarcinoma

certain therapies, because of the damage to healthy tissue that can lead to complications such as pancreatitis, vascular thrombosis, or enteric bowel damage. These concerns limit the use of certain techniques and augment other techniques based on the recent reports from numerous studies.

41.3 Irreversible Electroporation

IRE represents a new nonthermal injury [16] ablative technique with distinct advantages through the ability to definitively treat a soft tissue tumor with a decreased risk of thermal damage to vital structures adjacent to pancreatic tissue [13, 15]. The technique uses a series of short (70–90 us), high-voltage (2,250–3,000 V) pulses that are applied between two electrodes that are spaced 1.5–2.2 cm increasing the permeability of the cell membrane, which induces electrolyte disturbances across the cell leading to cell death via apoptosis [17, 18]. Reversible electroporation has been utilized in basic science labs as a technique that allows for transfer of genetic material or intracellular delivery of drugs [19–21]. The technique of reversible electroporation has a certain threshold to which the electrical energy induces permanent cell membrane porosity leading to irreversible permeabilization [22]. The IRE technique influences only the intracellular environment and not the extracellular matrix, thus allowing for cell repopulation and avoidance of luminal strictures of vital structures [17, 23–25].

Bower et al. [13] reported the first initial use of IRE in chronic non-tumor-bearing porcine pancreatic model. Six 70–80 kg pigs underwent a general anesthesia procedure, and through a midline incision either two to three 19-gauge monopolar or one 16-gauge bipolar electrodes was placed under ultrasound guidance to avoid mechanical damage and to ensure bracketing of the vital structures. The electrodes were placed within the pancreatic tissue in a distance of 1 mm from the portal vein or the mesenteric artery. Monopolar electrodes were spaced at 1.5 and 2 cm. The electroporation generator

Table 41.5 Studies of radiofrequency ablation in pancreatic ductal adenocarcinoma

Study	Patients	*n*	Route of administration	Device	RFA temp	RFA duration (min)	Outcome	Complication
Matsui et al.	Unresectable PDAC	20 LA:9 M:11	At laparotomy 4 RFA probes were inserted into the tumor 2 cm apart	A 13.56-MHz RFA pulse was produced by the heating apparatus	50	15	Survival: 3 months	Mortality: 10% (septic shock and gastrointestinal bleeding)
Hadjicostas et al.	Locally advanced and unresectable PDAC	4	Intraoperative – followed by palliative bypass surgery	Cool-tip™ RF Ablation system	NR	2–8	All patients were alive 1 year post-RFA	No complications encountered
Wu et al.	Unresectable PDAC	16 LA:11 M:5	Intraoperative	Cool-tip™ RF Ablation system	30–90	12 at 30 °C then 1 at 90 °C	Pain relief: back pain improved (6/12)	Mortality: 25% (4/16 pancreatic fistula: 18.8% (3/16)
Spiliotis et al.	Stage III and IV PDAC receiving palliative therapy	12 LA: 8 M:4	Intraoperative – followed by palliative bypass surgery	Cool-tip™ RF Ablation system	90	5–7	Mean survival: 33 months	Morbidity: 16% (biliary leak) Mortality: 0 %
Girelli et al.	Unresectable locally advanced PDAC	50	Intraoperative – followed by palliative bypass surgery	Cool-tip™ RF Ablation system	105 (25 pts) 90 (25 pts)	Not reported	Not reported	Morbidity 40% in the first 25 patients. Probe temperature decreased from 105 to 90 °C. Morbidity 8% in second cohort of 25 patients 30-day mortality: 2%
Girelli et al.	Unresectable locally advanced PDAC	100	Intraoperative – followed by palliative bypass surgery	Cool-tip™ RF Ablation system	90	56–10	Median overall survival: 20 months	Morbidity: 15%. Mortality: 3%

Giardino et al.	Unresectable PDAC, 47 RFA alone, 60 had RFA + RCT and/or IASC	107	Intraoperative – followed by palliative bypass surgery	Cool-tip™ RF Ablation system	90	5–10	Median overall survival: 14.7 months in RFA alone but 25.6 months in those receiving RFA + RCT and/or IADC ($P = 0.004$)	Mortality 1,8% (liver failure and duodenal perforation) morbidity: 28%
Arcidiacono et al.	Locally advanced PDAC	22	EUS-guided	Cryotherm probe; bipolar RFA + cryogenic cooling	NR	2–15	Feasible in 16/22 (72.8%)	Pain (3/22)
Steel et al.	Unresectable malignant bile duct obstruction (16/22 due to PDAC)	22	RFA + SEMS placement at ERCP	Habib EndoHPB wire-guided catheter	NR	Sequential 2-min treatments – median 2 (range 1–4)	Success ful biliary decompression (21/22)	Minor bleeding (1/22) asymptomatic biochemical pancreatitis (1/22), percutaneous gallbladder drainage (2/22). At 90 days, 2/22 had died, one with a patent SEMS
Figueroa-Barojas et al.	Unresectable malignant bile duct obstruction (7/20 due to PDAC	20	RFA + SEMS placement at ERCP	Habib EndoHPB wire-guided catheter	NR	Sequential 2-min treatments	SEMS occlusion at 90 days (3/22), bile duct diameter increased by 3.5 mm post-RFA ($P = 0.0001$)	Abdominal pain (5/20), mild post-ERCP pancreatitis and cholecystitis (1/20)
Pai et al.	Locally advanced PDAC	7	EUS guided	Habib EUS-RFA catheter	NR	Sequential 90-s treatments – median 3 (range 2–4)	2/7 tumors decreased in size	Mild pancreatitis: (1/7)

PDAC pancreatic ductal adenocarcinoma, *LA* locally advanced PDAC, *M* metastatic PDAC, *SEMS* self-expanding metal stent, *RFA* radiofrequency ablation, *EUS* endoscopic ultrasound, *ERCP* endoscopic retrograde cholangiopancreatography, *IASC* intra-arterial systemic chemotherapy

Table 41.6 Studies of high-intensity focused ultrasound in pancreatic ductal adenocarcinoma

Study	*n*	Study	Outcome and survival	Complications
Wang et al. (non-English article)	15	HIFU monotherapy in late-stage PDAC	Pain relief: 13/13 (100%)	Mild abdominal pain (2/15)
Xie et al. (non-English article)	41	HIFU alone + HIFU + gemcitabine in local advanced PDAC	Pain relief: HIFU (66.7%) HIFU + gemcitabine (76.6%)	None
Xu et al. (non-English article)	37	HIFU monotherapy in advanced PDAC	Pain relief: 24/30 (80%)	None
Yuan et al. (non-English article)	40	HIFU monotherapy	Pain relief: 32/40 (80%)	None
Wu et al.	8	HIFU in advanced PDAC	Median survival: 11.25 months Pain relief: 8/8	None
Xiong et al.	89	HIFU in unresectable PDAC	Median survival: 26.0 months (stage II), 1.2 months (stage III), and 5.4 months (stage IV)	Superficial skin burns (3.4%), subcutaneous fat sclerosis (6.5), asymptomatic pseudocyst (1.1%),
Zhao et al.	37	Phase II study of gemcitabine + HIFU in locally advanced PDAC	Overall survival: 12.6 months (95%) CI: 10.2–15.0 months), pain relief 78.6%	16.2 % experienced grade 3 or 43 neutropenia, 5.4% developed grade 3 thrombocytopenia, 8% had nausea vomiting
Orsi et al.	6	HIFU in unresectable PDAC	Pain relief: 6/6 (100 %)	Portal vein thrombosis (1/6)
Sung et al.	46	Stage III or IV PDAC	Median survival: 12.4 months. Overall survival at 12 months was 30.4%	Minor complications (abdominal pain, fever, and nausea):57.1!% (28/29). Major complications (pancreaticoduodenal fistula, gastric ulcer, or skin burns): 10.2% (5/49)
Wang et al.	40	Advanced PDAC	Median overall survival: 10 months (stage III) and 6 months (stage IV) pain relief: 35//40 (87.5%)	None
Lee et al.	12	HIFU monotherapy in unresectable PDAC (33/12 received chemotherapy)	Median overall survival for those receiving HIFU alone (9/12 pts): 10.3 months	Pancreatitis 1/12
Li et al.	25	Unresectable PDAC	Median overall survival: 10 months 42% survived more than 1 year, performance status and pain levels improved: 23/25	1st-degree skin burn: 12% Mortality: 0%
Wang et al.	224	Advanced PDAC	Not reported	Abdominal distension, anorexia and nausea: 10/224 (4.5%) asymptomatic vertebral injury: 2/224
Gao et al.	39	Locally advanced PDAC	Pain relief: 79.5% Median overall survival: 11 month 30.8% survived more than 1 year	None

HIFU high-intensity focused ultrasound, *PDAC* pancreatic ductal adenocarcinoma

was the NanoKnife System (AngioDynamics, Queensbury, NY), which utilized an energy output of a maximum of 3,000 V and maximum current of 50 amps. The system is utilized with cardiac synchronization in order to deliver electrical pulses during the refractory phase of the cardiac rhythm and not during the venerable phase in order to prevent cardiac arrhythmias. The goal of treatment is to deliver enough pulses (range 110–220) in groups of ten in order to see a change in resistance of the target tissue [26]. All animals tolerated the IRE procedure of the pancreas, and the animals had a transient (peak at 48 h) increase in pancreatic enzymes (normalized at 72 h in most animals). The animals survived to 72 h, 7 days, and 14 days after the procedure. Pathology demonstrated complete electroporation with nonthermal injury-induced necrosis of pancreatic cells adjacent to vascular structures. There was no evidence of thermal injury to the vessels or bile ducts. The authors were able to conclude from this preliminary study that IRE might be used in the ablation of pancreatic tissue without significant risk of pancreatitis or vascular thrombosis. Provided that IRE end user is knowledgeable and well training as to the thresholds or IRE, since misuse or lack of attention can lead to attempts of high-current energy delivery, which could result in thermal injury.

The initial clinical use of IRE was reported by Martin et al. in which 27 patients, 13 women and 14 men, underwent IRE with median age of 61 (45–80 years of age) were treated [27] (Table 41.7). Eight patients underwent margin accentuation with IRE in combination with left-sided

Table 41.7 Current reports with overall survival with the use of IRE in locally advanced pancreatic cancer

Author, year	Was ablation success reported and defined	Overall survival (Y/N) median	Local recurrence	Mortality	Complications
Strobel (2013) [36]	–	16.4 months	59%	0.9%	Pancreatic fistula, wound infections, burns, UTI, intra-abdominal abscess
Martin (2012)	54 patients IRE successfully	20 months	(15/54) 28%	2%	None
Martin (2012)	27 patients 100% success	All lived to 90-day post-op scan	0% at 90 days	(1/27) 3.7%	Hematologic, ileus, bile leak, portal vein thrombosis, deep venous thrombosis, pulmonary, renal failure, wound infection
Dunki-Jacobs (2014)	65 patients 100% success	The median local disease-free survival was 5.5 months in patients who had recurrence compared with 12.6 months in patients who did not recur ($p = 0.03$)	(17/65) 26%	–	Ileus, bile leak, portal vein thrombosis, pulmonary, renal failure, wound infection, liver insufficiency, dehydration
Narayanan (2013)	14 patients treated percutaneously	Median DFS 6.7 (0.7–12.7)	Not reported	0% at 30 days	Pancreatitis and pneumothorax
Martin (2015)	200 patients 150 in situ 50 margin 100% IRE energy success	With a median follow-up of 29 months, median overall survival (OS) was 24.9 months (range 4.9–85 months)	Six (3%) have experienced local recurrence	0% 90 days for margin and 3/150 90 days for in situ	Gastrointestinal, liver, vascular, and wound

resection (N = 4) or pancreatic head resection (n = 4). Nineteen patients had in situ IRE. All patients underwent successful IRE, with intraoperative imaging confirming effective delivery of therapy. All 27 patients demonstrated nonclinically relevant elevation of their amylase and lipase, which peaked at 48 h and returned to normal at 72 h post-procedure. There has been one 90-day mortality. No patient has shown evidence of clinical pancreatitis or fistula formation. After all patients have completed 90-day follow-up, there has been 100% ablation success. They concluded that IRE ablation of LAP tumors is a safe and feasible primary local treatment in unresectable, locally advanced disease.

Martin et al. reported on a larger study of 54 patients who underwent a combination of chemotherapy and chemoradiation therapy with consolidative IRE in comparison to a control group of chemotherapy/chemoradiation therapy for LAPC [28]. All patients were confirmed stage III LAPC based on staging CT and/or MRI due to encasement of the superior mesenteric artery, celiac axis, or long-segment occlusion of the SMV/PV. IRE was performed through an open supine midline incision or in a laparoscopic fashion. After a median follow-up time of 15 months, 15 of the 54 patients appeared to have local disease recurrence. The adverse events that were IRE-related were two cases of bile leakage and two cases of duodenal leakage. However, the duodenal leaks occurred after the removal of a duodenal stent and placement of the IRE needle. The 90-day mortality in the IRE patients was one (2%). In a comparison of IRE patients to standard therapy, we have seen an improvement in local progression-free survival (14 vs 6 months, P = 0.01), distant progression-free survival (15 vs 9 months, p = 0.02), and overall survival (20 vs 13 months, p = 0.03). The investigators concluded that IRE as a consolidative therapy of locally advanced pancreatic tumors remains safe. In the appropriate patient who has undergone standard induction therapy for a minimum of 4 months, IRE can achieve greater local palliation and potential improved overall survival when compared to standard chemoradiation-chemotherapy treatments.

Dunki-Jacobs and Martin also recently published on the temperature effects and the ability to treat around metal structures such as metal biliary stents, clips, and fiducials [16]. In vivo continuous temperature assessments of 86 different IRE procedures were performed on porcine liver, pancreas, kidney, and retroperitoneal tissue. Tissue temperature was measured continuously throughout IRE by means of two thermocouples placed at set distances (0.5 cm or less and 1 cm) from the IRE probes within the treatment field. Thermal injury was defined as a tissue temperature of 54 °C lasting at least 10 s. Tissue type, pulse length, probe exposure length, number of probes, and retreatment were evaluated for associations with thermal injury. In addition, IRE ablation was performed with metal clips or metal stents within the ablation field to determine their effect on thermal injury. An increase in tissue temperature above the animals' baseline temperature (median 36.0 °C) was generated during IRE in all tissues studied, with the greatest increase found at the thermocouple placed within 0.5 cm in all instances. On univariable and multivariable analysis, ablation in kidney tissue (maximum temperature 62.8 °C), ablation with a pulse length setting of 100 μs (maximum 54.7 °C), probe exposure of at least 3.0 cm (maximum 52.0 °C), and ablation with metal within the ablation field (maximum 65.3 °C) were all associated with a significant risk of thermal injury. IRE can generate thermal energy, and even thermal injury, based on tissue type, probe exposure lengths, pulse lengths, and proximity to metal. Awareness of probe placement regarding proximity to critical structures as well as probe exposure length and pulse length is necessary to ensure safety and prevent thermal injury. A probe exposure of 2.5 cm or less for liver IRE, and 1.5 cm or less for the pancreas, with maximum pulse length of 90 μs will result in safe and nonthermal energy delivery with spacing of 1.5–2.6 cm between probe pairs.

Similar work has also been performed to adequately define a clinical endpoint for IRE [26]. Since intraoperative evaluation of successful pancreatic tumor ablation, using irreversible IRE is difficult secondary to lack of visual confirmation. The IRE generator provides feedback by reporting

current (amperage), which can be used to calculate changes in tumor tissue resistance. They used a change in resistance to predict successful tumor ablation during IRE for pancreatic cancers.

All patients undergoing pancreatic IRE from March 2010 to December 2012 were evaluated using a prospective database. Intraoperative information, including change in tumor resistance during ablation and slope of the resistance curve, were used to evaluate effectiveness of tumor ablation in terms of local failure or recurrence (LFR) and disease-free survival (DFS). A total of 65 patients underwent IRE for locally advanced pancreatic cancer. Median follow-up was 23 months. Local failure or recurrence was seen in 17 patients at 3, 6, or 9 months post-IRE. Change in tumor tissue resistance and the slope of the resistance curve were both significant in predicting LFR (p 1⁄4 0.02 and p 1⁄4 0.01, respectively). The median local disease-free survival was 5.5 months in patients who had recurrence compared with 12.6 months in patients who did not recur (p 1⁄4 0.03). Neither mean change in tumor tissue resistance nor the slope of the resistance curve significantly predicted overall DFS. Mean change in tumor tissue resistance and the slope of the resistance curve could be used intraoperatively to assess successful tumor ablation during IRE. Larger sample size and longer follow-up are needed to determine if these parameters can be used to predict DFS.

All of these factors lead to the most recent data of the use of IRE in LAPC by Martin et al. From July 2010 to October 2014, patients with radiographic stage III LAPC were treated with IRE and monitored under a multicenter, prospective IRB-approved registry. Perioperative 90-day outcomes, local failure, and overall survival were recorded. A total of 200 patients with LAPC underwent IRE alone (n = 150) or pancreatic resection plus IRE for margin enhancement (n = 50). All patients underwent induction chemotherapy, and 52% received chemoradiation therapy as well, for a median of 6 months (range 5–13 months) prior to IRE. IRE was successfully performed in all patients. Thirty-seven percent sustained complications, with a median grade of 2 (range 1–5). Median length of stay was 6 days (range 4–36). With a median follow-up of 29 months, six (3%) have experienced local recurrence. Median overall survival (OS) was 24.9 months (range 4.9–85 months). This was significantly better than the most recent review of standard chemotherapy and chemoradiotherapy (Fig. 41.1).

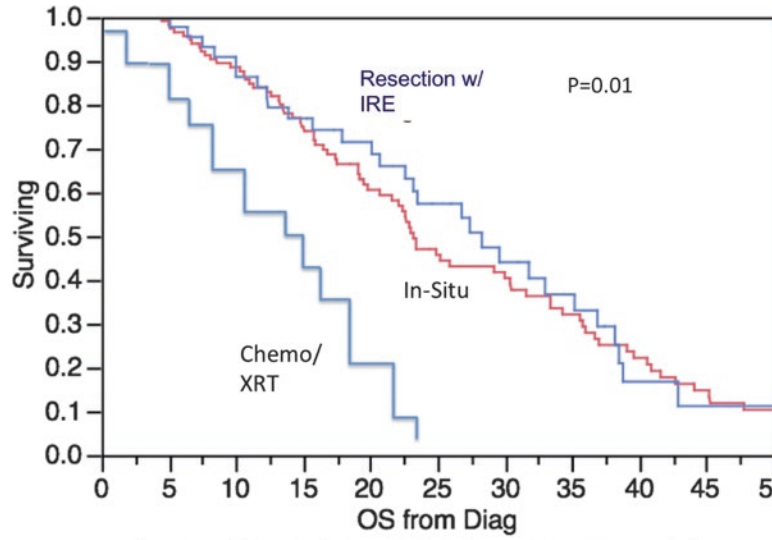

Fig. 41.1 Overall survival in the 200 LAPC treated with trimodality therapy (chemotherapy/IRE/radiation therapy) either with margin accentuation or in situ compared to the most systematic review of chemotherapy-radiation only

They concluded that patients with LAPC (stage III) with the addition of IRE to conventional chemotherapy and radiation therapy result in substantially prolonged survival compared to historical controls. These results suggest that ablative control of the primary tumor may prolong survival.

Another option is the use of a percutaneous access approach. Narayanan et al. [29] performed a study of 14 patients who received CT-guided percutaneous treatment with IRE for locally advanced pancreatic cancer. The indications for treatment were downstaging of the locally advanced cancer, control of local recurrence after previous Whipple procedure, and/or intolerance to systemic chemotherapy. All patients had received previous cycles of chemotherapy, and 10 of 14 also received previous radiation therapy. The median tumor size treated was 3.3 cm (range 2.5–7). In six cases, the tumor was located in the pancreatic head; in seven cases it was located in the body, and in one case it was located in the uncinate process. In three cases, small-volume metastatic disease was present, whereas patients with extensive metastatic disease were not included in the study. No severe complications occurred after the procedure. Complications included pneumothorax, a small subcutaneous hematoma, and self-limiting pancreatitis. There were four deaths during the course of the follow-up; however, no deaths were attributed to the procedure. Three other patients with intolerance to chemotherapy showed stable disease and did not require any further treatment. The median overall survival was reported as 6 months. With these results the investigators concluded that patients with metastatic disease do not appear to benefit from IRE and that patients with extensive varices need to be excluded from a percutaneous approach, thus indicating that a safe CT "window" is not enough for percutaneous IRE of locally advanced pancreatic cancer.

These results in avoiding treating patients with metastatic disease or incompletely electroporation patients cannot be overstated. A recent report from Philips et al. created the first ever heterotopic murine model by inoculating BALB/c nude mice in the hind limb with a subcutaneous injection of PANC-1 cells, an immortalized human pancreatic adenocarcinoma cell line [30]. Tumors were allowed to grow from 0.75 to 1.5 cm and then treated with the goal of complete ablation or partial ablation using standard IRE settings. Animals were recovered and survived for 2 ($n = 6$), 7 ($n = 6$), 14 ($n = 6$), 21 ($n = 6$), 30 ($n = 8$), and 60 ($n = 8$) days. All 40 animals/tumors underwent successful IRE under general anesthesia with muscle paralysis. The mean tumor volume of the animals undergoing ablation was 1,447.6 mm^3±884). Histologically, in the 14-, 21-, 30-, and 60-day survival groups, the entire tumor was nonviable, with a persistent tumor nodule completely replaced fibrosis. In the group treated with partial ablation, incomplete electroporation/recurrences ($N = 10$ animals) were seen, of which 66% had confluent tumors, and this was a significant predictor of recurrence ($p < 0.001$). Recurrent tumors were also significantly larger (mean 4,578 mm^3 ± SD 877 vs completed electroporated tumors 925.8 ± 277, $p < 0.001$). Recurrent tumors had a steeper growth curve (slope = 0.73) compared with primary tumors (0.60, $p = 0.02$). Recurrent tumors also had a significantly higher percentage of EpCAM expression, suggestive of stem cell activation. The authors concluded that tumors that recur after incomplete electroporation demonstrate a biologically aggressive tumor that could be more resistant to standard of care chemotherapy. Clinical correlation of this data is limited, but should be considered when IRE of pancreatic cancer is being considered.

The established technique for IRE of LAPC has been well published and described. Recent from Martin et al. reported on the optimal technique for both the LAPC of the pancreatic head (Fig. 41.2) and LAPC of the pancreatic neck/body (Fig. 41.3) [31, 32]. Representative case would involve a patient who presents a LAPC of the pancreatic head who has been treated with induction chemotherapy, who now has a mass of <3.5 cm in size with clear vascular involvement (Fig. 41.3). Given the size of the tumor, at least four needles are placed in a bracketing fashion, covering the

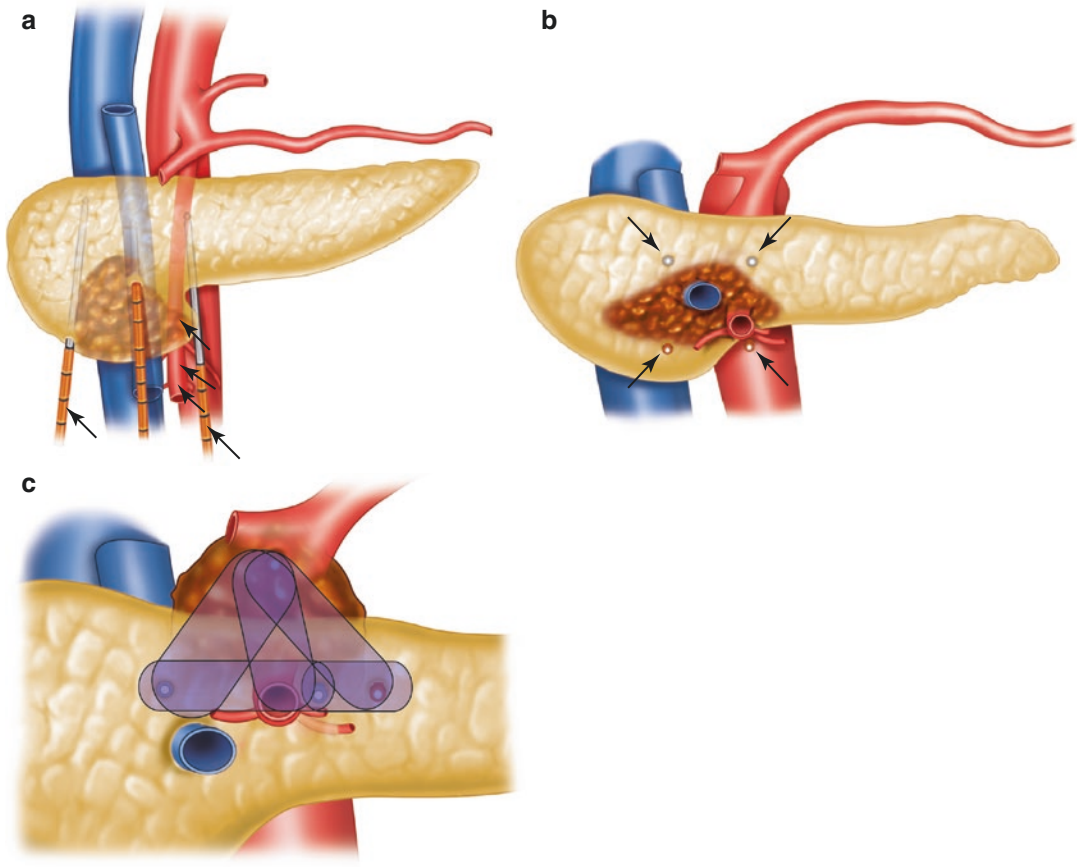

Fig. 41.2 (**a**) Coronal plane of standard 4-probe technique with SMA encasement. Care should be taken so that the needles are not placed past the extent of tumor involvement, thus preventing injury to the aorta. (**b**) Axial plane of classical 4 probe – box technique for a locally advanced pancreatic head tumor with SMA and SMV encasement with four probes bracketing the tumor and the SMA with max probe exposure of 1 cm

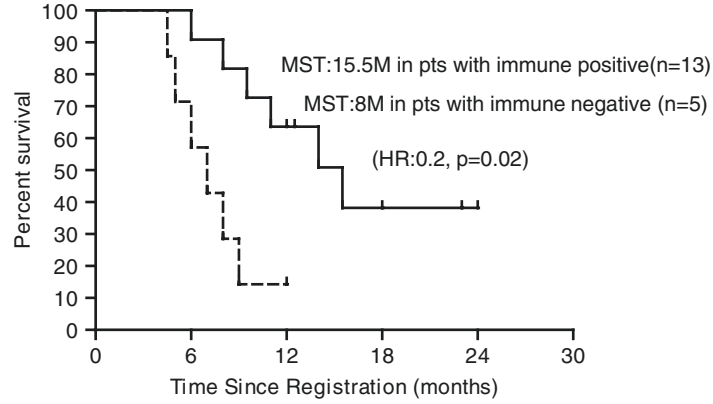

Fig. 41.3 Axial plane of a four probe – triangle technique for a locally advanced pancreatic mid-body tumor with just celiac encasement and SMA involvement with four probes bracketing the tumor and the celiac axis with max probe exposure of 1–1.5 cm, with example of energy delivery that occurs between probes

entire tumor and the vital structures, which in this case would include the SMA, SMV, and bile duct.

Similar presentation can occur with LAPC of the neck, which again should be extensively staged and then treated with initial induction chemotherapy. After appropriate selection the needle placement again is in a bracketed fashion to cover the entire tumor and the vital structures that the tumor invades (Fig. 41.3). After optimal needle placement, with precise spacing [33], the energy is delivered between the probes in a sequential fashion until a change in resistance is seen [26].

However, there does remain a learning curve with IRE that cannot be underestimated. A recent analysis of Philips et al. evaluated 150 consecutive patients over seven institutions from September 2010 to July 2012 and divided these into three groups A (1st 50 patients treated), B (2nd 50 patients treated), and C (3rd 50 patients treated chronologically and analyzed for outcomes [34]. Over time, complex treatments of larger lesions and lesions with greater vascular involvement were performed without a significant increase in adverse effects or impact on local relapse-free survival. This evolution demonstrated the safety profile of IRE and speed of graduation to more complex lesions, which was greater than five cases by institution. IRE is a safe and effective alternative to conventional ablation with a demonstrable learning curve of at least five cases to become proficient.

Lastly the imaging for post-IRE also continues to evolve. Since IRE is relatively new to the field of locoregional therapy, post-IRE imaging findings are limited [35]. In a most recent review by our institution for less than 30-day imaging, three distinct abnormalities are seen.

The most common finding overall was of direct vascular change, specifically, that of a significant post-procedural narrowing in caliber (estimated to be at least 50%) or even occlusion of a major peripancreatic vessel. The portal vein and confluence, superior mesenteric artery, and superior mesenteric vein were the most commonly affected. A few occurrences involving the celiac artery and hepatic artery were also noted. In eight instances there was development of significant intravascular thrombus, and six pseudoaneurysms were identified. Indirect vascular findings manifested as end-organ infarcts were seen in four cases, all involving the spleen.

The next most common category of findings were related to the gastrointestinal tract, most frequently with a nonspecific edematous appearance to the bowel wall, most commonly the stomach, as well as adjacent bowel loops in several cases. However, potentially more ominous findings related to the GI tract in descending order of frequency include bowel perforation, portal venous gas, GI hemorrhage, and pneumatosis intestinalis.

The remaining findings were associated with postoperative fluid collections within the abdominopelvic cavity, including nine rim-enhancing fluid collections suspicious for abscess formation and eight bland-appearing fluid collections. Biliary findings were infrequent, with two cases of common bile duct dilatation.

With improved survival of these patients, this potentially represents an increasingly relevant scenario for the practicing radiologist to recognize and even anticipate significant findings in the post-procedural evaluation of the peri-electroporation bed, for the benefit of both patients and clinical researchers, even beyond the specialized environments of tertiary and quaternary care centers.

For longer-term imaging post-IRE, the post-ablation bed is larger than the original ablated tumor. This ablation zone may get smaller in size (due to decreased edema and hyperemia) in the following months and, more importantly, remains stable provided there is no recurrence [35]. The evaluation of response rates for IRE using RECIST criteria is limited given the lack of true decrease in size based on the pancreatic tumor stroma, fibrosis, and vasculature. Thus we have defined a complete response of IRE with no residual solid-enhancing tumor and free of metastasis. Partial response would be a decrease of 30% or more of the solid-enhancing mass, stable disease <30% decrease, or <20% increase when compared to the first follow-up scan which is performed at 3 months post-IRE. In cases of recurrent disease, there is increased size of the ablation bed, mass effect, and new or worsening vascular encasement or occlusion.

CT imaging remains the best current imaging modality to assess post-IRE ablation changes. Serial imaging over at least 2–6 months must be employed to detect recurrence by comparing with prior studies in conjunction with clinical and serum studies. Larger imaging studies are underway to evaluate for a more ideal imaging modality for this unique patient population.

Conclusion

LAPC remains a distinct disease with a clear different biology than stage IV pancreatic cancer. Demands to separate these two distinct diseases are required to better risk stratify and care for thus subset of patients. Surgical evaluation at the time of diagnosis in conjunction with high-quality imaging is required, in conjunction with repeated evaluation at 203-month intervals while on induction chemotherapy. Only after the biology of the disease is determined, i.e., lack of progression within the first 4–6 months, should any type of local therapy – XRT or IRE – be considered. Currently, with the inability to control the distribution of the thermal-based injury, RFA and MWA have no role in the management, care, or palliation of patients with LAPC. Attempting to extrapolate what is known about RFA and MWA in the liver in regard to universally recognized and intentionally radical "safety halo" of necrosis is achieved around the target lesion which does not translate into the pancreas. The inability to obtain that "safety halo" without running excessive risks of perioperative complications is the most important limitation of any thermal ablative technique in the pancreas. HIFU has potential; however given that this is a thermal-based technique, there remain concerns that HIFU can truly eradicate all disease in a LAPC that is surrounding the artery or vein and not induce thermal injury to those structures. IRE can have a clear role in the local control of stage III and borderline pancreatic adenocarcinoma *IF AND ONLY IF* used responsibly with the highest technical quality with extensive knowledge of IRE clinical endpoints and management of LAPC. Significant limitations remain in 2015 with IRE: The capital generator expense and probe expense are outside of the norm when compared to other thermal injury-based probes, but much cheaper than radiation therapy units. Intra-procedural targeting is limited at this time and represents a limitation to the wider expansion based on the high-technical ability that is currently required. Last is the limited ability to confirm IRE success and IRE recurrence with the current imaging modalities and will require expansion into higher-quality molecular imaging. Thus in conclusion, local consolidative therapy for LAPC can be effective in local disease control when performed in collaboration with a multidisciplinary team and appropriate sequencing of all three therapies – chemotherapy, radiation therapy, and IRE.

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