Pancreatic Masses

Advances in Diagnosis and Therapy

Mihir S. Wagh
Peter V. Draganov
Editors

Springer

Pancreatic Masses

Mihir S. Wagh • Peter V. Draganov
Editors

Pancreatic Masses

Advances in Diagnosis and Therapy

Springer

Editors
Mihir S. Wagh, MD, FACG, FASGE
Division of Gastroenterology
University of Florida
Gainesville, FL, USA

Peter V. Draganov, MD, FASGE, AGAF, FACG
Division of Gastroenterology
University of Florida
Gainesville, FL, USA

ISBN 978-3-319-19676-3 ISBN 978-3-319-19677-0 (eBook)
DOI 10.1007/978-3-319-19677-0

Library of Congress Control Number: 2015950853

Springer Cham Heidelberg New York Dordrecht London

Printed on acid-free paper

Springer International Publishing AG Switzerland is part of Springer Science+Business Media (www.springer.com)

Preface

It is our distinct pleasure to present this book on pancreatic mass lesions and an honor to have the opportunity to work with world-renowned experts in this field. To begin, let us explain the two main reasons for putting this book together. As you know, pancreatic cancer is one of the deadliest of cancers and the fourth leading cause of cancer-related deaths. At the same time, imaging studies are identifying pancreatic masses more frequently, not all of which are neoplastic. Furthermore, these neoplasms are often associated with varying levels of malignant potential. Recently, there have been great advances in our understanding of pancreatic diseases, diagnostic capabilities, and treatment options. In this ever-changing world of sophisticated technological innovations and scientific progress, we thought it would be best to get a 360° view on pancreatic mass lesions and present a concise, yet thorough text for clinicians taking care of patients with these diseases.

This book is divided into four sections that cover the different types of pancreatic mass lesions, their diagnosis, treatment, and recent advances. Each chapter in these sections includes an abstract highlighting the salient features described in that segment of the book. We have incorporated illustrations and photographs to provide the reader with a visual understanding of key concepts, and diagnostic and therapeutic modalities, including radiographic images and endoscopic and surgical photos. We have presented relevant data and summarized their findings to help the clinician manage patients with these lesions. Finally, we have included recent advances in cytopathology, endoscopic ultrasonography (EUS), endoscopic retrograde cholangiopancreatography (ERCP), and other novel and innovative therapeutic strategies.

We are grateful to our panel of distinguished contributors, true international experts in this field, from America, Europe, and Asia, spanning various disciplines, including gastroenterology, interventional endoscopy, radiology, oncology, radiation oncology, and surgery. We extend a special thanks to our publishers (Springer), who helped bring our ideas to a tangible reality.

Gainesville, FL, USA

Mihir S. Wagh, MD, FACG, FASGE
Peter V. Draganov, MD, FASGE, AGAF, FACG

Contents

Contributors

Barham Abu-Dayyeh Division of Gastroenterology and Hepatology, Department of Medicine, Mayo Clinic College of Medicine, Rochester, MN, USA

Mohammad Al-Haddad Division of Gastroenterology and Hepatology, Indiana University School of Medicine, Indianapolis, IN, USA

Sunil Amin Division of Gastroenterology, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Urban Arnelo Division of Surgery, Department of Clinical Science, Intervention and Technology (CLINTEC), Karolinska Institutet, and Centre for Digestive Diseases, Karolinska University Hospital, Stockholm, Sweden

Michael Bartel Division of Gastroenterology and Hepatology, Mayo Clinic, Jacksonville, FL, USA

William R. Brugge Medicine and Gastrointestinal Unit, Pancreas Biliary Center, Massachusetts General Hospital, Boston, MA, USA

James L. Buxbaum Division of Gastroenterology, University of Southern California, Los Angeles, CA, USA

Kenneth J. Chang Division of Gastroenterology and Hepatology, H.H. Chao Comprehensive Digestive Disease Center, Universityof California, Irvine Medical Center, Orange, CA, USA

Saurabh Chawla Division of Digestive Diseases, Department of Medicine, Emory University School of Medicine, Atlanta, GA, USA

Christopher J. DiMaio Division of Gastroenterology, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Mohamad A. Eloubeidi Division of Gastroenterology and Hepatology, American University of Beirut School of Medicine, Beirut, Lebanon

James J. Farrell Yale Center for Pancreatic Disease, Yale School of Medicine, New Haven, CT, USA

Chris E. Forsmark Division of Gastroenterology, Hepatology, and Nutrition, University of Florida, Gainesville, FL, USA

Thomas J. George Jr. Division of Oncology, Department of Medicine, University of Florida, Gainesville, FL, USA

Ferga C. Gleeson Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN, USA

Emmanuel C. Gorospe Division of Gastroenterology and Hepatology, Department of Medicine, Mayo Clinic College of Medicine, Rochester, MN, USA

Shilpa Grover Division of Gastroenterology, Brigham and Women's Hospital, Boston, MA, USA

Harvard Medical School, Boston, MA, USA

Ihab I. El Hajj Department of Medicine, University of Colorado School of Medicine, Aurora, CO, USA

Steven N. Hochwald Department of Surgical Oncology, Roswell Park Cancer Institute, Buffalo, NY, USA

Takao Itoi Department of Gastroenterology and Hepatology, Tokyo Medical University, Tokyo, Japan

Abdurrahman Kadayifci Medicine and Gastrointestinal Unit, Pancreas Biliary Center, Massachusetts General Hospital, Boston, MA, USA

Division of Gastroenterology, University of Gaziantep, Gaziantep, Turkey

Michel Kahaleh Division of Gastroenterology and Hepatology, Weill Cornell Medical College, New York, NY, USA

Nikolaos Kartalis Division of Medical Imaging and Technology, Department of Clinical Science, Intervention and Technology (CLINTEC), Karolinska Institutet, and Department of Radiology, Karolinska University Hospital, Stockholm, Sweden

Masayuki Kitano Department of Gastroenterology and Hepatology, Kinki University Faculty of Medicine, Osaka, Japan

Pradermchai Kongkam Gastrointestinal Endoscopy Excellent Center, Department of Medicine, Faculty of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital, Thai Red Cross Society, Patumwan, Bangkok, Thailand

Moshim Kukar Department of Surgical Oncology, Roswell Park Cancer Institute, Buffalo, NY, USA

Milena Di Leo Division of Gastroenterology and Hepatology, Mayo Clinic, Jacksonville, FL, USA

Michael J. Levy Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN, USA

Johannes Matthias Löhr Division of Surgery, Department of Clinical Science, Intervention and Technology (CLINTEC), Karolinska Institutet, and Centre for Digestive Diseases, Karolinska University Hospital, Stockholm, Sweden

Parit Mekaroonkamol Division of Digestive Diseases, Department of Medicine, Emory University School of Medicine, Atlanta, GA, USA

Jennifer Nayor Division of Gastroenterology, Brigham and Women's Hospital, Boston, MA, USA

Population Sciences, Dana-Farber Cancer Institute, Boston, MA, USA

Harvard Medical School, Boston, MA, USA

R. Charles Nichols Department of Radiation Oncology, University of Florida Proton Therapy Institute, Jacksonville, FL, USA

Massimo Raimondo Department of Gastroenterology, Mayo Clinic, Jacksonville, FL, USA

Rungsun Rerknimitr Department of Medicine, Gastrointestinal Endoscopy Excellent Center, Department of Medicine, King Chulalongkorn Memorial Hospital, Thai Red Cross Society, Chulalongkorn University, Bangkok, Thailand

Wiriyaporn Ridtitid Division of Gastroenterology and Hepatology, Indiana University School of Medicine, Indianapolis, IN, USA

Chulalongkorn University, King Chulalongkorn Memorial Hospital, Thai Red Cross Society, Bangkok, Thailand

Jason B. Samarasena Division of Gastroenterology and Hepatology, H.H. Chao Comprehensive Digestive Disease Center, University of California, Irvine Medical Center, Orange, CA, USA

Thomas J. Savides Division of Gastroenterology, University of California, San Diego, La Jolla, CA, USA

Raj J. Shah Department of Medicine, University of Colorado School of Medicine, Aurora, CO, USA

Gastroenterology, Digestive Health Center, University of Colorado Hospital, Aurora, CO, USA

Sarunas Sliesoraitis Division of Oncology, Department of Medicine, University of Florida, Gainesville, FL, USA

Ioana Smith Division of Gastroenterology and Hepatology, University of Alabama, Birmingham, AL, USA

Louis M. Wong Kee Song Division of Gastroenterology and Hepatology, Department of Medicine, Mayo Clinic College of Medicine, Rochester, MN, USA

Sapna Syngal Division of Gastroenterology, Brigham and Women's Hospital, Boston, MA, USA

Population Sciences, Dana-Farber Cancer Institute, Boston, MA, USA

Harvard Medical School, Boston, MA, USA

Raymond S. Tang Institute of Digestive Disease, Prince of Wales Hospital, The Chinese University of Hong Kong, Shatin, New Territories, Hong Kong, China

Caroline Verbeke Division of Pathology, Department of Laboratory Medicine (LABMED), and Department of Clinical Pathology, Karolinska University Hospital, Stockholm, Sweden

Field F. Willingham Division of Digestive Diseases, Department of Medicine, Emory University School of Medicine, Atlanta, GA, USA

Ichiro Yasuda Department of Gastroenterology, Teikyo University Mizonokuchi Hospital, Kawasaki, Japan

Part I

Types of Lesions

Classification of Pancreatic Lesions

1

James J. Farrell

Introduction

The new revised WHO classification of tumors of the pancreas includes both exocrine and endocrine neoplasms in one classification (Table 1.1) [1]. This chapter will briefly review the major exocrine tumors, which are covered in more detail in subsequent chapters. A more detailed discussion of the classification of precursor pancreatic ductal lesions and pancreatic neuroendocrine tumors of the pancreas will also be provided in this chapter.

Classification of Solid Exocrine Tumors of the Pancreas

Ductal Adenocarcinoma

Ductal adenocarcinoma and its variants make up more than 90 % of all malignant exocrine pancreatic tumors. About two thirds of ductal adenocarcinomas occur in the head of the gland; the rest occur in the body or tail, or diffusely throughout the pancreas. They are characterized by an intense desmoplastic reaction in which duct-like structures of varying degrees of differentiation are seen. It comprises extracellular matrix together with a number of different host cell types, including fibroblasts, small endothelial-lined vessels, residual normal epithelia, and a variety of inflammatory cells which are both locally derived and recruited from the circulation [2]. The interplay between all these cells types and the pancreatic cancer cells influences new blood vessel formation, invasion, metastases, and evasion of the host immune system [3]. Because of their proximity to the intrapancreatic portion of the common bile duct, tumors in the head usually produce jaundice since they compress and obstruct the bile duct as they grow. They often obstruct the pancreatic duct as well, and although steatorrhea may result, there may not be any obvious symptoms. Tumors of the head of the pancreas are usually at least 2 cm in diameter when they are first diagnosed. Most tumors that are resected have a median diameter of 2.5–3.5 cm. Tumors of the body and tail commonly are larger (5–7 cm) and more advanced when they are discovered because they do not produce symptoms as early as head tumors do. The symptoms from tumors in the body and tail are usually caused by malignant infiltration of the retroperitoneal structures and nerves, which produces pain. By the time the diagnosis is made, almost all are unresectable. Nevertheless, there is evidence that resectable body tumors have a similar prognosis to resectable tumors in the head of

J.J. Farrell, M.D. (✉)
Yale Center for Pancreatic Disease,
Yale School of Medicine, 1080 LMP, 15 York St.,
New Haven, CT 06150, USA
e-mail: james.j.farrell@yale.edu

M.S. Wagh, P.V. Draganov (eds.), *Pancreatic Masses*, DOI 10.1007/978-3-319-19677-0_1

Table 1.1 WHO histologic classification of tumors of the exocrine and endocrine pancreas

1. Exocrine
(a) Epithelial tumors
• Benign
– Serous cystadenoma
– Mucinous cystadenoma
– Intraductal papillary-mucinous adenoma
– Mature teratoma
• Borderline (uncertain malignant potential)
– Mucinous cystic neoplasm with moderate dysplasia
– Intraductal papillary-mucinous neoplasm with moderate dysplasia
– Solid-pseudopapillary neoplasm
• Malignant
– Ductal adenocarcinoma
Mucinous noncystic carcinoma
Signet ring cell carcinoma
Adenosquamous carcinoma
Undifferentiated (anaplastic) carcinoma
Undifferentiated carcinoma with osteoclast-like giant cells
Mixed ductal–endocrine carcinoma
– Serous cystadenocarcinoma
– Mucinous cystadenocarcinoma
Noninvasive
Invasive
– Intraductal papillary mucinous carcinoma
Noninvasive
Invasive
– Acinar cell carcinoma
Acinar cell cystadenocarcinoma
Mixed acinar–endocrine carcinoma
– Pancreatoblastoma
– Solid-pseudopapillary carcinoma
– Others
(b) Nonepithelial tumors
• Mesenchymal tumors
– Lymphangioma
– Lipoma
– Solitary fibrous tumor
– Ewing sarcoma
– Desmoplastic small round cell tumor
– Perivascular epithelioid cell neoplasm
• Lymphomas
– Diffuse large B-cell lymphoma (DLBCL)
(c) Secondary tumors
2. Endocrine
(a) Pancreatic neuroendocrine microadenoma
(b) Neuroendocrine tumor G1 (NET G1)/Carcinoid
(c) Neuroendocrine tumor G2 (NET G2)

(continued)

Table 1.1 (continued)

(d) Neuroendocrine carcinoma
• Large cell neuroendocrine carcinoma
• Small cell neuroendocrine carcinoma
(e) Functional PNET
• Gastrinoma, malignant
• Glucagonoma, malignant
• Insulin-producing carcinoma (insulinoma)
• Somatostatinoma, malignant
• Vipoma, malignant

the gland. Approximately 70–80 % of adenocarcinomas of the head of the pancreas have metastasized to regional lymph nodes by the time they are discovered, which worsens the prognosis but does not preclude cure. These tumors also commonly invade lymphatic channels and perineural spaces. The prognosis is also influenced by the degree of tumor differentiation and by the presence of invasion of the retroperitoneal tissues adjacent to the cancer. The best outcome is seen in patients who have well-differentiated neoplasms, without retroperitoneal invasion or lymph node metastases. Distant metastases (e.g., lung) may occur, but pancreatic cancer typically infiltrates locally into the adjacent structures (e.g., stomach, duodenum, colon, transverse mesocolon, portal and superior mesenteric veins, superior mesenteric artery). The liver is the most common site of intraabdominal metastasis, and peritoneal seeding of the tumor is also seen. In patients without distant spread, vascular invasion by tumor is the most common reason for unresectability.

The most widely accepted staging system for pancreatic cancer is the American Joint Committee on Cancer (in cooperation with the TNM committee of the International Union Against Cancer), which is shown in Table 1.2 [4]. Although this system is prognostic for overall survival, it is not particularly useful in guiding treatment, because some patients with advanced-stage disease (i.e., stage IVA) may be candidates for surgical resection, whereas others may not. For this reason, pancreatic cancer patients are generally classified by physicians as having resectable, locally advanced, or metastatic disease. Other histologic variants of pancreatic ductal adenocarcinoma have been described, including mucinous noncystic carcinoma, signet ring cell carcinoma, adenosquamous carcinoma, undifferentiated (anaplastic) carcinoma, undifferentiated carcinoma with osteoclast-like giant cells, and mixed ductal–endocrine carcinoma.

Acinar Cell Carcinoma

Acinar cell carcinomas are uncommon and characterized by acinar arrangement of cells supported by minimal fibrous stoma [5]. They represent 1–2 % of all exocrine pancreatic neoplasms in adults and are considered separate from pancreatic ductal adenocarcinoma. Zymogen granules are present, which may be identified by electron microscopy. Patients may have elevated serum lipase levels and associated nonsuppurative panniculitis of the extremities and bone marrow and manifest subcutaneous nodules and polyarthritis. These tumors usually occur in adults in their sixth to eighth decades of life, and are rare under the age of 40. They have a male predominance, with an M:F ratio of 2:1 [6]. Acinar cell carcinomas are generally well circumscribed and may be multinodular. Areas of necrosis and cystic degeneration may be present and extension into adjacent structure may occur. Metastases most commonly affect the regional lymph nodes and the liver.

Table 1.2 TNM classification of tumors of exocrine and endocrine pancreas

Primary tumor (*T*)			
T0	No evidence of primary tumor		
Tis	in situ tumor		
Tl	Tumor limited to the pancreas, <2 cm in greatest dimension		
T2	Tumor limited to the pancreas, >2 cm in greatest dimension		
T3	Tumor extends directly into duodenum, bile duct, or peripancreatic tissues		
T4	Tumor extends directly into stomach, spleen, colon, or celiac axis vessels		
Regional lymph nodes (*N*)			
N0	Regional lymph nodes not involved		
N1	Regional lymph nodes involved		
N1a	Metastasis in a single regional lymph node		
N1b	Metastases in multiple regional lymph nodes		
Distant metastases			
MX	Distant metastases cannot be assessed		
M0	No distant metastases		
M1	Distant metastases present		
Stage grouping			
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage II	T3	N0	M0
Stage III	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IVA	T4	Any N	M0
Stage IVB	Any T	Any N	M1

Other Uncommon Solid Pancreatic Tumors

Other solid exocrine tumors of the pancreas include epithelial types such as pancreatoblastoma, a rare malignant epithelial tumor generally affecting young children, composed of well-defined solid nests of cells with acinar formations and squamoid corpuscles, separated by stromal bands. This accounts for 30–50 % of all pancreatic neoplasms in young children [7]. Metastases to the pancreas account for 3–16 % of all pancreatic malignancies, either by direct invasion (stomach, liver, and adrenal gland) or by lymphatic or hematogenous spread, including breast cancer, lung cancer, and renal carcinoma. Renal carcinoma is unique as it may give rise to pancreatic metastases without overt metastases elsewhere. Nonepithelial tumors of the pancreas are rare, including mesenchymal tumors, leimyosarcoma, malignant gastrointestinal stromal tumors, and solitary fibrous tumors. Primary lymphoma of the pancreas is defined as an extranodal lymphoma arising from the pancreas and is usually of B phenotype [including low-grade lymphoma of diffuse small cell type, follicle center cell lymphoma, low-grade MALT lymphoma, and large B-cell lymphoma, seen in immunodeficiency setting (e.g., HIV infection and posttransplant lymphoproliferative disorders following solid organ transplantation)] [8].

Classification of Cystic Exocrine Tumors of the Pancreas

Cystic neoplasms of the pancreas (CNP) were once considered extremely rare (many textbooks perpetuated the notion that most cystic lesions of the pancreas were pseudocysts), and fewer than 10 % were neoplasms [9]. Studies using CT and MRI have shown that the prevalence of pancreatic cysts (in individuals without history of symptoms

Table 1.3 Classification of cystic neoplasms of the pancreas, including lesions that resemble them (clinically common and important diseases highlighted in bold text)

Epithelial neoplasms
Serous cystadenoma
Mucinous cystic neoplasm and MCN-associated carcinoma
Intraductal papillary mucinous neoplasm and IPMN-associated carcinoma
Solid pseudopapillary neoplasm
Pancreatic ductal adenocarcinoma with cystic degeneration
Cystic pancreatic endocrine neoplasm (CPEN)
Acinar cystadenoma and cystadenocarcinoma
Dermoid cyst (cystic teratoma)
Intraductal papillary variant of acinar cell carcinoma
Intraductal tubulopapillary neoplasm
Nonepithelial
Lymphangioma
Epidermoid cyst in intrapancreatic spleen
Cystic pancreatic hamartoma
Mesothelial cyst
Lesions resembling pancreatic cystic neoplasms
Pseudocyst
Lymphoepithelial cyst (epidermoid cyst)
Mucinous nonneoplastic cyst
Enteric duplication cysts
Endometrial cyst
Hydatid cyst
Retention cyst
Accessory splenic cyst
Cystic pheochromocytoma
Cystic gastrointestinal stromal tumor
Retention cyst
Squamoid cyst

of pancreatic disease) is about 2.5 % [10, 11], and that this increases with age to the point that 10 % of persons 70 years or older have a pancreatic cyst [10]. Although the WHO classifies pancreatic cysts based on well-defined neoplastic pathologies, there is a clinical classification which includes both neoplastic and nonneoplastic pancreatic cysts including pseudocysts (Table 1.3) [9].

Serous Cystadenoma

Serous cystadenoma of the pancreas (SCA) is a benign, slow-growing tumor that affects predominantly women (~75 %); the mean age of resected patients has been 62 years [12–15]. This is discussed in further detail elsewhere in this book.

Intraductal Papillary Mucinous Neoplasm

The term "mucinous ductal ectasia" was used for many years to describe an entity characterized by gross dilation of the pancreatic duct due to overproduction of mucus from a proliferative epithelium with papillary growth. This disease is now recognized to be an advanced form of main-duct intraductal papillary mucinous neoplasm (MD-IPMN), and we now recognize that this neoplastic proliferation can involve the side branches of the pancreatic ductal system, either alone (branch-duct IPMN or BD-IPMN) or in combination (mixed or combined IPMN) [16]. This is discussed in further detail elsewhere in this book.

Mucinous Cystic Neoplasm

The mucinous cystic neoplasm of the pancreas (MCN) is a relatively uncommon tumor that comprises about a quarter of all resected cystic neoplasms of the pancreas in large surgical series [17]. This tumor is predominantly seen in women (>95 %) and in the distal pancreas (>95 %), and, unlike branch-duct IPMNs, is always a single lesion [18–20]. This is discussed in further detail elsewhere in this book.

Solid Pseudopapillary Neoplasm

The solid pseudopapillary neoplasm of the pancreas (SPN) is a very uncommon lesion that comprises less than 4 % of resected pancreatic cystic tumors. Prior to its inclusion in the World Health Organization (WHO) classification, it had previously been known by a variety of different names, including papillary epithelial neoplasm of the pancreas, solid and cystic tumor of the pancreas, adenocarcinoma of the pancreas of childhood, papillary-cystic tumor, and solid and papillary epithelial neoplasm [21]. It predominantly affects women (>80 %), and the median age has been between 30 and 38 years, with about 20–25 % of cases being seen in the pediatric population [22–24]. This is discussed in further detail elsewhere in this book.

Classification of Pancreatic Ductal Precursor Lesions

The presumed precursor lesions of pancreatic ductal adenocarcinoma are not discussed in detail in the ICD-10. Pancreatic cancer precursor lesions, also known as pancreatic intraepithelial eoplasia (PanIN), are seen more commonly in patients with pancreatic cancer compared with not (Fig. 1.1) [25, 26]. Pancreatic Intraepithelial Neoplasia (PanIN) precursor lesions can be graded from PanIN-1A (flat mucinous epithelium) to PanIN-2 (columnar epithelium with nuclear atypia) to PanIN-3 (in situ carcinoma) [26]. Normal ductal and ductular epithelium is a cuboidal to low-columnar epithelium with amphophilic cytoplasm, without the features of evolving PanIN such as mucinous cytoplasm, nuclear crowding, and atypia. A transitional squamous metaplasia has also been described, known as squamous metaplasia, in which the normal cuboidal ductal epithelium is replaced by mature squamous or transitional epithelium without atypia (Table 1.4).

In pancreatic intraepithelial neoplasia 1-A (PanIN 1-A), flat epithelial lesions composed of tall columnar cells with basally located nuclei and abundant supranuclear mucin are seen. The nuclei are small and round to oval in shape. When oval, the nuclei are oriented perpendicular to the basement membrane. In pancreatic intraepithelial

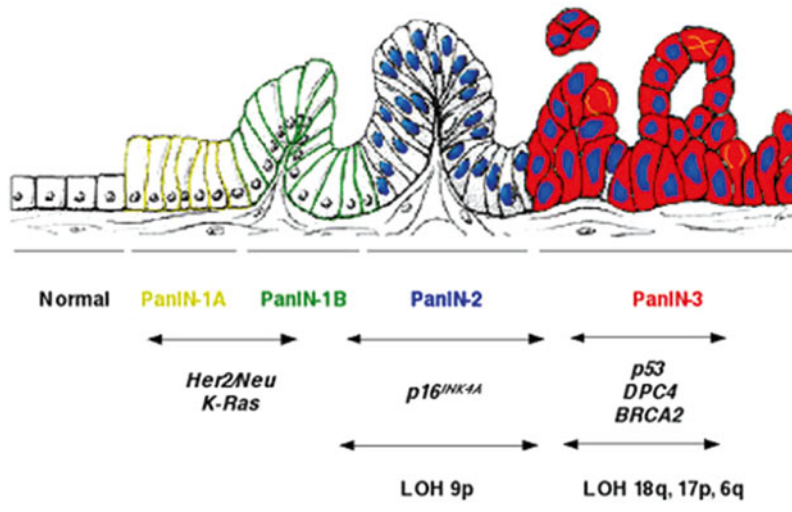

Fig. 1.1 Pancreatic cancer carcinogenesis. Progression of pancreatic intraepithelial lesions (PanIN) from normal to invasive cancer

Table 1.4 Recommended terms for pancreatic intraepithelial neoplasia (Panin)

Recommended WHO term	Previous terminology
Squamous metaplasia	Squamous metaplasia, epidermoid metaplasia, focal epithelial hyperplasia
PanIN-1A	Mucinous cell hypertrophy, mucinous cell hyperplasia, nonpapillary ductal hyperplasia
PanIN-1B	Ductal papillary hyperplasia, adenomatoid ductal hyperplasia, ductular cell hyperplasia
PanIN-2	Any PanIN lesion with moderate dysplasia
PanIN-3	Severe ductal dysplasia, carcinoma-in-situ

neoplasia 1-B (PanIN 1-B), these epithelial lesions have a papillary, micropapillary, or basally pseudostratified architecture but are otherwise identical to PanIN-1A. For pancreatic intraepithelial neoplasia 2 (PanIN-2), these mucinous epithelial lesions may be flat or papillary, but with defined nuclear abnormalities, including some loss of polarity, nuclear crowding, enlarged nuclei, pseudostratification, and hyperchromatism. These nuclear abnormalities fall short of those seen in PanIN-3. Mitoses are rare, but when present are nonluminal (not apical) and not atypical. Pancreatic intraepithelial neoplasia 3 (PanIN-3) typically shows papillary or micropapillary architecture, with true cribriforming, budding off small clusters of epithelial cells into the lumen and luminal necroses. Cytologically, these lesions are characterized by a loss of nuclear polarity, dystrophic goblet cells (goblet cells with nuclei oriented toward the lumen and mucinous cytoplasm oriented toward the basement membrane), mitoses which may occasionally be abnormal, nuclear irregularities, and prominent (macro) nucleoli.

This histologic- and cytologic-based model of pancreatic precursor is supported by molecular analyses (mutational analysis, immunohistochemical analysis, and loss of heterozygosity studies) which have demonstrated most of the molecular changes seen in invasive ductal adenocarcinoma identified in PanIN lesions, with the prevalence of these genetic alterations increasing with increasing degrees of cytologic and architectural atypia in the duct lesions in PanIN.

Classification of Pancreatic Neuroendocrine Tumors

Pancreatic neuroendocrine tumors (pancreatic NETs) which arise from the endocrine tissues of the pancreas represent up to 3 % of primary pancreatic tumors. They can secrete a variety of peptide hormones, including insulin, gastrin, glucagon, and vasoactive intestinal peptide (VIP), associated with a clinical syndrome, so-called functioning pancreatic NET. However, between 50 and 75 % of pancreatic NETs are nonfunctioning (i.e., unassociated with a hormonal syndrome) [27]. This is discussed in further detail elsewhere in this book.

References

1. Chapter 12—Tumours of the pancreas. In: Bosman FT, Carneiro F, Hruban RH, Theise ND, editors. WHO classification of tumours of the digestive system. Lyon: IARC; 2010.
2. Chu GC, Kimmelman AC, Hezel AF, DePinho RA. Stromal biology of pancreatic cancer. J Cell Biochem. 2007;101(4):887–907.
3. Mueller MM, Fusenig NE. Friends or foes—bipolar effects of the tumour stroma in cancer. Nat Rev Cancer. 2004;4(11):839–49.
4. Edge S, Byrd DR, Compton CC, et al., editors. American Joint Committee on Cancer staging manual. 7th ed. New York: Springer; 2010.
5. Colombo P, Arizzi C, Roncalli M. Acinar cell cystadenocarcinoma of the pancreas: report of rare case and review of the literature. Hum Pathol. 2004;35(12):1568–71.
6. Holen KD, Klimstra DS, Hummer A, Gonen M, Conlon K, Brennan M, et al. Clinical characteristics and outcomes from an institutional series of acinar cell carcinoma of the pancreas and related tumors. J Clin Oncol. 2002;20(24):4673–8.
7. Balasundaram C, Luthra M, Chavalitdhamrong D, Chow J, Khan H, Endres PJ. Pancreatoblastoma: a rare tumor still evolving in clinical presentation and histology. JOP. 2012;13(3):301–3.
8. Naito Y, Okabe Y, Kawahara A, Taira T, Yamagushi T, Abe H, et al. Guide to diagnosing primary pancreatic lymphoma, B-cell type: immunocytochemistry improves the diagnostic accuracy of endoscopic ultrasonography-guided fine needle aspiration cytology. Diagn Cytopathol. 2012;40(8):732–6.
9. Farrell JJ, Fernandez-del Castillo C. Pancreatic cystic neoplasms: management and unanswered questions. Gastroenterology. 2013;144(6):1303–15.
10. de Jong K, Nio C, Mearadji B, Phoa S, Engelbrecht M, Dijkgraaf M, et al. Disappointing interobserver agreement among radiologists for a classifying

diagnosis of pancreatic cysts using magnetic resonance imaging. Pancreas. 2012;41(2):278–82.
11. Laffan TA, Horton KM, Klein AP, Berlanstein B, Siegelman SS, Kawamoto S. Prevalence of unsuspected pancreatic cysts on MDCT. Am J Roentgenol. 2008;191:802–7.
12. Galanis C, Zamani A, Cameron JL, Campbell KA, Lillemoe KD, Caparelli D, et al. Resected serous cystic neoplasms of the pancreas: a review of 158 patients with recommendations for treatment. J Gastrointest Surg. 2007;11:820–6.
13. Tseng JF, Warshaw AL, Sahani DV, Lauwers GY, Rattner DW, Fernandez-del Castillo C. Serous cystadenoma of the pancreas: tumor growth rates and recommendations for treatment. Ann Surg. 2005; 242(3):413–9; discussion 419–21.
14. Le Borgne J, de Calan L, Partensky C, FSA. Cystadenomas and cystadenocarcinomas of the pancreas: a multiinstitutional restrospective study of 398 cases. Ann Surg. 1999;230:152–61.
15. Bassi C, Salvia R, Molinari E, Biasutti C, Falconi M, Pederzoli P. Management of 100 consecutive cases of pancreatic serous cystadenoma: wait for symptoms and see at imaging or vice versa? World J Surg. 2003;27:319–23.
16. Fernández-del Castillo C, Adsay NV. Intraductal papillary mucinous neoplasms of the pancreas. Gastroenterology. 2010;139:708–13.
17. Valsangkar NP, MoralesOyarvide V, Thayer SP, Ferrone CR, Wargo JA, Warshaw AL, et al. 851 resected cystic tumors of the pancreas: a 33-year experience at the Massachusetts General Hospital. Surgery. 2012;152:S4–12.
18. Crippa S, Salvia R, Warshaw AL, Dominguez I, Bassi C, Falconi M, et al. Mucinous cystic neoplasm of the pancreas is not an aggressive entity: lessons from 163 resected patients. Ann Surg. 2008;247:571–9.
19. Yamao K, Yanagisawa A, Takahashi K, Kimura W, Doi R, Fukushima N, et al. Clinicopathological features and prognosis of mucinous cystic neoplasm with ovarian-type stroma: a multi-institutional study of the Japan Pancreas Society. Pancreas. 2011;40:67–71.
20. Le Baleur Y, Couvelard A, Vullierme MP, Sauvanet A, Hammel P, Rebours V, et al. Mucinous cystic neoplasms of the pancreas: definition of preoperative imaging criteria for high-risk lesions. Pancreatology. 2011;11:495–9.
21. Vassos N, Agaimy A, Klein P, Hohenberger W, Croner RS. Solid-pseudopapillary neoplasm (SPN) of the pancreas: case series and literature review on an enigmatic entity. Int J Clin Exp Pathol. 2013;6(6): 1051–9.
22. Papavramidis T, Papavramidis S. Solid pseudopapillary tumors of the pancreas: review of 718 patients reported in English literature. J Am Coll Surg. 2005;200(6):965–72.
23. Reddy S, Cameron JL, Scudiere J, Hruban RH, Fishman EK, Ahuja N, et al. Surgical management of solid-pseudopapillary neoplasms of the pancreas (Franz or Hamoudi tumors): a single-institutional series. J Am Coll Surg. 2009;208:950–9.
24. Butte JM, Brennan MF, Gonen M, Tang LH, D'Angelica M, Fong Y, et al. Solid pseudopapillary tumors of the pancreas. Clinical features, surgical outcomes, and long-term survival in 45 consecutive patients from a single center. J Gastrointest Surg. 2011;15:350–7.
25. Sommers SM, Murphy SA, Warren S. Pancreatic duct hyperplasia and cancer. Arch Pathol. 1954;27: 629–40.
26. Hruban RH, Takaori K, Klimstra DS, Adsay NV, Albores-Saavedra J, Biankin AV, et al. An illustrated consensus on the classification of pancreatic intraepithelial neoplasia and intraductal papillary mucinous neoplasms. Am J Surg Pathol. 2004;28(8):977–87.
27. Fesinmeyer MD, Austin MA, Li CI, De Roos AJ, Bowen DJ. Differences in survival by histologic type of pancreatic cancer. Cancer Epidemiol Biomarkers Prev. 2005;14(7):1766–73.

Pancreatic Adenocarcinoma

2

Sunil Amin and Christopher J. DiMaio

Introduction

Pancreatic adenocarcinoma remains a highly lethal disease, with a 5-year survival rate of 6 %. Surgical resection is the only curative option. Unfortunately, localized, potentially resectable disease often presents without overt signs or symptoms. Too often, patients are diagnosed late in their disease course with already metastasized cancers. As such, early detection of high-risk lesions remains the focus of considerable research. In this chapter, we will provide a comprehensive review of pancreatic adenocarcinoma, with a focus on recent progress in the field.

Epidemiology

Pancreatic cancer is the fourth leading cause of cancer-related deaths in the United States. In 2013, an estimated 45,220 cases were diagnosed, with 38,460 deaths [1]. Although pancreatic cancer rarely presents before age 45, the overall incidence rises sharply thereafter. From 2006 to 2010, the SEER age-adjusted incidence rate of pancreatic adenocarcinoma was 12.2/100,000. However, for individuals over age 65 the incidence rate is 69.4/100,000, and for individuals 80–84, the incidence rate is as high as 93.1/100,000 [2]. Hence, age is an important risk factor for the development of pancreatic cancer. Pancreatic cancer is slightly more prevalent among males than females (13.9 vs. 10.9 per 100,000) and blacks than whites (15.8 vs. 12.1 per 100,000) [2]. Despite several available treatment modalities (surgery, chemotherapy, radiation), the 5-year survival rate from pancreatic cancer remains dismal. The current rate of 6.5 % is only slightly improved from the 2.4 % documented between 1975 and 1977 [2].

Biology

The molecular biology of pancreatic adenocarcinoma is exceedingly complex, with an average of 63 genetically relevant mutations per tumor [3]. However, central to our understanding of carcinogenesis is the simplified concept that pancreatic adenocarcinoma is the final product of the progression of precursor lesions. These lesions are referred to as pancreatic intraepithelial neoplasia (PanIN) and progress through a series of sequential genetic alterations in the ductal epithelium (Fig. 2.1). The most well-studied effector of these alterations is the oncogenic KRAS gene, which was first associated with pancreatic cancer over two decades ago [4, 5]. Along with inactivation of the tumor suppressor genes CDKN2A,

S. Amin, M.D., M.P.H. • C.J. DiMaio, M.D. (✉)
Division of Gastroenterology, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, Box 1069, New York, NY, 10029, USA
e-mail: Christopher.DiMaio@mssm.edu

M.S. Wagh, P.V. Draganov (eds.), *Pancreatic Masses*, DOI 10.1007/978-3-319-19677-0_2

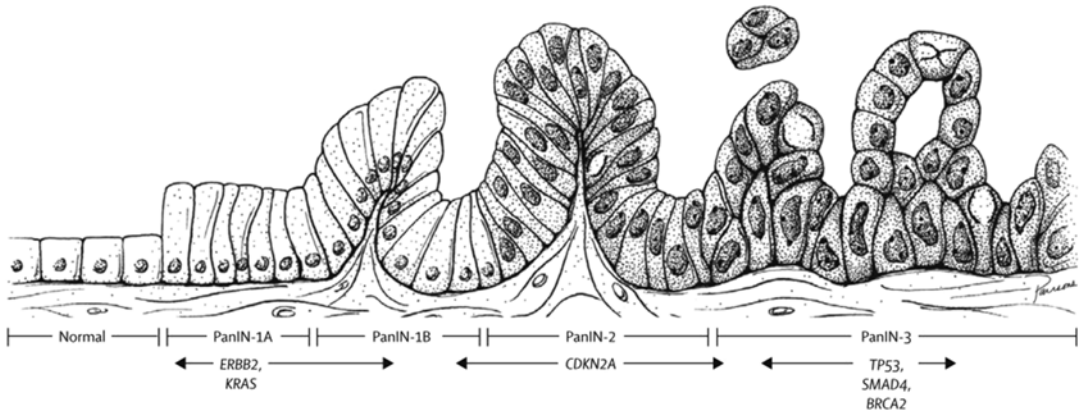

Fig. 2.1 PanIN progression model, showing genetic alterations. *PanIN,* pancreatic intraepithelial neoplasia (Pending permission from American Association for Cancer Research—RH Hruban, M Goggins, J Parsons, SE Kern. Progression model for pancreatic cancer. Clin Cancer Res, 6 (2000), pp. 2969–2972)

TP53, and SMAD4 (SMAD family member 4 gene, also known as deleted in pancreatic cancer 4, DPC4), the ductal epithelium is able to transform from minimally dysplastic PanIN grades 1A and 1B lesions to the more severely dysplastic grades 2 and 3 lesions. A recently published computational model based on data generated from the genome project estimates the time interval from initial mutation in the ductal epithelium (PanIN1) to the development of infiltrating carcinoma to be 11.7 years. Approximately 6.7 years is then required for a metastatic subclone to develop within the primary carcinoma, and a further 2.7 years to progress from metastatic dissemination to the patient's death [6]. Unfortunately, the majority of pancreatic adenocarcinoma patients are diagnosed toward the end of this sequence.

The oncogenic KRAS mutation is present in nearly all pancreatic adenocarcinoma [4, 7]. Through transcription of an abnormal RAS protein that is constituently active, a number of downstream signaling pathways lead to aberrant cell proliferation. Similarly, inactivation of the tumor suppressor gene CDK2NA is present in more than 90 % of pancreatic cancers [8]. These mutations lead to loss of the p16 protein, which plays an essential role in cell cycle regulation. TP53 mutations occur in approximately 75 % of pancreatic cancer and lead to dysregulation of the cellular stress response [7, 9]. SMAD4/DPC4 mutations occur in approximately 55 % of cases and lead to disruption of cell signaling in the transforming growth factor B (TGF-B) pathway [8, 10]. SMAD4/DPC4 mutations are associated with a poor prognosis in pancreatic adenocarcinoma [11]. Whereas KRAS is generally an earlier mutation, the loss of tumor suppressor genes occurs later in the sequence of dysplasia [12, 13].

Risk Factors

Both inherited and environmental risk factors have been implicated in the pathogenesis of pancreatic adenocarcinoma. Hereditary susceptibility may account for up to 10 % of pancreatic cancer cases and includes both genetic cancer syndromes [Lynch syndrome, familial atypical multiple mole melanoma syndrome (FAMMM), Peutz–Jeghers syndrome (PJS), hereditary breast-ovarian cancer syndrome (HBOC), familial adenomatous polyposis (FAP)] as well as familial pancreatic cancer [14]. Environmental risk factors such as smoking and alcohol as well as the co-morbid conditions of diabetes, obesity, and chronic pancreatitis have all been associated with an increased risk of pancreatic adenocarcinoma.

Table 2.1 Genetic syndromes associated with pancreatic adenocarcinoma

Syndrome	Relative risk of pancreatic cancer	Genes implicated
Familial adenomatous polyposis	4–6×	APC
Lynch (formerly HNPCC)	8–9×	MLH 1, MSH2, MSH6, PMS2
Hereditary breast–ovarian cancer	3.5–10×	BRCA1, BRCA2, PALB2
Familial atypical multiple mole melanoma	13–22×	P16/CDKN2A
Hereditary pancreatitis	25–60×	PRSS1, SPINK1
Peutz–Jeghers syndrome	132×	STK11/LKB1

Source: Adapted from Hidalgo M., Pancreatic cancer. N. Engl. J. Med. 2010;362(17):1605–1617

Inherited Risk Factors

Several hereditary cancer syndromes have been associated with pancreatic adenocarcinoma (Table 2.1). Hereditary pancreatic cancer is characterized by a known genetic defect that increases the risk of pancreatic cancer. Familial pancreatic cancer (FPC), conversely, describes a family with at least two first-degree relatives with pancreatic cancer without an identifiable gene mutation or cancer syndrome [15].

Lynch syndrome, formerly known as HNPCC, arises from mutations in one of the DNA mismatch repair (MMR) genes MLH1, MSH2, MSH6, or PMS2. In addition to early-onset colorectal cancer, individuals with Lynch syndrome are predisposed to cancers of the pancreas, ovary, stomach, urinary tract, endometrium, and small bowel. Specifically, the risk of pancreatic cancer among individuals with Lynch syndrome is 1.31 % up to age 50 and 3.7 % up to age 70, which represents an 8.6-fold increase over the general U.S. population [16, 17].

Peutz–Jeghers syndrome (PJS) is an autosomal dominant hamartomatous polyposis syndrome caused by inherited mutations in the STK11/LKB1 gene on chromosome 19p13.3. Individuals with PJS have distinctive mucocutaneous pigmentation and are at increased risk for a number of GI malignancies, including colorectal cancer, gastric cancer, small bowel adenocarcinoma, and pancreatic cancer. The lifetime incidence of pancreatic cancer among patients with PJS has been estimated to be as high as 36 % [18].

Familial atypical multiple mole melanoma (FAMMM) syndrome is an autosomal dominant condition associated with germline mutations in the p16/CDKN2A gene. Nevertheless, there is wide variability in the prevalence of the CDKN2A mutations among patients with FAMMM. Individuals with FAMMM have multiple dysplastic nevi that predispose them to malignant melanoma. In addition, these patients are at increased risk for pancreatic adenocarcinoma, lung and breast cancer, and sarcomas [16, 19]. Specifically, individuals with a germline p16 mutation have an approximately 17 % lifetime risk of developing pancreatic cancer [20].

Hereditary breast–ovarian cancer (HBOC) syndrome is an autosomal dominant condition associated with germline mutations in the BCRCA1 and BRCA2 genes. Patients with BRCA1 or 2 mutations present with early-onset breast and ovarian cancer. Studies have also linked both of these mutations with an increased risk of pancreatic adenocarcinoma. Of the two mutations, the association with pancreas cancer is most robust for BRCA2, which carries an approximately 3.5 times increased risk over the general population [21]. In addition, 5.5 % of Ashkenazi Jewish patients with resected PDAC have been shown to have founder mutations of BRCA1/2, compared to 1.1 % of cancer-free controls [22]. As such, screening such high-risk groups for germline mutations in the absence of a family history of breast or ovarian cancer has been proposed.

Familial adenomatous polyposis (FAP) syndrome is an autosomal dominant condition associated with inherited mutations of the APC tumor suppressor gene. Individuals with FAP develop colon cancer at a very early age but are also at increased risk for duodenal, thyroid, hepatic, and pancreatic cancer. The relative risk of pancreatic adenocarcinoma among FAP patients and at-risk relatives has been estimated at 4.5 times that of

the general population (RR, 4.45; 95 % CI, 1.2–11.4), with an absolute risk of 26.8/100,000 person years [23].

Hereditary pancreatitis (HP) is characterized by recurrent attacks of acute pancreatitis in childhood and adolescence with the eventual development of chronic pancreatitis over time. The autosomal dominant form of this disorder is associated with germline mutations of the PRSS1 gene, which encodes for cationic trypsinogen [24]. The risk of pancreatic cancer among patients with hereditary pancreatitis is significant, estimated at 19 % at age 60 and 53 % at age 75 [25]. This elevated risk may be secondary to inflammation, which has been shown to enhance cancer progression and amplify pathologic RAS activity [26, 27]. Among patients with hereditary pancreatitis, smoking and diabetes are preexisting risk factors that increase the risk of pancreatic cancer significantly [15, 28, 29].

Environmental Risk Factors

Several environmental factors predispose to pancreatic adenocarcinoma. Of these, cigarette smoking is the most well studied and perhaps the most significant, causing approximately 20–25 % of all pancreatic cancers [30]. A pooled analysis of 12 case-control studies from the International Pancreatic Cancer Case-Control Consortium (PanC4) showed a twofold increased risk of pancreatic cancer among current smokers compared to never smokers (OR, 2.2; 95 % CI, 1.7–2.8) [31]. While former smokers are also at increased risk (OR, 1.2; 95 % CI, 1.0–1.3), this risk is attenuated to the level of normal smokers 20 years after quitting [31].

Another significant risk factor for pancreatic adenocarcinoma is diabetes mellitus. A recent meta-analysis of 36 cohort studies concluded that diabetes mellitus is associated with a 1.96-fold increase in pancreatic cancer (RR, 1.96; 95 % CI, 1.66–2.27), controlling for several co-founders including alcohol consumption, BMI, and smoking status [32]. Furthermore, several studies have shown that the risk of pancreatic cancer is negatively correlated with the duration of diabetes. Individuals with the shortest history of diabetes (<4 years) appear to have a 1.5-fold greater risk (OR, 1.5; 95 % CI, 1.3–1.8) of developing pancreatic cancer than individuals with diabetes for 5 and 10 years, and a 2.1-fold greater risk than individuals with diabetes for more than 10 years (OR, 2.1; 95 % CI, 1.9–2.3) [32, 33].

Elevated BMI has also been linked to an increased risk of pancreatic cancer, independent of the increased risk associated with diabetes [34–36]. Compared to individuals with a BMI between 18.5 and 24.9, those with a BMI >35 have a 1.55-fold increased risk of pancreatic cancer (OR, 1.55; 95% CI, 1.16–2.07) [36]. Centralized fat distribution, particularly in women, as well as early adulthood obesity have both been linked to an increased risk of pancreatic cancer, with the latter predisposing to earlier onset of disease [36, 37].

Alcohol increases one's risk of pancreatic cancer, but only when consumed in large quantities. Mild to moderate alcohol consumption may even be protective. A meta-analysis of 21 case-control and 11 cohort studies reported a pooled relative risk of 1.22 (95 % CI, 1.12–1.34) for those who consumed equal to or greater than three drinks per day, but only 0.92 (0.86–0.97) for those who consumed less than this amount [38]. This association appears to be independent of confounding chronic pancreatitis or smoking history.

Chronic pancreatitis is a well-known risk factor for pancreatic cancer. Although the risk is highest for patients with autosomal dominant hereditary pancreatitis (discussed above), patients with acquired chronic pancreatitis are also at risk. A pooled analysis of 10 case-control studies reported a nearly threefold increased risk of pancreatic cancer (OR, 2.71; 95 % CI, 1.96–3.74) among patients diagnosed with pancreatitis more than 2 years before their cancer diagnosis [39]. However, the population attributable fraction was estimated at only 1.34 %, suggesting that only a small portion of pancreatic cancer is secondary to chronic pancreatitis. Of note, via reverse causation, new-onset pancreatitis may also be a consequence of tumor-related duct obstruction, and thus a possible presentation of pancreatic cancer.

Finally, an association has also been reported between colonization of CagA-negative *Helicobacter pylori* infection and pancreatic cancer [40]. This association appears to be strongest among individuals with non-O blood types.

Clinical Presentation

Patients with pancreatic adenocarcinoma present with nonspecific complaints. Often, patients may describe vague abdominal discomfort and nausea in the setting of weight loss. When the location of the tumor is within the head of the pancreas (approximately 75 % of cases), patients may present with jaundice from obstruction of the intra-pancreatic portion of the common bile duct [41]. A prospective study of 185 patients with newly diagnosed exocrine pancreatic cancer identified the most frequent presenting symptoms as asthenia (86 %), anorexia (85 %), weight loss (85 %), abdominal pain (79 %), and choluria (59 %) [42]. Less frequently, pancreatic cancer may present as gastrointestinal bleeding from gastric varices secondary to splenic vein thrombosis [43]. Up to 80 % of patients are either hyperglycemic or frankly diabetic at the time of diagnosis, which has important implications for early detection and screening efforts [44].

As the natural history of pancreatic cancer progresses, patients are at risk for several more complications. In addition to cholestasis from biliary obstruction, patients may also develop acute pancreatitis from obstruction of the pancreatic duct. In one series, 18 % of patients who underwent EUS-FNA following an episode of nonalcohol-, nongallstone-related acute pancreatitis were found to have pancreatic carcinoma [45]. Up to 10 % of patients may develop gastric outlet obstruction or duodenal obstruction from tumor expansion [46]. There is a bidirectional interaction between pancreatic cancer and diabetes. If not present at diagnosis, diabetes may emerge either as a complication of tumor-induced insulin resistance and islet cell dysfunction or as chronic obstruction of the pancreatic duct with upstream glandular atrophy and loss of islet cells [47, 48]. Similarly, patients with pancreatic adenocarcinoma, pre- or postresection, may complain of steatorrhea from exocrine insufficiency and are also at increased risk for superficial or deep venous thrombosis.

On physical exam, patients may have jaundice, lymphadenopathy, temporal wasting, hepatomegaly, or even ascites. Laboratory studies are similarly nonspecific and may show anemia, hyperglycemia, or mild elevations in liver tests. Biomarkers such as CA 19-9 may also be elevated and are discussed below.

Serum Tumor Markers

The routine use of serum biomarkers is limited in the management of pancreatic adenocarcinoma. At present, carbohydrate antigen 19-9 (CA 19-9) is the only clinicially useful biomarker for this purpose. CA 19-9 is a sialylated Lewis (a) antigen normally absorbed onto the surface of erythrocytes [49]. Since CA 19-9 is also present on various mucins secreted by pancreatic adenocarcinoma cells, it has been used as a marker of prognosis and disease burden for pancreatic adenocarcinoma since the 1980s [49, 50]. An elevated CA 19-9 value of greater than 70 U/mL has a sensitivity and specificity of 70 % and 87 %, respectively, for the diagnosis of pancreatic cancer [51]. With its low sensitivity and the fact that it can be elevated in benign pancreaticobiliary disease, CA 19-9 is not an effective screening test; however, it is useful as a marker of disease progression or recurrence following resection. Postresection CA 19-9 level also predicts overall survival among patients treated with adjuvant radiation. A large prospective study of 385 patients demonstrated a 72 % reduction in the risk of death for patients with a CA 19-9 lower than 180 compared to those with a postoperative CA 19-9 level greater than 180 (HR, 2.53; $p<0.0001$) [52]. Even patients with preoperative CA 19-9 levels as high as 900 can live as long as patients with normal values provided their postoperative CA 19-9 19-9 level falls within the normal range [53]. Other commonly used antigens such as CEA and CA 125, with sensitivities ranging from 30 to 60 % and specificities of

approximately 80 %, are less useful in the management of pancreatic adenocarcinoma, and not routinely used in clinical practice [54, 55]. In the future, newer technologies such as posttranscriptional gene regulation and next-generation gene sequencing will likely produce more promising, clinically relevant biomarkers to aid in early detection of pancreatic cancer and personalized treatment regimens [49].

Pathology

Pancreatic ductal adenocarcinomas are highly infiltrative tumors. Grossly, these tumors are solid and firm; however, microscopically, their edges are poorly defined (Figs. 2.2 and 2.3). Often tongues of carcinoma extend beyond the main tumor [56, 57]. Invasion often occurs before the time of diagnosis along lymphatic and perineural spaces, as well as small veins.

The histological hallmark of pancreatic ducal adenocarcinoma is the associated intense desmoplastic reaction within the tumor (Fig. 2.4) [56]. This reaction is composed of fibroblasts, inflammatory cells, endothelial cells, and complex extracellular matrix, which combined produce an elevated interstitial fluid pressure within the tumor [58]. Consequently, this elevated interstitial pressure induces vascular collapse and is thought to reduce perfusion to the tumor [58]. Reduced perfusion, in turn, has been implicated as a potential barrier to the adequate delivery of chemotherapeutic agents. On immunohistochemistry, pancreatic cancers may express CEA, cytokeratin, CA 19-9, B72.3 (TAG-72), CA 125, DUPAN2, as well as a number of mucins [56, 57].

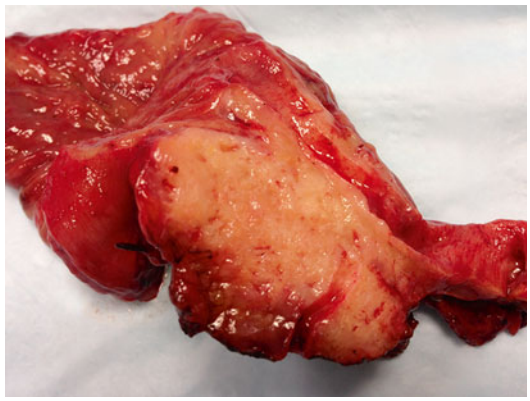

Fig. 2.2 Gross image of resected pancreatic ductal adenocarcinoma. Tumor has practically replaced the entire head of pancreas and blocked the main pancreatic duct, while the common bile remained open (Photo courtesy of Hongfa Zhu, MD, Icahn School of Medicine at Mount Sinai)

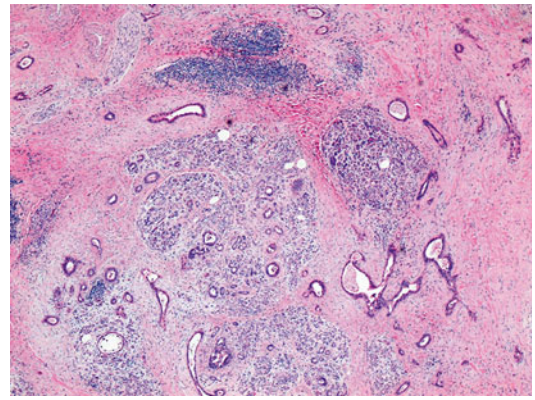

Fig. 2.3 Low-power image of infiltrating pancreatic ductal carcinoma in the background of parenchymal atrophy and prominent fibrosis (original magnification: ×40) (Photo courtesy of Hongfa Zhu, M.D., Icahn School of Medicine at Mount Sinai)

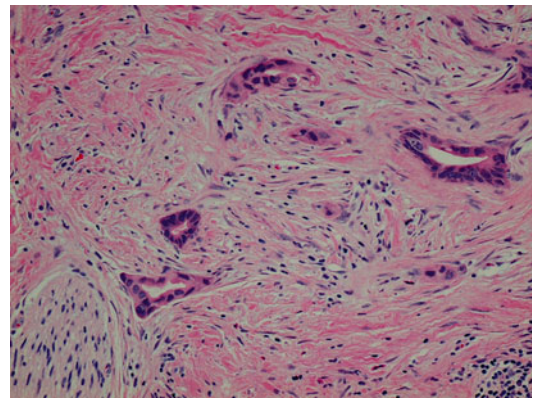

Fig. 2.4 Pancreatic cancer typically consists of infiltrating angulated glands surrounded by desmoplastic stroma, which makes the tumor less accessible to chemotherapy. Pancreatic cancer is also prone to perineural invasion (*left low corner*) (original magnification: ×200) (Photo courtesy of Hongfa Zhu, M.D., Icahn School of Medicine at Mount Sinai)

Staging

Pancreatic cancer is staged according to the American Joint Committee on Cancer (AJCC) tumor-node-metastasis classification (TNM) (Table 2.2) [59, 60]. The objective of the AJCC system is to generate a reproducible classification scheme based on which accurate predictions of prognosis and subsequent treatment recommendations can be generated. At present, this system is based on an assessment of resectability by helical CT scan. Whereas T1, T2, and T3 lesions are potentially resectable, T4 tumors, which involve the celiac axis or superior mesenteric artery, are not. Lesions that involve the superior mesenteric vein, splenic vein, and portal vein, provided they are patent, may be resectable depending on the expertise of the center and comfort of the surgeon with performing complex vascular reconstruction. A large-scale validation of the current system using the National Cancer Database (NCDB) found good 5-year survival discrimination by stage ($p<0.001$). Stage 1A patients survived a median of 10 months, whereas stage IV patients had a median survival of 2.5 months [61].

A critique of the current system is the highly variable survival among resected patients of the same AJCC stage. To this end, a nomogram which incorporated additional factors such as tumor grade or degree of differentiation was proposed and was found to predict postresection survival more accurately than the AJCC system [62]. This nomogram was based on a prospective cohort of 555 consecutive patients and validated with a retrospective cohort of 424 patients [62]. More recent studies using the SEER database have proposed a TNMG classification after showing that for each AJCC stage, survival is significantly worse for high-grade vs. low-grade tumors [63, 64].

Table 2.2 TNM staging system for exocrine and endocrine tumors of the pancreas

Primary tumor (T)			
TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
Tis	Carcinoma in situ[a]		
T1	Tumor limited to the pancreas, ≤2 cm in greatest dimension		
T2	Tumor limited to the pancreas, >2 cm in greatest dimension		
T3	Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery		
T4	Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)		
Regional lymph nodes (N)			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Regional lymph node metastasis		
Distant metastasis (M)			
M0	No distant metastasis		
M1	Distant metastasis		
Anatomic stage/prognostic groups			
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage III	T4	Any N	M0
Stage IV	Any T	Any N	M1

Source: Used with permission from Compton CC et al., Exocrine and endocrine pancreas. AJCC Cancer Staging Atlas. Springer; 2012

[a]This includes lesions classified as PanInIII classification

Management

A multidisciplinary approach to care is essential in the management of pancreatic adenocarcinoma. Gastroenterologists, surgeons, oncologists, radiation oncologists, pathologists, primary care providers, and pain specialists must all play a coordinated role in prognostication, treatment, and palliation if necessary. Several studies have shown that such a coordinated effort often results in reinterpretation of data, changes in therapeutic recommendations, and improved survival [65, 66]. Management is discussed in detail in various chapters in the treatment section of this book.

Screening/Prevention

Routine screening of pancreatic cancer in average-risk individuals is not recommended. The low incidence of pancreatic cancer combined with the lack of a low-cost screening modality makes such a strategy prohibitive. In contrast, screening to detect T1N0M0 disease and noninvasive precursor lesions such as PanIN and IPMN may be beneficial for those with an increased risk of pancreatic cancer. To date, several studies have looked at the utility of screening for pancreatic cancer in asymptomatic patients who have a significant family history and/or genetic predisposition for pancreatic cancer. A prospective study from the American Cancer of the Pancreas Consortium (CAPS) of 225 asymptomatic high-risk individuals identified 92 patients (42 %) with at least one pancreatic mass or dilated pancreatic duct by computed tomography (CT), magnetic resonance imaging (MRI), or endoscopic ultrasound (EUS). Of the 85 proven or suspected neoplasms, the vast majority were IPMNs (96 %), with the remaining lesions reported as pancreatic endocrine tumors [67]. Not all screening programs have resulted in such a high yield, however. A similar 5-year prospective study of 76 high-risk individuals from families with familial pancreatic cancer from the National German Familial Pancreatic Cancer Registry (FaPaCa) found only three PanIN lesions and one IPMN using a similar EUS/MR/MRCP-based screening program [68] (Fig. 2.5).

Regardless, the most recent International CAPS Consortium guidelines recommend that appropriate candidates for screening are (1) first-degree relatives (FDRs) of patients with PC from a familial PC kindred with at least two affected FDRs, (2) patients with PJS syndrome, or (3) p16, BRCA2, or HNPCC mutation carriers with at least one affected FDR [69]. Although EUS and/or MRI or magnetic resonance cholangiopancreatography (MRCP) were agreed upon as first-line screening modalities, no consensus was reached regarding appropriate age to start screening or stop surveillance, the appropriate interval for screening, or which screening abnormalities were concerning enough to warrant surgery [69].

Conclusion

Pancreatic adenocarcinoma remains a devastating and difficult-to-treat disease associated with a high mortality. Unfortunately, the majority of patients do not have resectable disease at the time of diagnosis. Although advances in surgical technology and chemotherapeutic regimens have resulted in incremental gains in survival, the current 5-year rate remains dismal at 6 %. In the future, an improved understanding of the biology and genetics of this disease will hopefully provide a foundation for improvements in targeted and more effective chemotherapeutic regimens. Furthermore, it is hoped that the identification and study of high-risk individuals will result in appropriate screening efforts and earlier detection of resectable lesions.

References

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin. 2013;63(1):11–30.
2. Howlader N, Noone AM, Krapcho M, Garshell J, Neyman N, Altekruse SF, et al., editors. SEER cancer statistics review (CSR) 1975–2010. Bethesda: National Cancer Institute.
3. Jones S, Zhang X, Parsons DW, Lin JC-H, Leary RJ, Angenendt P, et al. Core signaling pathways in human pancreatic cancers revealed by global genomic analyses. Science. 2008;321(5897):1801–6.
4. Di Magliano MP, Logsdon CD. Roles for KRAS in pancreatic tumor development and progression. Gastroenterology. 2013;144(6):1220–9.
5. Almoguera C, Shibata D, Forrester K, Martin J, Arnheim N, Perucho M. Most human carcinomas of the exocrine pancreas contain mutant c-K-ras genes. Cell. 1988;53(4):549–54.
6. Iacobuzio-Donahue CA. Genetic evolution of pancreatic cancer: lessons learnt from the pancreatic cancer genome sequencing project. Gut. 2012;61(7):1085–94.
7. Rall CJ, Yan YX, Graeme-Cook F, Beauchamp R, Yandell DW, Povoski SP, et al. Ki-ras and p53 mutations in pancreatic ductal adenocarcinoma. Pancreas. 1996;12(1):10–7.
8. Wood LD, Hruban RH. Pathology and molecular genetics of pancreatic neoplasms. Cancer J. 2012;18(6):492–501.
9. Scarpa A, Capelli P, Mukai K, Zamboni G, Oda T, Iacono C, et al. Pancreatic adenocarcinomas frequently show p53 gene mutations. Am J Pathol. 1993; 142(5):1534.
10. Hahn SA, Schutte M, Hoque AS, Moskaluk CA, da Costa LT, Rozenblum E, et al. DPC4, a candidate

tumor suppressor gene at human chromosome 18q21.1. Science. 1996;271(5247):350–3.
11. Blackford A, Serrano OK, Wolfgang CL, Parmigiani G, Jones S, Zhang X, et al. SMAD4 gene mutations are associated with poor prognosis in pancreatic cancer. Clin Cancer Res. 2009;15(14):4674–9.
12. Hidalgo M. Pancreatic cancer. N Engl J Med. 2010;362(17):1605–17.
13. Feldmann G, Beaty R, Hruban RH, Maitra A. Molecular genetics of pancreatic intraepithelial neoplasia. J Hepatobiliary Pancreat Surg. 2007;14(3):224–32.
14. Lucas AL, Chang MM, Lipsyc MD, Frucht H. The prevention and genetics of pancreatic cancer: a programmatic approach. In: Su GH, editor. Pancreatic cancer—methods and protocols. 2nd ed. New York: Springer; 2013.
15. Solomon S, Das S, Brand R, Whitcomb DC. Inherited pancreatic cancer syndromes. Cancer J. 2012;18(6):485–91.
16. Grover S, Syngal S. Hereditary pancreatic cancer. Gastroenterology. 2010;139(4):1076–80.
17. Kastrinos F, Mukherjee B, Tayob N, Wang F, Sparr J, Raymond VM, et al. Risk of pancreatic cancer in families with Lynch syndrome. JAMA. 2009;302(16):1790–5.
18. Giardiello FM, Brensinger JD, Tersmette AC, Goodman SN, Petersen GM, Booker SV, et al. Very high risk of cancer in familial Peutz–Jeghers syndrome. Gastroenterology. 2000;119(6):1447–53.
19. Lynch HT, Brand RE, Hogg D, Deters CA, Fusaro RM, Lynch JF, et al. Phenotypic variation in eight extended CDKN2A germline mutation familial atypical multiple mole melanoma-pancreatic carcinoma-prone families: the familial atypical multiple mole melanoma-pancreatic carcinoma syndrome. Cancer. 2002;94(1):84–96.
20. Vasen HFA, Gruis NA, Frants RR, van der Velden PA, Hille ETM, Bergman W. Risk of developing pancreatic cancer in families with familial atypical multiple mole melanoma associated with a specific 19 deletion of p16 (p16-Leiden). Int J Cancer. 2000;87(6):809–11.
21. Consortium TBCL. Cancer risks in BRCA2 mutation carriers. J Natl Cancer Inst. 1999;91(15):1310–6.
22. Ferrone CR, Levine DA, Tang LH, Allen PJ, Jarnagin W, Brennan MF, et al. BRCA germline mutations in Jewish patients with pancreatic adenocarcinoma. J Clin Oncol. 2009;27(3):433–8.
23. Giardiello FM, Offerhaus GJ, Lee DH, Krush AJ, Tersmette AC, Booker SV, et al. Increased risk of thyroid and pancreatic carcinoma in familial adenomatous polyposis. Gut. 1993;34(10):1394–6.
24. Whitcomb DC, Gorry MC, Preston RA, Furey W, Sossenheimer MJ, Ulrich CD, et al. Hereditary pancreatitis is caused by a mutation in the cationic trypsinogen gene. Nat Genet. 1996;14(2):141–5.
25. Rebours V, Lévy P, Ruszniewski P. An overview of hereditary pancreatitis. Dig Liver Dis. 2012;44(1):8–15.
26. Daniluk J, Liu Y, Deng D, Chu J, Huang H, Gaiser S, et al. An NF-κB pathway-mediated positive feedback loop amplifies Ras activity to pathological levels in mice. J Clin Invest. 2012;122(4):1519–28.
27. Rhim AD, Mirek ET, Aiello NM, Maitra A, Bailey JM, McAllister F, et al. EMT and dissemination precede pancreatic tumor formation. Cell. 2012;148(1–2):349–61.
28. Lowenfels AB, Maisonneuve P, Whitcomb DC, Lerch MM, DiMagno EP. Cigarette smoking as a risk factor for pancreatic cancer in patients with hereditary pancreatitis. JAMA. 2001;286(2):169–70.
29. Rebours V, Boutron-Ruault M-C, Jooste V, Bouvier A-M, Hammel P, Ruszniewski P, et al. Mortality rate and risk factors in patients with hereditary pancreatitis: uni- and multidimensional analyses. Am J Gastroenterol. 2009;104(9):2312–7.
30. Maisonneuve P, Lowenfels AB. Epidemiology of pancreatic cancer: an update. Dig Dis. 2010;28(4–5):645–56.
31. Bosetti C, Lucenteforte E, Silverman DT, Petersen G, Bracci PM, Ji BT, et al. Cigarette smoking and pancreatic cancer: an analysis from the International Pancreatic Cancer Case-Control Consortium (Panc4). Ann Oncol. 2012;23(7):1880–8.
32. Ben Q, Xu M, Ning X, Liu J, Hong S, Huang W, et al. Diabetes mellitus and risk of pancreatic cancer: a meta-analysis of cohort studies. Eur J Cancer. 2011;47(13):1928–37.
33. Huxley R, Ansary-Moghaddam A, Berrington de Gonzalez A, Barzi F, Woodward M. Type-II diabetes and pancreatic cancer: a meta-analysis of 36 studies. Br J Cancer. 2005;92(11):2076–83.
34. Aune D, Greenwood DC, Chan DSM, Vieira R, Vieira AR, Navarro Rosenblatt DA, et al. Body mass index, abdominal fatness and pancreatic cancer risk: a systematic review and non-linear dose-response meta-analysis of prospective studies. Ann Oncol. 2012;23(4):843–52.
35. Larsson SC, Orsini N, Wolk A. Body mass index and pancreatic cancer risk: a meta-analysis of prospective studies. Int J Cancer. 2007;120(9):1993–8.
36. Arslan AA, Helzlsouer KJ, Kooperberg C, Shu X-O, Steplowski E, Bueno-de-Mesquita HB, et al. Anthropometric measures, body mass index and pancreatic cancer: a pooled analysis from the Pancreatic Cancer Cohort Consortium (PanScan). Arch Intern Med. 2010;170(9):791–802.
37. Li D, Morris JS, Liu J, Hassan MM, Day RS, Bondy ML, et al. Body mass index and risk, age of onset, and survival in patients with pancreatic cancer. JAMA. 2009;301(24):2553–62.
38. Tramacere I, Scotti L, Jenab M, Bagnardi V, Bellocco R, Rota M, et al. Alcohol drinking and pancreatic cancer risk: a meta-analysis of the dose-risk relation. Int J Cancer. 2010;126(6):1474–86.
39. Duell EJ, Lucenteforte E, Olson SH, Bracci PM, Li D, Risch HA, et al. Pancreatitis and pancreatic cancer risk: a pooled analysis in the International Pancreatic

Cancer Case-Control Consortium (PanC4). Ann Oncol. 2012;23(11):2964–70.
40. Risch HA, Yu H, Lu L, Kidd MS. ABO blood group, *Helicobacter pylori* seropositivity, and risk of pancreatic cancer: a case-control study. J Natl Cancer Inst. 2010;102(7):502–5.
41. Brennan MF, Moccia RD, Klimstra D. Management of adenocarcinoma of the body and tail of the pancreas. Ann Surg. 1996;223(5):506–11; discussion 511–2.
42. Porta M, Fabregat X, Malats N, Guarner L, Carrato A, de Miguel A, et al. Exocrine pancreatic cancer: symptoms at presentation and their relation to tumour site and stage. Clin Transl Oncol. 2005;7(5):189–97.
43. Smith TA, Brand EJ. Pancreatic cancer presenting as bleeding gastric varices. J Clin Gastroenterol. 2001;32(5):444–7.
44. Pannala R, Basu A, Petersen GM, Chari ST. New-onset diabetes: a potential clue to the early diagnosis of pancreatic cancer. Lancet Oncol. 2009;10(1):88–95.
45. Tummala P, Tariq SH, Chibnall JT, Agarwal B. Clinical predictors of pancreatic carcinoma causing acute pancreatitis. Pancreas. 2013;42(1):108–13.
46. Wong YT, Brams DM, Munson L, Sanders L, Heiss F, Chase M, et al. Gastric outlet obstruction secondary to pancreatic cancer: surgical vs endoscopic palliation. Surg Endosc. 2002;16(2):310–2.
47. Park JW, Jang J-Y, Kim E-J, Kang MJ, Kwon W, Chang YR, et al. Effects of pancreatectomy on nutritional state, pancreatic function and quality of life. Br J Surg. 2013;100(8):1064–70.
48. Muniraj T, Chari S. Diabetes and pancreatic cancer. Minerva Gastroenterol Dietol. 2012;58(4):331–45.
49. Winter JM, Yeo CJ, Brody JR. Diagnostic, prognostic, and predictive biomarkers in pancreatic cancer. J Surg Oncol. 2013;107(1):15–22.
50. Glenn J, Steinberg WM, Kurtzman SH, Steinberg SM, Sindelar WF. Evaluation of the utility of a radioimmunoassay for serum CA 19-9 levels in patients before and after treatment of carcinoma of the pancreas. J Clin Oncol. 1988;6(3):462–8.
51. Pleskow DK, Berger HJ, Gyves J, Allen E, McLean A, Podolsky DK. Evaluation of a serologic marker, CA19-9, in the diagnosis of pancreatic cancer. Ann Intern Med. 1989;110(9):704–9.
52. Berger AC, Garcia Jr M, Hoffman JP, Regine WF, Abrams RA, Safran H, et al. Postresection CA 19-9 predicts overall survival in patients with pancreatic cancer treated with adjuvant chemoradiation: a prospective validation by RTOG 9704. J Clin Oncol. 2008;26(36):5918–22.
53. Turrini O, Schmidt CM, Moreno J, Parikh P, Matos JM, House MG, et al. Very high serum CA 19-9 levels: a contraindication to pancreaticoduodenectomy? J Gastrointest Surg. 2009;13(10):1791–7.
54. Haglund C. Tumour marker antigen CA125 in pancreatic cancer: a comparison with CA19-9 and CEA. Br J Cancer. 1986;54(6):897–901.
55. Benini L, Cavallini G, Zordan D, Rizzotti P, Rigo L, Brocco G, et al. A clinical evaluation of monoclonal (CA19-9, CA50, CA12-5) and polyclonal (CEA, TPA) antibody-defined antigens for the diagnosis of pancreatic cancer. Pancreas. 1988;3(1):61–6.
56. Hruban RH, Pitman MB, Klimstra DS, editors. Tumors of the pancreas. Atlas of tumor pathology. Washington, DC: American Registry of Pathology in collaboration with the Armed Forces Institute of Pathology; 2007.
57. Maitra A, Hruban RH. Pancreatic cancer. Annu Rev Pathol. 2008;3:157–88.
58. Provenzano PP, Cuevas C, Chang AE, Goel VK, Von Hoff DD, Hingorani SR. Enzymatic targeting of the stroma ablates physical barriers to treatment of pancreatic ductal adenocarcinoma. Cancer Cell. 2012;21(3):418–29.
59. Edge S, Byrd DR, Compton CC, et al., editors. AJCC cancer staging manual. New York: Springer; 2010.
60. Compton CC, Byrd DR, Garcia-Aguilar J, Kurtzman SH, Olawaiye A, Washington MK, editors. Exocrine and endocrine pancreas. AJCC cancer staging atlas. New York: Springer; 2012. p. 297–308.
61. Bilimoria KY, Bentrem DJ, Ko CY, Ritchey J, Stewart AK, Winchester DP, et al. Validation of the 6th edition AJCC pancreatic cancer staging system: report from the National Cancer Database. Cancer. 2007;110(4):738–44.
62. Ferrone CR, Kattan MW, Tomlinson JS, Thayer SP, Brennan MF, Warshaw AL. Validation of a postresection pancreatic adenocarcinoma nomogram for disease-specific survival. J Clin Oncol. 2005;23(30):7529–35.
63. Wasif N, Ko CY, Farrell J, Wainberg Z, Hines OJ, Reber H, et al. Impact of tumor grade on prognosis in pancreatic cancer: should we include grade in AJCC staging? Ann Surg Oncol. 2010;17(9):2312–20.
64. Rochefort MM, Ankeny JS, Kadera BE, Donald GW, Isacoff W, Wainberg ZA, et al. Impact of tumor grade on pancreatic cancer prognosis: validation of a novel TNMG staging system. Ann Surg Oncol. 2013;20(13):4322–9.
65. Pawlik TM, Laheru D, Hruban RH, Coleman J, Wolfgang CL, Campbell K, et al. Evaluating the impact of a single-day multidisciplinary clinic on the management of pancreatic cancer. Ann Surg Oncol. 2008;15(8):2081–8.
66. Katz MHG, Wang H, Fleming JB, Sun CC, Hwang RF, Wolff RA, et al. Long-term survival after multidisciplinary management of resected pancreatic adenocarcinoma. Ann Surg Oncol. 2009;16(4):836–47.
67. Canto MI, Hruban RH, Fishman EK, Kamel IR, Schulick R, Zhang Z, et al. Frequent detection of pancreatic lesions in asymptomatic high-risk individuals. Gastroenterology. 2012;142(4):796–804; quiz e14–5.
68. Langer P, Kann PH, Fendrich V, Habbe N, Schneider M, Sina M, et al. Five years of prospective screening of high-risk individuals from families with familial pancreatic cancer. Gut. 2009;58(10):1410–8.
69. Canto MI, Harinck F, Hruban RH, Offerhaus GJ, Poley J-W, Kamel I, et al. International Cancer of the Pancreas Screening (CAPS) Consortium summit on the management of patients with increased risk for familial pancreatic cancer. Gut. 2013;62(3):339–47.

Less Common Solid Tumors of Pancreas

3

Saurabh Chawla, Parit Mekaroonkamol, and Field F. Willingham

Introduction

Pancreatic adenocarcinoma arising from the ductal cells in the pancreas remains the most common pancreatic malignancy and accounts for 85–90 % of all pancreatic neoplasms. While pancreatic adenocarcinoma has a poor prognosis, nonductal solid pancreatic tumors may be associated with a considerably better prognosis and can be differentiated from the more common adenocarcinoma based on imaging and pathological characteristics. This chapter reviews these less common solid tumors, including pancreatic neuroendocrine tumors (PNETs), acinar cell carcinomas (ACCs), solid pseudopapillary tumors (SPTs), primary pancreatic lymphomas (PPLs), and isolated pancreatic metastases.

Pancreatic Neuroendocrine Tumors

Neuroendocrine neoplasms of the pancreas were traditionally referred to as pancreatic carcinoids or islet cell tumors, assumed to arise from the islet cells, and were thought to have an indolent course. As the heterogeneous nature of this lesion was recognized, the term "neuroendocrine tumor" was proposed in place of "carcinoid" as it conveys the potential malignant nature and histopathology of the tumor more accurately [1]. These tumors are now classified as pancreatic neuroendocrine tumors (PanNETs) and are believed to be a group of epithelial neoplasms that are derived from multipotential stem cells of endodermal origin with predominant neuroendocrine differentiation [2]. PanNETs account for approximately 3 % of all pancreatic neoplasms [3]. There is vast heterogeneity among these tumors; despite sharing a common histological appearance, they differ in biologic behavior, histologic differentiation, and functionality. PanNETs can be further categorized into functional and nonfunctional tumors based on the secretion of biologically active peptides and hormones, resulting in specific clinical syndromes [4, 5]. The WHO 2010 PanNET classification was revised to include mixed adenoneuroendocrine carcinomas, previously referred to as mixed-form carcinoid adenocarcinoma or mixed exocrine–endocrine carcinoma. This type of neoplasm is comprised of both adenocarcinoma and neuroendocrine carcinoma, with at least 30 % of each component [6].

Epidemiology

PanNETs are rare tumors with a reported incidence of 1–2 cases/10^6 population/year though a much higher rate ranging from 0.07 to 10 % has

S. Chawla, M.D. • P. Mekaroonkamol, M.D.
F.F. Willingham, M.D., M.P.H. (✉)
Division of Digestive Diseases, Department of Medicine, Emory University School of Medicine, Atlanta, GA, USA
e-mail: field.willingham@emoryhealthcare.org

M.S. Wagh, P.V. Draganov (eds.), *Pancreatic Masses*, DOI 10.1007/978-3-319-19677-0_3

been reported in surgical and autopsy series [7, 8]. This variation underscores the limitation in determining the exact incidence and prevalence of PanNETs as the majority of these tumors are small and indolent and may remain asymptomatic. Registry data from Europe, the United States, and Japan showed a rising incidence of these tumors, which probably correlates with the increased use of cross-sectional imaging and more frequent detection of incidental and asymptomatic tumors [9]. Older European studies report an incidence rate (per 100,000) of approximately 0.1 while more recent studies report an incidence rate of 0.3. A similar increase is reflected in the SEER database, with a rise in incidence from 0.17 (1970s) to 0.43 (2003–2007) [9]. A stratified sample survey in Japan reported a much higher incidence rate of 1.01/100,000, with a prevalence rate of 2.23/100,000 [10]. 24 % of patients in this survey had an incidental diagnosis of their tumors.

The median age at diagnosis for PanNETs is 60 years, with a peak incidence rate occurring between the sixth and eighth decades. These tumors are slightly more common among men (53 %) than women (47 %) [11, 12]. Most PanNETs are nonfunctional and sporadic though they may be associated with hereditary endocrinopathies such as multiple endocrine neoplasia (MEN; Type 1), von Hippel–Lindau (VHL) disease, neurofibromatosis type 1 (NF1), and tuberous sclerosis [13]. Patients with these endocrinopathies have an increased risk of developing neuroendocrine tumors ranging from 35 to 75 % of MEN 1, 20 % for VHL disease, 10 % for NF1, and 1 % for tuberous sclerosis [5, 14]. In these patients, PanNETs tend to occur at a younger age, are multiple, and are likely to be diagnosed earlier because of surveillance in carriers of the mutations.

The incidence of functional PanNETs varies by tumor type with insulinoma being the most common (1–4 cases/10^6 population/year), followed by gastrinoma (0.5–2 cases/10^6 population/year), VIPoma (0.05–0.2 cases/10^6 population/year), and glucagonoma (0.01–0.1 cases/10^6 population/year), respectively [12]. The true incidence of rarer types of PanNETs such as somatostatinoma, GRHoma, ACTHoma, and PTHrPoma is difficult to estimate given their rarity.

Since the majority of PanNETs are nonfunctional, most patients present at an advanced stage with mass effect or metastatic disease, and the 5-year survival has been reported between 27 and 62 % [9]. The 5-year survival after surgical resection of noninsulinoma PanNETs has been reported as 65 %, with a 10-year survival of 45 % [15].

Classification

Functional PanNETs

Functionality of PanNETs depends on the clinical symptoms rather than the level or type of hormones secreted. Each type of functional PanNETs produces a distinct clinical hormonal hypersecretion syndrome, which will be described in detail later in this chapter.

Nonfunctional PanNETs

In contrast to functional PanNETs, nonfunctional PanNETs may not cause clinical syndromes; however, they may secrete hormones and other peptides such as chromogranins, neuron-specific endolase, pancreatic polypeptide (such as insulin, gastrin, glucagon, vasoactive intestinal polypeptide), or ghrelin. Usually these do not have clinical significance. However, the tumor itself or its metastatic lesions may manifest compressive symptoms from locoregional mass effect, resulting in abdominal pain, jaundice, pruritus, anorexia, nausea, weight loss, watery diarrhea, or peptic ulcer disease.

Patients with nonfunctional PanNETs are usually asymptomatic at presentation. In symptomatic patients, obstructive symptoms from mass effect are usually the main presentation [16, 17]. As nonfunctional PanNETs do not cause hypersecretory syndromes, they tend to be diagnosed incidentally late in the course of the disease.

The most common presenting symptom is abdominal pain (up to 78 %), which is usually caused by mass effect from the tumor itself. However, when the pain is more localized in the right upper quadrant, it should raise suspicion for a metastatic lesion to the liver causing capsule distension. Other common presenting symptoms include anorexia, nausea, and vomiting, which can be due to a compressive effect from the mass on the duodenum (45 %) [18, 19]. Rarely, PanNETs can present with upper gastrointestinal bleeding from ruptured gastric varices, caused by splenic vein thrombosis. Jaundice from bile duct compression is more commonly seen in PanNETs arising from the pancreatic head.

Functional PanNETs

1. *Insulinoma*
   Insulinomas are functional PanNETs that secrete proinsulin, causing a hypoglycemic hormonal syndrome, also known as Whipple's triad. Whipple et al. first described these features in 1938 of low plasma glucose together with hypoglycemic symptoms, reversible with normalization of the serum glucose level. The triad served as a clue to the diagnosis of insulinoma. The hypoglycemic symptoms include blurred vision, lightheadedness, dizziness, confusion, amnesia, abnormal behavior, loss of consciousness, seizure, and sympatoadrenal symptoms from catecholamine release in response to hypoglycemia such as palpitation, anxiety, diaphoresis, and tremor.

   Despite its rarity, with an incidence of 1–4 cases/10^6 population/year [12, 20], pancreatic insulinoma is still the most common functioning PanNET [21]. The tumor is more prevalent in women (57 %), with a median age of 50 years old. The majority are sporadic; however, up to 6 % may be associated with MEN-1 syndrome [22]. Insulinomas are usually indolent neoplasms. However, metastatic lesions can be found in up to 6 % upon initial diagnosis, and a more aggressive course may be seen in male patients [20, 22].

2. *Gastrinoma*
   The overall incidence of gastrinoma is 0.5–2 cases/10^6 population/year with a slight male predominance and a mean age of diagnosis at 41 years old [23, 24]. Approximately 20 % are associated with MEN-1 syndrome [25]. It is typically indolent; however, up to 33 % have been reported to have metastatic disease upon initial diagnosis. The most common site of metastasis is the liver, followed by the axial bones [26]. It usually arises in the pancreatic head and uncinate process [27].

   As its name implies, gastrinomas predominantly secrete gastrin, causing hypersecretion of gastric acid via stimulation of histamine-releasing enterochromaffin-like cells, in turn acting on the acid-secreting parietal cells. The syndromic features of gastrin hypersecretion are also known as the Zollinger–Ellison syndrome [28]. Presenting symptoms of gastrinomas include refractory peptic ulcer disease and associated complications (bleeding, stricture, perforation), steatorrhea (the overt acidic environment causing inactivation of pancreatic enzymes), chronic secretory diarrhea (disruption of sodium and water reabsorption in the small intestine secondary to high gastrin levels), gastroesophageal reflux, severe heartburn, abdominal pain, anorexia, and weight loss [24]. Approximately 0.1–1 % of patients with peptic ulcer disease have gastrinoma [20].

3. *VIPoma*
   Pancreatic VIPoma is a functional PanNET that predominantly secretes vasoactive intestinal peptide (VIP), which is a 28-amino-acid polypeptide which activates cellular adenylate cyclase and cAMP production in intestinal epithelial cells, leading to a net hypersecretion of free water, sodium, and chloride. It stimulates secretion and inhibits absorption in the bowel, inhibits gastric acid secretion, induces vasodilation, stimulates bone resorption, and promotes hepatic glycogenolysis [29, 30]. This malabsorption and secretory dysfunction lead to the VIPoma syndrome, which is also known as Verner–Morrison syndrome, watery diarrhea–hypokalemia–achlorhydria syndrome (WDHA), and pancreatic cholera

syndrome [31]. Patients typically present with large-volume secretory diarrhea that is not improved with fasting, leading to electrolyte imbalance (hypokalemia, hypochlorhydria, and hypercalcemia) and symptoms such as flushing, lethargy, nausea, vomiting, muscle weakness, and muscle cramps.

Compared to other PanNETS, VIPomas are much more aggressive, with 60–80 % of patients having metastatic lesions at the initial diagnosis. The primary tumor is usually large (>3 cm) and is commonly found in the pancreatic tail (75 %) [32, 33]. Fortunately, it is very rare, with an incidence of 0.05–0.2 cases/10^6 population/year [34]. Five percent of patients with VIPoma also have the MEN-1 syndrome [35].

4. *Glucagonoma*
Glucagonoma is a neoplasm arising from the alpha cells of the pancreas that secrete glucagon, an anabolic 29-amino-acid polypeptide that stimulates glycogenolysis, gluconeogenesis, ketogenesis, lipolysis, amino acid oxidation, and catecholamine secretion. Thus, hypersecretion of glucagon causes hyperglycemia and hypoaminoacidemia. One of the unique manifestations, which can be seen in up to 70 % of patients with glucagonoma, is necrolytic migratory erythema (NME), a painful migratory erythematous plaque (or papules) involving the face, perineum, and extremities. The typical lesions coalesce with central clearing within 1–2 weeks, leaving indurated bronze-colored scars with crusted or blistering borders. Mucosal involvement such as angular cheilitis, glossitis, stomatitis, blepharitis, hair thinning, and dystrophic nails can be seen with NME. Skin biopsy is rarely needed and has a low yield; however, if done properly at the edge of the lesion, it may reveal the classic superficial necrolysis with lymphocytic and histiocytic perivascular infiltration and separation of the outer epidermal layers [36]. NME is believed to be a result of hypoaminoacidemia and a hypometabolic state caused by excessive glucagon.

Other manifestations of the glucagonoma syndrome include normocytic normochromic anemia from decreased erythropoietin, weight loss, venous thromboembolism, abdominal pain, anorexia, constipation, proximal muscle weakness, and neuropsychiatric symptoms such as ataxia, dementia, and optic atrophy [37, 38].

Similar to VIPoma, glucagonoma is a very rare tumor with an aggressive behavior. The common sites of metastasis are liver, bones, and lymph nodes [39]. The mean age of diagnosis is 50 years old, with a slight female preponderance [37, 38]. It almost exclusively arises from the pancreas, typically from the pancreatic tail.

5. *Somatostatinoma*
Somatostatinoma is a rare PanNET that arises from the D-cells of the pancreas, commonly in the pancreatic head. An extrapancreatic somatostatinoma is not uncommon (45 % of all tumors) and is usually found in the duodenum and periampullary areas. It secretes somatostatin, a 14-amino-acid polypeptide with widespread inhibitory effects on other hormones via paracrine signaling, especially acing on insulin, glucagon, gastrin, growth hormone, cholecystokinin-stimulated pancreatic enzymes, pancreatic bicarbonate, gallbladder contraction, intestinal contractility, intestinal amino acid absorption, and gastric acid secretion [40]. However, these inhibitory properties may not cause clinical symptoms. Only 10 % of somatostatinomas are associated with somatostatinoma syndrome [41, 42], which include diabetes mellitus, cholelithiasis, steatorrhea, and gastric hypochlorhydria, abdominal pain, anorexia, and obstructive jaundice [40].

6. *Corticotropinoma* (*ACTHoma*)
Corticotropinoma is a rare neuroendocrine tumor that is usually found in the adrenal gland or pituitary gland. Only 1–16 % of corticotropinomas are localized to the pancreas [43]. As its name implies, it secretes adrenocorticotropic hormone (corticotrophin), a polypeptide that stimulates production of glucocorticoids from the adrenal cortex, leading to a florid Cushing syndrome. The clinical presentation includes obesity, hypertension, glucose intolerance, osteoporosis, muscular atrophy, and hyperpigmentation [44].

7. *PTHrP-producing NET* (*PTHrPoma*)
   PTHrPoma is a very rare PanNET, with less than 50 cases reported worldwide [45]. It is usually found as a single large tumor in the pancreatic body (32 %) or pancreatic tail (53 %) [45]. It secretes parathyroid hormone–related peptide (PTHrP), which is a single monomeric peptide with multiple isoforms. Some of these isoforms have identical N-terminal domains as parathyroid hormone (PTH) and thus can stimulate PTH receptors [46]. Patients with PTHrPoma may present with hyperparathyroidism. These manifestations include malignant hypercalcemia, altered mental status, confusion, constipation, abdominal pain, nausea, vomiting, ureteric stones, osteolytic lesions, and renal failure.

Diagnostic Approach

The wide spectrum of clinical presentations and variability of the types can make the diagnosis and classification of PanNETs challenging. With widespread use of cross-sectional imaging techniques, the incidence of PanNETs has increased due to incidental detection. However, in order to accurately diagnose and classify the type of the tumor, a multimodality diagnostic approach is essential. Such an approach includes the use of serum biomarkers and radiologic studies and, in rare cases, arterial stimulation venous sampling (ASVS).

Role of Biomarkers

When a pancreatic neoplasm is detected and a clinical syndrome is present, the serum marker of the specific peptide can help confirm the diagnosis. These markers and their associated clinical presentations are summarized in Table 3.1. Caution should be exercised when interpreting the level of these peptides as they are all physiologic hormones and therefore can vary according to patients' physiologic changes.

For example, even though an insulin-to-glucose ratio of more than 32.2 (pmol/L)/(mmol/L) and C-peptide-to-glucose ratio of more than 0.24 (nmol/L)/(mmol/L) are highly suggestive of insulinoma [with new cutoff values of 53.6 (pmol/L)/(mmol/L) and 0.61 (nmol/L)/(mmol/L), respectively, being proposed to increase the specificity and positive predictive value], a sulfonylurea level should always be measured to exclude medication-induced hyperinsulinemia (insulin and C-peptide levels should be high while sulfonylurea should be undetectable in true hypoglycemia from insulinoma) [37, 47].

For gastrinoma, a serum gastrin level of greater than 1000 pg/mL (475 pmol/L) when gastric pH is less than 2 is virtually diagnostic. However, a falsely elevated serum gastrin level can be seen in patients with atrophic gastritis, pernicious anemia, *H. pylori* infection, proton-pump inhibitor (PPI) use, and status-post small bowel resection. Therefore, it is recommended to measure serum gastrin level while fasting and after stopping PPI for at least 7 days. A secretin or calcium stimulation test can be used to confirm the diagnosis in equivocal cases [23].

A glucagon level greater than 1000 pg/mL in patients with suggestive clinical symptoms (NME and/or hyperglycemia) is virtually diagnostic of glucagonoma. However, as glucagon secretion is a normal physiologic response for stress, it can be misleadingly elevated (usually less than 500 pg/mL) in patients with sepsis, burns, trauma, surgery, and fasting [48]. In the setting of diabetes, steatorrhea, and cholelithiasis, a somatostatin level higher than 160 pg/mL is highly suggestive of somatostatinoma [41].

It is more challenging when the PanNET is not functional or when the clinical presentation is vague and nonspecific. Among several biomarkers studied in the past, chromogranin A (CgA), neuron-specific enolase (NSE), and pancreatic polypeptide (PP) are the most promising [49–51].

CgA is elevated in both functional and nonfunctional PanNETs. Moreover, its level also correlates well with tumor burden and metastatic disease. Therefore, it is used to monitor response to therapy and progression-free survival [49, 52, 53]. However, CgA has some limitations and should not be used alone for diagnosis. False-negative results can be seen in insulinomas, MEN-1–associated PanNETs, and poorly

Table 3.1 Summary of characteristics of functional PanNETs

Functional PanNETs	Clinical syndrome	Laboratory diagnostics
Insulinoma	• Whipple's triad	• Elevated insulin and C-peptide during hypoglycemic episodes
	• Neuroglycopenic symptoms	• Insulin-to-glucose ratio < 0.3
	• Sympatoadrenal symptoms	• Undetectable sulfonylurea
Gastrinoma	• Zollinger–Ellison syndrome	• Serum gastrin >1000 pg/mL (475 pmol/L)
	• Diarrhea	• Gastric pH < 2
	• Hypergastrinemia	• Serum gastrin increases >200 pg/mL after secretin stimulation test
	• Gastric acid hypersecretion	• Serum gastrin increases >395 pg/mL after calcium stimulation test
	• Peptic ulcer diathesis	
VIPoma	• Verner–Morrison syndrome/WDHA syndrome	• Stool osmolal gap < 50 mOsm/kg
	• Watery diarrhea	• VIP > 75 ph/mL
	• Hypokalemia	
	• Achlorhydria	
Glucagonoma	• Glucagonoma syndrome (4D syndrome)	• Glucagon level >1000 pg/mL
	• Dermatitis (necrolytic migratory erythema) and mucositis	
	• Diabetes mellitus	
	• Deep vein thrombosis	
	• Depression (neuropsychiatric symptoms)	
Somatostatinoma	• Somatostatinoma syndrome	• Somatostatin level > 160 pg/mL
	• Diabetes mellitus	
	• Gastric hypochlorhydria	
	• Cholelithiasis	
	• Steatorrhea	
Corticotropinoma	• Cushing syndrome	• Plasma ACTH > 20 pg/mL
	• Diabetes mellitus	• Negative high-dose dexamethasone suppression test
	• Obesity	• Negative CRH stimulation test
	• Hypertension	
	• Hyperpigmentation	
PTHrPoma	• Hyperparathyroidism, hypercalcemic crisis	• Hypercalcemia
	• Altered mental status, confusion	• Hypophosphatemia
	• Abdominal pain	• Elevated PTHrP
	• Nausea, vomiting	
	• Ureteric stones	
	• Osteolytic lesion	

differentiated neoplasms, while a falsely elevated level may be seen in patients with renal failure, proton-pump inhibitor use, atrophic gastritis, and pernicious anemia [49].

NSE is a cytoplasmic dimer of the glycolytic enzyme enolase. It is used as a marker of secretory activity of the tumor. Even though it is not specific enough to be a diagnostic marker, it can be used for follow-up after treatment. Pancreatic polypeptide is less specific than CgA and NSE, but when its level is higher than three times the age-matched normal fasting basal level, its specificity increases and should raise suspicion for a PanNET [49–51].

Radiologic Studies

Helical multiphasic contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI) are the first-line diagnostic modalities for PanNETs. Most PanNETs are isodense with pancreatic parenchyma on precontrast images but demonstrate avid arterial enhancement; therefore, dual or multiphase contrast-enhanced CT has higher sensitivity than conventional CT scan [54]. Nonfunctional PanNETs are easier to detect on these cross-sectional studies because of their larger size (median diameter of 8.4 cm compared to 1.3 cm with functional PanNETs) and more frequent distinctive features (i.e., necrosis, cystic changes, and calcifications) [55]. Therefore, endoscopic ultrasound (EUS) plays an important role in these small CT-negative tumors. It detects 91 % of CT-negative lesions, which typically appear as round, homogeneous, and hypoechoic mass lesions. A sequential approach of CT followed by EUS is recommended, which has been shown to have 100 % sensitivity in diagnosing these tumors [54, 56]

On MRI, PanNETs have a low signal intensity on T_1-weighted images and a high signal intensity on T_2-weighted images. The tumors are most conspicuous on the fat-suppressed T_1-weighted sequence, where they appear of low intensity against the bright pancreas [55]. Compared to CT scan, MRI is superior for metastatic disease [57, 58]. The performance characteristics of various imaging modalities for assessing local spread, resectability, and metastasis are similar to those reported earlier for pancreatic adenocarcinomas.

Nuclear imaging studies using radiolabeled octreotide scanning, referred to as somatostatin-receptor scintigraphy (SRS) or Octreoscan, is another diagnostic modality to detect PanNETs with somatostatin-receptor-rich tissue. This study is particularly helpful in determining which patients would benefit from somatostatin-based therapies such as ^{90}Y-edotreotide or Tyr^3-octrotate. Even though its sensitivity and specificity are lower than CT and MRI, a new application with single-photon emission computed tomography (SPECT) or positron emission tomography (PET) called SRS-SPECT has promising data with higher accuracy [59]. False negatives can occur in tumors with low expression of somatostatin receptors such as insulinoma and poorly differentiated PanNETs. Other nuclear imaging modalities such as glucagon-like peptide-1 (GLP-1) receptor scintigraphy and ^{18}F-fluorodeoxyglucose scintigraphy are under investigation to help detect such neoplasms [60]. Another useful modality is EUS, which has become a modality of choice in the evaluation and surveillance of PanNETs. It can detect lesions as small as 2 mm with a sensitivity of 82 % and a specificity of 92 %. The sensitivity of EUS is highest when the lesion is in the pancreatic head area. The biggest advantage is its ability to obtain a tissue diagnosis using fine-needle aspiration (FNA). EUS can also be used to tattoo the lesion preoperatively. However, the test may not be readily available in every center and its quality is operator-dependent [61].

Arterial Stimulation Venous Sampling (ASVS)

ASVS is an invasive test for tumor localization, which is rarely needed in the diagnosis of PanNET given the recent advancement of other modalities. The test is performed by directly stimulating the tumor via a selective arterial injection of a stimulant such as secretin for gastrinoma and calcium gluconate for insulinoma and subsequently measuring the hormonal response of the tumor by venous sampling of the hepatic venous effluent [62]. Other adjunct invasive modalities include intraoperative pancreatic ultrasound, which is sometimes required when other modalities fail [55].

Grading and Staging System

Classification of PNETs has evolved considerably over the past decade. Grading and staging systems proposed by the World Health Organization (WHO), European Neuroendocrine Tumour Society (ENETS), and American Joint Committee on Cancer (AJCC) share common schemes with minor differences (Table 3.2) [6, 63, 64].

Table 3.2 Histologic grading of pancreatic neuroendocrine tumors

Grade	Mitotic count (per 2 mm^2)	Ki-67 labeling index (%)
Low grade (G1)	<2	<3
Intermediate grade (G2)	2–20	3–20
High grade (G3)	>20	>20

Source: From [6, 63, 64]

Histologic features based on the proliferative rate determine the grading of PanNET, which reflects the biologic aggressiveness. The tumor staging systems reflect more on the extent of the disease based on vascular invasion, tumor size, and distant metastasis. Both systems are used independently to assess prognosis.

PanNETs are categorized into well-differentiated neuroendocrine tumors and poorly differentiated neuroendocrine carcinoma. Histologic features of well-differentiated neuroendocrine tumors include organized tumor cells in a trabecular or gyriform pattern with uniformly round or oval nuclei, coarsely stippled chromatin (salt-and-pepper chromatin), and finely granular cytoplasm with abundant neurosecretory granules [65]. They tend to have an indolent course with a much better prognosis, with an overall 5-year survival rate reaching up to 67 % [66]. However, it is not unusual for well-differentiated PNETs to present with metastatic disease [66].

Poorly differentiated neuroendocrine carcinomas have sheet-like or diffuse tumor cell arrangements with irregularly nonuniform nuclei, and less cytoplasmic granularity. These tumors have a more aggressive behavior with a rapid clinical course that resembles small or large cell neuroendocrine carcinoma of the lung [65].

Histologically, it is not possible to differentiate between benign and malignant tumors as morphology alone cannot predict the tumor behavior. Well-differentiated PNETs can have an aggressive clinical course while metastatic tumors may show little or no cellular pleomorphism, hyperchromasia, or increased mitotic activity [67]. Therefore, the terms "benign" and "malignant" are discouraged in histological grading of PNETs. WHO has updated its grading system to further subcategorize well-differentiated neuroendocrine tumors into low-grade (G1) and intermediate-grade (G2) subgroups based on their proliferative rate (mitotic count and Ki-67 index) [6]. This grading scheme, together with the staging system, is used for prognosis. The parameters used in this grading system as described in Table 3.2 are also endorsed by the AJCC and ENETS.

Based on this new grading system, poorly differentiated carcinomas are all high-grade neoplasms (G3) and are no longer defined by local vascular invasion or metastasis. The term "neuroendocrine tumor grade 3" is therefore a misnomer because, by definition, neuroendocrine tumors are well differentiated [6]. The Ki-67 protein is a large nuclear protein that is closely involved in cell cycle regulation and organization of the nucleolus. Ki-67 is expressed in G1, S, G2, and M phases, with a peak level during mitosis, hence its use as a surrogate marker of cellular proliferation [6, 63]. According to WHO and ENETS guidelines, 2000 cells in the area of highest proliferative rate (hot spots) should be counted to determine the Ki-67 labeling index [6, 63].

Mitotic count is the most direct marker of the proliferative activity of the tumor. It is recommended to perform an average count over 40–50 HPF, assuming that 10 HPF equals 2 mm^2. However, in contrast to Ki-67–labeled cells, the mitotic count is usually not as abundant and may not be able to be measured in a limited specimen such as with fine-needle aspiration [68].

If the mitotic count and Ki-67 labeling index yield different grades, the neoplasm should be regarded as the higher one. Other prognostic parameters such as tumor necrosis and lymphovascular and perineural invasion are not included in the grading criteria [6, 63].

Staging Systems

There are currently two widely accepted TNM staging systems by AJCC and ENETS, with only minor differences in primary tumor (T) staging

Table 3.3 Comparison between TNM staging systems of the AJCC and ENETS

		AJCC	ENETS
Primary tumor (T)	T_x	Primary tumor cannot be assessed.	Primary tumor cannot be assessed.
	T_0	No evidence of primary tumor.	No evidence of primary tumor.
	T_1	Tumor limited to pancreas, ≤2 cm.	Tumor limited to pancreas, ≤2 cm.
	T_2	Tumor limited to pancreas, >2 cm.	Tumor limited to pancreas, 2–4 cm.
	T_3	Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery.	Tumor limited to the pancreas and is larger than 4 cm or invading duodenum or bile duct.
	T_4	Tumor involves the celiac axis or the superior mesenteric artery.	Tumor invading adjacent organs (stomach, spleen, colon, adrenal gland) or the wall of large vessels (celiac axis or superior mesenteric artery).
Regional lymph node (N)	N_x	Regional lymph node cannot be assessed.	Regional lymph node cannot be assessed.
	N_0	No regional lymph node metastasis.	No regional lymph node metastasis.
	N_1	Regional lymph node metastasis.	Regional lymph node metastasis.
Distant metastasis (M)	M_x	No M_x categorized.	Distant metastasis cannot be assessed.
	M_0	No distant metastasis.	No distant metastasis.
	M_1	Distant metastasis.	Distant metastasis.

Staging systems for pancreatic neuroendocrine tumor [63, 64]

AJCC				ENETS			
Stage	T	N	M	Stage	T	N	M
IA	T_1	N_0	M_0	I	T_1	N_0	M_0
IB	T_2	N_0	M_0	IIA	T_2	N_0	M_0
IIA	T_3	N_0	M_0	IIB	T_3	N_0	M_0
IIB	T_1, T_2, T_3	N_1	M_0	IIIA	T_4	N_0	M_0
III	T_4	N_{ANY}	M_0	IIIB	T_{ANY}	N_1	M_0
IV	T_{ANY}	N_{ANY}	M_1	IV	T_{ANY}	N_{ANY}	M_1

Source: From [63, 64]

between the two, as shown in Table 3.3. The prognostic values of both systems have been extensively validated [69, 70]. Five-year overall survival rates for stages I, II, III, and IV disease of PNETs are 92 %, 84 %, 81 %, and 57 %, respectively, using AJCC staging and 100 %, 88 %, 85 %, and 57 %, respectively, using ENETS staging [70]. It is unclear which staging system has a better prognostic accuracy; therefore, applying the system that is widely used in a particular region is generally accepted.

The ENETS stages poorly differentiated neuroendocrine carcinoma in the same way as well-differentiated neuroendocrine tumors, while the AJCC stages poorly differentiated neuroendocrine carcinomas as adenocarcinomas. The functionality of the tumor plays no role in staging and grading systems.

Solid Pseudopapillary Tumor

Solid pseudopapillary tumors (SPTs) are rare pancreatic tumors characterized by unique clinicopathological features which were first reported by Franz in 1959. Historically, they have been classified by different names such as papillary cystic carcinoma, papillary-cystic epithelial neoplasm, and solid and papillary neoplasm. Most of these terms were descriptive and pertain to the cystic and papillary components of the tumors. In 1996, the WHO classification for exocrine pancreatic tumors classified them as "solid pseudopapillary tumors" of the pancreas and further defined malignant features associated with these tumors. This has led to a recent increase in the diagnosis of these tumors with a better characterization of their pathology.

Epidemiology

SPTs are rare tumors, accounting for only 0.13–2.7 % of pancreatic tumors. Though they have been reported across all age groups (range, 2–85 years), they characteristically affect young females (90 % females, mean age 22–27 years) [71, 72]. In one of the largest series, only 6 % of patients were more than 51 years of age, while 22 % of the patients were less than 19 years of age [71]. They are indolent, slow-growing tumors with a tumor-doubling time of 765 days; however, they have a malignant potential with metastases reported in 20 % of the patients [73]. The liver is the most common site of metastasis, followed by the portal vein and spleen. Local invasion into other organs such as the duodenum, omentum, colon, lung, peritoneum, and vasculature has been reported less frequently [71]. The prognosis, even with metastasis, local invasion, or recurrence, is good, with an overall 5-year survival greater than 95 % [71]. Long-term survival has also been reported in most patients with metastatic or locally advanced disease [74].

Molecular Genetics

The pathogenesis of SPTs has not been completely elucidated. The female preponderance led to the investigation of gender hormonal receptors; however, estrogen receptor (ER) expression in these tumors is variable and no gender-based differences in immunohistochemical staining for sex hormone receptor proteins have been demonstrated [75]. Furthermore, they exhibit a genetic profile distinct from pancreatic ductal adenocarcinoma in that they are not associated with mutations in K-ras, p-53, or DPC4 genes but, like colorectal and gastric cancer, demonstrate genetic abnormalities in the APC/B-catenin pathway [76]. Other hypotheses proposed for the pathogenesis of these tumors include chromosome abnormalities in the form of karyotype unbalance translocation and early incorporation of ovarian cells into the pancreatic tissue during the period of embryogenesis [77, 78].

Pathology

Typical SPTs are large, well-demarcated, soft tan to red masses with variable solid and cystic components demonstrating hemorrhagic changes surrounded by a fibrous capsule. Smaller tumors which are now commonly detected incidentally tend to be more solid and often lack the fibrous pseudocapsule which demarcates the larger tumors [71]. Microscopically, they are characterized by a solid growth pattern of discohesive polygonal cells arranged around fibrovascular septa which can undergo cystic degeneration and result in pseudopapillae formation [79]. Infiltration into surrounding tissues is common despite the well-circumscribed gross appearance and adjacent acini often appear separated from neoplastic cells by only a basement membrane [79]. Metastasizing tumors have a higher nuclear grade with more prominent necrobiotic nests characterized by cell aggregates with pyknotic nuclei and eosinophilic cytoplasm exhibiting high mitotic rates and true tumor necrosis [80]. Most SPTs stain for vimentin, CD10, neuron-specific enolase (NSE), CD56, progesterone receptors, and alpha-1 antitrypsin and can be differentiated from other pancreatic tumors by non-expression or only focal staining with keratin, chromogranin, synaptophysin, or endocrine and pancreatic enzymes [81].

Clinical Presentation and Diagnosis

Most patients present with nonspecific abdominal complaints likely caused by the bulky tumor compressing upon surrounding organs. The most common clinical presentation is abdominal pain (38–47 %), palpable mass (35–36 %), or abdominal discomfort (16–33 %) [71, 72]. Up to a third of patients are asymptomatic, and the tumor is diagnosed incidentally on abdominal imaging for another cause [72]. Other rare presentations include fever, jaundice secondary to bile duct obstruction, pancreatitis with pseudocyst formation, and hemoperitoneum due to tumor rupture [81]. The tumors are unifocal and are most

commonly found in the tail or the head of the pancreas though they can occur in all regions of the gland. Multifocal tumors may be present in 15 % of patients. The mean diameter of the tumor at the time of diagnosis is 6–8 cm (range, 0.5–34.5 cm) [71, 72]. Laboratory studies are not helpful in diagnosis as these tumors are not associated with elevation of known tumor-specific serum markers or pancreatic enzymes.

SPTs have characteristic imaging features though occasionally percutaneous or EUS-guided FNA may be required to differentiate them from necrotic neuroendocrine tumors. On US, they appear as a heterogeneous, encapsulated mass with solid echogenic and cystic hypoechoic components with peripheral calcifications [81]. The typical CT and MRI features of SPT are a large, well-encapsulated mass with varying solid and cystic components and early peripheral heterogeneous enhancement with progressive fill-in after contrast administration on dynamic examination [82]. Smaller SPTs have less typical imaging findings as they are predominantly solid, not well encapsulated, and less likely to demonstrate cystic degeneration. These may require preoperative tissue diagnosis using FNA. Local or extended resection, depending on the size of the tumor and involvement of adjacent organs or lymph nodes, is the mainstay of therapy and standard chemotherapeutic regimens are not established [71, 74].

Acinar Cell Carcinoma

Acinar cells secreting pancreatic enzymes account for 82 % of the pancreatic parenchyma and make up the bulk of the pancreas [83]. Malignant transformation of these cells is, however, exceedingly uncommon when compared to pancreatic ductal adenocarcinoma. ACCs are rare but biologically aggressive malignant tumors arising from the acinar cells in the pancreas.

Epidemiology

ACCs occur infrequently and account for 1–2 % of all adult malignant pancreatic neoplasms [84, 85]. They tend to present earlier than pancreatic adenocarcinoma, with a mean age of presentation of 58 years (range, 28–85 years) although they have also been reported in children [81, 83, 85]. In most series, there is a strong male predilection, and patients in the United States are more likely to be white (84.7 % white vs. 15.3 % others) [83]. ACCs are aggressive neoplasms; older, small, single-institution studies reported that approximately half of patients present with metastasis, most commonly to the liver, and most of the remaining patients develop metastasis on follow-up [84, 86]. A 2008 U.S. cancer database review of 333 patients reports nodal metastasis in 40 % and distant metastasis in 13 % of patients at presentation [87]. Based on a 2008 SEER database review of 672 patients, these tumors have a significantly better prognosis than ductal adenocarcinoma, with a median survival of 47 months (5-year survival, 42.8 %), which decreases to 25 months for unresectable tumors (5-year survival, 22 %) [83, 84]. The 5-year survival for resectable disease has also been encouragingly reported as 71.6–76.9 % (median, 123 months) [83, 85].

Molecular Genetics

Unlike pancreatic ductal adenocarcinomas, ACCs rarely contain mutations of K-ras, p-53, or p-16 or abnormalities of DPC4 protein expression [79]. Similar to pancreatoblastomas, loss of 11 p has been reported in 50 % of patients, and abnormalities in the APC/beta catenin pathway have been found in 24 % of patients [88, 89]. Other studies have demonstrated a loss of heterozygosity (LOH) at various chromosomes. In particular, chromosome 4q LOH was present in 75 % of ACCs compared to no patients with PanNETs and 17 % with pancreatic adenocarcinoma [90].

Pathology

Grossly, these tumors are well circumscribed, soft, and fleshy with scattered areas of hemorrhage and necrosis. On low-power microscopy, they have a high cellularity with a relative paucity of desmoplastic stroma. Histologically, several different architectural patterns may be present,

though the solid and acinar patterns are most common. Since these tumors arise from acinar cells, the cytoplasm contains abundant zymogen granules which appear intensely eosinophilic and granular [79]. Zymogen granules may be stained with periodic acid–Schiff (PAS) to confirm the diagnosis of ACC. In tumors with less abundant zymogen granules, the diagnosis may be confirmed with IHC staining for enzymes, especially trypsin and chymotrypsin, which is 95 % sensitive to detect acinar differentiation [91]. Some tumors may have more than one line of differentiation, which may cause diagnostic confusion when detected on IHC staining. If these elements exceed more than 25 % of the tumor, these tumors are classified as mixed carcinomas, of which acinar–endocrine carcinomas are best characterized, though mixed acinar–ductal or acinar–ductal–endocrine carcinomas have also been reported [79]. All these tumors are clinically aggressive and behave similarly to ACCs [79].

Clinical Presentation and Diagnosis

The clinical presentation is often nonspecific; most commonly patients may present with abdominal pain or bloating and a palpable abdominal mass on examination. Other reported symptoms include weight loss, nausea and vomiting, and, less commonly, a change in stool consistency or jaundice [84, 92]. Because this tumor arises from acinar cells, it is associated with the systemic release of pancreatic enzymes, including trypsin, chymotrypsin, amylase, and lipase, although the serum levels of these enzymes may not be elevated [81]. In 10 % of patients, this tumor can be functionally active and secrete lipase, resulting in signs related to excess lipase secretion which manifest with high serum lipase levels, diffuse subcutaneous nodules, and polyarthropathies and is referred to as the lipase hypersecretion syndrome [84]. Tumors tend to be focal, occur predominantly in the head or the tail, and tend to be larger than a pancreatic adenocarcinoma at presentation with a mean size of 4 cm (0.7–23.5 cm), but may be more than 10 cm at presentation in a third of the patients [84, 92]. Serum tumor markers such as CA 19-9, AFP, and CEA are variably expressed and are not specific to establish a diagnosis though they may be useful for evaluating recurrence if elevated [93]. On nonenhanced imaging, these tumors are well marginated, are exophytic, and appear homogeneous when small. When larger, they may be solid or heterogeneous with cystic components with occasional focal calcification due to necrosis and hemorrhage. With contrast, they enhance homogeneously though less than the pancreatic parenchyma, and hypervascular variants which may be confused with NETs have been reported [94]. Imaging studies are not always diagnostic for ACCs, and FNA or surgical pathology may be required to establish the diagnosis [94]. Aggressive surgical management with a goal of an R0 resection remains the mainstay of therapy. Anecdotally, neoadjuvant and adjuvant chemoradiotherapy regimens suggest some benefit; however, due to the low incidence of the tumor, large series to evaluate benefit are lacking [87, 92].

Primary Pancreatic Lymphoma

Around half of the patients with extranodal non-Hodgkin's lymphoma will have gastrointestinal involvement and secondary involvement of the pancreas is not infrequent [95]. Primary pancreatic lymphomas (PPLs), on the other hand, are a rare extranodal presentation of non-Hodgkin's lymphoma which may mimic pancreatic adenocarcinoma on presentation and pose a diagnostic dilemma.

Epidemiology

PPLs are extremely rare and compromise less than 0.5 % of all pancreatic tumors and less than 1 % of extranodal non-Hodgkin's lymphoma (NHL) [96, 97]. Most studies suggest a male predominance, with patients typically presenting in the sixth decade (range, 40–84 years) [98–100]. Survival in patients with PPLs is dependent on the stage of disease at the time of diagnosis and varies with treatment modalities used, with an

overall 3-year survival rate of 46 % using chemoradiation though newer chemotherapeutic agents were not included in these studies [101]. Some groups have reported dramatic response rates of 100 % with long-term survival rates of 94 % after surgery with early-stage, resectable pancreatic lymphomas [101].

Pathology

Histologically, most PPLs are intermediate or high-grade NHL with diffuse large cell lymphoma being the most common histotype (60 %). Rarer histotypes like anaplastic large cell (ALK) have also been reported [102]. Cytopathology is often employed to establish diagnosis and smears show a variable degree of cellularity. In most cases, the malignant lymphocytes appear as discohesive cells with large nuclei (greater than 3–4 times the size of a mature lymphocytic nucleus) with single to multiple prominent nucleoli in a background of abundant necrosis and karyorrhexis. Occasionally, a monotonous population of small mature lymphocytes may be seen and flow cytometry (FC) and immunophenotyping are often used to confirm diagnosis. By flow cytometry, most cases have Ig light chain restriction and CD20 expression, though expression of other cell surface markers has also been noted [99]. Immunophenotypically, most cases reported in the West have been B-cell lymphomas, while 21 % of cases reported in Japan are T-cell lymphomas and carry a worse prognosis [98].

Clinical Presentation and Diagnosis

The clinical presentation of PPL, like other uncommon solid pancreatic tumors, is nonspecific. Abdominal pain is the most common presenting symptom (83 %) followed by abdominal mass (58 %), weight loss (50 %), and jaundice (37 %). Less commonly, patients may present with pancreatitis, small bowel obstruction, and diarrhea. The classic B-type symptoms of nodal NHL such as fever, chills, and night sweats are uncommon [102]. They commonly present as large solitary masses varying in size from 2–15 cm with mean reported diameters across most series of greater than 8 cm [101]. The tumors frequently are confined to the head, though body or tail tumors and rarely diffuse involvement of the entire gland have also been reported [101]. On CT, the mass is hypodense and homogeneous and can extend into and infiltrate the peripancreatic vasculature and surrounding structures. Two patterns of CT appearance have been described: (1) a well-defined mass and (2) a large infiltrating lesion with poorly defined contours. On MRI, they appear as a low-signal-intensity homogeneous mass on T_1-weighted images with subtle postcontrast enhancement, and on T_2-weighted images, they show a more heterogeneous character with low- to intermediate-signal amplitude [103]. Due to their location, nonspecific clinical presentation, and imaging findings of a solitary pancreatic head mass, they may be mistaken for the more common pancreatic ductal adenocarcinoma. Imaging findings which may help differentiate a PPL from a pancreatic adenocarcinoma include a bulky localized tumor in the pancreatic head without significant dilatation of main pancreatic duct; enlargement of the lymph nodes below the level of the renal veins; invasive tumor growth not respecting anatomic boundaries and infiltrating the retroperitoneum or surrounding organs [103]. They can be differentiated from secondary involvement of the pancreas by lymphoma, which is much more frequent and can occur in up to a third of cases with non-Hodgkin's lymphoma by the following criteria: the absence of superficial or mediastinal lymphadenopathy; a normal peripheral leukocyte count; the main mass in the pancreas with lymph node involvement confined to the peripancreatic region; and no hepatic or splenic involvement [104]. A clinical suspicion of PPL should prompt percutaneous or EUS-guided FNA or core biopsy of the lesion with flow cytometry, which has been shown to reliably diagnose PPL and differentiate it from other pancreatic tumors. Once diagnosed, PPL is staged as other NHLs using the Ann Arbor staging system. Unlikely the pancreatic adenocarcinoma which it mimics, PPL is usually treated with a combination of chemotherapy and radiation therapy or stem cell transplantation and carries a much better prognosis [102].

Pancreatoblastoma

Pancreatoblastomas are rare pancreatic malignant neoplasms of presumed stem cell origin first reported in 1957 as "infantile pancreatic carcinoma." Due to the histological resemblance of this tumor to fetal pancreatic tissue, the name of "pancreatoblastoma" was first proposed in 1977 [105].

Epidemiology

Pancreatoblastoma is the most common pancreatic neoplasm of childhood, accounting for 25 % of all pancreatic tumors, with most patients being less than 10 years of age (mean age, 4 years) [106]. An association with Beckwith–Wiedemann syndrome has been reported [79]. These tumors have rarely been reported in adolescents and adults, and account for 0.5 % of all pancreatic exocrine neoplasms. In a recent review of published literature, the median age of adults was 37 years (range, 18–78 years) and no gender predilection was reported [105].

Pancreatoblastomas are aggressive tumors with more than half of patients presenting with locally advanced disease or metastases at initial diagnosis. The liver is the most common site for metastases followed by regional lymph nodes, lung, and peritoneum [105, 106]. The prognosis with a pancreatoblastoma is much better in children than in adults. In children, the 5-year event-free survival and overall survival were 58.8 % and 79.4 %, respectively, in a European registry, and the survival was not found to correlate with tumor site and size but was strongly influenced by the feasibility of complete resection [106]. The prognosis in adults is uniformly poor, with a median survival of 15 months (range, 1–108 months) [105].

Pathology

On gross examination, pancreatoblastomas are large, well circumscribed, lobulated, and soft and fleshy on cut section. Histologically, they are very cellular and are separated by broad fibrous bands into lobules, which have a geographic pattern of light and dark staining cells, reflecting the different cell types of pancreatoblastomas. A characteristic histological feature is the "squamoid nests" or "squamoid corpuscules" which are composed of spindle-shaped cells in whorled nests, giving a squamous appearance [79]. On IHC staining, pancreatoblastomas can have multiple lines of differentiation, including ductal, mesenchymal, acinar, and neuroendocrine. The molecular alterations in pancreatoblastomas are similar to ACC with LOH of the short arm of chromosome 11 p. Also, 50–80 % of tumors will manifest alteration in the beta catenin/APC pathway [79].

Clinical Presentation and Diagnosis

Abdominal pain (45 %), weight loss (29 %), jaundice (19 %), and a palpable abdominal mass (19 %) are the most frequent presenting symptoms and are typically related to mass effect from the tumor. Pancreatoblastomas are slow-growing tumors usually diagnosed when they are large, with a median size of 8 cm (range, 1.8–20 cm) [105]. They have most frequently been reported in the head (45 %) and tail of the pancreas (29 %). Elevation of alpha fetoprotein has been reported in up to 70 % of pediatric patients, but no tumor markers have been consistently shown to be elevated in adults [105, 106]. On imaging most of these tumors are well defined and at least partially circumscribed, seen as multilobulated masses with a mixed echotexture on US and enhancing septa on CT. On MR, the tumors appear heterogeneous with low to intermediate signal intensity on T_1-weighted sequences and high signal intensity on T_2-weighted images [107]. Complete tumor excision is associated with the best outcomes though chemoradiation may be beneficial to downstage tumors or in unresectable disease [106].

Isolated Pancreatic Metastasis

Pancreatic metastases occur most commonly from primary tumors in lung, kidney, or breast or with melanoma, though virtually any primary neoplasm can metastasize to the pancreas. The diagnosis is usually evident in the presence of the

primary tumor; however, occasionally isolated metastasis to the pancreas may occur years after resection of the primary tumor and may be mistaken for primary pancreatic neoplasm.

Epidemiology

Isolated pancreatic metastases can account for approximately 2 % of all pancreatic neoplasms in living patients [108]. Renal cell carcinoma (RCC) is the most common malignancy with isolated pancreatic metastasis (62.6 % of all tumors) followed by sarcoma (7.2 %), colorectal carcinoma (6.2 %), ovarian carcinoma (4.7 %), and melanoma (4 %) [109]. In a recent systematic review, the mean age of patients was 61.7 %, and these lesions were slightly more common in men (58 % men vs. 42 % women) [109]. The mean disease-free interval (DFI) for all tumors in this review was 66 months. This mean was probably skewed by a large proportion of RCC patients (62.6 %), which is characterized by a long disease-free interval (7–10 years) after nephrectomy for primary disease [81]. Resection of isolated pancreatic metastasis from RCC is associated with a good prognosis, with a 5-year survival of 68–75 %, whereas resection of pancreatic metastasis from other tumor sites carries a much worse prognosis, with a median survival of 2 years [81].

Pathology

Histologically, the metastatic tumor may resemble the primary tumor though it can mimic a pancreatic adenocarcinoma and IHC may be required for confirmation of the tissue of origin. RCC presents as sheets of tumor cells separated into solid acini, or variously into cystic, papillary, pseudopapillary, tubular, or sarcomatoid growth patterns, with polygonal or cuboidal tumor cells [81].

Clinical Presentation and Diagnosis

Lesions may be diagnosed during routine surveillance or by the presence of nonspecific symptoms and imaging findings may be similar to the primary tumor. On CT scan, metastatic RCC appears as a large hypervascular spherical mass with well-defined margins and central low attenuation that can mimic other hypervascular lesions of the pancreas such as PanNETs [110]. In patients with a history of resected RCC, this presentation is usually diagnostic and tissue biopsy is not required though percutaneous or EUS biopsy may be obtained for suspected metastasis from non-RCC malignancies or if diagnostic confusion exists. Once the diagnosis of pancreatic metastasis has been established, pancreatic resection may be considered after a careful search has excluded concurrent extrapancreatic metastatic lesions [109].

References

1. Capella C, Heitz PU, Hofler H, Solcia E, Kloppel G. Revised classification of neuroendocrine tumours of the lung, pancreas and gut. Virchows Arch. 1995;425(6):547–60.
2. Sadaria MR, Hruban RH, Edil BH. Advancements in pancreatic neuroendocrine tumors. Expert Rev Gastroenterol Hepatol. 2013;7(5):477–90.
3. Fesinmeyer MD, Austin MA, Li CI, De Roos AJ, Bowen DJ. Differences in survival by histologic type of pancreatic cancer. Cancer Epidemiol Biomarkers Prev. 2005;14(7):1766–73.
4. Oberg K. Pancreatic endocrine tumors. Semin Oncol. 2010;37(6):594–618.
5. Metz DC, Jensen RT. Gastrointestinal neuroendocrine tumors: pancreatic endocrine tumors. Gastroenterology. 2008;135(5):1469–92.
6. Bosman FT. WHO classification of tumours of the digestive system. 4th ed. Lyon: International Agency for Research on Cancer; 2010. p. 417.
7. Halfdanarson TR, Rabe KG, Rubin J, Petersen GM. Pancreatic neuroendocrine tumors (PNETs): incidence, prognosis and recent trend toward improved survival. Ann Oncol. 2008;19(10):1727–33.
8. Kimura W, Kuroda A, Morioka Y. Clinical pathology of endocrine tumors of the pancreas. Analysis of autopsy cases. Dig Dis Sci. 1991;36(7):933–42.
9. Fraenkel M, Kim MK, Faggiano A, Valk GD. Epidemiology of gastroenteropancreatic neuroendocrine tumours. Best Pract Res Clin Gastroenterol. 2012;26(6):691–703.
10. Ito T, Sasano H, Tanaka M, Osamura RY, Sasaki I, Kimura W, et al. Epidemiological study of gastroenteropancreatic neuroendocrine tumors in Japan. J Gastroenterol. 2010;45(2):234–43.
11. Yao JC, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE, et al. One hundred years after "carcinoid":

epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol. 2008;26(18):3063–72.
12. Yao JC, Eisner MP, Leary C, Dagohoy C, Phan A, Rashid A, et al. Population-based study of islet cell carcinoma. Ann Surg Oncol. 2007;14(12):3492–500.
13. Lawrence B, Gustafsson BI, Chan A, Svejda B, Kidd M, Modlin IM. The epidemiology of gastroenteropancreatic neuroendocrine tumors. Endocrinol Metab Clin North Am. 2011;40(1):1–18. 1.
14. Pieterman CR, Vriens MR, Dreijerink KM, van der Luijt RB, Valk GD. Care for patients with multiple endocrine neoplasia type 1: the current evidence base. Fam Cancer. 2011;10(1):157–71.
15. de Wilde RF, Edil BH, Hruban RH, Maitra A. Well-differentiated pancreatic neuroendocrine tumors: from genetics to therapy. Nat Rev Gastroenterol Hepatol. 2012;9(4):199–208.
16. Vagefi PA, Razo O, Deshpande V, McGrath DJ, Lauwers GY, Thayer SP, et al. Evolving patterns in the detection and outcomes of pancreatic neuroendocrine neoplasms: the Massachusetts General Hospital experience from 1977 to 2005. Arch Surg. 2007;142(4):347–54.
17. Cheema A, Weber J, Strosberg JR. Incidental detection of pancreatic neuroendocrine tumors: an analysis of incidence and outcomes. Ann Surg Oncol. 2012;19(9):2932–6.
18. Madura JA, Cummings OW, Wiebke EA, Broadie TA, Goulet Jr RL, Howard TJ. Nonfunctioning islet cell tumors of the pancreas: a difficult diagnosis but one worth the effort. Am Surg. 1997;63(7):573–7. discussion 7–8.
19. Matthews BD, Heniford BT, Reardon PR, Brunicardi FC, Greene FL. Surgical experience with nonfunctioning neuroendocrine tumors of the pancreas. Am Surg. 2000;66(12):1116–22. discussion 22–3.
20. Service FJ, McMahon MM, O'Brien PC, Ballard DJ. Functioning insulinoma—incidence, recurrence, and long-term survival of patients: a 60-year study. Mayo Clin Proc. 1991;66(7):711–9.
21. DeVita Jr VT, Lawrence TS, Rosenberg SA, editors. DeVita, Hellman, and Rosenberg's cancer: principles & practice of oncology. Philadelphia: Lippincott Williams & Wilkins; 2008. Available from: http://catdir.loc.gov/catdir/enhancements/fy0811/2008006079-d.html. http://catdir.loc.gov/catdir/enhancements/fy0811/2008006079-d.html, http://www.lww.com/product/DeVita-Hellman-and-Rosenbergs-Cancer/?978-0-7817-7207-5.
22. Placzkowski KA, Vella A, Thompson GB, Grant CS, Reading CC, Charboneau JW, et al. Secular trends in the presentation and management of functioning insulinoma at the Mayo Clinic, 1987–2007. J Clin Endocrinol Metab. 2009;94(4):1069–73.
23. Berna MJ, Hoffmann KM, Serrano J, Gibril F, Jensen RT. Serum gastrin in Zollinger–Ellison syndrome: I. Prospective study of fasting serum gastrin in 309 patients from the National Institutes of Health and comparison with 2229 cases from the literature. Medicine. 2006;85(6):295–330.
24. Roy PK, Venzon DJ, Shojamanesh H, Abou-Saif A, Peghini P, Doppman JL, et al. Zollinger–Ellison syndrome. Clinical presentation in 261 patients. Medicine. 2000;79(6):379–411.
25. Norton JA. Neuroendocrine tumors of the pancreas and duodenum. Curr Probl Surg. 1994;31(2):77–156.
26. Gibril F, Doppman JL, Reynolds JC, Chen CC, Sutliff VE, Yu F, et al. Bone metastases in patients with gastrinomas: a prospective study of bone scanning, somatostatin receptor scanning, and magnetic resonance image in their detection, frequency, location, and effect of their detection on management. J Clin Oncol. 1998;16(3):1040–53.
27. Norton JA, Alexander HR, Fraker DL, Venzon DJ, Gibril F, Jensen RT. Possible primary lymph node gastrinoma: occurrence, natural history, and predictive factors: a prospective study. Ann Surg. 2003;237(5):650–7. discussion 7–9.
28. Zollinger RM, Ellison EH. Primary peptic ulcerations of the jejunum associated with islet cell tumors of the pancreas. 1955. CA Cancer J Clin. 1989;39(4):231–47.
29. Meriney DK. Pathophysiology and management of VIPoma: a case study. Oncol Nurs Forum. 1996;23(6):941–8. quiz 9–50.
30. Bloom SR, Yiangou Y, Polak JM. Vasoactive intestinal peptide secreting tumors. Pathophysiological and clinical correlations. Ann N Y Acad Sci. 1988;527:518–27.
31. Verner JV, Morrison AB. Islet cell tumor and a syndrome of refractory watery diarrhea and hypokalemia. Am J Med. 1958;25(3):374–80.
32. Perry RR, Vinik AI. Clinical review 72: diagnosis and management of functioning islet cell tumors. J Clin Endocrinol Metab. 1995;80(8):2273–8.
33. Smith SL, Branton SA, Avino AJ, Martin JK, Klingler PJ, Thompson GB, et al. Vasoactive intestinal polypeptide secreting islet cell tumors: a 15-year experience and review of the literature. Surgery. 1998;124(6):1050–5.
34. Friesen SR. Update on the diagnosis and treatment of rare neuroendocrine tumors. Surg Clin North Am. 1987;67(2):379–93.
35. Lecorguille M, Hammel P, Couvelard A, O'Toole D, Ratouis A, Belghiti J, et al. [Jejunal vipoma]. Gastroenterologie clinique et biologique. 2004;28(8–9):797–800.
36. Wilkinson DS. Necrolytic migratory erythema with carcinoma of the pancreas. Trans St Johns Hosp Dermatol Soc. 1973;59(2):244–50.
37. Boden G. Glucagonomas and insulinomas. Gastroenterol Clin North Am. 1989;18(4):831–45.
38. Stacpoole PW. The glucagonoma syndrome: clinical features, diagnosis, and treatment. Endocr Rev. 1981;2(3):347–61.
39. Pujol RM, Wang CY, el-Azhary RA, Su WP, Gibson LE, Schroeter AL. Necrolytic migratory erythema: clinicopathologic study of 13 cases. Int J Dermatol. 2004;43(1):12–8.
40. Yamada T, Alpers DH. Textbook of gastroenterology. Hoboken: Blackwell; 2009. Available from:

http://site.ebrary.com/id/10300962. Materials specified: ebrary http://site.ebrary.com/id/10300962.
41. Harris GJ, Tio F, Cruz Jr AB. Somatostatinoma: a case report and review of the literature. J Surg Oncol. 1987;36(1):8–16.
42. Soga J, Yakuwa Y. Somatostatinoma/inhibitory syndrome: a statistical evaluation of 173 reported cases as compared to other pancreatic endocrinomas. J Exp Clin Cancer Res. 1999;18(1):13–22.
43. Ehehalt F, Saeger HD, Schmidt CM, Grutzmann R. Neuroendocrine tumors of the pancreas. Oncologist. 2009;14(5):456–67.
44. Filippella M, Davi MV, Doveri G, Lillaz E, Ciccarelli A, Massimetti E, et al. Hyperinsulinemic hypoglycemia associated with ectopic Cushing's syndrome due to a pancreatic endocrine tumor in a Type 2 diabetes mellitus patient: clinical implications of a rare association. J Endocrinol Invest. 2011;34(3):175–9.
45. Papazachariou IM, Virlos IT, Williamson RC. Parathyroid hormone-related peptide in pancreatic neuroendocrine tumours associated with hypercalcaemia. HPB (Oxford). 2001;3(3):221–5.
46. Wu TJ, Lin CL, Taylor RL, Kvols LK, Kao PC. Increased parathyroid hormone-related peptide in patients with hypercalcemia associated with islet cell carcinoma. Mayo Clin Proc. 1997;72(12):1111–5.
47. Nauck MA, Meier JJ. Diagnostic accuracy of an "amended" insulin–glucose ratio for the biochemical diagnosis of insulinomas. Ann Intern Med. 2012;157(11):767–75.
48. Wermers RA, Fatourechi V, Wynne AG, Kvols LK, Lloyd RV. The glucagonoma syndrome. Clinical and pathologic features in 21 patients. Medicine. 1996;75(2):53–63.
49. Ardill JE, O'Dorisio TM. Circulating biomarkers in neuroendocrine tumors of the enteropancreatic tract: application to diagnosis, monitoring disease, and as prognostic indicators. Endocrinol Metab Clin North Am. 2010;39(4):777–90.
50. Bajetta E, Ferrari L, Martinetti A, Celio L, Procopio G, Artale S, et al. Chromogranin A, neuron specific enolase, carcinoembryonic antigen, and hydroxyindole acetic acid evaluation in patients with neuroendocrine tumors. Cancer. 1999;86(5):858–65.
51. Friesen SR, Tomita T, Kimmel JR. Pancreatic polypeptide update: its roles in detection of the trait for multiple endocrine adenopathy syndrome, type I and pancreatic polypeptide-secreting tumors. Surgery. 1983;94(6):1028–37.
52. Nehar D, Lombard-Bohas C, Olivieri S, Claustrat B, Chayvialle JA, Penes MC, et al. Interest of chromogranin A for diagnosis and follow-up of endocrine tumours. Clin Endocrinol (Oxford). 2004;60(5):644–52.
53. Kouvaraki MA, Ajani JA, Hoff P, Wolff R, Evans DB, Lozano R, et al. Fluorouracil, doxorubicin, and streptozocin in the treatment of patients with locally advanced and metastatic pancreatic endocrine carcinomas. J Clin Oncol. 2004;22(23):4762–71.
54. Gouya H, Vignaux O, Augui J, Dousset B, Palazzo L, Louvel A, et al. CT, endoscopic sonography, and a combined protocol for preoperative evaluation of pancreatic insulinomas. Am J Roentgenol. 2003;181(4):987–92.
55. Rockall AG, Reznek RH. Imaging of neuroendocrine tumours (CT/MR/US). Best Pract Res Clin Endocrinol Metab. 2007;21(1):43–68.
56. Khashab MA, Yong E, Lennon AM, Shin EJ, Amateau S, Hruban RH, et al. EUS is still superior to multidetector computerized tomography for detection of pancreatic neuroendocrine tumors. Gastrointest Endosc. 2011;73(4):691–6.
57. Ichikawa T, Peterson MS, Federle MP, Baron RL, Haradome H, Kawamori Y, et al. Islet cell tumor of the pancreas: biphasic CT versus MR imaging in tumor detection. Radiology. 2000;216(1):163–71.
58. Dromain C, de Baere T, Lumbroso J, Caillet H, Laplanche A, Boige V, et al. Detection of liver metastases from endocrine tumors: a prospective comparison of somatostatin receptor scintigraphy, computed tomography, and magnetic resonance imaging. J Clin Oncol. 2005;23(1):70–8.
59. Reidy-Lagunes DL, Gollub MJ, Saltz LB. Addition of octreotide functional imaging to cross-sectional computed tomography or magnetic resonance imaging for the detection of neuroendocrine tumors: added value or an anachronism? J Clin Oncol. 2011;29(3):e74–5.
60. Sundin A. Imaging of neuroendocrine tumors. Expert Opin Med Diagn. 2012;6(5):473–83.
61. Kim EY. Role of repeated endoscopic ultrasound-guided fine needle aspiration for inconclusive initial cytology result. Clin Endosc. 2013;46(5):540–2.
62. Abboud B, Boujaoude J. Occult sporadic insulinoma: localization and surgical strategy. World J Gastroenterol. 2008;14(5):657–65.
63. Jensen RT, Cadiot G, Brandi ML, de Herder WW, Kaltsas G, Komminoth P, et al. ENETS Consensus Guidelines for the management of patients with digestive neuroendocrine neoplasms: functional pancreatic endocrine tumor syndromes. Neuroendocrinology. 2012;95(2):98–119.
64. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A, editors. AJCC cancer staging handbook. 7th ed. Chicago: American Joint Committee on Cancer; 2010.
65. Klimstra DS, Modlin IR, Coppola D, Lloyd RV, Suster S. The pathologic classification of neuroendocrine tumors: a review of nomenclature, grading, and staging systems. Pancreas. 2010;39(6):707–12.
66. Ramage JK, Ahmed A, Ardill J, Bax N, Breen DJ, Caplin ME, et al. Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours (NETs). Gut. 2012;61(1):6–32.
67. Reid MD, Balci S, Saka B, Adsay NV. Neuroendocrine tumors of the pancreas: current concepts and controversies. Endocr Pathol. 2014;25(1):65–79.
68. Travis WD, Rush W, Flieder DB, Falk R, Fleming MV, Gal AA, et al. Survival analysis of 200 pulmonary neuroendocrine tumors with clarification of criteria for atypical carcinoid and its separation from typical carcinoid. Am J Surg Pathol. 1998;22(8):934–44.

69. Strosberg JR, Cheema A, Weber JM, Ghayouri M, Han G, Hodul PJ, et al. Relapse-free survival in patients with nonmetastatic, surgically resected pancreatic neuroendocrine tumors: an analysis of the AJCC and ENETS staging classifications. Ann Surg. 2012;256(2):321–5.
70. Strosberg JR, Cheema A, Weber J, Han G, Coppola D, Kvols LK. Prognostic validity of a novel American Joint Committee on Cancer Staging Classification for pancreatic neuroendocrine tumors. J Clin Oncol. 2011;29(22):3044–9.
71. Papavramidis T, Papavramidis S. Solid pseudopapillary tumors of the pancreas: review of 718 patients reported in English literature. J Am Coll Surg. 2005;200(6):965–72.
72. Yu PF, Hu ZH, Wang XB, Guo JM, Cheng XD, Zhang YL, et al. Solid pseudopapillary tumor of the pancreas: a review of 553 cases in Chinese literature. World J Gastroenterol. 2010;16(10):1209–14.
73. Kato T, Egawa N, Kamisawa T, Tu Y, Sanaka M, Sakaki N, et al. A case of solid pseudopapillary neoplasm of the pancreas and tumor doubling time. Pancreatology. 2002;2(5):495–8.
74. Madan AK, Weldon CB, Long WP, Johnson D, Raafat A. Solid and papillary epithelial neoplasm of the pancreas. J Surg Oncol. 2004;85(4):193–8.
75. Tien YW, Ser KH, Hu RH, Lee CY, Jeng YM, Lee PH. Solid pseudopapillary neoplasms of the pancreas: is there a pathologic basis for the observed gender differences in incidence? Surgery. 2005;137(6):591–6.
76. Abraham SC, Klimstra DS, Wilentz RE, Yeo CJ, Conlon K, Brennan M, et al. Solid-pseudopapillary tumors of the pancreas are genetically distinct from pancreatic ductal adenocarcinomas and almost always harbor beta-catenin mutations. Am J Pathol. 2002;160(4):1361–9.
77. Maitra A, Weinberg AG, Schneider N, Patterson K. Detection of t(11;22)(q24;q12) translocation and EWS-FLI-1 fusion transcript in a case of solid pseudopapillary tumor of the pancreas. Pediatr Dev Pathol. 2000;3(6):603–5.
78. Kosmahl M, Seada LS, Janig U, Harms D, Kloppel G. Solid-pseudopapillary tumor of the pancreas: its origin revisited. Virchows Arch. 2000;436(5):473–80.
79. Klimstra DS. Nonductal neoplasms of the pancreas. Mod Pathol. 2007;20 Suppl 1:S94–112.
80. Nishihara K, Nagoshi M, Tsuneyoshi M, Yamaguchi K, Hayashi I. Papillary cystic tumors of the pancreas. Assessment of their malignant potential. Cancer. 1993;71(1):82–92.
81. Mortenson MM, Katz MH, Tamm EP, Bhutani MS, Wang H, Evans DB, et al. Current diagnosis and management of unusual pancreatic tumors. Am J Surg. 2008;196(1):100–13.
82. Yao X, Ji Y, Zeng M, Rao S, Yang B. Solid pseudopapillary tumor of the pancreas: cross-sectional imaging and pathologic correlation. Pancreas. 2010;39(4):486–91.
83. Wisnoski NC, Townsend Jr CM, Nealon WH, Freeman JL, Riall TS. 672 patients with acinar cell carcinoma of the pancreas: a population-based comparison to pancreatic adenocarcinoma. Surgery. 2008;144(2):141–8.
84. Holen KD, Klimstra DS, Hummer A, Gonen M, Conlon K, Brennan M, et al. Clinical characteristics and outcomes from an institutional series of acinar cell carcinoma of the pancreas and related tumors. J Clin Oncol. 2002;20(24):4673–8.
85. Kitagami H, Kondo S, Hirano S, Kawakami H, Egawa S, Tanaka M. Acinar cell carcinoma of the pancreas: clinical analysis of 115 patients from Pancreatic Cancer Registry of Japan Pancreas Society. Pancreas. 2007;35(1):42–6.
86. Klimstra DS, Heffess CS, Oertel JE, Rosai J. Acinar cell carcinoma of the pancreas. A clinicopathologic study of 28 cases. Am J Surg Pathol. 1992;16(9):815–37.
87. Schmidt CM, Matos JM, Bentrem DJ, Talamonti MS, Lillemoe KD, Bilimoria KY. Acinar cell carcinoma of the pancreas in the United States: prognostic factors and comparison to ductal adenocarcinoma. J Gastrointest Surg. 2008;12(12):2078–86.
88. Abraham SC, Wu TT, Hruban RH, Lee JH, Yeo CJ, Conlon K, et al. Genetic and immunohistochemical analysis of pancreatic acinar cell carcinoma: frequent allelic loss on chromosome 11p and alterations in the APC/beta-catenin pathway. Am J Pathol. 2002;160(3):953–62.
89. Abraham SC, Wu TT, Klimstra DS, Finn LS, Lee JH, Yeo CJ, et al. Distinctive molecular genetic alterations in sporadic and familial adenomatous polyposis-associated pancreatoblastomas: frequent alterations in the APC/beta-catenin pathway and chromosome 11p. Am J Pathol. 2001;159(5):1619–27.
90. Rigaud G, Moore PS, Zamboni G, Orlandini S, Taruscio D, Paradisi S, et al. Allelotype of pancreatic acinar cell carcinoma. Int J Cancer. 2000;88(5):772–7.
91. Hoorens A, Lemoine NR, McLellan E, Morohoshi T, Kamisawa T, Heitz PU, et al. Pancreatic acinar cell carcinoma. An analysis of cell lineage markers, p53 expression, and Ki-ras mutation. Am J Pathol. 1993;143(3):685–98.
92. Seth AK, Argani P, Campbell KA, Cameron JL, Pawlik TM, Schulick RD, et al. Acinar cell carcinoma of the pancreas: an institutional series of resected patients and review of the current literature. J Gastrointest Surg. 2008;12(6):1061–7.
93. Chiou YY, Chiang JH, Hwang JI, Yen CH, Tsay SH, Chang CY. Acinar cell carcinoma of the pancreas: clinical and computed tomography manifestations. J Comput Assist Tomogr. 2004;28(2):180–6.
94. Tatli S, Mortele KJ, Levy AD, Glickman JN, Ros PR, Banks PA, et al. CT and MRI features of pure acinar cell carcinoma of the pancreas in adults. Am J Roentgenol. 2005;184(2):511–9.
95. Zucca E, Roggero E, Bertoni F, Cavalli F. Primary extranodal non-Hodgkin's lymphomas. Part 1: gastrointestinal, cutaneous and genitourinary lymphomas. Ann Oncol. 1997;8(8):727–37.

96. Freeman C, Berg JW, Cutler SJ. Occurrence and prognosis of extranodal lymphomas. Cancer. 1972;29(1):252–60.
97. Baylor SM, Berg JW. Cross-classification and survival characteristics of 5,000 cases of cancer of the pancreas. J Surg Oncol. 1973;5(4):335–58.
98. Nishimura R, Takakuwa T, Hoshida Y, Tsujimoto M, Aozasa K. Primary pancreatic lymphoma: clinicopathological analysis of 19 cases from Japan and review of the literature. Oncology. 2001;60(4):322–9.
99. Nayer H, Weir EG, Sheth S, Ali SZ. Primary pancreatic lymphomas: a cytopathologic analysis of a rare malignancy. Cancer. 2004;102(5):315–21.
100. Behrns KE, Sarr MG, Strickler JG. Pancreatic lymphoma: is it a surgical disease? Pancreas. 1994;9(5):662–7.
101. Koniaris LG, Lillemoe KD, Yeo CJ, Abrams RA, Colemann J, Nakeeb A, et al. Is there a role for surgical resection in the treatment of early-stage pancreatic lymphoma? J Am Coll Surg. 2000;190(3):319–30.
102. Saif MW. Primary pancreatic lymphomas. JOP. 2006;7(3):262–73.
103. Merkle EM, Bender GN, Brambs HJ. Imaging findings in pancreatic lymphoma: differential aspects. Am J Roentgenol. 2000;174(3):671–5.
104. Dawson IM, Cornes JS, Morson BC. Primary malignant lymphoid tumours of the intestinal tract. Report of 37 cases with a study of factors influencing prognosis. Br J Surg. 1961;49:80–9.
105. Salman B, Brat G, Yoon YS, Hruban RH, Singhi AD, Fishman EK, et al. The diagnosis and surgical treatment of pancreatoblastoma in adults: a case series and review of the literature. J Gastrointest Surg. 2013;17(12):2153–61.
106. Bien E, Godzinski J, Dall'igna P, Defachelles AS, Stachowicz-Stencel T, Orbach D, et al. Pancreatoblastoma: a report from the European cooperative study group for paediatric rare tumours (EXPeRT). Eur J Cancer. 2011;47(15):2347–52.
107. Montemarano H, Lonergan GJ, Bulas DI, Selby DM. Pancreatoblastoma: imaging findings in 10 patients and review of the literature. Radiology. 2000;214(2):476–82.
108. Roland CF, van Heerden JA. Nonpancreatic primary tumors with metastasis to the pancreas. Surg Gynecol Obstet. 1989;168(4):345–7.
109. Adler H, Redmond CE, Heneghan HM, Swan N, Maguire D, Traynor O, et al. Pancreatectomy for metastatic disease: a systematic review. Eur J Surg Oncol. 2014;40(4):379–86.
110. Ghavamian R, Klein KA, Stephens DH, Welch TJ, LeRoy AJ, Richardson RL, et al. Renal cell carcinoma metastatic to the pancreas: clinical and radiological features. Mayo Clin Proc. 2000;75(6):581–5.

Cystic Lesions of the Pancreas

4

Wiriyaporn Ridtitid and Mohammad Al-Haddad

Introduction

In recent years, the diagnosis of cystic lesions of the pancreas (CLPs) has increased dramatically due to the widespread use of cross-sectional radiologic imaging technologies [1]. In the radiology literature, the prevalence of CLPs on computed tomography (CT) and magnetic resonance imaging (MRI) is estimated to range between 2.4 and 14 % [2–4]. Furthermore, small CLPs have been reported iwith a high frequency (up to 39 %) during screening of asymptomatic individuals with a high risk of pancreatic malignancy [5]. A recent population-based study demonstrated that the overall frequency of detecting malignancy in CLPs at 2.9 % in patients surveyed for known pancreatic cysts, with an annual incidence of 0.4 % per year [6]. Based on the presence of epithelial tissue, the World Health Organization (WHO) classifies) CLPs into epithelial and non-epithelial lesions [7]. Inflammatory pancreatic fluid collections (pancreatitis-associated pseudocysts) are not considered true cysts due to the absence of an epithelial component.

A combination of clinical and imaging findings in addition to cyst fluid markers can help appropriately classify CLPs. In this chapter we will expand on each one of the main types of epithelial CLPs, including the commonly encountered types in clinical practice from the mucinous and nonmucinous subtypes.

Mucinous Cystic Lesions of the Pancreas

Mucinous CLPs are mucin-producing neoplasms, which are composed of two distinct groups: intraductal papillary-mucinous neoplasms (IPMNs) and mucinous cystic neoplasms (MCNs). Despite the fact that mucinous CLPs are considered premalignant, many of them remain indolent and do not exhibit an aggressive biological behavior. Because of this malignant potential, however, mucinous CLPs require a baseline investigation to assess the risk of malignant transformation and the interval for follow-up. Furthermore, these tumors sometimes need surgical resection if already malignant at the time of diagnosis or strongly suspected to be so based on preoperative

W. Ridtitid, M.D.
Division of Gastroenterology and Hepatology,
Indiana University School of Medicine,
550 N. University Blvd, Suite 4100, Indianapolis,
IN 46202, USA

Chulalongkorn University, King Chulalongkorn Memorial Hospital, Thai Red Cross Society,
Bangkok, Thailand

M. Al-Haddad, M.D., M.Sc., F.A.S.G.E. (✉)
Division of Gastroenterology and Hepatology,
Indiana University School of Medicine,
550 N. University Blvd, Suite 4100, Indianapolis,
IN 46202, USA
e-mail: alhaddad_mo@yahoo.com

M.S. Wagh, P.V. Draganov (eds.), *Pancreatic Masses*, DOI 10.1007/978-3-319-19677-0_4

testing. Therefore, it is necessary to distinguish between mucinous and nonmucinous CLPs prior to making final management recommendations.

Intraductal Papillary-Mucinous Neoplasms

Histopathologic Features

IPMNs are defined as intraductal papillary mucin-producing neoplasms, arising in the main pancreatic duct or its major branches [7]. Based on the WHO classification, IPMNs are histologically categorized as benign, borderline, or malignant; the malignant ones encompass noninvasive and invasive lesions [7]. According to the consensus on the pathologic classification [8], IPMNs are categorized based on the presence or absence of invasive adenocarcinoma in the resected specimen due to its impacts on local recurrence and patient survival. In addition, the consensus suggested classifying noninvasive IPMN into low-grade dysplasia (adenomas in the previous classification), moderate dysplasia (borderline tumors in the previous classification), or high-grade dysplasia (carcinoma in situ), based on the maximal degree of dysplasia in the lining epithelium. From a pathological and morphological perspective, IPMNs can be classified as main-duct (MD-IPMN), branched-duct (BD-IPMN), or mixed IPMN [9]. Macroscopically, IPMNs exhibit various degrees of main- or side-branch ductal dilation with mucin-filled cystic cavities [7]. The lining of the lesion may be smooth or exhibit classic papillary growth. The histopathologic hallmark of IPMN is the intraductal proliferation of columnar mucin-producing cells [7]. The premalignant papillary projections within IPMN lesions can be categorized into four histopathological subtypes: the gastric, intestinal, pancreatobiliary, and oncocytic subtypes [10, 11]. The gastric subtype is the most common variant seen in BD-IPMN, which often demonstrates benign behavior, whereas the intestinal subtype is the most common type in MD-IPMN and has a higher malignant potential compared to the gastric type. The pancreatobiliary subtype is less commonly seen but could be considered a highly dysplastic variant of the gastric type, which typically exhibits aggressive biological behavior once it becomes invasive. The oncocytic subtype, on the other hand, typically displays noninvasive behavior. Most invasive carcinoma arising from IPMN presents as either the tubular or colloid type. The histological and biological behavior of the tubular type is similar to the common ductal adenocarcinoma. The colloid type contains pools of mucin intervening between scant carcinoma cells, which usually predicts a better prognosis.

Clinical Characteristics

MD-IPMN and mixed-type IPMN are slightly more prevalent in men [9, 12], with a peak age of incidence in the sixth to seventh decade (Table 4.1) [12, 13]. IPMNs are slightly more frequently seen in the pancreatic head. The majority of patients with IPMNs are asymptomatic and most BD-IPMNs are incidentally diagnosed on imaging studies [12, 14]. However, IPMNs can present with symptoms such as abdominal pain, jaundice, weight loss, diabetes, steatorrhea, and pancreatitis [14]. Recently, a multicenter case-control study identified possible risk factors relevant for the development of IPMN, including a previous history of diabetes, especially with insulin use, chronic pancreatitis, and family history of pancreatic ductal adenocarcinoma [15]. The overall malignancy risk in MD-IPMN has been reported as up to 92 % in surgical patients, with most studies placing this between 40 and 50 % [16–20]. In BD-IPMN, this risk varied in surgical literature but is believed to be 20 % or less [16, 18, 20, 21]. Nevertheless, many experts believe that these reported risks are inflated, citing selection bias in these mostly surgical series.

It is believed that IPMN lesions grow slowly and follow an adenoma-to-carcinoma sequence [22]. Based on the 2006 international consensus guidelines [23], clinical factors associated with invasive cancer in patients with IPMNs include jaundice and weight loss, intramural nodules, progressive dilation of the main duct, and positive cytology on fine-needle aspiration (FNA).

Table 4.1 Clinical and histopathologic features of the different types of cystic pancreatic neoplasms

	IPMNs	MCNs	SCNs	cPNETs	SPTPs
Age range	60s–70s	50s–70s	60s–70s	50s–60s	30s
Gender	Male > Female	Female > Male	Female > Male	Male = Female	Female > Male
Presentations	Mostly asymptomatic with BD-IPMNs	Asymptomatic if small Pain/weight loss if larger	Frequently asymptomatic	Nonfunctioning lesions and often asymptomatic	Asymptomatic or abdominal pain
Macroscopic findings	Various degrees of ductal dilation in MD-IPMNs; mucin-filled cystic cavity in BD-IPMNs	A smooth surface and a fibrous pseudocapsule with variable thickness septations	A few/numerous small cysts filled with serous fluid around a central fibronodular core	A single locule, surrounded by a rim of neoplastic parenchyma, filled with clear to straw-colored fluid	Cystic areas of hemorrhage and necrosis with a well-defined fibrous pseudocapsule
Microscopic findings	Intraductal proliferation of columnar mucin-producing cells	Benign: no mitosis Malignant: changes of high-grade intraepithelial neoplasia or invasive adenocarcinoma	A single layer of cuboidal or flattened epithelial cells with clear cytoplasm; positive PAS staining	Monotonous cells with granular chromatin and plasmacytoid morphology, positive synaptophysin and chromogranin A stains	Pseudopapillary structures composed of tumor cells surrounding small central vessels
Location	Head > body, tail	Body, tail > head	Body, tail ≥ head	Body, tail > head	Throughout the pancreas

MD-IPMN main duct intraductal papillary mucinous neoplasm, *SB-IPMN* side branch intraductal papillary mucinous neoplasm, *cPNETs* cystic neuroendocrine tumors of the pancreas, *SPTPs* solid pseudopapillary tumors of the pancreas, *PAS* periodic acid Schiff

Although BD-IPMN is associated with a lower risk of malignancy, PDAC has been reported concomitantly in patients with BD-IPMN [24–26]. Those cancers were detected in a location distant from the IPMN lesion. During follow-up, the 3- and 5-year rates of IPMN-concomitant PDAC occurrence were 4.0 % and 8.8 %, respectively [24]. However; the natural history of IPMN remains unclear due to the rather short span of follow-up, which is less than 6 years in most published studies [27–30].

Radiological Findings

On CT imaging, MD-IPMN demonstrates diffuse or focal dilation of the main pancreatic duct with possible intraductal heterogeneous densities, representing mucin or intraductal tumor growth (Table 4.2) [31]. BD-IPMN can be either unifocal or multifocal [14, 32]. MRI technology is better suited to outline the morphology of the main duct and its side branches, as well as determine the presence of septations, mural nodules, or mass [31, 33]. IPMN lesions usually appear as well-circumscribed uni- or multiloculated hyperintensities on T2-weighted (W) images (Fig. 4.1a). On magnetic resonance cholangiopancreatograhy (MRCP), a communication between the cystic lesion and the main pancreatic duct (Fig. 4.1b) or its side branches can be often demonstrated in BD-IPMN. MCNs and BD-IPMNs may be difficult to differentiate on imaging alone since both can appear as simple unilocular cystic lesions, with variable cystic wall thickness [34]. Communication with a side branch of the main pancreatic duct is the hallmark of BD-IPMNs but is not always seen. Mucinous cystic neoplasms, on the other hand, rarely exhibit any communication with the pancreatic ductal system. Intramural filling defects seen on imaging of BD-IPMNs can be either mucin or mural nodules. Based on earlier studies [33, 35–40], CT or MRI features associated with malignancy in IPMNs include lesion size more than 3 cm, main duct dilation more than 6 mm, irregularly thickened wall, mural nodule larger than 5 mm, ductal wall enhancement, common bile duct dilation, and bulging papilla. A recent meta-analysis evaluated imaging features for differentiating malignant from benign BD-IPMNs [41] and found that the presence of mural nodules was the most suggestive finding for malignancy [odds ratio (OR), 6.0], followed by main pancreatic duct dilatation (OR, 3.4), thick septum or cyst wall (OR, 2.3), and cyst size greater than 3 cm (OR, 2.3). According to the 2012 international consensus guidelines for the management of IPMNs and MCNs [42], "high-risk stigmata" included enhanced solid component and the size of main pancreatic duct ≥10 mm, or "worrisome features," including cyst o≥3 cm, thickened enhanced cyst walls, nonenhanced mural nodules, the main pancreatic duct size of 5–9 mm, abrupt change in the main pancreatic duct caliber with distal pancreatic duct atrophy, and lymphadenopathy.

EUS Morphology

The classic endoscopic finding of fish-mouth appearance of the papilla, which is characterized by the presence of mucin exuding from a patulous major or minor papilla (Fig. 4.2) with or without papillary tissue protrusion (fish-egg appearance), is diagnostic of MD-IPMN. EUS characteristics include a macrocystic morphology of the cyst, with or without septations, which could communicate with a dilated pancreatic duct (MD or BD) (Fig. 4.3, Table 4.3) [43]. A mucin nodule may be seen (Fig. 4.4). The differential diagnosis of a unilocular pancreatic cyst on EUS includes commonly macrocystic serous cystic neoplasm, mucinous cystic neoplasm, and inflammatory cyst [44]. Other less common differential diagnoses include cystic solid tumor (neuroendocrine or solid pseudopapillary) and lymphoepithelial cyst. Previous retrospective studies reported a strong association between the presence of a mural nodule (height >10 mm, lateral spread >15 mm) and malignancy in BD-IPMN [45, 46].

Due to the difficulty in differentiating such tumors based on morphology alone, FNA is generally recommended in this case to accrue fluid for cytology and tumor markers. The integration of cyst fluid cytology and tumor markers for the appropriate classification of CLPs is discussed elsewhere in this book.

Table 4.2 Radiological characteristics of the different types of cystic pancreatic neoplasms

	IPMNs	MCNs	SCNs	cPNETs	SPTPs
CT	MD-IPMNs: diffuse or focal dilatation of MPD with intraductal heterogeneous densities	Solitary lesion consisting of a thick enhancing wall, ± septation, ± peripheral calcification, ± mural nodules	Polycystic, honeycomb or oligocystic pattern, with septations, ± central scar ± calcifications	A cystic lesion with peripheral arterial enhancement ± a solid component	A solid part in the periphery with central cystic component, surrounded by well-demarcated capsule
	BD-IPMNs: unifocal or multifocal cystic lesions				
MRI	MD-IPMN: diffusely or segmentally dilated main pancreatic duct; BD-IPMN: Well-circumscribed single or multiloculated hyperintensity on T2W	Round, homogeneous, with high signal intensity on T2W, with regular rim enhancement on delayed T1W	Microcystic with honey comb appearance and central scar on T2W or macrocystic, unilocular or oligolocular on T2W. Enhancement of thin septations radiating from a central scar on gadolinium-T1W	Homogenous unilocular, thick wall lesion on T2W. Wall enhancement in arterial phase on gadolinium-T1W	High and low signal intensity with thick fibrous capsule. Heterogeneous peripheral capsule enhancement on T1W post-gadolinium
MRCP	Cyst usually communicating with pancreatic duct	Cyst rarely communicating with pancreatic duct	No communication with the pancreatic duct	No communication with the pancreatic duct	No communication with the pancreatic duct

MD-IPMN main duct intraductal papillary mucinous neoplasm, *SB-IPMN* side branch intraductal papillary mucinous neoplasm, *cPNETs* cystic neuroendocrine tumors of the pancreas, *SPTPs* solid pseudopapillary tumors of the pancreas, *PAS* periodic acid Schiff

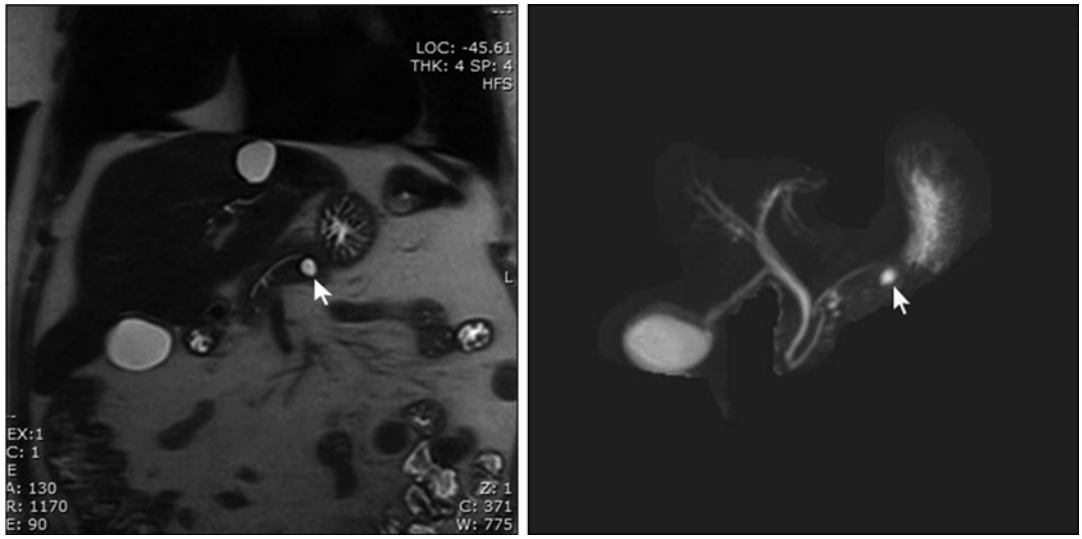

Fig. 4.1 Radiological characteristics of side-branch IPMNs. (**a**) MRI of a 35-year-old asymptomatic female patient shows a 9-mm cystic lesion (*white arrow*), in close proximity to the main pancreatic duct. (**b**) Communication between the pancreatic cyst and the main pancreatic duct seen on MRCP (*white arrow*)

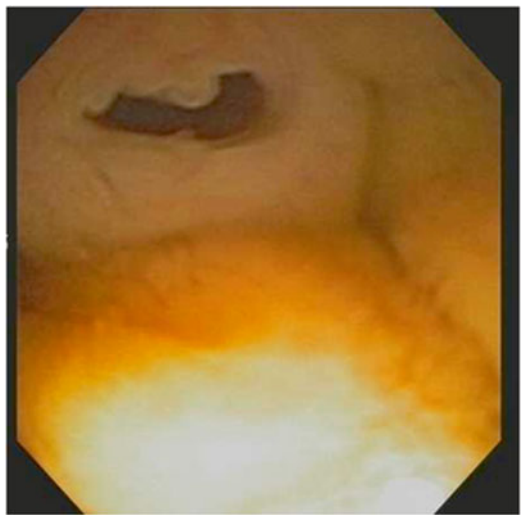

Fig. 4.2 Endoscopic finding of fish-mouth appearance of the major papilla, characterized by the presence of mucin exuding from a patulous papilla in a patient with main-duct IPMN

Mucinous Cystic Neoplasms

Histopathologic Features

MCNs are defined as cystic epithelial neoplasms with no communication with the pancreatic ductal system and are composed of columnar, mucin-producing epithelium, supported by ovarian-type stroma [7]. These tumors are usually associated with extracellular mucin production with variable degrees of cyst wall epithelial atypia. The histopathologic hallmark of MCN is the presence of ovarian stroma underlying the mucinous columnar cyst epithelium and is required to differentiate this tumor from IPMN [47]. Similar to IPMNs, MCNs are classified as noninvasive (low-grade dysplasia, moderate dysplasia, and high-grade dysplasia) and invasive lesions. Gross morphology demonstrates a round mass with a smooth surface and a fibrous pseudocapsule with variable thickness and frequent calcifications [7]. Histologically, MCNs exhibit columnar epithelium with basally located nuclei and absent or minimal mitosis, whereas mucinous cystadenocarcinomas show changes of high-grade intraepithelial neoplasia (nuclear stratification, severe nuclear atypia, and frequent mitoses), which are usually focal [7].

Clinical Characteristics

Females are more frequently affected with MCNs, particularly in their fifth to seventh decades

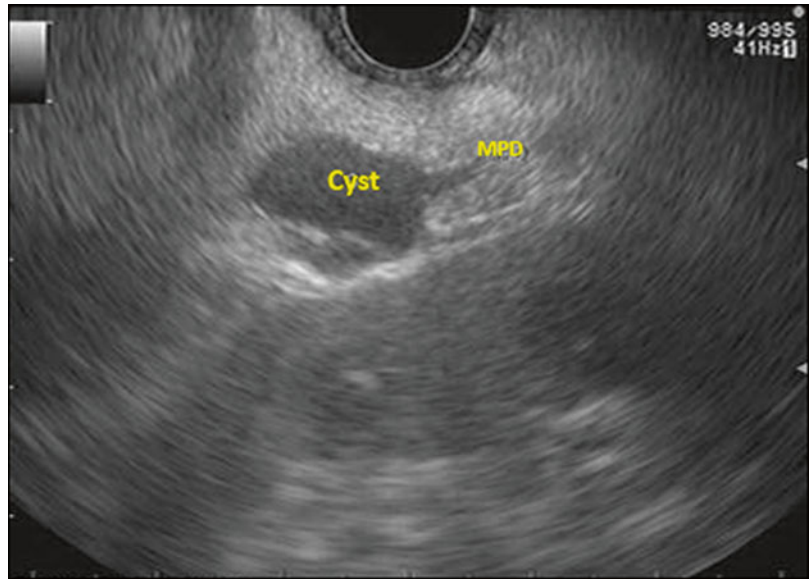

Fig. 4.3 EUS morphology of SB-IPMNs. A 14-mm × 12-mm cystic lesion was identified in the pancreatic tail in a 66-year-old male presenting with abdominal pain. The cyst was found to communicate with the main pancreatic duct through a small side branch, suggestive of branched duct IPMN

Table 4.3 EUS morphology in the different types of cystic pancreatic neoplasm

	IPMNs	MCNs	SCNs	cPNETs	SPTPs
Typical features	Fish-mouth appearance on endoscopy. Macrocystic, septated cyst with dilated PD (main or side branch)	Macrocystic cyst with a visible wall	A well-demarcated lesion with multiple small fluid-filled cavities, ± central calcified scar	Uni- or multilocular lesion with a visible wall	Well-defined, mixed echogenicity lesion, ± internal or peripheral calcifications
Echogenicity	Anechoic	Anechoic	Usually anechoic Hypoechoic if solid variant	Anechoic, hypoechoic, or mixed	Anechoic, hypoechoic, or mixed
Wall thickness	Thin	Mostly thick	Thin	Mostly thick	Mostly thick
Septation	Yes	Yes	Yes	Yes	No
Nodule	Mucin aggregation; ± true soft tissue mural nodule	± Mural nodule	Rare	± Mural nodule	± Mural nodule
Communication with the pancreatic duct	Usually seen	Rarely seen	Not seen	Not seen	Not seen

MD-IPMN main duct intraductal papillary mucinous neoplasm, *SB-IPMN* side branch intraductal papillary mucinous neoplasm, *cPNETs* cystic neuroendocrine tumors of the pancreas, *SPTPs* solid pseudopapillary tumors of the pancreas, *PAS* periodic acid Schiff

[48–50]. The tumors occur most frequently in the pancreatic body and tail [13]. MCNs can be incidentally found [47]; however, they can present with abdominal pain, palpable mass, and weight loss, particularly in association with large lesions [9, 13]. Pancreatitis is infrequent with MCNs but can be seen in up to 10–20 % of cases [48, 51, 52]. A recent study demonstrated factors predictive of high-grade dysplasia and/or invasive carcinoma in MCNs, which included the presence of symptoms, obstructive jaundice, and elevated serum CEA and CA 19-9 [53]. Although MCNs have malignant

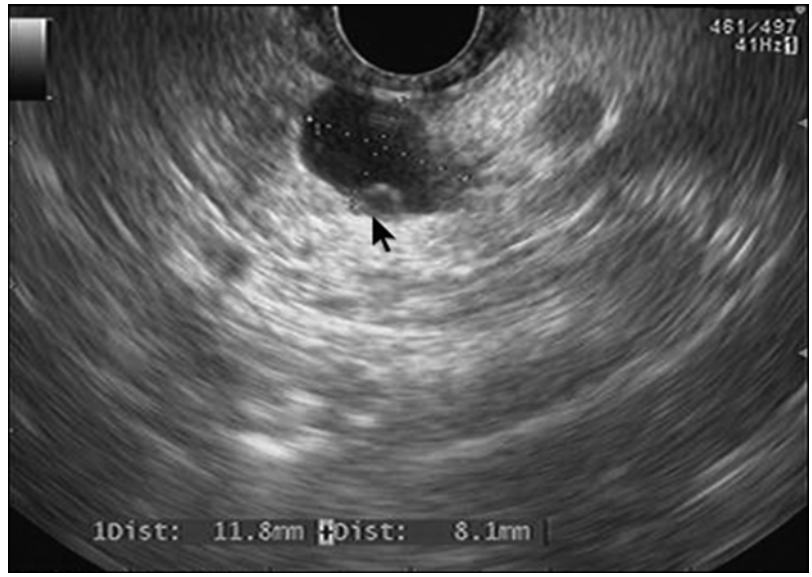

Fig. 4.4 EUS morphology of IPMNs. A 12-mm × 8-mm cystic lesion with mucin aggregate (*black arrow*; this was suspicious for soft tissue mural nodule on MRI) within the fluid-filled cavity of the cyst, consistent with SB-IPMN. Mucin "balls" typically have a hyperechoic rim and hypoechoic core

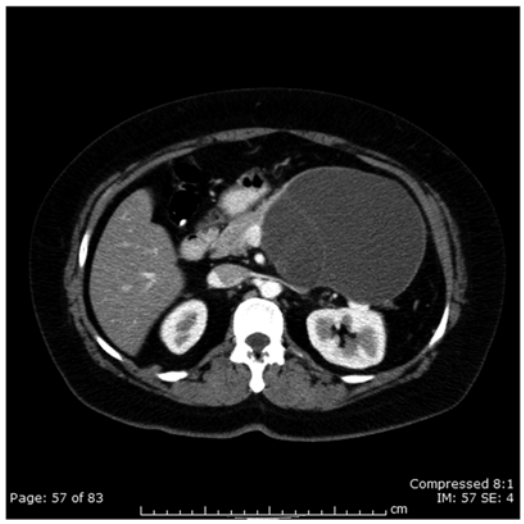

Fig. 4.5 Radiological characteristics of MCNs. CT demonstrated a large 11-cm septated cystic lesion in the pancreatic tail in a middle-aged female patient presenting with left upper quadrant discomfort

potential, they carry a lower overall risk of malignancy in comparison with MD-IPMNs [47]. In a study of 163 patients undergoing surgery, the prevalence of malignancy in such tumors was found to be 17.5 % (5.5 % with carcinoma in situ and 12 % with invasive cancer) [51].

Radiological Findings

CT typically shows a unilocular cystic lesion in the pancreatic body or tail, with or without septations and a thick enhancing wall (Fig. 4.5). Peripheral calcifications can be present in 15–23 % and occasionally can be linear, taking the shape of an eggshell [48, 52]. Mural nodules within MCN on CT scan strongly suggest malignancy [52]. MCN appears round, homogeneous, with high signal intensity on T2W MRI (Fig. 4.6), with regular rim enhancement on delayed T1W images [54]. MRCP usually demonstrates no communication between the cyst and the pancreatic ductal system [31, 54].

EUS Morphology

MCNs presents as a macrocystic lesion with a visible wall and septations of variable thickness on EUS (Fig. 4.7a) [13, 43]. A solid component (Fig. 4.7b) or mural nodule (Fig. 4.7a) may be seen. Peripheral calcifications can be present focally or as a rim but are only seen in up to 15 % of lesions [48]. Mucinous cystadenocarcinomas are more likely to appear as a hypoechoic cystic/solid mass or complex cyst and are frequently

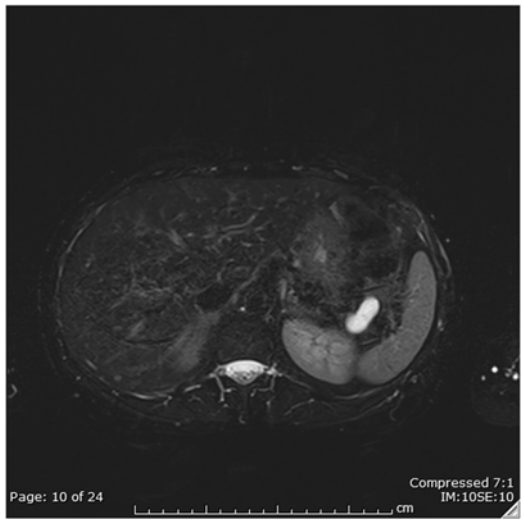

Fig. 4.6 Radiological characteristics of MCNs. T2-weighted MRI showed a round, homogeneous cyst with high signal intensity in the pancreatic tail. EUS-FNA of this lesion confirmed the mucinous nature due to an elevated cyst fluid CEA and the presence of a low-clonality K-ras mutation

associated with a dilated main pancreatic duct upstream from the lesion [55]. Furthermore, regional lymphadenopathy can be seen during EUS examination in malignant lesions [56].

Nonmucinous Cystic Lesions of the Pancreas

Nonmucinous CLPs vary greatly in their clinical, radiologic, and EUS characteristics due to variable underlying pathologies. Serous cystadenomas (SCAs) are the most commonly encountered nonmucinous true cystic tumors of the pancreas. Other nonmucinous pure cystic or mixed solid–cystic tumors such as pancreatic neuroendocrine tumors (PNETs) and solid pseudopapillary tumors of the pancreas (SPTPs) will be discussed in this chapter as well.

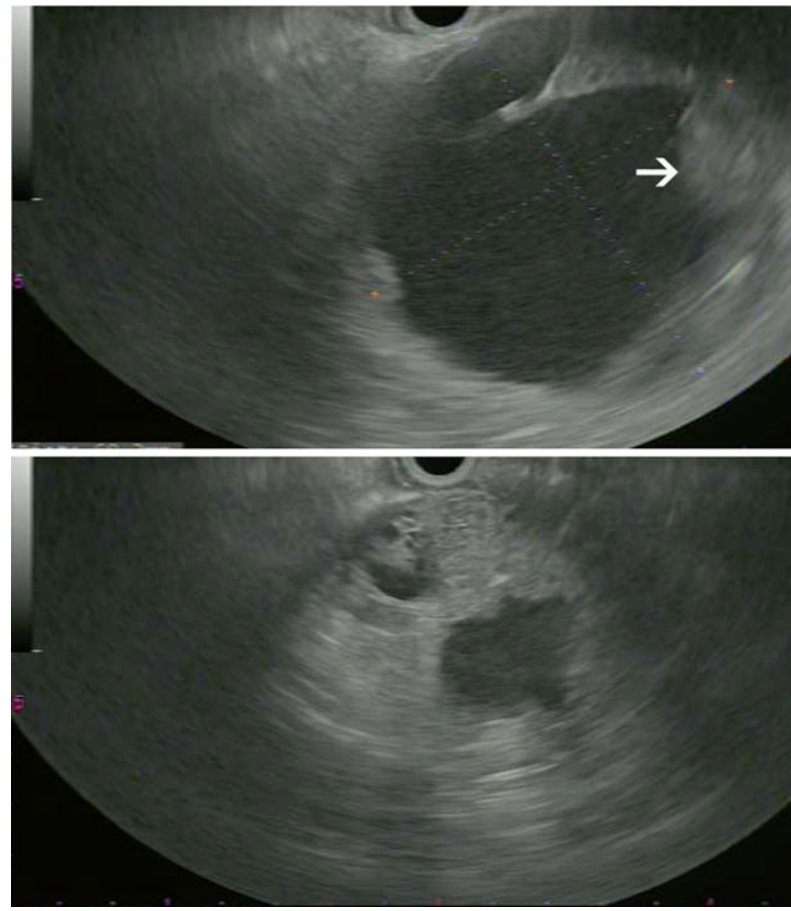

Fig. 4.7 EUS morphology of MCN. (**a**) A mixed cystic–solid septated 70-mm ×70-mm lesion was seen in the pancreatic tail with thickened wall and mural nodules (*white arrow*) within the cavity, not communicating with the pancreatic duct. (**b**) A tangential view through the cyst demonstrates the thickened wall and septum

Serous Cystadenomas

Histopathologic Features

SCAs are defined as cystic epithelial neoplasms composed of glycogen-rich, ductular-type epithelial cells that produce a watery fluid similar to serum [7]. Gross pathology often demonstrates a few or numerous small cysts filled with serous fluid around a central fibrous core with fine septations (central scars) [7]. By histology, the cysts are lined with a single layer of cuboidal or flattened epithelial cells with a clear cytoplasm. The periodic acid–Schiff stain is positive due to their intracytoplasmic glycogen [7]. Morphologically, microcystic SCAs (typically with individual cysts measuring less than 5 mm in size) are more common, whereas the macroscopic variant (over 2 cm in size) is relatively infrequent. Microcystic tumors are usually well delineated with multiple small fluid-filled cavities, which are separated by thin septa and lined with cuboidal epithelial cells [14]. Macrocystic SCAs may not be indistinguishable from MCNs or BD-IPMNs based on morphology alone. The presence of any intramural nodules, cyst wall thickening, floating debris, mucin, or associated pancreatic duct dilation or communication can indicate a mucinous lesion [55, 57].

Clinical Characteristics

SCAs frequently occur in females around the sixth to seventh decade of life [9, 13, 58] and are believed to be predominantly located in the pancreatic body and tail [9, 12]. However, a 2012 multicenter study from Japan reported a similar distribution in the pancreas head (39 %), body (35 %), and tail (22 %) [58]. Patients are usually asymptomatic, with SCAs being an incidental finding on imaging studies [13, 58]. Among symptomatic patients, abdominal pain is the most common presentation (12 %) [58], but other symptoms include back pain, jaundice, pancreatitis, or palpable mass [9, 12, 58]. Malignant SCAs of the pancreas are very rare, and these tumors are therefore considered to have a negligible malignant potential [59–61]. A recent study showed a steady rate of growth of pancreatic SCAs over time, with an estimated time of doubling in size of 12 years [62].

Radiological Findings

SCAs can appear as polycystic (70 %), honeycomb (20 %), or oligocystic (<10 %) on imaging [63]. On CT, the polycystic lesion is characterized by multiple cysts measuring 2 cm or smaller with septations (Fig. 4.8) [63]. A central scar may be seen on delayed-phase imaging [64]. The honeycomb appearance is described as numerous subcentimeter cysts, separated by fibrous septa [31, 63]; however, this may appear as a well-delineated mass with mixed attenuation and a sharp interface with vascular structures on CT scan [63]. The oligocystic pattern is recognized by fewer large cysts measuring >2 cm, which may appear like MCNs or BD-IPMNs [63]. T2W MRI can demonstrate a microcystic (cysts <2 cm) morphology with a honeycomb appearance and central scar or a macrocystic (cysts >2 cm) oligocystic pattern (unilocular or bilocular; Fig. 4.5) [54]. Enhancement

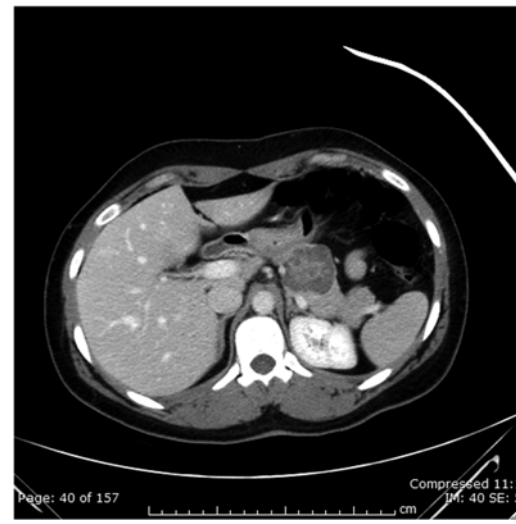

Fig. 4.8 Radiological characteristics of SCA. CT imaging in a patient with incidental lesion on the pancreas, which showed a heterogeneous, multiseptated, low-density cystic lesion in the junction of the pancreatic body and tail of the pancreas, measuring 3.7 cm in diameter, with central stellate scarring appearance

of the thin septations that radiate from a central scar may be seen on gadolinium T1W images. MRCP usually shows no communication with the pancreatic duct.

EUS Morphology

The typical SCA is a well-demarcated lesion on EUS with multiple small fluid-filled cavities, which are separated by thin septations (Fig. 4.9) [13, 44]. The honeycomb pattern is noted in most of the microcystic lesions by EUS [58]. A central calcified scar may exhibit a "sunburst" appearance (Fig. 4.9) [13, 44]. A macrocystic morphology is less commonly seen (Fig. 4.10). The solid variant of SCAs has been rarely reported but can lead to misdiagnosis as a solid tumor [44, 58, 63, 65–67]. Nevertheless, the presence of a mural nodule, wall thickening, ductal dilation, or mucin-filled cavity is atypical manifestations for SCAs and should raise the suspicion of a mucinous lesion [44, 63].

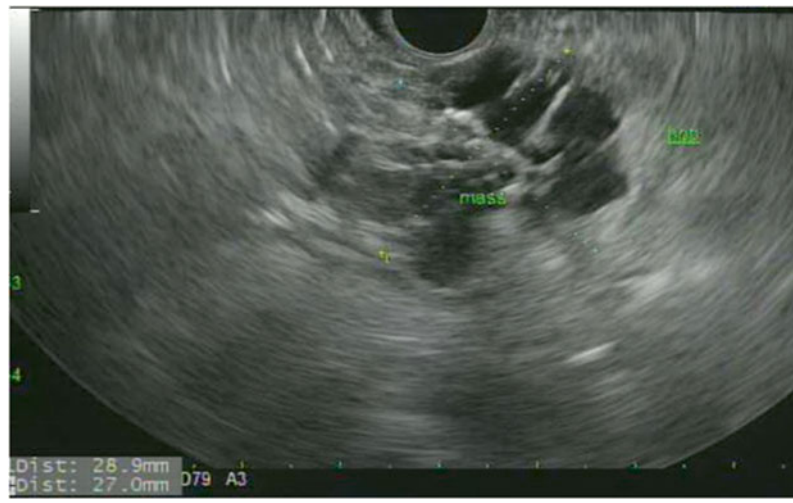

Fig. 4.9 EUS morphology of SCA. A 29-mm ×27-mm multiloculated cystic lesion was identified in the pancreatic head with central calcification, consistent with microcystic serous cystadenoma

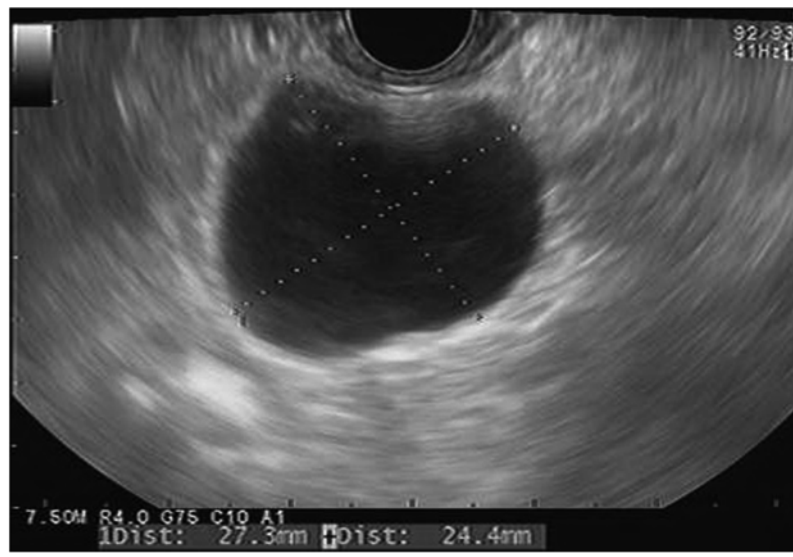

Fig. 4.10 EUS morphology of SCA. A 27-mm ×25-mm macrocystic lesion was demonstrated in the pancreatic head on EUS in this 62-year-old female patient. Cyst fluid CEA was 2.6 ng/mL, which is consistent with a serous lesion

Cystic Pancreatic Neuroendocrine Tumors

Histopathologic Features

Grossly, cystic pancreatic neuroendocrine tumors (cPNETs) are typically)comprised of a single locule, surrounded by a rim of neoplastic parenchyma, which are filled with clear to straw-colored fluid. The histopathology of solid PNETs typically shows small or medium-sized monotonous cells with granular chromatin (salt and pepper) and a plasmacystoid morphology [68]. Tumor cells may be difficult to detect in the cystic fluid [69]. However, the diagnosis can be confirmed by synaptophysin and chromogranin A staining, which is practically diagnostic of this condition [31, 69, 70]. In comparison with ductal adenocarcinomas, tumor necrosis, perineural invasion, vascular invasion, and regional lymph node metastasis are less likely to be seen in cPNETs [71, 72].

Clinical Characteristics

PNETs make up to 1–2 % of all pancreatic neoplasms, which may have a cystic component in less than 10 % of cases [1, 7, 69, 73, 74]. In a previous study of a 33-year experience at Massachusetts General Hospital, cPNETs accounted for 3 % of cystic neoplasms in the 1970s and 1980s but comprised more than 8 % of cystic tumors of the pancreas between 2005 and 2011 [1]. The majority of cases are incidentally detected on imaging studies [9]. Compared to solid neuroendocrine tumors, cPNETs tend to be larger, are more likely to be nonfunctional, and are more frequently associated with multiple endocrine neoplasia type 1 [75]. Furthermore, cPNETs have been reported in 4–15 % of patients with von Hippel–Lindau disease (VHL) [76, 77]. Similar to solid tumors, they occur nearly equally among males and females, with 50–60 years of age at diagnosis [9, 70, 71]. Patients may present with abdominal pain, pancreatitis, or symptoms related to the functioning cPNETs [69, 70, 74]. The pancreatic body and tail are the most common locations among patients with cPNETs.

Radiological Findings

CT usually demonstrates a cystic lesion with peripheral arterial enhancement (Fig. 4.11) [31, 78]. Septations or solid components are occasionally identified [79]. Compared with solid pancreatic neoplasms, cPNETs are less likely to be associated with lymph node or liver metastases [78]. MRI shows a homogeneous unilocular, thick wall lesion on T2W [54]. On gadolinium T1W, wall enhancement is seen on the arterial phase. No communication with the pancreatic ductal system is typically detected on MRCP.

EUS Morphology

By EUS, cPNETs can appear as a uni- or multilocular, anechoic, mixed solid–cystic, or hypoechoic lesion (Fig. 4.12) [69, 70, 74, 80]. Wall thickening and a nodule may be present in 60 % of cases [70]. Most of them (80 %) are thinly septated. The surrounding pancreatic parenchyma as well as the pancreatic ductal system are usually unremarkable.

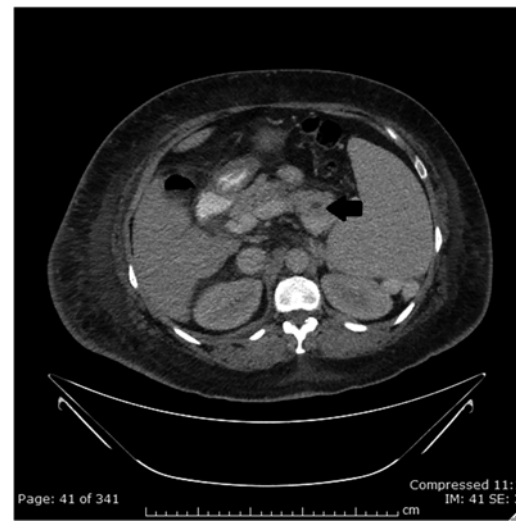

Fig. 4.11 Radiological characteristics of cystic pancreatic neuroendocrine tumor (CPNET). CT showed a low-density lesion measuring 1.0 cm with a thick wall at the junction of the pancreatic body and tail (*black arrow*)

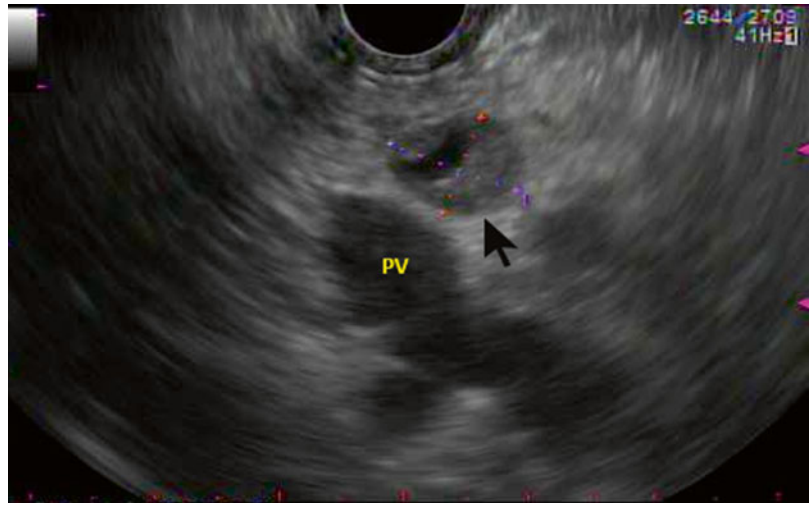

Fig. 4.12 EUS morphology of CPNET. A 12-mm ×8-mm mixed cystic–solid lesion was seen in the pancreatic neck with a thick wall (*black arrow*). Cyst fluid cytology confirmed this diagnosis after immunocytochemical stains

Solid Pseudopapillary Tumors of the Pancreas

Histopathologic Features

SPTPs are uncommon neoplasms, composed of monomorphic cells forming solid and pseudopapillary structures, frequently undergoing hemorrhagic-cystic changes [7]. Macroscopically, larger tumors are more likely to contain cystic areas of hemorrhage and necrosis but usually have a well-defined fibrous pseudocapsule [81]. Microscopically, SPTPs are composed of solid nests of uniform neuroendocrine-looking epithelial cells around delicate fibrovascular stalks [81]. Larger counterparts show pesudopapillary structures composed of tumor cells surrounding small central vessels.

Clinical Characteristics

SPTPs predominantly affect young women in their third decade of life [9, 12]. Patients may be asymptomatic, with such a lesion presenting incidentally on imaging studies. Abdominal pain is the most common presenting symptom, followed by abdominal mass, pancreatitis, and weight loss [81–83]. The tumors can occur throughout the pancreas. SPTPs are usually of low-grade pathology, but high-grade carcinomas have been rarely reported [82, 84–87].

Radiological Findings

SPTPs are typically of mixed-density on imaging, with a solid part in the periphery and a cystic component in the center on CT scan (Fig. 4.13) [81]. Large tumors are well demarcated by the capsule from the surrounding normal parenchyma. These tumors often demonstrate peripheral or central calcifications [82]. MRI usually shows areas of high and low signal intensity, corresponding to cystic and solid components, respectively, with a thick fibrous capsule [54, 81]. Heterogeneous peripheral capsule enhancement is seen on T1W postgadolinium. MRCP does not show communication with the pancreatic duct, and pancreatic duct dilation, vessel encasement, and metastasis may be used to differentiate solid pseudopapillary carcinomas from benign SPTPs [87].

EUS Morphology

SPTPs are endosonographically well-defined, echo-poor lesions [83] and can be solid, mixed solid–cystic, or cystic in nature (Fig. 4.14). Internal or peripheral calcifications may be seen with postacoustic shadowing. EUS-ENA is useful for definitive preoperative diagnosis of SPTPs [88]. The largest series of EUS-FNA for the diagnosis of SPTPs demonstrated a preoperative diagnostic accuracy of 75 % [83].

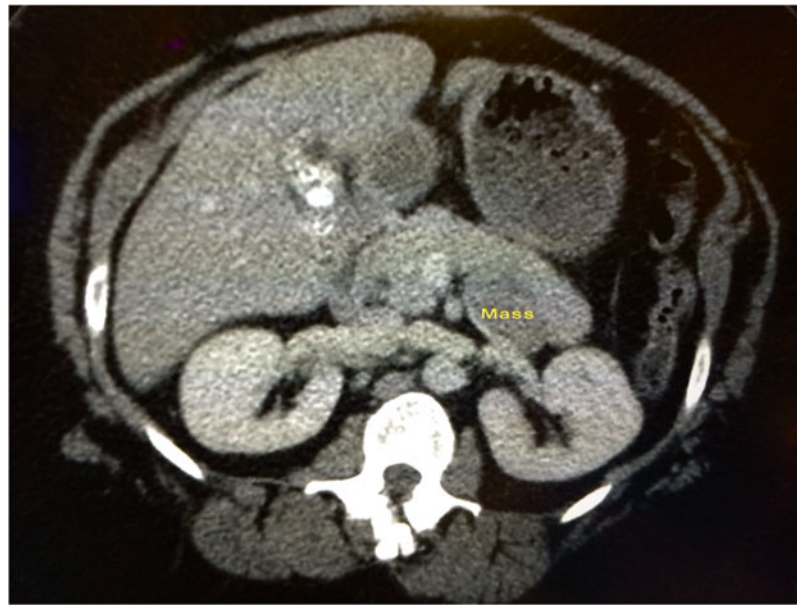

Fig. 4.13 Radiological characteristics of solid pseudopapillary tumor (PSPT) in a 28-year-old female patient. CT demonstrated an oval-shaped area of mixed-density measuring 3.5 cm in the pancreatic body, which was well demarcated by the capsule from the surrounding normal parenchyma

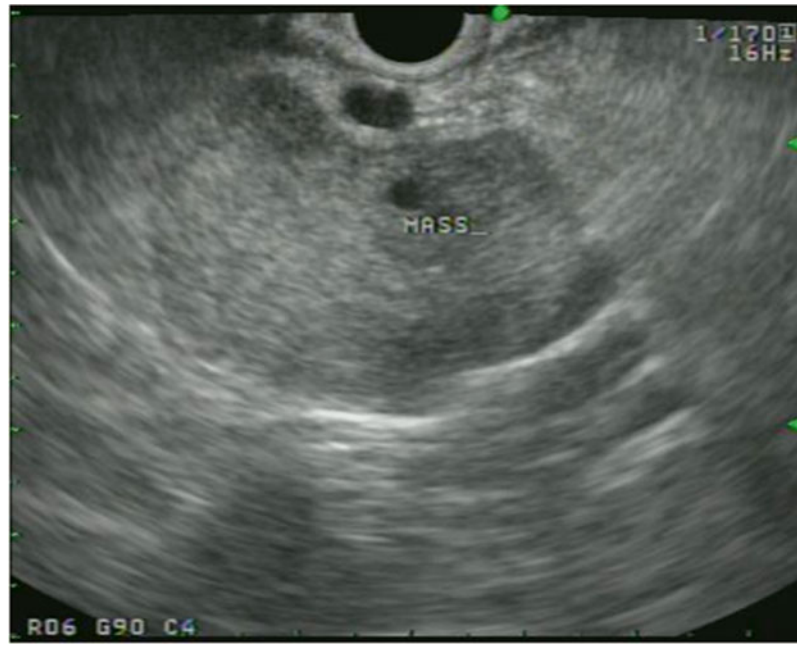

Fig. 4.14 EUS morphology of PSPT. A 3-cm lesion in the pancreatic body, with more than 90 % solid component with a small cystic space. Final cytopathology from fine-needle aspiration and core biopsy confirmed solid pseudopapillary neoplasm

Less Frequently Encountered Cystic Lesions of the Pancreas

Lymphoepithelial cysts (LECs) of the pancreas are rare benign lesions. They are composed mainly of keratinous material and can occur throughout the pancreas. Histologically, the cysts are lined by stratified squamous epithelium and surrounded by dense epithelial lymphoid tissue containing lymphoid follicles [89]. Since the first case was reported in 1985 [90], 109 patients with LECs have been described in the literature [91]. Such lesions are predominantly seen in middle-aged

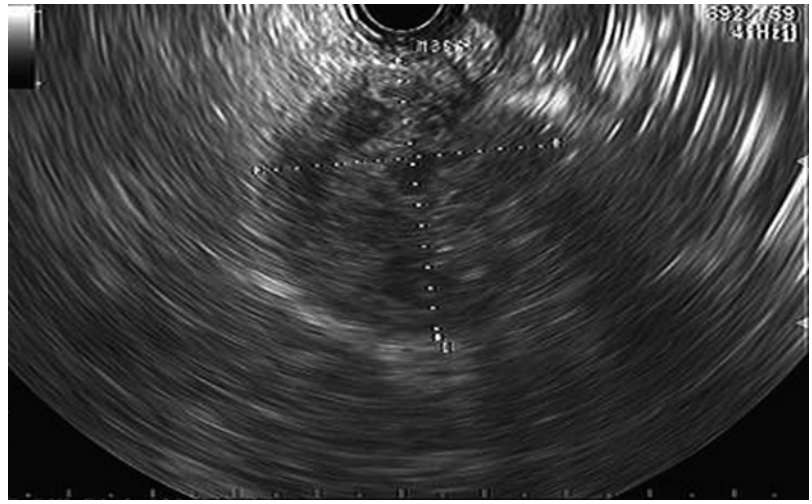

Fig. 4.15 EUS morphology of lymphoepithelial cyst. A 3.6-cm hypoechoic lesion with fine hyperechoic debris within the cyst in the body of the pancreas. Final cytology confirmed lymphoepithelial cyst

men [92]. Although the most common presentation is abdominal pain, nausea, vomiting, anorexia, and back pain may occur [89]. LECs exhibit a benign behavior and are not considered a risk factor for the development of pancreatic cancer [91]. On CT scan, LECs can appear as either a cystic or solid lesion of low attenuation, which may be uni- or multiloculated [91, 93]. The imaging characteristics of LECs on CT can be similar to that of a pseudocyst or a MCN [91]. EUS typically shows a hypoechoic, uniloculated, or multiloculated lesion with fine or coarse hyperechoic debris within the cyst (Fig. 4.15) [89, 94]. Thick milky, creamy fluid may be seen during EUS-FNA [93].

von Hippel–Lindau (VHL) is a rare autosomal dominant hereditary disorder resulting from a germline mutation in the VHL gene [95]. Pancreatic cysts can occur in approximately 70 % of VHL patients [96, 97] and include simple cysts (47 %) and SCAs (11 %), which are benign lesions [77]. In addition, cPNETs have been reported in 4–15 % of patients with VHL, which have malignant potential [76, 77]. Therefore, surgical treatment may be required in some cases. Nevertheless, unlike sporadic nonfunctioning PNETs without VHL, PNETs in VHL patients are believed to be of lower metastatic risk [98]. Most pancreatic lesions in VHL are asymptomatic; however, abdominal pain and jaundice may be present [95]. Pancreatic involvement in previous series of VHL detected by CT and MRI has varied from 20 to 80 % [99–101]. Simple cysts appear as unilocular, homogeneous, fluid-attenuation or fluid signal lesions with a thin wall and no calcification or enhancement [100]. SCAs and PNETs in this context have a similar morphology to those identified without VHL and as previously described in this chapter. EUS can be helpful to better characterize the cystic lesions and may influence clinical management [102]. Nevertheless, these pancreatic cysts often do not influence the outcome of the majority of VHL patients [101].

Conclusion

CLPs are increasingly detected by imaging studies among asymptomatic and symptomatic patients. Depending on the pathological type of the cyst, the clinical features, radiological characteristics, and EUS morphology vary significantly. In combination with minimally invasive investigations like EUS-FNA, clinical and imaging findings are essential to provide an accurate diagnosis of CLPs and improve early detection of cancer in the potentially malignant ones. Therefore, patients with CLPs should be evaluated thoroughly to determine the appropriate management, ideally in a multidisciplinary approach.

References

1. Valsangkar NP, Morales-Oyarvide V, Thayer SP, Ferrone CR, Wargo JA, Warshaw AL, et al. 851 resected cystic tumors of the pancreas: a 33-year experience at the Massachusetts General Hospital. Surgery. 2012;152(3 Suppl 1):S4–12.
2. Laffan TA, Horton KM, Klein AP, Berlanstein B, Siegelman SS, Kawamoto S, et al. Prevalence of unsuspected pancreatic cysts on MDCT. Am J Roentgenol. 2008;191(3):802–7.
3. Lee KS, Sekhar A, Rofsky NM, Pedrosa I. Prevalence of incidental pancreatic cysts in the adult population on MR imaging. Am J Gastroenterol. 2010;105(9):2079–84.
4. de Jong K, Nio CY, Hermans JJ, Dijkgraaf MG, Gouma DJ, van Eijck CH, et al. High prevalence of pancreatic cysts detected by screening magnetic resonance imaging examinations. Clin Gastroenterol Hepatol. 2010;8(9):806–11.
5. Canto MI, Hruban RH, Fishman EK, Kamel IR, Schulick R, Zhang Z, et al. Frequent detection of pancreatic lesions in asymptomatic high-risk individuals. Gastroenterology. 2012;142(4):796–804. quiz e14–5.
6. Wu BU, Sampath K, Berberian CE, Kwok KK, Lim BS, Kao KT, et al. Prediction of malignancy in cystic neoplasms of the pancreas: a population-based cohort study. Am J Gastroenterol. 2014;109(1):121–9. quiz 30.
7. Bosman FT, World Health Organization, International Agency for Research on Cancer. WHO classification of tumours of the digestive system. 4th ed. Lyon: IARC; 2010.
8. Hruban RH, Takaori K, Klimstra DS, Adsay NV, Albores-Saavedra J, Biankin AV, et al. An illustrated consensus on the classification of pancreatic intraepithelial neoplasia and intraductal papillary mucinous neoplasms. Am J Surg Pathol. 2004;28(8):977–87.
9. Farrell JJ, Fernandez-del Castillo C. Pancreatic cystic neoplasms: management and unanswered questions. Gastroenterology. 2013;144(6):1303–15.
10. Adsay NV, Merati K, Basturk O, Iacobuzio-Donahue C, Levi E, Cheng JD, et al. Pathologically and biologically distinct types of epithelium in intraductal papillary mucinous neoplasms: delineation of an "intestinal" pathway of carcinogenesis in the pancreas. Am J Surg Pathol. 2004;28(7):839–48.
11. Furukawa T, Hatori T, Fujita I, Yamamoto M, Kobayashi M, Ohike N, et al. Prognostic relevance of morphological types of intraductal papillary mucinous neoplasms of the pancreas. Gut. 2011;60(4):509–16.
12. Yoon WJ, Brugge WR. Pancreatic cystic neoplasms: diagnosis and management. Gastroenterol Clin North Am. 2012;41(1):103–18.
13. Al-Haddad M, El II H, Eloubeidi MA. Endoscopic ultrasound for the evaluation of cystic lesions of the pancreas. JOP. 2010;11(4):299–309.
14. Al-Haddad M, Schmidt MC, Sandrasegaran K, Dewitt J. Diagnosis and treatment of cystic pancreatic tumors. Clin Gastroenterol Hepatol. 2011;9(8):635–48.
15. Capurso G, Boccia S, Salvia R, Del Chiaro M, Frulloni L, Arcidiacono PG, et al. Risk factors for intraductal papillary mucinous neoplasm (IPMN) of the pancreas: a multicentre case-control study. Am J Gastroenterol. 2013;108(6):1003–9.
16. Kobari M, Egawa S, Shibuya K, Shimamura H, Sunamura M, Takeda K, et al. Intraductal papillary mucinous tumors of the pancreas comprise 2 clinical subtypes: differences in clinical characteristics and surgical management. Arch Surg. 1999;134(10):1131–6.
17. Doi R, Fujimoto K, Wada M, Imamura M. Surgical management of intraductal papillary mucinous tumor of the pancreas. Surgery. 2002;132(1):80–5.
18. Sugiyama M, Izumisato Y, Abe N, Masaki T, Mori T, Atomi Y. Predictive factors for malignancy in intraductal papillary-mucinous tumours of the pancreas. Br J Surg. 2003;90(10):1244–9.
19. Salvia R, Fernandez-del Castillo C, Bassi C, Thayer SP, Falconi M, Mantovani W, et al. Main-duct intraductal papillary mucinous neoplasms of the pancreas: clinical predictors of malignancy and long-term survival following resection. Ann Surg. 2004;239(5):678–85. discussion 85–7.
20. Schmidt CM, White PB, Waters JA, Yiannoutsos CT, Cummings OW, Baker M, et al. Intraductal papillary mucinous neoplasms: predictors of malignant and invasive pathology. Ann Surg. 2007;246(4):644–51. discussion 51–4.
21. Matsumoto T, Aramaki M, Yada K, Hirano S, Himeno Y, Shibata K, et al. Optimal management of the branch duct type intraductal papillary mucinous neoplasms of the pancreas. J Clin Gastroenterol. 2003;36(3):261–5.
22. Sohn TA, Yeo CJ, Cameron JL, Hruban RH, Fukushima N, Campbell KA, et al. Intraductal papillary mucinous neoplasms of the pancreas: an updated experience. Ann Surg. 2004;239(6):788–97. discussion 97–9.
23. Tanaka M, Chari S, Adsay V, Fernandez-del Castillo C, Falconi M, Shimizu M, et al. International consensus guidelines for management of intraductal papillary mucinous neoplasms and mucinous cystic neoplasms of the pancreas. Pancreatology. 2006;6(1–2):17–32.
24. Kamata K, Kitano M, Kudo M, Sakamoto H, Kadosaka K, Miyata T, et al. Value of EUS in early detection of pancreatic ductal adenocarcinomas in patients with intraductal papillary mucinous neoplasms. Endoscopy. 2014;46(1):22–9.
25. Yamaguchi K, Ohuchida J, Ohtsuka T, Nakano K, Tanaka M. Intraductal papillary-mucinous tumor of the pancreas concomitant with ductal carcinoma of the pancreas. Pancreatology. 2002;2(5):484–90.
26. Uehara H, Nakaizumi A, Ishikawa O, Iishi H, Tatsumi K, Takakura R, et al. Development of ductal carcinoma of the pancreas during follow-up of branch duct intraductal papillary mucinous neoplasm of the pancreas. Gut. 2008;57(11):1561–5.
27. Kobayashi G, Fujita N, Maguchi H, Tanno S, Mizuno N, Hanada K, et al. Natural history of branch duct intraductal papillary mucinous neoplasm with mural nodules: a Japan pancreas society multicenter study. Pancreas. 2014;43(4):532–8.

28. Traverso LW, Moriya T, Hashimoto Y. Intraductal papillary mucinous neoplasms of the pancreas: making a disposition using the natural history. Curr Gastroenterol Rep. 2012;14(2):106–11.
29. Maguchi H, Tanno S, Mizuno N, Hanada K, Kobayashi G, Hatori T, et al. Natural history of branch duct intraductal papillary mucinous neoplasms of the pancreas: a multicenter study in Japan. Pancreas. 2011;40(3):364–70.
30. Tanno S, Nakano Y, Nishikawa T, Nakamura K, Sasajima J, Minoguchi M, et al. Natural history of branch duct intraductal papillary-mucinous neoplasms of the pancreas without mural nodules: long-term follow-up results. Gut. 2008;57(3):339–43.
31. Kucera JN, Kucera S, Perrin SD, Caracciolo JT, Schmulewitz N, Kedar RP. Cystic lesions of the pancreas: radiologic-endosonographic correlation. Radiographics. 2012;32(7):E283–301.
32. Rodriguez JR, Salvia R, Crippa S, Warshaw AL, Bassi C, Falconi M, et al. Branch-duct intraductal papillary mucinous neoplasms: observations in 145 patients who underwent resection. Gastroenterology. 2007;133(1):72–9. quiz 309–10.
33. Ku YM, Shin SS, Lee CH, Semelka RC. Magnetic resonance imaging of cystic and endocrine pancreatic neoplasms. Top Magn Reson Imaging. 2009;20(1):11–8.
34. Minami M, Itai Y, Ohtomo K, Yoshida H, Yoshikawa K, Iio M. Cystic neoplasms of the pancreas: comparison of MR imaging with CT. Radiology. 1989;171(1):53–6.
35. Ogawa H, Itoh S, Ikeda M, Suzuki K, Naganawa S. Intraductal papillary mucinous neoplasm of the pancreas: assessment of the likelihood of invasiveness with multisection CT. Radiology. 2008;248(3):876–86.
36. Sahani DV, Kadavigere R, Blake M, Fernandez-Del Castillo C, Lauwers GY, Hahn PF. Intraductal papillary mucinous neoplasm of pancreas: multi-detector row CT with 2D curved reformations—correlation with MRCP. Radiology. 2006;238(2):560–9.
37. Lee CJ, Scheiman J, Anderson MA, Hines OJ, Reber HA, Farrell J, et al. Risk of malignancy in resected cystic tumors of the pancreas < or =3 cm in size: is it safe to observe asymptomatic patients? A multi-institutional report. J Gastrointest Surg. 2008;12(2):234–42.
38. Lee JH, Lee KT, Park J, Bae SY, Lee KH, Lee JK, et al. Predictive factors associated with malignancy of intraductal papillary mucinous pancreatic neoplasms. World J Gastroenterol. 2010;16(42):5353–8.
39. Liu Y, Lin X, Upadhyaya M, Song Q, Chen K. Intraductal papillary mucinous neoplasms of the pancreas: correlation of helical CT features with pathologic findings. Eur J Radiol. 2010;76(2):222–7.
40. Manfredi R, Graziani R, Motton M, Mantovani W, Baltieri S, Tognolini A, et al. Main pancreatic duct intraductal papillary mucinous neoplasms: accuracy of MR imaging in differentiation between benign and malignant tumors compared with histopathologic analysis. Radiology. 2009;253(1):106–15.
41. Kim KW, Park SH, Pyo J, Yoon SH, Byun JH, Lee MG, et al. Imaging features to distinguish malignant and benign branch-duct type intraductal papillary mucinous neoplasms of the pancreas: a meta-analysis. Ann Surg. 2014;259(1):72–81.
42. Tanaka M, Fernandez-del Castillo C, Adsay V, Chari S, Falconi M, Jang JY, et al. International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas. Pancreatology. 2012;12(3):183–97.
43. Nakai Y, Isayama H, Itoi T, Yamamoto N, Kogure H, Sasaki T, et al. Role of endoscopic ultrasonography in pancreatic cystic neoplasms: where do we stand and where will we go? Dig Endosc. 2014;26(2):135–43.
44. Levy MJ. Pancreatic cysts. Gastrointest Endosc. 2009;69(2 Suppl):S110–6.
45. Kobayashi N, Sugimori K, Shimamura T, Hosono K, Watanabe S, Kato S, et al. Endoscopic ultrasonographic findings predict the risk of carcinoma in branch duct intraductal papillary mucinous neoplasms of the pancreas. Pancreatology. 2012;12(2):141–5.
46. Zhong N, Zhang L, Takahashi N, Shalmiyev V, Canto MI, Clain JE, et al. Histologic and imaging features of mural nodules in mucinous pancreatic cysts. Clin Gastroenterol Hepatol. 2012;10(2):192–8. 8 e1–2.
47. Reddy RP, Smyrk TC, Zapiach M, Levy MJ, Pearson RK, Clain JE, et al. Pancreatic mucinous cystic neoplasm defined by ovarian stroma: demographics, clinical features, and prevalence of cancer. Clin Gastroenterol Hepatol. 2004;2(11):1026–31.
48. Sarr MG, Carpenter HA, Prabhakar LP, Orchard TF, Hughes S, van Heerden JA, et al. Clinical and pathologic correlation of 84 mucinous cystic neoplasms of the pancreas: can one reliably differentiate benign from malignant (or premalignant) neoplasms? Ann Surg. 2000;231(2):205–12.
49. Zamboni G, Scarpa A, Bogina G, Iacono C, Bassi C, Talamini G, et al. Mucinous cystic tumors of the pancreas: clinicopathological features, prognosis, and relationship to other mucinous cystic tumors. Am J Surg Pathol. 1999;23(4):410–22.
50. Khalid A, Brugge W. ACG practice guidelines for the diagnosis and management of neoplastic pancreatic cysts. Am J Gastroenterol. 2007;102(10):2339–49.
51. Crippa S, Salvia R, Warshaw AL, Dominguez I, Bassi C, Falconi M, et al. Mucinous cystic neoplasm of the pancreas is not an aggressive entity: lessons from 163 resected patients. Ann Surg. 2008;247(4):571–9.
52. Le Baleur Y, Couvelard A, Vullierme MP, Sauvanet A, Hammel P, Rebours V, et al. Mucinous cystic neoplasms of the pancreas: definition of preoperative imaging criteria for high-risk lesions. Pancreatology. 2011;11(5):495–9.
53. Goh BK, Thng CH, Tan DM, Low AS, Wong JS, Cheow PC, et al. Evaluation of the Sendai and 2012 international consensus guidelines based on cross-sectional imaging findings performed for the initial triage of mucinous cystic lesions of the pancreas: a

single institution experience with 114 surgically treated patients. Am J Surg. 2014;208(2):202–9.
54. Barral M, Soyer P, Dohan A, Laurent V, Hoeffel C, Fishman EK, et al. Magnetic resonance imaging of cystic pancreatic lesions in adults: an update in current diagnostic features and management. Abdom Imaging. 2014;39(1):48–65.
55. Gress F, Gottlieb K, Cummings O, Sherman S, Lehman G. Endoscopic ultrasound characteristics of mucinous cystic neoplasms of the pancreas. Am J Gastroenterol. 2000;95(4):961–5.
56. Jacobson BC, Baron TH, Adler DG, Davila RE, Egan J, Hirota WK, et al. ASGE guideline: the role of endoscopy in the diagnosis and the management of cystic lesions and inflammatory fluid collections of the pancreas. Gastrointest Endosc. 2005;61(3):363–70.
57. Song MH, Lee SK, Kim MH, Lee HJ, Kim KP, Kim HJ, et al. EUS in the evaluation of pancreatic cystic lesions. Gastrointest Endosc. 2003;57(7):891–6.
58. Kimura W, Moriya T, Hirai I, Hanada K, Abe H, Yanagisawa A, et al. Multicenter study of serous cystic neoplasm of the Japan Pancreas Society. Pancreas. 2012;41(3):380–7.
59. Bramis K, Petrou A, Papalambros A, Manzelli A, Mantonakis E, Brennan N, et al. Serous cystadenocarcinoma of the pancreas: report of a case and management reflections. World J Surg Oncol. 2012;10:51.
60. Rathore MU, Arif A, Umair B. Serous cystadenocarcinoma of pancreas. J Coll Physicians Surg Pak. 2013;23(6):430–1.
61. Bano S, Upreti L, Puri SK, Chaudhary V, Sakuja P. Imaging of pancreatic serous cystadenocarcinoma. Jpn J Radiol. 2011;29(10):730–4.
62. El-Hayek KM, Brown N, O'Rourke C, Falk G, Morris-Stiff G, Walsh RM. Rate of growth of pancreatic serous cystadenoma as an indication for resection. Surgery. 2013;154(4):794–800; discussion 800–2.
63. Choi JY, Kim MJ, Lee JY, Lim JS, Chung JJ, Kim KW, et al. Typical and atypical manifestations of serous cystadenoma of the pancreas: imaging findings with pathologic correlation. Am J Roentgenol. 2009;193(1):136–42.
64. Sarr MG, Kendrick ML, Nagorney DM, Thompson GB, Farley DR, Farnell MB. Cystic neoplasms of the pancreas: benign to malignant epithelial neoplasms. Surg Clin North Am. 2001;81(3):497–509.
65. Sanaka MR, Kowalski TE, Brotz C, Yeo CJ, McCue P, Palazzo J. Solid serous adenoma of the pancreas: a rare form of serous cystadenoma. Dig Dis Sci. 2007;52(11):3154–6.
66. Gabata T, Terayama N, Yamashiro M, Takamatsu S, Yoshida K, Matsui O, et al. Solid serous cystadenoma of the pancreas: MR imaging with pathologic correlation. Abdom Imaging. 2005;30(5):605–9.
67. Yamaguchi M. Solid serous adenoma of the pancreas: a solid variant of serous cystadenoma or a separate disease entity? J Gastroenterol. 2006;41(2):178–9.
68. Chatzipantelis P, Salla C, Konstantinou P, Karoumpalis I, Sakellariou S, Doumani I. Endoscopic ultrasound-guided fine-needle aspiration cytology of pancreatic neuroendocrine tumors: a study of 48 cases. Cancer. 2008;114(4):255–62.
69. Yoon WJ, Daglilar ES, Pitman MB, Brugge WR. Cystic pancreatic neuroendocrine tumors: endoscopic ultrasound and fine-needle aspiration characteristics. Endoscopy. 2013;45(3):189–94. Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't.
70. Ho HC, Eloubeidi MA, Siddiqui UD, Brugge WR, Rossi F, Bounds BW, et al. Endosonographic and cyst fluid characteristics of cystic pancreatic neuroendocrine tumours: a multicentre case series. Dig Liver Dis. 2013;45(9):750–3.
71. Singhi AD, Chu LC, Tatsas AD, Shi C, Ellison TA, Fishman EK, et al. Cystic pancreatic neuroendocrine tumors: a clinicopathologic study. Am J Surg Pathol. 2012;36(11):1666–73.
72. Boninsegna L, Partelli S, D'Innocenzio MM, Capelli P, Scarpa A, Bassi C, et al. Pancreatic cystic endocrine tumors: a different morphological entity associated with a less aggressive behavior. Neuroendocrinology. 2010;92(4):246–51.
73. Brugge WR, Lauwers GY, Sahani D, Fernandez-del Castillo C, Warshaw AL. Cystic neoplasms of the pancreas. N Engl J Med. 2004;351(12):1218–26.
74. Kongkam P, Al-Haddad M, Attasaranya S, O'Neil J, Pais S, Sherman S, et al. EUS and clinical characteristics of cystic pancreatic neuroendocrine tumors. Endoscopy. 2008;40(7):602–5.
75. Bordeianou L, Vagefi PA, Sahani D, Deshpande V, Rakhlin E, Warshaw AL, et al. Cystic pancreatic endocrine neoplasms: a distinct tumor type? J Am Coll Surg. 2008;206(3):1154–8.
76. Graziani R, Mautone S, Vigo M, Manfredi R, Opocher G, Falconi M. Spectrum of magnetic resonance imaging findings in pancreatic and other abdominal manifestations of von Hippel–Lindau disease in a series of 23 patients: a pictorial review. J Pancreas. 2014;15(1):1–18.
77. Charlesworth M, Verbeke CS, Falk GA, Walsh M, Smith AM, Morris-Stiff G. Pancreatic lesions in von Hippel–Lindau disease? A systematic review and meta-synthesis of the literature. J Gastrointest Surg. 2012;16(7):1422–8.
78. Kawamoto S, Johnson PT, Shi C, Singhi AD, Hruban RH, Wolfgang CL, et al. Pancreatic neuroendocrine tumor with cystlike changes: evaluation with MDCT. Am J Roentgenol. 2013;200(3):W283–90.
79. Gaujoux S, Tang L, Klimstra D, Gonen M, Brennan MF, D'Angelica M, et al. The outcome of resected cystic pancreatic endocrine neoplasms: a case-matched analysis. Surgery. 2012;151(4):518–25. Comparative Study Research Support, Non-U.S. Gov't.
80. Morales-Oyarvide V, Yoon WJ, Ingkakul T, Forcione DG, Casey BW, Brugge WR, et al. Cystic pancreatic neuroendocrine tumors: the value of cytology in preoperative diagnosis. Cancer Cytopathol. 2014; 122(6):435–44.

81. Sunkara S, Williams TR, Myers DT, Kryvenko ON. Solid pseudopapillary tumours of the pancreas: spectrum of imaging findings with histopathological correlation. Br J Radiol. 2012;85(1019):e1140–4.
82. Raman SP, Kawamoto S, Law JK, Blackford A, Lennon AM, Wolfgang CL, et al. Institutional experience with solid pseudopapillary neoplasms: focus on computed tomography, magnetic resonance imaging, conventional ultrasound, endoscopic ultrasound, and predictors of aggressive histology. J Comput Assist Tomogr. 2013;37(5):824–33.
83. Jani N, Dewitt J, Eloubeidi M, Varadarajulu S, Appalaneni V, Hoffman B, et al. Endoscopic ultrasound-guided fine-needle aspiration for diagnosis of solid pseudopapillary tumors of the pancreas: a multicenter experience. Endoscopy. 2008;40(3):200–3.
84. Nishihara K, Tsuneyoshi M. Papillary cystic tumours of the pancreas: an analysis by nuclear morphometry. Virchows Arch A Pathol Anat Histopathol. 1993;422(3):211–7.
85. Das G, Bhuyan C, Das BK, Sharma JD, Saikia BJ, Purkystha J. Spleen-preserving distal pancreatectomy following neoadjuvant chemotherapy for papillary solid and cystic neoplasm of pancreas. Indian J Gastroenterol. 2004;23(5):188–9.
86. Tang LH, Aydin H, Brennan MF, Klimstra DS. Clinically aggressive solid pseudopapillary tumors of the pancreas: a report of two cases with components of undifferentiated carcinoma and a comparative clinicopathologic analysis of 34 conventional cases. Am J Surg Pathol. 2005;29(4):512–9.
87. Lee JH, Yu JS, Kim H, Kim JK, Kim TH, Kim KW, et al. Solid pseudopapillary carcinoma of the pancreas: differentiation from benign solid pseudopapillary tumour using CT and MRI. Clin Radiol. 2008;63(9):1006–14.
88. Hosokawa I, Shimizu H, Ohtsuka M, Kato A, Yoshitomi H, Furukawa K, et al. Preoperative diagnosis and surgical management for solid pseudopapillary neoplasm of the pancreas. J Hepatobiliary Pancreat Sci. 2014;17.
89. Foley KG, Christian A, Roberts SA. EUS-FNA diagnosis of a pancreatic lymphoepithelial cyst: three-year imaging follow-up. J Pancreas. 2012;13(6):681–3.
90. Luchtrath H, Schriefers KH. A pancreatic cyst with features of a so-called branchiogenic cyst. Pathologe. 1985;6(4):217–9.
91. Kavuturu S, Sarwani NE, Ruggeiro FM, Deshaies I, Kimchi ET, Kaifi JT, et al. Lymphoepithelial cysts of the pancreas. Can preoperative imaging distinguish this benign lesion from malignant or pre-malignant cystic pancreatic lesions? J Pancreas. 2013;14(3):250–5.
92. Adsay NV, Hasteh F, Cheng JD, Bejarano PA, Lauwers GY, Batts KP, et al. Lymphoepithelial cysts of the pancreas: a report of 12 cases and a review of the literature. Mod Pathol. 2002;15(5):492–501.
93. Nasr J, Sanders M, Fasanella K, Khalid A, McGrath K. Lymphoepithelial cysts of the pancreas: an EUS case series. Gastrointest Endosc. 2008;68(1):170–3.
94. Ahlawat SK. Lymphoepithelial cyst of pancreas. Role of endoscopic ultrasound guided fine needle aspiration. J Pancreas. 2008;9(2):230–4.
95. van Asselt SJ, de Vries EG, van Dullemen HM, Brouwers AH, Walenkamp AM, Giles RH, et al. Pancreatic cyst development: insights from von Hippel–Lindau disease. Cilia. 2013;2(1):3.
96. Hammel PR, Vilgrain V, Terris B, Penfornis A, Sauvanet A, Correas JM, et al. Pancreatic involvement in von Hippel–Lindau disease. The Groupe Francophone d'Etude de la Maladie de von Hippel–Lindau. Gastroenterology. 2000;119(4):1087–95.
97. Horton WA, Wong V, Eldridge R. von Hippel–Lindau disease: clinical and pathological manifestations in nine families with 50 affected members. Arch Intern Med. 1976;136(7):769–77.
98. Tamura K, Nishimori I, Ito T, Yamasaki I, Igarashi H, Shuin T. Diagnosis and management of pancreatic neuroendocrine tumor in von Hippel–Lindau disease. World J Gastroenterol. 2010;16(36):4515–8. Research Support, Non-U.S. Gov't.
99. Mukhopadhyay B, Sahdev A, Monson JP, Besser GM, Reznek RH, Chew SL. Pancreatic lesions in von Hippel–Lindau disease. Clin Endocrinol (Oxf). 2002;57(5):603–8.
100. Davenport MS, Caoili EM, Cohan RH, Hoff CN, Ellis JH. Pancreatic manifestations of von Hippel–Lindau disease—effect of imaging on clinical management. J Comput Assist Tomogr. 2010;34(4):517–22.
101. Kobayashi N, Sato T, Kato S, Watanabe S, Hosono K, Shimamura T, et al. Imaging findings of pancreatic cystic lesions in von Hippel–Lindau disease. Intern Med. 2012;51(11):1301–7.
102. Elli L, Buscarini E, Portugalli V, Reduzzi L, Reduzzi C, Brambilla G, et al. Pancreatic involvement in von Hippel–Lindau disease: report of two cases and review of the literature. Am J Gastroenterol. 2006;101(11):2655–8.

Autoimmune Pancreatitis

5

Urban Arnelo, Caroline Verbeke, Nikolaos Kartalis, and Johannes Matthias Löhr

Introduction

Autoimmune pancreatitis (AIP) represents a rare form of chronic pancreatitis having distinct and characteristic clinical, radiologic, chemical, and histological features. The pancreas has no organ-residing immune system like the hollow gut system (MALT). However, in acute and even more so in chronic pancreatitis as well as in pancreatic cancer, a dense inflammatory infiltrate can be observed [1]. While the autoimmune diseases of the liver have been known for decades and their particular immunopathology is rather well understood [2], AIP seems to have appeared at the end of the last century as a novel disease. However, 50 years ago Henry Sarles had already discovered autoantibodies in some of his patients with chronic pancreatitis [3, 4], and sometime later associations of pancreatitis with primary biliary cirrhosis (PBC) [5] and Sjögren's syndrome [6, 7] were described. Furthermore, pancreatitis is part of some syndromes of polyglandular autoimmune diseases (PGAD) [8]. In the 1990s, a "lymphoplasmacellular sclerosing pancreatitis" in conjunction with cholangitis was described [9] and in 1995 the term "autoimmune pancreatitis" was introduced [10]. AIP can be considered an enigmatic disease, widening the possible spectrum of inflammatory diseases of the pancreas. This might explain the unforeseen interest in the disease, where the number of publications exceeds the number of patients [11].

After the formation of national guidelines, which were sometimes conflicting [12–17], the three major societies [i.e., JPS (Japan), APA (USA), and EPC (Europe)] came together for an "International Consortium for Diagnostic Criteria" (ICDC) of autoimmune pancreatitis [18]. As a major result, two subtypes of AIP were acknowledged that are defined both by histology and by clinical picture [19] (Table 5.1). Type 1 is IgG/IgG4-positive (both serum and tissue) [20] with more "other organ involvement" (OOI) as it represents a systemic "immunogammopathy" [21]. AIP type 2 is eosinophilic infiltration in the pancreas (see below).

U. Arnelo (✉) • J.M. Löhr
Division of Surgery, Department of Clinical Science, Intervention and Technology (CLINTEC), Karolinska Institutet, and Centre for Digestive Diseases, Karolinska University Hospital, Stockholm 141 86, Sweden
e-mail: urban.arnelo@ki.se

C. Verbeke
Division of Pathology, Department of Laboratory Medicine (LABMED), and Department of Clinical Pathology, Karolinska University Hospital, Stockholm 141 86, Sweden

N. Kartalis
Division of Medical Imaging and Technology, Department of Clinical Science, Intervention and Technology (CLINTEC), Karolinska Institutet, and Department of Radiology, Karolinska University Hospital, Stockholm 141 86, Sweden

M.S. Wagh, P.V. Draganov (eds.), *Pancreatic Masses*, DOI 10.1007/978-3-319-19677-0_5

Table 5.1 ICDC diagnostic criteria of definite and probable AIP type 1

Diagnosis	Primary basis for diagnosis	Imaging evidence	Collateral evidence
Definitive type 1 AIP	Histology	Typical/indeterminate	Histologically confirmed LPSP (level 1 H)
	Imaging	Typical	Any non-D level 1/level 2
		Indeterminate	Two or more from level 1 (+level 2 D[a])
	Response to steroid	Indeterminate	Level 1 S/OOI + Rt or level 1 D + level 2 S/OOI/H + Rt
Probable type 1 AIP		Indeterminate	Level 2 S/OOI/H + Rt

Source: From [18]
[a]Level 2 D is counted as level 1 in this setting

Etiology and Pathogenesis

The pathogenesis of AIP is unclear in contrast to other forms of pancreatitis [22]. Similar to Sjögren's syndrome and primary sclerosing cholangitis (PSC), CD4+ Th1 cells dominate. Patients with AIP, especially in Japan, demonstrate HLA loci [23], with two of them carrying an increased risk of developing AIP: HLA class II haplotype DRB1*0405-DBQB1*0401, and the ABCF1 gene, localized on the proximal part of the telomere region C3-2-11 in HLA-E class I [23, 24].

As is the nature of any autoimmune disease, several common autoantibodies have been detected, such as antinuclear autoantibodies (ANA). Disease-specific autoantibodies in AIP are against ductal antigens such as lactoferrin (ALF) and carbonic anhydrase type 2 (ACA-II) [25] as well as against acinar antigens such as SPINK1 [26, 27], ubiquitin-protein ligase E3 component n-recognin 2 (UBR2) [28], and trypsinogens [27]. Most of these autoantibodies will be of IgG as this Ig class is elevated, especially IgG4 [20]. Lactoferrin and carbonic anhydrase type 2 are characteristic for so-called specialized secretory epithelium that, besides the pancreas, also is found in the salivary glands, the lung, the renal tubule, and the bile ducts—tissues that can all become sites of systemic autoimmune disease [29] as "other organ involvement" in type 1 AIP with a lymphoplasma cellular IgG4-positive inflammatory infiltrate [30]. As in other immune-triggered systemic diseases such as mixed connective tissue disease (MCTD) or soft-tissue rheumatism, the spectrum of organ manifestations is wide. There is a limitation: Not all patients with an IgG4+ infiltrate in the pancreas (or elsewhere) present with increased blood levels of IgG4 [20, 31–33].

The autoimmune character of the disease is not fully understood: Thymectomy in neonatal mice and immunization with lactoferrin and carbonic anhydrase type II led to AIP [34]. Lymphotoxin can induce AIP [35]. While T-cell-negative I-A-chain$^{-/-}$(Ab0) mice develop AIP spontaneously, HLA-DRB1*0405 is the predisposing factor [36]. In the MRL/Mp model, suppressing regulatory T cells increases the severity of AIP [37]. However, the triggering factors are unclear. The histology seems suggestive of exogenous factors. Consequently, viral and other xenobiotic factors have been studied. With a murine retrovirus, an "exocrinopathy" could be developed, including pancreatitis and Sjögren-like changes [27, 38], resembling AIP. Immunization of mice with apathogenic *E. coli* caused autoantibodies against carbonic anhydrase type II [39].

One of the most fascinating theories is proposing *Helicobacter pylori* as being the causative agent [40], the rationale being a "molecular mimicry" [41] between the *H. pylori* enzyme CA and the human carbonic anhydrase type II (CA-II), the lead enzyme of pancreatic duct cells [42] and one of the described autoantibodies in AIP. Interestingly, this sequence incorporates a binding motif of HLA DRB1*0405 that is associated with some patients with AIP [23, 24]. However, *H. pylori* DNA or RNA could not be detected in the pancreas of patients with AIP [43]. Another host protein, UBR2 (ubiquitin-protein ligase E3 component n-recognin 2), shows a high homology with the cagA protein of *H. pylori* [28]. Even if *H. pylori* itself could not

be found in pancreatic tissue in AIP, the concept of "molecular mimicry" is suggestive for the pathogenesis of AIP. Another attempt to hit an exogenous, disease-causing agent failed as well in that varicella zoster virus (VZV) could not be detected in the tissue of patients with AIP [44].

Pathology

Macropathology

Upon gross pathology, AIP may resemble pancreatic ductal adenocarcinoma (PDAC). In 50–80 % of AIP, a tumorous mass is described in the pancreatic head. Together with obstructive jaundice [30] and enlarged lymph nodes, the diagnosis of PDAC is highly suggestive. It must be noted that the typical dilation of the main pancreatic duct (MPD) is missing in AIP and the pancreas typically lacks pseudocysts and calcifications, which are described rarely.

Histopathology

A histological grading system has been proposed [30] and reevaluated [45] (Table 5.2). The histopathological features of AIP are lymphoplasmacellular infiltrates, destroying ductal and later even acinar tissue. The exocrine pancreas is replaced by fibrotic tissue (Fig. 5.1). Granulocytic epithelial lesions (GEL) mark a specific histopathological finding. Focal destructions of the epithelial lining are caused by neutrophilic granulocytes. GEL also incorporate eosinophils.

As a major result of the ICDC [18], AIP was classified in two distinct subtypes [46]: a lymphoplasmacytic sclerosing pancreatitis (LPSP, type 1) with IgG4-positive cells (Fig. 5.2) and an idiopathic ductocentric chronic pancreatitis (IDCP, type 2) with GEL and eosinophils.

Epidemiology

There are no reliable data on the incidence and prevalence of AIP; however, AIP can be considered a rare disease. Depending on the reference group of patients (acute or chronic pancreatitis), the prevalence was described between 4.7 and 10 % [14, 31, 32, 47].

AIP is more common among males, even more pronounced in the Asia-Pacific population. The peak seems to be above the age of 50 [48], but with a wide range spanning essentially all ages.

Clinical Picture

As a spinoff of ICDC, the data of close to 1000 patients were gathered. The clinical picture and initial presentation can vary widely. Abdominal pain seems to be the major symptom [19]. Another feature, albeit sometimes misleading the diagnosis, is painless jaundice, found in 48–86 % of cases [47, 49]. Cholangitis can be the leading symptom, preceding the diagnosis of IAP by months. AIP can present as acute pancreatitis as well [50], maybe more often in younger patients [51]. Nausea and weight loss are also typical, the latter in about a third of cases. The inflammatory pancreatic head tumor can be the cause of a gastric outlet syndrome (obstruction). The disease is sometimes diagnosed best by analyzing the associated diseases (OOI), at least in type 1 AIP, as these may be the dominant symptoms.

Association with Other Autoimmune Diseases/Organ Involvement

Other organ involvement is a typical feature of type 1 AIP [19], found in 37–50 % of all patients (Fig. 5.3).

Crohn's disease (CD) and ulcerative colitis (UC) are associated with AIP [52]; it looks as if UC is more associated with type 1 and CD with type 2 AIP [19]. Inflammatory bowel disease (IBD) is the next most frequent OOI following cholangitis. The association between AIP and CD is more frequently observed in younger patients [52, 53]. Pancreatic exocrine insufficiency is present in most AIP patients and in about 40 % of IBD patients [54].

Diabetes mellitus (DM) is an autoimmune disease on its own but is also observed frequently in

Table 5.2 ICDC Levels 1 and 2 diagnostic criteria for AIP type 1 according to ICDC

	Criterion	Level 1	Level 2
P	Parenchymal imaging	Typical:	Indeterminate (including atypical[a]):
		Diffuse enlargement with delayed enhancement (sometimes associated with rim-like enhancement)	Segmental/focal enlargement with delayed enhancement
D	Ductal imaging (ERP)	Long (>1/3 length of the main pancreatic duct) or multiple strictures without marked upstream dilatation	Segmental/focal narrowing without marked upstream dilatation (duct size, <5 mm)
S	Serology	IgG4, >2× upper limit of normal value	IgG4, 1–2× upper limit of normal value
		(a) or (b)	(a) or (b)
OOI	Other organ involvement	(a) Histology of extrapancreatic organs	(a) Histology of extrapancreatic organs including endoscopic biopsies of bile duct[b]:
		Any three of the following:	Both of the following:
		(1) Marked lymphoplasmacytic infiltration with fibrosis and without granulocytic infiltration	(1) Marked lymphoplasmacytic infiltration without granulocytic infiltration
		(2) Storiform fibrosis	(2) Abundant (>10 cells/HPF) IgG4-positive cells
		(3) Obliterative phlebitis	
		(4) Abundant (>10 cells/HPF) IgG4-positive cells	
		(b) Typical radiological evidence	(b) Physical or radiological evidence
		At least one of the following:	At least one of the following:
		(1) Segmental/multiple proximal (hilar/intrahepatic) or proximal and distal bile duct stricture	(1) Symmetrically enlarged salivary/lachrymal glands
		(2) Retroperitoneal fibrosis	(2) Radiological evidence of renal involvement described in association with AIP
H	Histology of the pancreas	LPSP (core biopsy/resection)	LPSP (core biopsy/resection)
		At least three of the following:	Any two of the following:
		(1) Periductal lymphoplasmacytic infiltrate without granulocytic infiltration	(1) Periductal lymphoplasmacytic infiltrate without granulocytic infiltration
		(2) Obliterative phlebitis	(2) Obliterative phlebitis
		(3) Storiform fibrosis	(3) Storiform fibrosis
		(4) Abundant (>10 cells/HPF) IgG4-positive cells	(4) Abundant (>10 cells/HPF) IgG4-positive cells
Response to steroid (Rt)[c]		Diagnostic steroid trial	
		Rapid (≤2 weeks) radiologically demonstrable resolution or marked improvement in pancreatic/extrapancreatic manifestations	

Source: From [18]

[a]Atypical: Some AIP cases may show low-density mass, pancreatic ductal dilation, or distal atrophy. Such atypical imaging findings in patients with obstructive jaundice and/or pancreatic mass are highly suggestive of pancreatic cancer. Such patients should be managed as pancreatic cancer unless there is strong collateral evidence for AIP and a thorough workup for cancer is negative (see algorithm)

[b]Endoscopic biopsy of duodenal papilla is a useful adjunctive method because ampulla often is involved pathologically in AIP

[c]Diagnostic steroid trial should be conducted carefully by pancreatologists with caveats (see text) only after negative workup for cancer including EUS-guided FNA

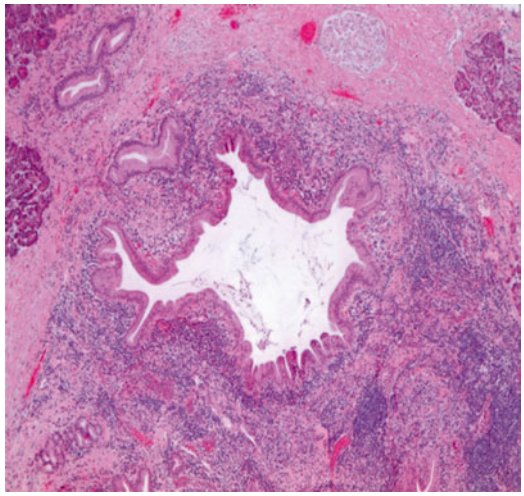

Fig. 5.1 Overview of autoimmune pancreatitis (H&E staining) with the typical lymphocellular infiltrates around a pancreatic duct and storiform fibrosis

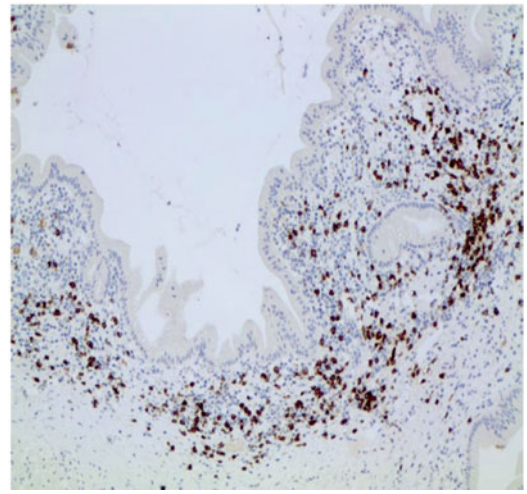

Fig. 5.2 Immunohistochemistry for IgG in AIP type 1

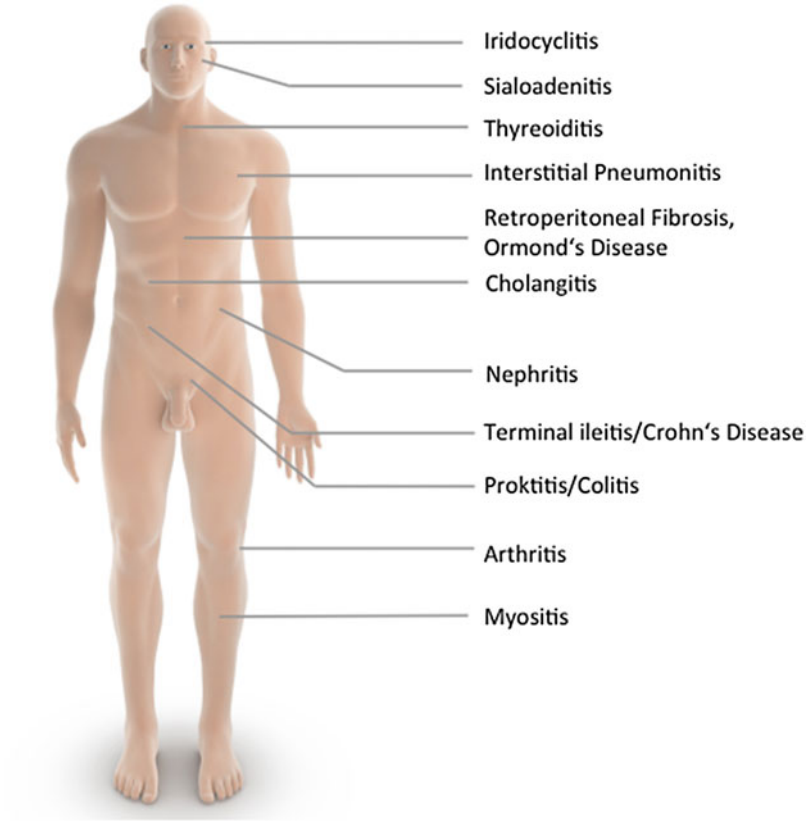

Fig. 5.3 Possible affection of other organs (other organ involvement, OOI) in autoimmune pancreatitis

AIP. Most of these patients exhibit the typical criteria of DM type 1 with autoantibodies against islet cells (ICA), glutamic acid decarboxylase (GAD), and the tyrosine phosphatase-like protein [19]. It has been reported that diabetes mellitus in AIP ameliorates under steroid therapy [55].

Associations between AIP and autoimmune hepatitis or primary biliary cirrhosis are rare [19].

Affection of the biliary tract by IgG4-associated cholangitis (IAC) is the most frequent overall OOI in AIP, naturally occurring in type 1AIP, hence warranting special attention [19]. IAC occurs both in the intra- and extrahepatic bile ducts as well as in the gallbladder wall [56]. The findings in the bile ducts in AIP may mimic PSC [57]. Due to the fact that IAC/AIP responds well to steroids, in contrast to PSC, the differential diagnosis is pivotal.

Extraintestinal manifestations of the AIP include lung and kidney lesions (Fig. 5.3). The pulmonary lesions are made up of diffuse small nodules, infiltrates, and/or hilar adenopathy that can clinically impress as interstitial pneumonia. Lesions in the kidney appear as tubulointerstitial nephritis leading to mild renal insufficiency. Renal lesions have a distinct morphology on multidetector CT (MDCT) [58].

Further OOI as manifestations of IgG immunopathy in AIP type 1 are idiopathic retroperitoneal fibrosis, scleroderma, lymphadenopathy, as well as inflammatory pseudotumors of the hypophysis, lungs, and liver [59]. Rare autoimmune conditions accompanying AIP are systemic lupus erythematosus (SLE), autoimmune hepatitis (AIH), idiopathic thrombocytopenic purpura (ITP), rheumatoid arthritis (RA), and thyroiditis [60].

Diagnosis

Laboratory Diagnostics

Serum amylase and lipase in AIP are normal or slightly elevated. Patients may have signs of obstructive jaundice (transaminases, bilirubin, alkaline phosphatase, GGT) [19, 47]. Eosinophilia and increased serum IgE can be found [50]. A pathological glucose tolerance (OGTT) or type II diabetes can be diagnosed in conjunction with AIP (54–76 %) [19, 47]. Pancreatic exocrine insufficiency can develop [19] and may be transient [61, 62].

Serology

The most predominant findings in AIP are elevated serum IgG and IgG4 [20], also found in other autoimmune diseases [63]. The specificity of IgG4 to discriminate AIP from PDAC is said to be 98 %, with a sensitivity of 90.4 %. The sensitivity of total gamma globulin (IgG) in serum was estimated between 59.1 and 73.3 % [33]. Further generic autoantibodies are antinuclear antibodies (ANA) (76 %; $n=13/17$), rheumatoid factor (RF) (29 %; $n=5/17$), and antibodies against smooth muscle (ASMA) (18 %; $n=3/17$).

As mentioned above, there are several specific autoantibodies described. Those are directed against antigens in the pancreatic ducts such as lactoferrin and carbonic anhydrase type II (ACA-II) [25]. Further autoantibodies have been described against acinar antigens, such as SPINK1 [26, 27], ubiquitin-protein ligase E3 component n-recognin 2 (UBR2) [28], and trypsinogens [27]. The frequency described in the few studies varies: lactoferrin (ALF) in 76 % ($n=13/17$) and carbonic anhydrase type II in 59 % ($n=10/17$) [64]. It seems as if patients in Europe do not express these autoantibodies as often as patients from the Asia-Pacific region [65]. The acinar antigens or respective autoantigens cannot be tested with commercial kits. Therefore, as confirmatory studies are currently lacking (but are under way), these autoantibodies, which could greatly simplify the diagnosis of AIP, have no clinical impact at present.

Imaging

AIP presents in about 60 % of patients with a pancreatic head tumor; therefore, PDAC is the most important differential diagnosis in cross-sectional imaging [58, 66, 67]. Nevertheless, there is a distinct, not to say pathognomonic picture of AIP: In both MRI and MDCT, a capsular

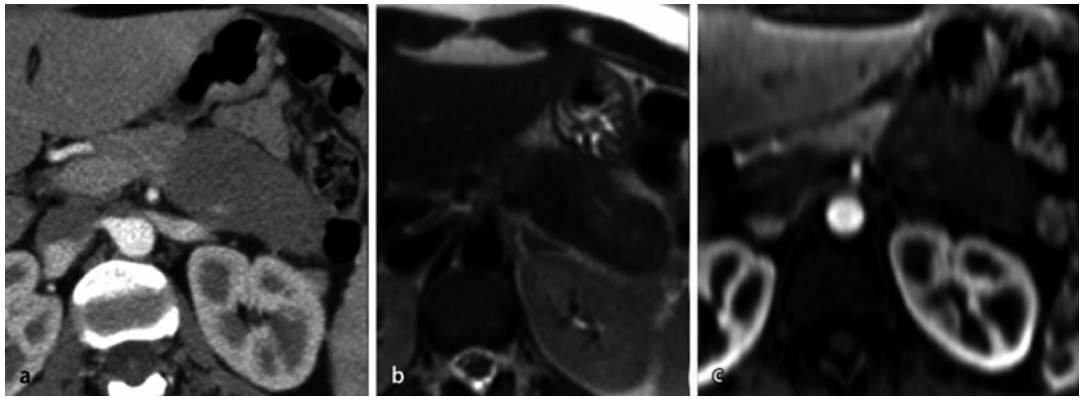

Fig. 5.4 Imaging in autoimmune pancreatitis. (**a**) MDCT with contrast and a hypodense swelling of the pancreatic tail. (**b**) T2-weighted MRI, demonstrating the segmental vanishing of the MPD and a reduction of signal. (**c**) T1-weighted MRI with contrast, demonstrating reduced uptake in the pancreatic tail similar to MDCT (all images are from the same patient)

enhancement can be detected [68] (Fig. 5.4). Sometimes a peripheral hypoattenuation ("halo") can be seen. Another typical picture is a diffuse swelling of the entire pancreas ("German bratwurst") or parts thereof that can be accompanied by obliteration or affection of the MPD and/or distal bile duct (Fig. 5.4). In both magnetic resonance cholangiopancreatography (MRCP) or endoscopic retrograde cholangiopancreatography (ERCP), a small MPD with strictures can be seen. A typical finding is a distinct contrast enhancement of the distal bile duct as a sign of the AIP-associated cholangitis (IAC) [69].

Any possible finding in the pancreas may occur: from acute pancreatitis to atrophy of the gland. Pancreatic pseudocysts and MPD dilatations, however, are atypical, as are calcifications. Ordinary transabdominal ultrasound seems not to be helpful; however, both contrast-enhanced ultrasound as well as elastography are claimed to allow for a more robust diagnosis and distinction from PDAC [70].

Endoscopic ultrasound (EUS) will show a hypoechogenic, **sausage-like enlarged pancreas** [71, 72]. The parenchymal pattern is said to be typical of contrast-enhanced ultrasound as well as elastography. EUS offers the option of taking a biopsy [45, 73]. A histological diagnosis is an important part of establishing the diagnosis according to ICDC (Figs. 5.1 and 5.2). The yield of EUS-guided FNA or Trucut biopsy in establishing the diagnosis of AIP or IAC is around 50 % [74, 75].

In Japan, ERCP is still used as a diagnostic tool. It would show the same findings as in MRCP: segmental, irregular narrowing of the MPD and stenosis of the CBD. ERCP, however, has little or no value in the differential diagnosis of autoimmune cholangitis (IAC) versus PSC [76].

Classification and Diagnostic Criteria

There have been several proposals to classify and diagnose chronic pancreatitis. All had their impact in their respective time. For AIP, a panel of experts reached a consensus (ICDC), addressing both the diagnosis and the classification of AIP [18]. In addition, we developed a scoring system for chronic pancreatitis allowing for the grading of disease activity [77]. This tool can be used to monitor disease activity according to therapy.

The classification of AIP requires clear criteria for diagnosis according to ICDC. According to the clinical reality, two categories are formed: "definite" versus "probable" with morphological criteria (histology, imaging) (Tables 5.1 and 5.3). These criteria have been further detailed (Tables 5.2 and 5.4). The criteria are described separately for AIP type 1 (Tables 5.1 and 5.3) and

Table 5.3 ICDC diagnostic criteria for AIP type 2 (definitive and probable)

Diagnosis	Imaging evidence	Collateral evidence
Definitive type 2 AIP	Typical/indeterminate	Histologically confirmed IDCP (level 1 H) or clinical inflammatory bowel disease + level 2 H + Rt
Probable type 2 AIP	Typical/indeterminate	Level 2 H/clinical inflammatory bowel disease + Rt

Source: From [18]

Table 5.4 ICDC levels 1 and 2 diagnostic criteria for AIP type 2

	Criterion	Level 1	Level 2
P	Parenchymal imaging	Typical:	Indeterminate (including atypical[a]):
		Diffuse enlargement with delayed enhancement (sometimes associated with rim-like enhancement)	Segmental/focal enlargement with delayed enhancement
D	Ductal imaging (ERP)	Long (>1/3 length of the main pancreatic duct) or multiple strictures without marked upstream dilatation	Segmental/focal narrowing without marked upstream dilatation (duct size, <5 mm)
OOI	Other organ involvement		Clinically diagnosed inflammatory bowel disease
H	Histology of the pancreas (core biopsy/resection)	IDCP:	Both of the following:
		Both of the following:	(1) Granulocytic and lymphoplasmacytic acinar infiltrate
		(1) Granulocytic infiltration of duct wall (GEL) with or without granulocytic acinar inflammation	(2) Absent or scant (0–10 cells/HPF) IgG4-positive cells
		(2) Absent or scant (0–10 cells/HPF) IgG4-positive cells	
Response to steroid (Rt)[b]		Diagnostic steroid trial: Rapid (≤2 weeks) radiologically demonstrable resolution or marked improvement in manifestations	

Source: From [18]

[a]Atypical: Some AIP cases may show low-density mass, pancreatic ductal dilation, or distal atrophy. Such atypical imaging findings in patients with obstructive jaundice and/or pancreatic mass are highly suggestive of pancreatic cancer. Such patients should be managed as pancreatic cancer unless there is strong collateral evidence for AIP and a thorough workup for cancer is negative (see algorithm)

[b]Diagnostic steroid trial should be conducted carefully by pancreatologists with caveats (see text) only after negative workup for cancer including EUS-guided FNA

AIP type 2 (Tables 5.2 and 5.4). Based on these criteria, diagnostic algorithms are proposed, separately for AIP type 1 (Figs. 5.5 and 5.6) and AIP type 2 (Fig. 5.7). Application of these ICDC in the years to come will prove whether they are adequate to diagnose and classify AIP [78].

Therapy

Treatment with steroids should be considered in patients who fulfill the ICDC criteria and who are symptomatic (pain, jaundice). It should be noted that even if there is a significant bile duct stricture leading to obstructive jaundice but the diagnosis of AIP is secured, patients can be treated with steroids first without the need for immediate stenting. The changes in the MPD as well as focal lesions in the lungs and kidney will respond quickly to steroid treatment. A pancreatic head tumor will also respond; however, if there is any doubt about the diagnosis of AIP according to the ICDC, cross-sectional imaging must be performed after 2 weeks to ensure appropriate shrinking of the inflammatory pancreatic head tumor—and not missing a pancreatic cancer.

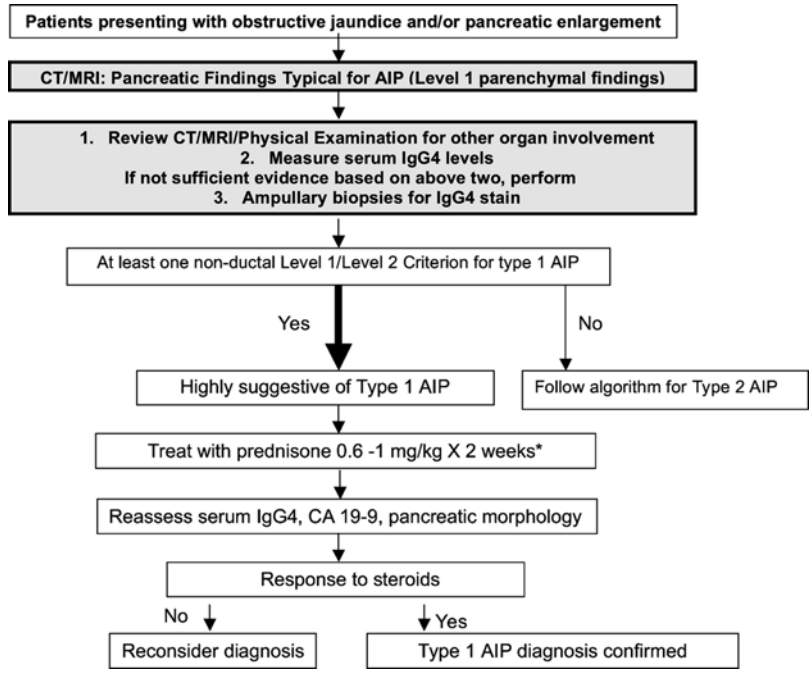

Fig. 5.5 ICDC algorithm to diagnose AIP type 1 in patients with jaundice and typical findings (level 1) [18]

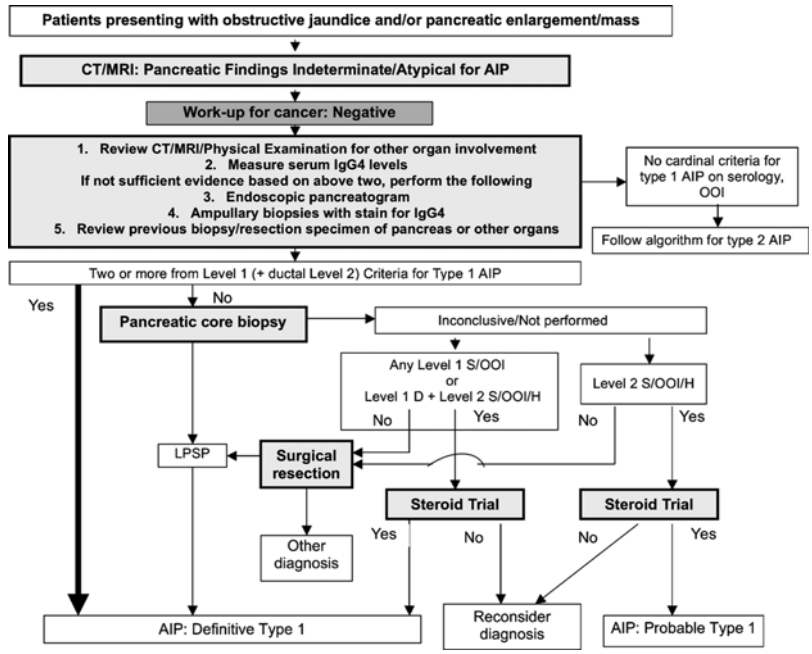

Fig. 5.6 ICDC algorithm to diagnose AIP type 1 in patients with jaundice and atypical imaging (level 2) [18]

Prednisone is the corticosteroid of choice. The recommended initial dose is 40 mg once daily (≈0.5 mg/kg BW) for 4 weeks, with tapering thereafter in 10-mg steps [79–81]. The scheme is following the recommendations for Crohn's disease (Table 5.5).

A significant proportion of patients will experience a relapse of AIP during the steroid taper. The recurrence rate is around 30 %, higher in type 1 AIP, especially in those where the initially elevated IgG/IgG4 is not normalized [62]. Those patients may be in need of

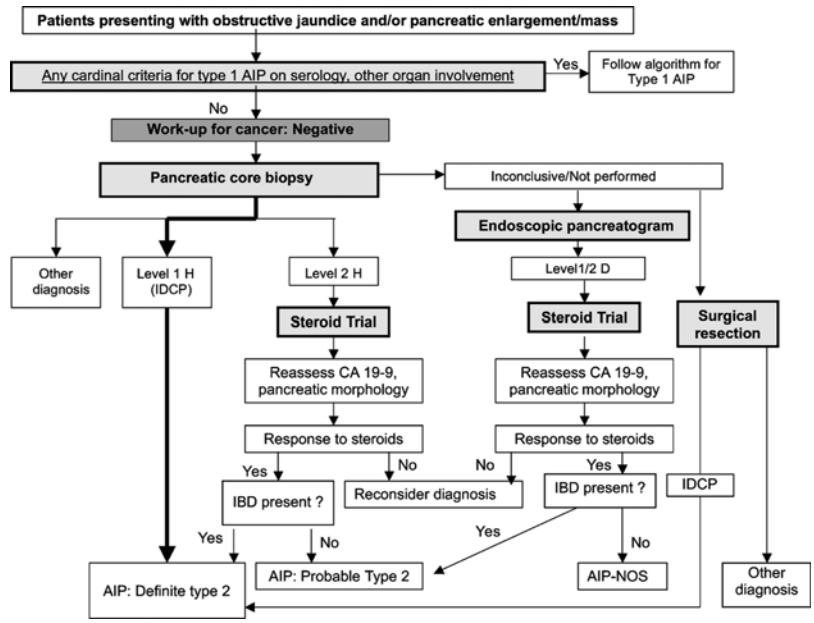

Fig. 5.7 ICDC algorithm to diagnose AIP type 2 in patients with jaundice and both typical and atypical imaging (levels 1 and 2) [18]

Table 5.5 General treatment scheme for steroid therapy in AIP

	Europe	Asian Pacific
General	IBD guidelines	IBD guidelines
Dose (mg/kg)	0.6–0.75	≤0.5
Starting dose (mg)	50–60	35–40
Duration (weeks)	4	4
Reduction	10 mg/week	5 mg/week
Maintenance	Not generally recommended	2.5–5 mg/6–24 months

Source: From [18]

maintenance therapy with low-dose steroids (5–10 mg prednisone daily) [47]. The OOI will also respond well to steroid therapy [49]. As an alternative, other immune suppressants can be used [81, 82]. Azathioprine would be the first choice, even if this drug itself rarely could cause pancreatitis.

In AIP with cholangitis (IAC) [83] steroids may not suffice. Relapse rates seem to be higher, especially after (unintentional) operation [84]. Jaundice as a presenting symptom is a determining factor for relapse after successful steroid medication [49], making the use of other immunosuppressive drugs necessary, such as azathioprine or mycophenolate mofetil [81, 82]. The addition of ursodesoxycholic acid (UDA) is recommended in analogy to other forms of cholangitis [45].

Natural Course and Prognosis

In contrast to pancreatic cancer, AIP is a benign diagnosis. However, the diagnosis must be safely established. There are no long-term studies on AIP at present. It is generally accepted that AIP has a good prognosis. There are case reports on pancreatic cancer in AIP. Most of the cancers occurred within a 1–2-year period of the diagnosis of AIP. In principle, it is feasible to assume that AIP could develop into PDAC, in analogy to colorectal cancer in UC; however, we are far from calling AIP a premalignant lesion [19]. Nevertheless, this differential diagnosis must be taken seriously in order to leave all patients with the option of surgical removal of a malignant tumor. PDAC as a differential diagnosis must be considered in IgG/IgG4-negative disease, i.e., type 2 AIP. If in doubt, surgery must be the choice of treatment, especially if EUS-guided biopsy is inconclusive [85].

References

1. Emmrich J, Weber I, Nausch M, Sparmann G, Koch K, Seyfarth M, Lohr M, Liebe S. Immunohistochemical characterization of the pancreatic cellular infiltrate in normal pancreas, chronic pancreatitis and pancreatic carcinoma. Digestion. 1998;59(3):192–8.
2. Emmrich J, Jaster R. Autoimmune diseases in gastroenterology. Curr Pharm Des. 2012;18(29):4542–5.
3. Ball WP, Baggenstoss AH, Bargen JA. Pancreatic lesions associated with chronic ulcerative colitis. Arch Pathol. 1950;50:345–8.
4. Sarles H, Sarles JC, Muratore R, Guien C. Chronic inflammatory sclerosis of the pancreas—an autonomous pancreatic disease? Am J Dig Dis. 1961;6:688–98.
5. Epstein O, Chapman RWG, Lake-Bakaar G, Foo AY, Rosalki SB, Sherlock S. The pancreas in primary biliary cirrhosis and primary sclerosing cholangitis. Gastroenterology. 1982;83:1177–82.
6. Montefusco PP, Geiss AC, Bronzo RL, Randall S, Kahn E, McKinley MJ. Sclerosing cholangitis, chronic pancreatitis and Sjögren's syndrome: a syndrome complex. Am J Surg. 1984;147:822–6.
7. Sartori N, Löhr M, Basan B, Holle A, Liebe S. Pancreatitis in systemic scleroderma. Z Gastroenterol. 1997;35(9):677–80.
8. Löhr M, Schmitt P, Klöppel G. Island changes in insulin-dependent diabetes in old age. Immunocytochemical pancreas studies in a diabetic patient with hypothyroidism. Pathologe. 1988;9(2):103–8.
9. Kawaguchi K, Koike M, Tsuruta K, Okamoto A, Tabata I, Fujita N. Lymphoplasmacytic sclerosing pancreatitis with cholangitis: a variant of primary sclerosing cholangitis extensively involving pancreas. Hum Pathol. 1991;22(4):387–95.
10. Yoshida K, Toki F, Takeuchi T, Watanabe S, Shiratori K, Hayashi N. Chronic pancreatitis caused by an autoimmune abnormality. Proposal of the concept of autoimmune pancreatitis. Dig Dis Sci. 1995;40:1561–8.
11. Keim V, Teich N. Idiopathic vs. hereditary pancreatitis. JAMA. 2003;289(8):983–4. Author reply 985.
12. Otsuki M. Chronic pancreatitis in Japan: epidemiology, prognosis, diagnostic criteria, and future problems. J Gastroenterol. 2003;38(4):315–26.
13. Otsuki M. Chronic pancreatitis. The problems of diagnostic criteria. Pancreatology. 2004;4(1):28–41.
14. Chari ST, Smyrk TC, Levy MJ, Topazian MD, Takahashi N, Zhang L, Clain JE, Pearson RK, Petersen BT, Vege SS, Farnell MB. Diagnosis of autoimmune pancreatitis: the Mayo Clinic experience. Clin Gastroenterol Hepatol. 2006;4(8):1010–6. quiz 1934.
15. Kamisawa T, Chung JB, Irie H, Nishino T, Ueki T, Takase M, Kawa S, Nishimori I, Okazaki K, Kim MH, Otsuki M. Japan–Korea symposium on autoimmune pancreatitis (KOKURA 2007). Pancreas. 2007;35(3):281–4.
16. Otsuki M, Chung JB, Okazaki K, Kim MH, Kamisawa T, Kawa S, Park SW, Shimosegawa T, Lee K, Ito T, Nishimori I, Notohara K, Naruse S, Ko SB, Kihara Y. Asian diagnostic criteria for autoimmune pancreatitis: consensus of the Japan–Korea Symposium on Autoimmune Pancreatitis. J Gastroenterol. 2008;43(6):403–8.
17. Shimosegawa T, Kataoka K, Kamisawa T, Miyakawa H, Ohara H, Ito T, Naruse S, Sata N, Suda K, Hirota M, Takeyama Y, Shiratori K, Hatori T, Otsuki M, Atomi Y, Sugano K, Tanaka M. The revised Japanese clinical diagnostic criteria for chronic pancreatitis. J Gastroenterol. 2010;45(6):584–91.
18. Shimosegawa T, Chari ST, Frulloni L, Kamisawa T, Kawa S, Mino-Kenudson M, Kim MH, Kloppel G, Lerch MM, Löhr M, Notohara K, Okazaki K, Schneider A, Zhang L. International consensus diagnostic criteria for autoimmune pancreatitis: guidelines of the International Association of Pancreatology. Pancreas. 2011;40(3):352–8.
19. Kamisawa T, Chari ST, Giday SA, Kim MH, Chung JB, Lee KT, Werner J, Bergmann F, Lerch MM, Mayerle J, Pickartz T, Löhr M, Schneider A, Frulloni L, Webster GJM, Reddy DN, Liao WC, Wang HP, Okazaki K, Shomosegawa T, Kloeppel G, Go VL. Clinical profile of autoimmune pancreatitis and its histological subtypes: an international multicentre survey. Pancreas. 2011;40:809–14.
20. Hamano H, Kawa S, Horiuchi A, Unno H, Furuya N, Akamatsu T, Fukushima M, Nikaido T, Nakayama K, Usuda N, Kiyosawa K. High serum IgG4 concentrations in patients with sclerosing pancreatitis. N Engl J Med. 2001;344(10):732–8.
21. Stone JH, Zen Y, Deshpande V. IgG4-related disease. N Engl J Med. 2012;366(6):539–51.
22. Witt H, Apte MV, Keim V, Wilson JS. Chronic pancreatitis: challenges and advances in pathogenesis, genetics, diagnosis, and therapy. Gastroenterology. 2007;132(4):1557–73.
23. Kawa S, Ota M, Yoshizawa K, Horiuchi A, Hamano H, Ochi Y, Nakayama K, Tokutake Y, Katsuyama Y, Saito S, Hasebe O, Kiyosawa K. HLA DRB10405-DQB10401 haplotype is associated with autoimmune pancreatitis in the Japanese population. Gastroenterology. 2002;122(5):1264–9.
24. Ota M, Katsuyama Y, Hamano H, Umemura T, Kimura A, Yoshizawa K, Kiyosawa K, Fukushima H, Bahram S, Inoko H, Kawa S. Two critical genes (HLA-DRB1 and ABCF1) in the HLA region are associated with the susceptibility to autoimmune pancreatitis. Immunogenetics. 2007;59(1):45–52.
25. Kino-Ohsaki J, Nishimori I, Morita M, Okazaki K, Yamamoto Y, Onishi S, Hollingsworth MA. Serum antibodies to carbonic anhydrase I and II in patients with idiopathic chronic pancreatitis and Sjögren's syndrome. Gastroenterology. 1996;110:1579–86.
26. Asada M, Nishio A, Uchida K, Kido M, Ueno S, Uza N, Kiriya K, Inoue S, Kitamura H, Ohashi S, Tamaki H, Fukui T, Matsuura M, Kawasaki K, Nishi T, Watanabe N, Nakase H, Chiba T, Okazaki K. Identification of a novel autoantibody against pancreatic secretory trypsin inhibitor in patients with autoimmune pancreatitis. Pancreas. 2006;33(1):20–6.

27. Löhr JM, Faissner R, Koczan D, Bewerunge P, Bassi C, Brors B, Eils R, Frulloni L, Funk A, Halangk W, Jesnowski R, Kaderali L, Kleeff J, Kruger B, Lerch MM, Losel R, Magnani M, Neumaier M, Nittka S, Sahin-Toth M, Sanger J, Serafini S, Schnölzer M, Thierse HJ, Wandschneider S, Zamboni G, Klöppel G. Autoantibodies against the exocrine pancreas in autoimmune pancreatitis: gene and protein expression profiling and immunoassays identify pancreatic enzymes as a major target of the inflammatory process. Am J Gastroenterol. 2010;105(9):2060–71.
28. Frulloni L, Lunardi C, Simone R, Dolcino M, Scattolini C, Falconi M, Benini L, Vantini I, Corrocher R, Puccetti A. Identification of a novel antibody associated with autoimmune pancreatitis. N Engl J Med. 2009;361(22):2135–42.
29. Jonas L, Kruger B, Tessenow W. Immunohistochemical detection of lactoferrin in different human glandular tissues with special reference to the exocrine pancreas. Acta Histochem. 1993;95(1):53–9.
30. Zamboni G, Luttges J, Capelli P, Frulloni L, Cavallini G, Pederzoli P, Leins A, Longnecker D, Kloppel G. Histopathological features of diagnostic and clinical relevance in autoimmune pancreatitis: a study on 53 resection specimens and 9 biopsy specimens. Virchows Arch. 2004;445(6):552–63.
31. Pearson RK, Longnecker DS, Chari ST, Smyrk TC, Okazaki K, Frulloni L, Cavallini G. Controversies in clinical pancreatology: autoimmune pancreatitis: does it exist? Pancreas. 2003;27(1):1–13.
32. Kleeff J, Welsch T, Esposito I, Löhr M, Singer R, Büchler MW, Friess H. Autoimmune pancreatitis—a surgical disease? Chirurg. 2006;77(2):154–65.
33. Choi EK, Kim MH, Lee TY, Kwon S, Oh HC, Hwang CY, Seo DW, Lee SS, Lee SK. The sensitivity and specificity of serum immunoglobulin G and immunoglobulin G4 levels in the diagnosis of autoimmune chronic pancreatitis: Korean experience. Pancreas. 2007;35(2):156–61.
34. Uchida K, Okazaki K, Nishi T, Uose S, Nakase H, Ohana M, Matsushima Y, Omori K, Chiba T. Experimental immune-mediated pancreatitis in neonatally thymectomized mice immunized with carbonic anhydrase II and lactoferrin. Lab Invest. 2002;82(4):411–24.
35. Seleznik GM, Reding T, Romrig F, Saito Y, Mildner A, Segerer S, Sun LK, Regenass S, Lech M, Anders HJ, McHugh D, Kumagi T, Hiasa Y, Lackner C, Haybaeck J, Angst E, Perren A, Balmer ML, Slack E, MacPherson A, Manz MG, Weber A, Browning JL, Arkan MC, Rulicke T, Aguzzi A, Prinz M, Graf R, Heikenwalder M. Lymphotoxin beta receptor signaling promotes development of autoimmune pancreatitis. Gastroenterology. 2012;143(5):1361–74.
36. Freitag TL, Cham C, Sung HH, Beilhack GF, Durinovic-Bello I, Patel SD, Bronson RT, Schuppan D, Sonderstrup G. Human risk allele HLA-DRB1*0405 predisposes class II transgenic Ab0 NOD mice to autoimmune pancreatitis. Gastroenterology. 2010;139(1):281–91.
37. Schwaiger T, van den Brandt C, Fitzner B, Zaatreh S, Kraatz F, Dummer A, Nizze H, Evert M, Broker BM, Brunner-Weinzierl MC, Wartmann T, Salem T, Lerch MM, Jaster R, Mayerle J. Autoimmune pancreatitis in MRL/Mp mice is a T cell-mediated disease responsive to cyclosporine A and rapamycin treatment. Gut. 2014;63(3):494–505.
38. Watanabe S, Suzuki K, Kawauchi Y, Yamagiwa S, Yoneyama H, Kawachi H, Okada Y, Shimizu F, Asakura H, Aoyagi Y. Kinetic analysis of the development of pancreatic lesions in mice infected with a murine retrovirus. Clin Immunol. 2003;109(2):212–23.
39. Haruta I, Yanagisawa N, Kawamura S, Furukawa T, Shimizu K, Kato H, Kobayashi M, Shiratori K, Yagi J. A mouse model of autoimmune pancreatitis with salivary gland involvement triggered by innate immunity via persistent exposure to avirulent bacteria. Lab Invest. 2010;90(12):1757–69.
40. Kountouras J, Zavos C, Gavalas E, Tzilves D. Challenge in the pathogenesis of autoimmune pancreatitis: potential role of *Helicobacter pylori* infection via molecular mimicry. Gastroenterology. 2007;133(1):368–9.
41. Fujinami RS, von Herrath MG, Christen U, Whitton JL. Molecular mimicry, bystander activation, or viral persistence: infections and autoimmune disease. Clin Microbiol Rev. 2006;19(1):80–94.
42. Guarneri F, Guarneri C, Benvenga S. *Helicobacter pylori* and autoimmune pancreatitis: role of carbonic anhydrase via molecular mimicry? J Cell Mol Med. 2005;9(3):741–4.
43. Jesnowski R, Isaksson B, Möhrcke C, Bertsch B, Bulajic M, Schneider-Brachert W, Klöppel G, Lowenfels AB, Maisonneuve P, Löhr JM. *Helicobacter pylori* in autoimmune pancreatitis and pancreatic carcinoma. Pancreatology. 2010;10:462–6.
44. Patel NC, Palmer WC, Krishna M, Lewis MD, Wallace MB. Lack of an association between autoimmune pancreatitis and varicella zoster virus. JOP. 2011;12(6):614–5.
45. Detlefsen S, Mohr Drewes A, Vyberg M, Kloppel G. Diagnosis of autoimmune pancreatitis by core needle biopsy: application of six microscopic criteria. Virchows Arch. 2009;454(5):531–9.
46. Chari ST, Kloeppel G, Zhang L, Notohara K, Lerch MM, Shimosegawa T. Histopathologic and clinical subtypes of autoimmune pancreatitis: the Honolulu consensus document. Pancreatology. 2010;10(6):664–72.
47. Church NI, Pereira SP, Deheragoda MG, Sandanayake N, Amin Z, Lees WR, Gillams A, Rodriguez-Justo M, Novelli M, Seward EW, Hatfield AR, Webster GJ. Autoimmune pancreatitis: clinical and radiological features and objective response to steroid therapy in a UK series. Am J Gastroenterol. 2007;102(11):2417–25.
48. Weber SM, Cubukcu-Dimopulo O, Palesty JA, Suriawinata A, Klimstra D, Brennan MF, Conlon K. Lymphoplasmacytic sclerosing pancreatitis: inflammatory mimic of pancreatic carcinoma. J Gastrointest Surg. 2003;7(1):129–37; discussion 137–9.
49. Hirano K, Tada M, Isayama H, Yagioka H, Sasaki T, Kogure H, Nakai Y, Sasahira N, Tsujino T, Yoshida H,

Kawabe T, Omata M. Long-term prognosis of autoimmune pancreatitis with and without corticosteroid treatment. Gut. 2007;56(12):1719–24.
50. Nahon Uzan K, Levy P, O'Toole D, Belmatoug N, Vullierme MP, Couvelard A, Ponsot P, Palazzo L, Abbas A, Hammel P, Ruszniewski P. Is idiopathic chronic pancreatitis an autoimmune disease? Clinical Gastroenterol Hepatol. 2005;3(9):903–9.
51. Kamisawa T, Wakabayashi T, Sawabu N. Autoimmune pancreatitis in young patients. J Clin Gastroenterol. 2006;40(9):847–50.
52. Seyrig JA, Jian R, Madigliani R, et al. Idiopathic pancreatitis associated with inflammatory bowel disease. Dig Dis Sci. 1985;30:1121–6.
53. Rasmussen HH, Fonager K, Sorensen HT, Pedersen L, Dahlerup JF, Steffensen FH. Risk of acute pancreatitis in patients with chronic inflammatory bowel disease. A Danish 16-year nationwide follow-up study. Scand J Gastroenterol. 1999;34(2):199–201.
54. Angelini G, Cavallini G, Bovo P, Brocca G, Castagnini A, Lavarini E, Merigo F, Tallon N, Scuro LA. Pancreatic function in chronic inflammatory bowel disease. Int J Pancreatol. 1988;3:185–93.
55. Tanaka S, Kobayashi T, Nakanishi K, Okubo M, Murase T, Hashimoto M, Takeuchi K. Corticosteroid-responsive diabetes mellitus associated with autoimmune pancreatitis. Lancet. 2000;356(9233):910–1.
56. Abraham SC, Cruz-Correa M, Argani P, Furth EE, Hruban RH, Boitnott JK. Lymphoplasmacytic chronic cholecystitis and biliary tract disease in patients with lymphoplasmacytic sclerosing pancreatitis. Am J Surg Pathol. 2003;27(4):441–51.
57. Klöppel G, Sipos B, Zamboni G, Kojima M, Morohoshi T. Autoimmune pancreatitis: histo- and immunopathological features. J Gastroenterol. 2007;42 Suppl 18:28–31.
58. Sahani DV, Kalva SP, Farrell J, Maher MM, Saini S, Mueller PR, Lauwers GY, Fernandez CD, Warshaw AL, Simeone JF. Autoimmune pancreatitis: imaging features. Radiology. 2004;233(2):345–52.
59. Kamisawa T, Okamoto A. Autoimmune pancreatitis: proposal of IgG4-related sclerosing disease. J Gastroenterol. 2006;41(7):613–25.
60. Ohara H, Nakazawa T, Sano H, Ando T, Okamoto T, Takada H, Hayashi K, Kitajima Y, Nakao H, Joh T. Systemic extrapancreatic lesions associated with autoimmune pancreatitis. Pancreas. 2005;31(3):232–7.
61. Nishino T, Toki F, Oyama H, Shimizu K, Shiratori K. Long-term outcome of autoimmune pancreatitis after oral prednisolone therapy. Intern Med. 2006;45(8):497–501.
62. Maire F, Le Baleur Y, Rebours V, Vullierme MP, Couvelard A, Voitot H, Sauvanet A, Hentic O, Levy P, Ruszniewski P, Hammel P. Outcome of patients with type 1 or 2 autoimmune pancreatitis. Am J Gastroenterol. 2011;106(1):151–6.
63. Aalberse RC, Schuurman J. IgG4 breaking the rules. Immunology. 2002;105(1):9–19.
64. Okazaki K, Uchida K, Ohana M, Nakase H, Uose S, Inai M, Matsushima Y, Katamura K, Ohmori K, Chiba T. Autoimmune-related pancreatitis is associated with autoantibodies and a Th1/Th2-type cellular immune response. Gastroenterology. 2000;118(3):573–81.
65. Aparisi L, Farre A, Gomez-Cambronero L, Martinez J, De Las Heras G, Corts J, Navarro S, Mora J, Lopez-Hoyos M, Sabater L, Ferrandez A, Bautista D, Perez-Mateo M, Mery S, Sastre J. Antibodies to carbonic anhydrase and IgG4 levels in idiopathic chronic pancreatitis: relevance for diagnosis of autoimmune pancreatitis. Gut. 2005;54(5):703–9.
66. Hur BY, Lee JM, Lee JE, Park JY, Kim SJ, Joo I, Shin CI, Baek JH, Kim JH, Han JK, Choi BI. Magnetic resonance imaging findings of the mass-forming type of autoimmune pancreatitis: comparison with pancreatic adenocarcinoma. J Magn Reson Imaging. 2012;36(1):188–97.
67. Perez-Johnston R, Sainani NI, Sahani DV. Imaging of chronic pancreatitis (including groove and autoimmune pancreatitis). Radiol Clin North Am. 2012;50(3):447–66.
68. Carbognin G, Girardi V, Biasiutti C, Camera L, Manfredi R, Frulloni L, Hermans JJ, Mucelli Pozzi R. Autoimmune pancreatitis: imaging findings on contrast-enhanced MR, MRCP and dynamic secretin-enhanced MRCP. Radiol Med. 2009;114(8):1214–31.
69. Kim JH, Byun JH, Lee SJ, Park SH, Kim HJ, Lee SS, Kim MH, Kim J, Lee MG. Differential diagnosis of sclerosing cholangitis with autoimmune pancreatitis and periductal infiltrating cancer in the common bile duct at dynamic CT, endoscopic retrograde cholangiography and MR cholangiography. Eur Radiol. 2012;22(11):2502–13.
70. Finkelberg DL, Sahani D, Deshpande V, Brugge WR. Autoimmune pancreatitis. N Engl J Med. 2006;355(25):2670–6.
71. Farrell JJ, Garber J, Sahani D, Brugge WR. EUS findings in patients with autoimmune pancreatitis. Gastrointest Endosc. 2004;60(6):927–36.
72. Iglesias-Garcia J, Lindkvist B, Larino-Noia J, Dominguez-Munoz JE. The role of EUS in relation to other imaging modalities in the differential diagnosis between mass forming chronic pancreatitis, autoimmune pancreatitis and ductal pancreatic adenocarcinoma. Rev Esp Enferm Dig. 2012;104(6):315–21.
73. Löhr JM, Klöppel G. Indications for pancreatic biopsy. Uncommon, but increasingly more important. Pathologe. 2005;26(1):67–72.
74. Levy MJ, Reddy RP, Wiersema MJ, Smyrk TC, Clain JE, Harewood GC, Pearson RK, Rajan E, Topazian MD, Yusuf TE, Chari ST, Petersen BT. EUS-guided trucut biopsy in establishing autoimmune pancreatitis as the cause of obstructive jaundice. Gastrointest Endosc. 2005;61(3):467–72.
75. Nishino T, Oyama H, Hashimoto E, Toki F, Oi I, Kobayashi M, Shiratori K. Clinicopathological differentiation between sclerosing cholangitis with autoimmune pancreatitis and primary sclerosing cholangitis. J Gastroenterol. 2007;42(7):550–9.
76. Kalaitzakis E, Levy M, Kamisawa T, Johnson GJ, Baron TH, Topazian MD, Takahashi N, Kanno A, Okazaki K, Egawa N, Uchida K, Sheikh K, Amin Z, Shimosegawa T, Sandanayake NS, Church NI,

Chapman MH, Pereira SP, Chari S, Webster GJ. Endoscopic retrograde cholangiography does not reliably distinguish IgG4-associated cholangitis from primary sclerosing cholangitis or cholangiocarcinoma. Clin Gastroenterol Hepatol. 2011;9(9):800–3. e802.

77. Schneider A, Löhr JM, Singer MV. The M-ANNHEIM classification of chronic pancreatitis: introduction of a unifying classification system based on a review of previous classifications of the disease. J Gastroenterol. 2007;42(2):101–19.
78. Ikeura T, Detlefsen S, Zamboni G, Manfredi R, Negrelli R, Amodio A, Vitali F, Gabbrielli A, Benini L, Kloppel G, Okazaki K, Vantini I, Frulloni L. Retrospective comparison between preoperative diagnosis by international consensus diagnostic criteria and histological diagnosis in patients with focal autoimmune pancreatitis who underwent surgery with suspicion of cancer. Pancreas. 2014;43(5):698–703.
79. Ghazale A, Chari ST. Optimising corticosteroid treatment for autoimmune pancreatitis. Gut. 2007;56(12):1650–2.
80. Kamisawa T, Takeuchi T. Treatment of autoimmune pancreatitis with the anecdotes of the first report. Int J Rheumatol. 2012;2012:597643.
81. Sodikoff JB, Keilin SA, Cai Q, Bharmal SJ, Lewis MM, Raju GS, Willingham FF. Mycophenolate mofetil for maintenance of remission in steroid-dependent autoimmune pancreatitis. World J Gastroenterol. 2012;18(18):2287–90.
82. Khosroshahi A, Carruthers MN, Deshpande V, Unizony S, Bloch DB, Stone JH. Rituximab for the treatment of IgG4-related disease: lessons from 10 consecutive patients. Medicine (Baltimore). 2012;91(1):57–66.
83. Zen Y, Harada K, Sasaki M, Sato Y, Tsuneyama K, Haratake J, Kurumaya H, Katayanagi K, Masuda S, Niwa H, Morimoto H, Miwa A, Uchiyama A, Portmann BC, Nakanuma Y. IgG4-related sclerosing cholangitis with and without hepatic inflammatory pseudotumor, and sclerosing pancreatitis-associated sclerosing cholangitis: do they belong to a spectrum of sclerosing pancreatitis? Am J Surg Pathol. 2004;28(9):1193–203.
84. Detlefsen S, Löhr JM, Drewes AM, Frokjaer JB, Kloppel G. Current concepts in the diagnosis and treatment of type 1 and type 2 autoimmune pancreatitis. Recent Pat Inflamm Allergy Drug Discov. 2011;5(2):136–49.
85. Zyromski NJ. Autoimmune pancreatitis (AIP) masquerading as pancreatic cancer: cutting is not a crime … for now. Dig Dis Sci. 2012;57(9):2246–7.

Pancreatitis-Related Pancreatic Masses: Chronic Pancreatitis

6

Chris E. Forsmark

The evaluation of a pancreatic mass is centered on promptly and accurately identifying the presence of malignancy. While the majority of pancreatic mass lesions are malignant, patients with chronic pancreatitis may also present with an apparent mass on cross-sectional imaging. These inflammatory masses need to be differentiated from pancreatic ductal adenocarcinoma and other, rarer pancreatic malignancies. This situation most commonly presents in one of three clinical scenarios: (1) a patient with pancreatic ductal adenocarcinoma who has developed atrophy of the pancreas and a dilated pancreatic duct (i.e., "chronic pancreatitis") upstream from the cancer, and who is misdiagnosed as having chronic pancreatitis; (2) a patient with chronic pancreatitis who develops a large inflammatory mass which mimics the imaging features of adenocarcinoma; or (3) a patient with established chronic pancreatitis who develops a secondary superimposed pancreatic malignancy. These three clinical scenarios are not easily distinguishable based on symptoms or clinical features—in each situation patients may present with abdominal pain, weight loss, steatorrhea, diabetes, and even jaundice. These three scenarios may also not be easily distinguishable by cross-sectional imaging (e.g., CT or MRI) (Fig. 6.1). In each scenario, the clinical challenge is in differentiating the patient with malignant disease from the one with only chronic pancreatitis, and doing this efficiently so that time is not wasted without initiating appropriate treatment.

Patients with chronic pancreatitis are at increased risk of pancreatic adenocarcinoma, with an overall lifetime risk of approximately 4 % [1–3] and an overall hazard ratio of around 10 [1, 4]. This risk is especially magnified in patients who also smoke [1], and in some genetic syndromes. As an example, in patients with a PRSS1 mutation (hereditary pancreatitis) with a paternal pattern of inheritance, and who also smoke, the lifetime risk may approach 70 % [1, 5, 6]. The risk of pancreatic cancer presumably accumulates over time, although many cancers are diagnosed within a few years of the diagnosis of chronic pancreatitis. Some of these cancers, particularly those diagnosed within 1 year of the diagnosis of chronic pancreatitis, likely reflect cancer being mistakenly diagnosed as chronic pancreatitis as in the first scenario noted above. It can be difficult in natural history studies to differentiate these prevalent cancers misdiagnosed as chronic pancreatitis from incident cancers occurring in patients with preexisting chronic pancreatitis. The increased risk of pancreatic cancer is greatest 2–4 years after the diagnosis of chronic pancreatitis but remains elevated even after 15 years of disease [4]. Smoking lowers the

C.E. Forsmark, M.D. (✉)
Division of Gastroenterology, Hepatology, and Nutrition, University of Florida, 1329 SW 16th St., Suite 5251, PO Box 100214, Gainesville, FL 32610-0214, USA
e-mail: chris.forsmark@medicine.ufl.edu

M.S. Wagh, P.V. Draganov (eds.), *Pancreatic Masses*, DOI 10.1007/978-3-319-19677-0_6

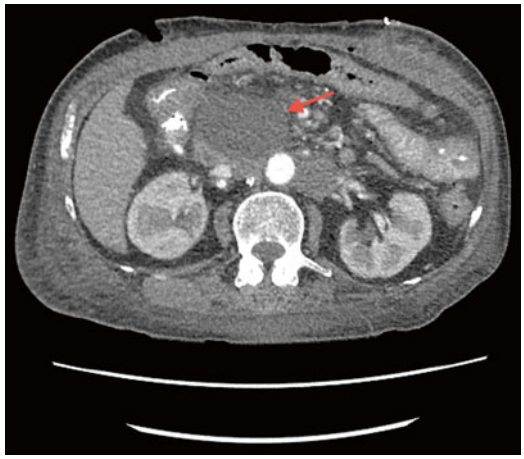

Fig. 6.1 A CT scan demonstrates a hypodense mass in the pancreatic head (*arrow*). This lesion is due to chronic pancreatitis and resolved on subsequent imaging tests

mean age of presentation of pancreatic cancer in patients with chronic pancreatitis, compared to nonsmokers, by one to two decades [1, 7]. Smoking is also a strong independent risk factor for chronic pancreatitis [1, 8, 9], and more than half of adult patients with chronic pancreatitis are active smokers [1]. This shared risk factor partially explains the strong association of chronic pancreatitis and pancreatic cancer. Thus it is not uncommon to find pancreatic malignancy occurring in patients with chronic pancreatitis, although this still accounts for only a small fraction (<5 %) of all pancreatic cancers [1]. In population-based studies, the mortality from chronic pancreatitis is three- to fivefold higher than age-matched controls, and cancer is a frequent cause of death [1, 4]. In particular, pancreatic cancer has the highest excess risk in these patients and is the most frequent cause of cancer-related death in patients with chronic pancreatitis [4]. While this risk is substantial, death in these patients is also commonly caused by complications of coexistent cirrhosis, cardiovascular disease, pulmonary disease, other cancers (particularly lung), and various postoperative complications [1, 4]. Routine surveillance for pancreatic cancer has not been recommended in most patients with chronic pancreatitis, with the exception of certain genetic syndromes. The challenges for effective surveillance in these patients are numerous; the difficulty in visualizing a malignant pancreatic mass in the background of an already diseased pancreas, the cost of surveillance, the relative rarity of pancreatic cancer, and the lack of any evidence that surveillance and early detection reduces cancer mortality are major ones. The challenge in differentiating a benign from a malignant mass lesion in patients with preexisting chronic pancreatitis is the subject of this chapter.

Mass-forming chronic pancreatitis refers to the second scenario listed above. It implies a large inflammatory mass in the pancreas, which is distinguishable on cross-sectional imaging from the surrounding pancreas. The inflammatory mass may occur anywhere within the pancreas but is most common in the head of the gland. Some patients with chronic pancreatitis may have more than one mass-like lesion in the pancreas. The inflammatory mass may be associated with bile duct obstruction or duodenal obstruction, main pancreatic duct obstruction, or compression of the portal vein or superior mesenteric vein, thus mimicking most of the imaging features of pancreatic malignancy. The prevalence of mass-forming chronic pancreatitis is not known. It has been estimated that 5–10 % of patients with chronic pancreatitis will develop biliary or duodenal obstruction, and these patients usually have relative enlargement of the head of the pancreas. A second group of patients with so-called groove pancreatitis (inflammation and fluid in the groove between the duodenum and the pancreatic head) may also develop biliary and duodenal obstruction and may also be mistaken for malignancy [10]. The majority of reports of mass-forming chronic pancreatitis come from a few tertiary European referral centers. In a series of patients referred to one surgical center in Germany performing duodenum-preserving pancreatic head resections, more than 30 % of patients had an inflammatory mass in the head of the pancreas [11, 12]. There are other surgical case series of patients who have undergone pancreatic resection for presumed malignancy, with the pathologic specimen demonstrating chronic pancreatitis rather than malignancy.

Many of these case series are old, prior to the availability of endoscopic ultrasonography (EUS) or of high-resolution computed tomography (CT) and magnetic resonance imaging (MRI), and prior to the widespread recognition of autoimmune pancreatitis. These case series are also small. In one illustrative more recent report of 15 patients who underwent resection for presumed pancreatic malignancy but in whom no malignancy was found, half were found to have Type 1 autoimmune pancreatitis, and half mass-forming chronic pancreatitis without features of Type 1 autoimmune pancreatitis [13]. These patients represented 9.4 % of all patients at that institution who underwent pancreatic resection for presumed cancer during that same timeframe. In older case series, approximately 11–34 % of patients undergoing pancreatic resection for presumed malignancy were found to have benign disease [14–18]. In these earlier reports, autoimmune pancreatitis is not mentioned, but in the more recent reports, around half (or more) of these patients had a histologic pattern consistent with Type 1 autoimmune pancreatitis. Whether the rest also represent Type 1 autoimmune pancreatitis with nondiagnostic pathology, or Type 2 autoimmune pancreatitis, or other forms of chronic pancreatitis is not known. These limited data would suggest that around 1 in 10 patients with a mass large enough to lead to consideration of pancreatic resection for presumed malignancy suffers from chronic pancreatitis, and that at least half of these have autoimmune pancreatitis. The subject of masses due to autoimmune pancreatitis and their differentiation from malignancy is the subject of another chapter of this book.

The prevalence of mass-forming chronic pancreatitis may vary by geographic regions. The majority of the reports of this entity come from Europe. Some experts have suggested that this may reflect more than just referral bias and may reflect some differences between populations. Although unproven, it has been the experience of many pancreatologists that these patients with mass-forming chronic pancreatitis are more likely to have disease due to the combined effects of alcohol and smoking and are more likely to be male. Differences in the prevalence of this mass-forming variant of chronic pancreatitis may therefore reflect differences in these risk factors (or in genetic background) across these different populations.

A number of diagnostic tools are available to assist clinicians in distinguishing mass-forming chronic pancreatitis from malignancy. This diagnostic distinction is often challenging as all of our diagnostic techniques suffer from false-negative and false-positive results. Even more important in this setting is the negative predictive value (NPV) of the diagnostic test. The NPV combines both sensitivity and disease prevalence. Masses due to cancer are much more common than mass-forming pancreatitis. A high NPV means that a patient with a negative test is very unlikely to harbor malignancy. Unfortunately, we do not have a diagnostic test or strategy with a high NPV, which is an unavoidable consequence of the relative prevalence of these conditions. This leaves the clinician in a difficult dilemma, as it may not be possible to be absolutely sure (or even reasonably sure) that malignancy is not present.

The diagnostic tools include cross-sectional imaging [CT, positron emission tomography (PET), PET-CT, and MRI], pancreatography [endoscopic retrograde cholangiopancreatography (ERCP) or magnetic resonance cholangiopancreatography (MRCP)], EUS with fine-needle aspiration (FNA), and various biomarkers in tissue, serum, or pancreatic juice. One would assume that as these tests became more technically advanced and more widely available that the number of patients with mass-forming chronic pancreatitis undergoing pancreatic resection to rule out malignancy would decrease. This may not be the case. In one case series covering the years 1998–2011, there was no change in the percentage of patients with benign disease undergoing resection (averaging around 11 %) [19]. In this report, the use of EUS with FNA and ERCP with cytology increased substantially over time, but this was not associated with a decrease in pancreatic resection for presumed malignancy in patients who were ultimately found to have benign disease. A similar analysis [20] noted that the introduction of EUS with FNA improved the overall specificity of the evaluation but did not

lead to a reduction in rates of surgery for presumed malignancy that ultimately turned out to be benign disease. Finally, another recent report noted that the routine use of EUS and FNA in the diagnostic evaluation did not reduce the number of patients undergoing resection for presumed malignancy who were found to have mass-forming pancreatitis [21]. The EUS findings in the patients in this report included a visible mass in 70 %, enlarged lymph nodes in 27 %, and features suggesting vascular invasion in 13 %. EUS-FNA was indeterminate or suspicious for malignancy in 63 % of these patients who were ultimately found to have benign disease. This may reflect a major diagnostic weakness of EUS with FNA—the relatively frequent cytologic interpretation of an FNA specimen as "suspicious" or "indeterminate."

In reviewing these reports and others [13–19], we see that a number of themes are evident; these patients with mass-forming pancreatitis who ultimately go to pancreatic resection are most often men, between the ages of 40 and 60, who present with abdominal pain or painless obstructive jaundice, and often with weight loss. The most common location is a mass in the head of the pancreas. Of particular note, only about half have a history of preexisting pancreatitis, and cross-sectional imaging evidence of chronic pancreatitis is often not present in the rest of the pancreas. This is particularly true for those with underlying autoimmune pancreatitis, but less so for those with other etiologies of chronic pancreatitis (e.g., due to alcohol, smoking, or genetics). The majority of these patients have a history of alcohol or smoking. On imaging, the mass may be solid or may have cystic components, and may demonstrate abnormal enhancement with intravenous contrast. Enlarged lymph nodes and vascular compression occur in 10–20 %, and a dilated pancreatic duct in the upstream gland is not uncommon. Several clinical studies have attempted to develop predictive rules to identify these patients preoperatively, based on clinical features or radiographic imaging studies, with very little success. This is not surprising, as pancreatic cancer is much more common than mass-forming pancreatitis. Any predictive scheme (short of an FNA—which definitively demonstrates clear-cut malignancy) will be plagued by a high number of false-negative results and inadequate negative predictive value. Even the cytologic examination of an EUS-FNA often reaches a diagnosis of "suspicious" or "indeterminate," as noted in the study mentioned previously [21], and this leaves the clinician with little option but to recommend resection. This lack of a sufficiently high NPV explains why resective cancer surgery is still performed in patients who turn out to have benign disease. Indeed, recent surgical consensus statements focus on the need for accurate identification of autoimmune pancreatitis but conclude that biopsy proof is not needed prior to proceeding to a pancreaticoduodenectomy in patients with a mass lesion that is suspicious for malignancy [22].

In most patients, the diagnostic approach starts with a CT scan. Pancreatic cancer is a hypovascular tumor with a robust surrounding fibrous stroma. This stroma is similar to that seen in chronic pancreatitis, which explains part of the difficulty in differentiating these two conditions on imaging studies. The use of multidetector CT with a "pancreas protocol" is likely to reduce the chance of diagnostic error; however, it has not been specifically assessed in this situation or compared to older CT techniques. Pancreatic carcinoma typically is hypovascular, which is usually most evident 45 s after contrast injection ("pancreatic phase") [23]. Most tumors are hypoattenuating, although smaller cancers are often iso-intense, making it difficult to identify them [23]. Findings which are suggestive of malignancy include (1) a focal low-density mass, (2) pancreatic duct dilation upstream from the mass, (3) atrophy of the pancreas upstream from the mass, (4) the lack of features of chronic pancreatitis (especially calcification), (5) vascular compression or obstruction with the loss of the fat plane between blood vessels and the mass, and (6) metastatic disease (Fig. 6.1). Of these features, only the presence of obvious metastatic disease is specific for malignancy. The sensitivity of CT for the diagnosis of pancreatic cancer is around 80 % [23], yielding a substantial false-negative rate. One would assume that the addition of FDG-PET

to CT, or PEt alone, would improve the ability to differentiate benign from malignant pancreatic masses. In several studies, this appeared to be the case. In one study from India in 87 patients with a pancreatic mass, it was noted that focal (rather than diffuse) uptake of FDG by the lesion (cutoff SUVmax of 2.8) resulted in a sensitivity of 87.5 % and a specificity of 45 % to differentiate pancreatic cancer from mass-forming pancreatitis [24]. Other studies described even better accuracy [25]. In distinction to these findings, a recent analysis of 47 patients from Japan noted an inability to distinguish cancer from mass-forming pancreatitis [26], due to substantial overlap in SUVmax values. Analysis of PEt alone, without CT, has shown poor accuracy [27]. A recent meta-analysis of these data noted a pooled NPV for PEt alone at 76 %, and for combined PET/CT of 78 % [28], concluding that these techniques offer no benefit over current primary diagnostic tools such as CT, MR, and EUS. These data do not provide convincing evidence that PET-CT is sufficiently accurate to distinguish cancer from mass-forming pancreatitis.

MRI and MRCP allow a more detailed imaging of the pancreatic duct than CT; however, pancreatic calcifications are not visible on an MRI. The features of malignancy on MRI are typically an iso- or hypointense mass on T1 weighting and iso- or hyperintense on T2 weighting [23]. The other features are essentially the same as CT as noted above, with pancreatic duct dilation and atrophy upstream from the mass. The overall accuracy is around 80 %, with sensitivities and specificities very similar to multidetector CT (MDCT) [23, 29]. Both CT and MRI have greatly diminished accuracy for lesions under 2 cm [29]. The accuracy of MRI in differentiating pancreatic cancer from mass-forming pancreatitis may be able to be improved by a number of techniques, including intravenous contrast [30], quantitative analysis of time–intensity curves during contrast injection [31, 32], or by the related technique of diffusion-weighted imaging and use of diffusion coefficients [33–36]. At least some of these studies noted that it was possible to identify pancreatic cancer that had developed in some patients with preexisting chronic pancreatitis. Diffusion-weighted imaging and other MRI techniques have not yet gained widespread application in this group of patients. At the current time, MR imaging and MDCT imaging are equivalent in their ability to differentiate mass-forming pancreatitis from pancreatic cancer, with an NPV of approximately 70–80 %.

EUS has added significantly to the ability to differentiate mass-forming pancreatitis from pancreatic malignancies. Imaging characteristics alone are often insufficient to differentiate benign from malignant lesions (Fig. 6.2). The overall accuracy for EUS imaging characteristics alone to make this distinction is at best around 75 % [37, 38].

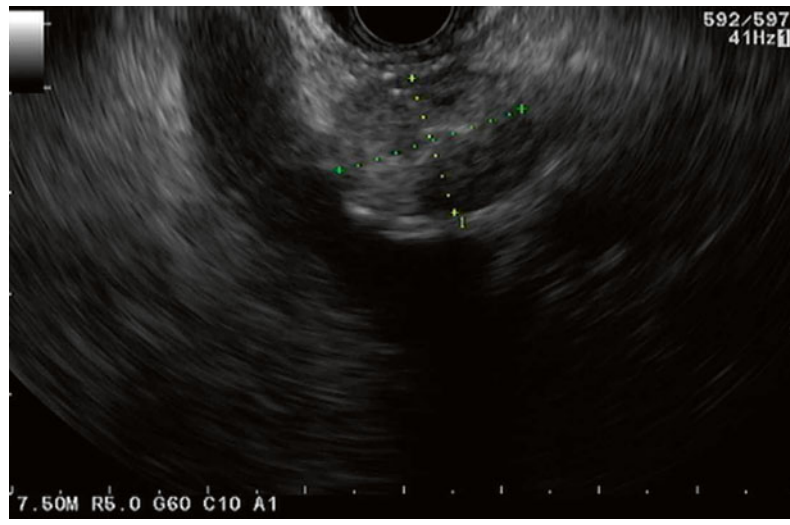

Fig. 6.2 An EUS image of a hypoechoic pancreatic head mass in a patient with mass-forming pancreatitis. FNA samples were negative, and the lesion resolved on subsequent imaging

The advantage of EUS is the ability to sample lesions and use cytological examination to identify malignancy. A systematic review and a meta-analysis [39, 40] of the accuracy of EUS with FNA have reported a pooled sensitivity of approximately 85 % and specificity of approximately 98 %, but with significant variability across studies. In some studies, the sensitivity was as low as 54 %, and specificity as low as 71 %. A systematic review of 53 studies noted that the negative predictive value of EUS-FNA in the diagnosis of pancreatic carcinoma is only around 60–70 % [39]. In particular, the overall accuracy of EUS and FNA is substantially reduced in patients with chronic pancreatitis [37, 41–45]. This has been documented in several studies. In one study [41] the sensitivity of EUS with FNA was 89 % in those without chronic pancreatitis, and 54 % in those with chronic pancreatitis. The ability to diagnose mass-forming pancreatitis requires a very high NPV, and as pancreatic cancer is more common than mass-forming pancreatitis, the NPV will remain stubbornly low. A number of variations of EUS and FNA have been studied as methods to improve the overall accuracy of this technique. EUS elastography is a technique to measure tissue elasticity or hardness and can be used to differentiate mass-forming pancreatitis from pancreatic adenocarcinoma. Cancers are generally "harder" than normal tissue, and potentially more than benign masses. It is worth pointing out that patients with mass-forming chronic pancreatitis often have substantial associated pancreatic fibrosis, and this may mimic the "hardness" of the tumor-associated fibrotic stroma. EUS elastography can be performed with a qualitative endpoint (based on color patterns) or quantitatively (based on numerical analysis). The initial studies of EUS elastography, utilizing a qualitative endpoint, suggested a very high sensitivity and specificity with NPVs of 90 % [37, 46–48]; however, not all studies demonstrated similar impressive results [49]. Several recent meta-analyses have also assessed the overall accuracy of EUS elastography [50–52]. The pooled sensitivity from these studies is approximately 95 % and specificity 67 %. There is heterogeneity among the primary studies analyzed in these meta-analyses, related to different qualitative standards used for diagnosis. It is also noteworthy that there are multiple potential opportunities for artifact in the performance of elastography, related to tissue compression, motion artifact, and adjacent organs with very high or very low elastographic characteristics. Quantitative EUS elastography utilizes analysis of a strain ratio, which requires the examiner to select areas of interest for comparison and analysis. This allows the introduction of potential bias even with the more quantitative analysis. Nonetheless, the accuracy of quantitative EUS elastography appears to be slightly better than a qualitative analysis in limited studies. Another technique to improve EUS images includes the use of contrast agents. This technique, contrast harmonic echo (CHE-EUS), may improve the visualization of small lesions, but the NPV to identify mass-forming pancreatitis does not appear much better than traditional EUS [53, 54]. A final way to improve the ability of EUS to identify mass-forming pancreatitis is by improving the tissue sampling. One method is to use larger needles for FNA, or to utilize core biopsy needles to obtain histopathology [55–57]. Unfortunately, these core biopsy needles are difficult to utilize in the head of the pancreas and whether this technique will allow more accurate diagnosis of mass-forming pancreatitis is not known.

Another method is to analyze the FNA specimen in a more detailed method, searching for biomarkers (DNA, specific mutations, miRNA, proteins, etc.) that identify a lesion as malignant, and the absence of these biomarkers could identify the lesion as benign [58]. This approach has been most well studied in relation to EUS-FNA in cystic neoplasms [59], but a wealth of data exists on pancreatic cancer [60]. Measurement of these genetic, protein, or metabolic markers could provide improved diagnostic accuracy, although perhaps their most significant use will be in personalizing cancer treatment based on individual cancer cell susceptibility to specific therapies. Biomarkers can be measured in many

tissues and fluids, including aspirated tissue, pancreatic juice, and serum. CA 19-9 is obviously a well-studied and widely used biomarker, but is not sufficiently accurate to differentiate mass-forming pancreatitis from pancreatic cancer. Nonetheless, it is often used as part of a screening procedure in individuals at high risk of pancreatic cancer. Differentiating mass-forming pancreatitis from pancreatic cancer utilizing CA 19-9 has not been well studied, but many of these patients may have coexistent biliary obstruction, which increases CA 19-9 even in those with benign disease. There are numerous reports of elevations in CA 19-9 to a level of >1000 ng/mL in benign disease, making it an inaccurate biomarker for the purpose of identifying patients with mass-forming pancreatitis. Activation of K-ras is very common in pancreatic cancer, and analysis of the presence of K-ras mutations in FNA specimens has been assessed [61] in a meta-analysis. K-ras analysis appears to be particularly helpful when the EUS-FNA findings are inconclusive, reducing the false-negative rate from 56 to 11 %. It should be pointed out that K-ras mutations may also be found in benign lesions. In the meta-analysis, the pooled specificity of K-ras was 93 %, so that on average 7 % of patients with benign disease have a positive K-ras analysis. In most recent series of patients going to surgery, around 10 % are ultimately found to have benign disease, which approximates the false-negative rate of EUS-FNA with or without K-ras measurement. These data point out the current limitations on diagnostic accuracy. Additional mutations can be assessed in FNA specimens as well, and one commercially available panel includes mutational profiling on K-ras and 16 microsatellite markers (known commercially as PathFinderTG, RedPath Integrated Pathology, Inc., Pittsburgh, PA). This approach has been used primarily for cystic lesions rather than solid mass lesions, but this type of analysis can be performed on solid tissue and even when the specimen is paucicellular, by assessing the supernatant [62]. Next-generation sequencing is also possible with EUS-FNA specimens [63], which will reduce cost and speed results. There are now many known potential biomarkers for pancreatic cancer, including circulating tumor cells, microRNAs, protein or serological signatures, and many others that are being assessed as methods of earlier detection of pancreatic cancer [64, 65]. Much of the work in this area has focused on both early detection as well as screening of high-risk individuals. Pancreatic cysts have been the subject of the most studies with these biomarkers, in an attempt to differentiate mucinous cysts from nonmucinous cysts and to differentiate malignant from nonmalignant or premalignant cysts. Analysis of DNA, miRNA, and proteomic and metabolomic profiling have had limited success to this point in improving diagnostic accuracy in that setting, but work has been very limited in solid mass lesions. Much is known about the molecular mechanisms of pancreatic cancer, and it is likely the clinical value of biomarkers will improve in the future.

EUS-FNA, EUS elastography, contrast-enhanced EUS, and biomarkers are discussed in detail in separate chapters elsewhere in this book.

To reiterate, it remains difficult to distinguish mass-forming pancreatitis from pancreatic cancer. As mentioned, a recent international surgical consensus conference reached the conclusion that biopsy proof is not required prior to resection in patients with a solid mass suspicious for malignancy [22]. This approach has traditionally led to 10 % of resections being performed for benign disease. Imaging studies, in the absence of obvious metastases, are often inconclusive in making the distinction between malignancy and mass-forming pancreatitis. EUS-FNA has the potential to allow more accurate diagnosis, but recent analyses continue to document that approximately 10 % of patients going to pancreatic resection for presumed pancreatic cancer have benign disease, so EUS-FNA has not moved the needle much. The role of better EUS, utilizing elastography and molecular analysis of FNA specimens, has the potential to improve diagnostic accuracy, but the best methods and best markers remain to be identified. In the future, the best approach is likely to include EUS with FNA and a robust panel of biomarkers.

References

1. Yadav D, Lowenfels AB. The epidemiology of pancreatitis and pancreatic cancer. Gastroenterology. 2013;144:1252–61.
2. Lowenfels AB, Maisonneuve P, Cavallini G, et al. Pancreatitis and the risk of pancreatic cancer: International Pancreatic Study Group. N Engl J Med. 1993;328:1434–7.
3. Duell EJ, Lucenteforte E, Olson SH, et al. Pancreatitis and pancreatic cancer risk: a pooled analysis in the International Pancreatic Cancer Case-Control Consortium (PanC4). Ann Oncol. 2012;23:2964–70.
4. Bang UC, Benfield T, Hyldstrup L, et al. Mortality, cancer, and comorbidities associated with chronic pancreatitis: a Danish nationwide matched-cohort study. Gastroenterology. 2014;146:989–94.
5. Lowenfels AB, Maisonneuve P, DiMagno EP, et al. Hereditary pancreatitis and the risk of pancreatic cancer: International Hereditary Pancreatitis Study Group. J Natl Cancer Inst. 1997;89:442–6.
6. Lowenfels AB, Maisonneuve P, Whitcomb DC, et al. Cigarette smoking as a risk factor for pancreatic cancer in patients with hereditary pancreatitis. JAMA. 2001;286:169–70.
7. Bosetti C, Lucenteforte E, Silverman DT, et al. Cigarette smoking and pancreatic cancer: an analysis from the International Pancreatic Cancer Case-Control Consortium (PanC4). Ann Oncol. 2012;23:1880–8.
8. Andriulli A, Botteri E, Almasio PL, et al. Smoking as a cofactor for causation of chronic pancreatitis. A meta-analysis. Pancreas. 2010;39:1205–10.
9. Cote GA, Yadav D, Slivka A, et al. Alcohol and smoking as risk factors in an epidemiology study of patients with chronic pancreatitis. Clin Gastroenterol Hepatol. 2011;9:266–73.
10. Raman SP, Salaria SN, Hruban RH, Fishman EK. Groove pancreatitis: spectrum of imaging findings and radiology-pathology correlation. AJR Am J Roentgenol. 2013;201:W29–39.
11. Buchler M, Malfertheiner P, Friess H, et al. Chronic pancreatitis with inflammatory mass in the head of the pancreas: a special entity? In: Beger JG, Buchler M, Ditschuneit H, Malfertheiner P, editors. Chronic pancreatitis. Berlin: Springer; 1990. p. 41–6.
12. Beger HG, Schlowsser W, Poch B, Gansauge F. Inflammatory mass in the head of the pancreas. In: Beger HG, Warshaw AL, Buchler MW, Carr-Locke DC, Neoptolemos JP, Russell C, Sarr MG, editors. The pancreas. London: Blackwell; 1998. p. 757–60.
13. Kajiwara M, Gotoda N, Konishi M, et al. Incidence of focal type of autoimmune pancreatitis and chronic pancreatitis suspected to be pancreatic carcinoma: experience of a single tertiary center. Scand J Gastroenterol. 2008;43:110–6.
14. Abraham SC, Wilentz RE, Yeo CJ, et al. Pancreaticoduodenectomy (Whipple resections) in patients without malignancy. Are they all "chronic pancreatitis"? Am J Surg Pathol. 2003;27:110–20.
15. Sasson AR, Gulizia JM, Galva A, et al. Pancreaticoduodenectomy for suspected malignancy: have advancements in radiographic imaging improved results? Am J Surg. 2006;192:888–93.
16. Kennedy T, Preczewski L, Stocker SJ, et al. Incidence of benign inflammatory disease in patients undergoing Whipple operation for clinically suspected carcinoma: a single-institution experience. Am J Surg. 2006;191:437–41.
17. Smith CD, Behrns KE, van Heerden JA, Sarr MG. Radical pancreatoduodenectomy for misdiagnosed pancreatic mass. Br J Surg. 1994;81:585–9.
18. Van Gulik TM, Reedes JW, Bosma A, et al. Incidence and clinical findings of benign, inflammatory disease in patients resected for presumed pancreatic head cancer. Gastrointest Endosc. 1997;46:417–23.
19. Yarandi SS, Runge T, Wang L, et al. Increased incidence of benign pancreatic pathology following pancreaticoduodenectomy for presumed malignancy over 10 years despite increased use of endoscopic ultrasound. Diagn Ther Endosc. 2014. doi:10.1155/2014/701535. Article ID 701535.
20. Manzia TM, Toti L, Lenci I, et al. Benign disease and unexpected histological findings after pancreaticoduodenectomy: the role of endoscopic ultrasound fine needle aspiration. Ann R Coll Surg Engl. 2010;92:295–301.
21. De la Fuente SG, Ceppa EP, Reddy SK, et al. Incidence of benign disease in patients that underwent resection for presumed pancreatic cancer diagnosed by endoscopic ultrasonography (EUS) and fine-needle aspiration (FNA). J Gastrointest Surg. 2010;14:1139–42.
22. Asbun HJ, Conlon K, Fernandez-Cruz L, et al. When to perform a pancreatoduodenectomy in the absence of positive histology? A consensus statement by the International Study Group of Pancreatic Surgery. Surgery. 2014;155:887–92.
23. Lee ES, Lee JM. Imaging diagnosis of pancreatic cancer: a state-of-the-art review. World J Gastroenterol. 2014;20:7864–77.
24. Santhosh S, Mitttal BR, Bhasin D, et al. Role of (18) F-fluorodeoxyglucose positron emission tomography/computed tomography in the characterization of pancreatic masses: experience from the tropics. J Gastroenterol Hepatol. 2013;28:255–61.
25. Kauhanen SP, Komar G, Seppanen MP, et al. A prospective diagnostic accuracy study of 18F-fluorodoxyglucose positron emission tomography/computed tomography, multidetector row computed tomography, and magnetic resonance imaging in the primary diagnosis and staging of pancreatic cancer. Ann Surg. 2009;250:957–63.
26. Kato K, Nihashi T, Ikeda M, et al. Limited efficacy of 18F-FDG PET/CT for differentiation between metastasis-free pancreatic cancer and mass forming pancreatitis. Clin Nucl Med. 2013;38:417–21.
27. Matsumo I, Shirakawa S, Shinzeki M, et al. 18-Fluorodeoxyglucose positron emission tomography does not aid in diagnosis of pancreatic ductal adenocarcinoma. Clin Gastroenterol Hepatol. 2013;11:712–8.

28. Rijkers AP, Valkema R, Duivenvoorden HJ, van Eijck CH. Usefulness of F-18-fluordeoxyglucosse positron emission tomography to confirm suspected pancreatic cancer: a meta-analysis. Eur J Surg Oncol. 2014;40: 794–904.
29. Shrikhande SV, Barreto SG, Goel M, Arya S. Multimodality imaging of pancreatic ductal adenocarcinoma: a review of the literature. HPB (Oxford). 2012;14:658–68.
30. Koelbinger C, Ba-Ssalamah A, Goetzinger P, et al. Gadobenate dimeglumine-enhanced 3.0-T MR imaging versus multiphasic 64-detector row CT: prospective evaluation in patients suspected of having pancreatic cancer. Radiology. 2011;259:757–66.
31. Liu K, Xie P, Peng W, Zhou A. Assessment of dynamic contrast-enhanced magnetic resonance imaging in the differentiation of pancreatic ductal adenocarcinoma from other pancreatic solid lesions. J Comput Assist Tomogr. 2014;38(5):681–6.
32. Tajima Y, Kuroki T, Tsutsumi R, et al. Pancreatic carcinoma coexisting with chronic pancreatitis vs. tumor-forming pancreatitis. Diagnostic utility of the time-signal intensity curve from dynamic contrast-enhanced MR imaging. World J Gastroenterol. 2007;14:858–65.
33. Sandrasegaran K, Nutakki K, Tahir B, et al. Use of diffusion-weighted MRI to differentiate chronic pancreatitis from pancreatic cancer. AJR Am J Roentgenol. 2013;201:1002–8.
34. Ma X, Zhao X, Ouyang H, et al. Quantified ADC histogram analysis: a new method for differentiating mass-forming pancreatitis form pancreatic cancer. Acta Radiol. 2014;55(7):785–92.
35. Wiggermann P, Grutzmann R, Weissenbock A, et al. Apparent diffusion coefficient measurements of the pancreas, pancreas carcinoma, and mass forming focal pancreatitis. Acta Radiol. 2012;53:135–9.
36. Fattahi R, Balci NC, Perman WH, et al. Pancreatic diffusion-weighted imaging (DWI): comparison between mass-forming focal pancreatitis (FP), pancreatic cancer (PC), and normal pancreas. J Magn Reson Imaging. 2009;29:350–6.
37. Iglesias-Garcia J, Lindkvist B, Larino-Noia J, Dominguez-Munoz JE. The role of endoscopic ultrasound (EUS) in relation to other imaging modalities in the differential diagnosis of mass forming chronic pancreatitis. Autoimmune pancreatitis and ductal pancreatic adenocarcinoma. Rev Esp Enferm Dig. 2012;104:315–21.
38. Varadarajulu S, Eloubeidi MA. The role of endoscopic ultrasonography in the evaluation of pancreaticobiliary cancer. Surg Clin North Am. 2010;90: 251–63.
39. Hartwig W, Schneider L, Diener MK, et al. Preoperative tissue diagnosis for tumors of the pancreas. Br J Surg. 2009;96:5–20.
40. Hewitt MJ, McPhail MJW, Possamai L, et al. EUS-guided FNA for the diagnosis of solid pancreatic neoplasms. A meta-analysis. Gastrointest Endosc. 2012;75:319–31.
41. Fritscher-Ravens A, Brand L, Knofel WT, et al. Comparison of endoscopic ultrasound-guided fine needle aspiration for focal pancreatic lesions in patients with normal parenchyma and chronic pancreatitis. Am J Gastroenterol. 2002;97:2768–75.
42. Varadarajulu S, Tamhane A, Eloubeidi MA. Yield of EUS guided FNA of pancreatic masses in the presence of the absence of chronic pancreatitis. Gastrointest Endosc. 2005;62:728–36.
43. Ardengh JC, Lopes CV, Campos AD, et al. Endoscopic ultrasound and fine needle aspiration in chronic pancreatitis: differential diagnosis between pseudotumoral masses and pancreatic cancer. JOP. 2007;8:413–21.
44. Krishna NB, Mehra M, Reddy AV, Agarwal B. EUS/EUSFNA for suspected pancreatic cancer: influence of chronic pancreatitis and clinical presentation with or without obstructive jaundice on performance characteristics. Gastrointest Endosc. 2009;70:70–9.
45. Takahashi K, Yamao K, Okubo K, et al. Differential diagnosis of pancreatic cancer and focal pancreatitis using EUS-guided FNA. Gastrointest Endosc. 2005; 61:76–9.
46. Giovannini M, Botelberge T, Bories E, et al. Endoscopic ultrasound elastography for evaluation of lymph nodes and pancreatic masses: a multicenter study. World J Gastroenterol. 2009;15:1587–93.
47. Iglesias-Garcia J, Larino-Noia J, Abdulkader I, et al. EUS-elastography for the characterization of solid pancreatic masses. Gastrointest Endosc. 2009;70:1101–8.
48. Swaftoiu A, Vilmann P, Gorunescu F, et al. Accuracy of endoscopic ultrasound elastography used for differential diagnosis of focal pancreatic masses: a multicenter study. Endoscopy. 2011;43:596–603.
49. Hirche TO, Ignee A, Barreiros AP, et al. Indications and limitations of endoscopic ultrasound elastography for evaluation of focal pancreatic lesions. Endoscopy. 2008;40:910–7.
50. Pei Q, Zou X, Zhang X, et al. Diagnostic value of EUS elastography in differentiation of benign and malignant pancreatic masses: a meta-analysis. Pancreatology. 2012;12:402–8.
51. Mei M, Ni J, Liu D, et al. EUS elastography for diagnosis of solid pancreatic masses: a meta-analysis. Gastrointest Endosc. 2013;77:578–89.
52. Ying L, Lin X, Xie Z-L, et al. Clinical utility of endoscopic ultrasound elastography for identification of malignant pancreatic masses: a meta-analysis. J Gastroenterol Hepatol. 2013;28:1434–43.
53. Saftoiu A, Dietrich CF, Vilmann P. Contrast-enhanced endoscopic ultrasound. Endoscopy. 2012;44:612–7.
54. Giovannini M. Contrast-enhanced and 3-dimensional endoscopic ultrasonography. Gastroenterol Clin North Am. 2010;39:845–58.
55. Holt BA, Varadarajulu S, Hebert-Magee S. High-quality endoscopic ultrasound-guided fine needle aspiration tissue acquisition. Adv Ther. 2014;31: 696–707.
56. Panic N, Larghi A. Techniques for endoscopic ultrasound-guided fine-needle biopsy. Gastrointest Endosc Clin N Am. 2014;24:83–107.

57. De la Fuente SG, Arnoletti JP. Beyond cytology: why and when does the oncologist require core tissue? Gastrointest Endosc Clin N Am. 2014;24:9–17.
58. Layfield LJ, Ehya H, Fillie AC, et al. Utilization of ancillary studies in the cytologic diagnosis of biliary and pancreatic lesions: the Papanicolau Society of Cytopathology guidelines for pancreatobiliary cytology. Diagn Cytopathol. 2014;42:351–62.
59. Matthaei H, Feldmann G, Lingohr P, Kalff JC. Molecular diagnostics for pancreatic cysts. Langenbecks Arch Surg. 2013;398:1021–7.
60. Fang Y, Yaoi Q, Chen Z, et al. Genetic and molecular alterations in pancreatic cancer: implications for personalized medicine. Med Sci Monit. 2013;19: 916–26.
61. Fuccio L, Hassan C, Laterza L, et al. The role of K-ras gene mutation analysis in EUS-guided FNA cytology specimens for the differential diagnosis of pancreatic solid masses: a meta-analysis or prospective studies. Gastrointest Endosc. 2013;78:596–608.
62. Deftereos G, Finkelstein SD, Jackson SA, et al. The value of mutational profiling of the cytocentrifugation supernatant fluid from fine-needle aspiration of pancreatic solid mass lesions. Mod Pathol. 2014;27: 594–601.
63. Di Biase D, Visani M, Baccarini P, et al. Next generation sequencing improves the accuracy of KRAS mutation analysis in endoscopic ultrasound fine needle aspiration pancreatic lesions. PLoS One. 2014; 9(2), e87651.
64. He XY, Yuan YZ. Advances in pancreatic cancer research: moving towards early detection. World J Gastroenterol. 2014;28:11241–8.
65. Herreros-Villanueva M, Gironella M, Castells A, Bujanda L. Molecular markers in pancreatic cancer diagnosis. Clin Chim Acta. 2013;418:22–9.

Part II

Diagnosis

Radiographic Imaging

7

Nikolaos Kartalis and Johannes Matthias Löhr

Introduction

For the radiological investigation of the various pancreatic masses, there is a wide variety of available imaging modalities, such as computed tomography (CT), magnetic resonance imaging (MRI), ultrasonography (US), and nuclear medicine. In this chapter, a short overview of the available techniques with an emphasis on recent advances will be presented, followed by a practical diagnostic imaging algorithm. Finally, the imaging features of the most common solid and cystic pancreatic lesions will be illustrated.

Imaging Techniques

In order to obtain optimal results, it is necessary to apply dedicated imaging protocols depending on the relevant clinical scenario, where careful attention should be paid to technical parameters related to the scanner, the patient, and the intravenous contrast material potentially to be used.

Computed Tomography

CT is the "workhorse" in the imaging of pancreatic masses. In modern scanners, multiple, parallel positioned detector rows (MDCT) combined with a fast rotating X-ray tube enable imaging of the thorax and abdomen within a single breathhold. Thus, breathing-related motion artifacts can be minimized and an optimal use of iodine-based contrast material achieved, according to well-defined imaging protocols.

For the investigation of pancreatic masses, the upper abdomen (defined as the abdominal area between the diaphragm and the iliac crest) is scanned before (unenhanced) and after the intravenous injection of iodine-based contrast material in the late arterial (parenchymal or portal venous inflow) phase and the whole abdomen in the venous (or portal venous) phase (dynamic contrast-enhanced CT, DCE-CT) [1]. In order to account for intraindividual variations of heart rate between patients, the use of individualized delay between contrast agent injection and image acquisition is encouraged [2]. The image acquisition is performed in the axial plane and the resulting images (the so-called raw data) have a slice thickness in the range of millimeters or even submillimeters. These are then reconstructed in thicker

N. Kartalis (✉)
Division of Medical Imaging and Technology, Department of Clinical Science, Intervention and Technology (CLINTEC), Karolinska Institutet, and Department of Radiology, Karolinska University Hospital, C1-46, KS Huddinge, Stockholm 14186, Sweden
e-mail: nikolaos.kartalis@karolinska.se

J.M. Löhr
Division of Surgery, Department of Clinical Science, Intervention and Technology (CLINTEC), Karolinska Institutet, and Centre for Digestive Diseases, Karolinska University Hospital, Stockholm, Sweden

M.S. Wagh, P.V. Draganov (eds.), *Pancreatic Masses*, DOI 10.1007/978-3-319-19677-0_7

slices, preferably ≤3 mm, two-dimensional (2D) images in the axial, coronal, and sagittal planes (multi-planar reformats, MPRs) [1]. Occasionally, curved planar reformats (CPR) along the ductal system and/or major vasculature may also be of value [3]. If needed, e.g., for the depiction of the vascular anatomy, 2D maximum intensity projection (MIP) and three-dimensional (3D) volume-rendering technique (VRT) images can easily be reconstructed from the same data and provide additional information about vessel engagement [4–7]. Recent advances in the commercially available hard- and software have made possible the more precise quantification of abdominal organ and tissue perfusion characteristics by applying CT perfusion technique. Parameters like blood flow, blood volume, mean transit time, and the permeability–surface area product can be calculated, providing potentially valuable information about the hemodynamic characteristics of organs, tissues, and tumors [8].

Magnetic Resonance Imaging

MRI is particularly useful in the investigation of pancreatic masses. Due to its superior soft tissue contrast resolution [i.e., the ability to distinguish different structures from each other based on their signal intensity (SI) differences on the various imaging sequences] compared to CT and to the fact that it does not expose the examined area to potentially harmful ionizing radiation, it has become a modality of great interest. Drawbacks related to its use are the limited availability and the timely image acquisition, compared to CT, as well as the considerable variation in image quality between various MRI scanners. The magnetic field strength in modern equipment is either 1.5 or 3 T and dynamic contrast imaging is feasible within reasonable timeframes (i.e., a single breath-hold).

Similarly to the DCE-CT, MR image sequences are obtained before and after the intravenous administration of gadolinium-based chelates in late arterial, portal venous, and, additionally, equilibrium phases (dynamic contrast-enhanced MRI, DCE-MRI) [9]. The sequences used for the dynamic contrast imaging are fat-saturated 3D T1-weighted and can be primarily obtained in any plane, preferably the axial, with a slice thickness of 2–3 mm. The possibility to obtain MPRs from the originally acquired axial images exists, but the results may be of lower quality compared with CT examinations due to the lower spatial resolution, at least on 1.5 T scanners. Apart from these, the protocol should include magnetic resonance cholangiopancreatography (MRCP) and T2-weighted sequences, in order to depict the relation of the lesion(s) to the main pancreatic (MPD) and common bile (CBD) ducts and to demonstrate the internal architecture of the lesions without needing to use intravenous contrast material. Diffusion-weighted imaging (DWI) is a relatively new sequence implemented in abdominal applications. It is based on the random translational movement of free water molecules (or Brownian motion), which is restricted in cases where the extracellular space is diminished (such as when there is tumor-related hypercellularity and/or increased fibrosis) [10]. By calculating the apparent diffusion coefficient (ADC), it is possible to obtain objective measurements of the diffusivity in a given tissue or organ. For this calculation, various models are available. Among them are the automated monoexponential model, which is easier and faster, and the biexponential (intravoxel incoherent motion, IVIM) model, which is more complex and accurate and allows for, besides ADC calculations, the extraction of the following parameters: the slow component of diffusion (D_{slow}), incoherent microcirculation, or otherwise pseudodiffusion, (D_{fast}), and perfusion fraction (f) [11]. Similarly to CT, the MRI perfusion technique has recently been made available in advanced scanners and the acquisition of quantitative information about perfusion characteristics is now possible [12]. Parameters that can be extracted from MRI perfusion data are the following: the volume transfer coefficient (K^{trans}), the volume of extracellular extravascular space (EES), the per-unit volume of tissue (v_e), and the flux rate constant between EES and plasma (k_{ep}) [13]. However, MRI perfusion is a technically more demanding method compared to its CT counterpart [14].

Ultrasonography

US can also be used in the investigation of pancreatic tumors. There are various approaches to perform pancreatic US, such as transabdominally (i.e., examination through the abdominal wall), endoscopically (by inserting the transducer via an endoscope, EUS), and intraoperatively (by direct contact with the organ surface during operation, IOUS). This modality is advantageous in that it does not expose the area under investigation to ionizing radiation and allows a dynamic examination of the organ of interest by injecting microbubble-containing contrast agents [15, 16]. Finally, US is useful in providing biopsy guidance (for both fine-needle aspiration and core biopsy). The use of low-frequency transducers is suggested for examining deeper areas, where higher penetration is required, and of high-frequency transducers for more superficial areas. Drawbacks include the high operator dependency, the fact that secondary readings and optimal communication of findings to clinicians are somehow difficult to perform, the insufficient visualization in cases of obese patients or due to obscuring overlying intestinal gas (in case of the transabdominal approach), and, finally, the limited availability (in the case of EUS).

Nuclear Medicine

Nuclear medicine imaging may be useful in the workup of pancreatic masses, particularly for the investigation of pancreatic neuroendocrine tumors (PNETs). In general, the technique is based on the use of radioactive tracers and can be, grossly, divided into two subcategories: (1) scintigraphy and (2) positron emission tomography (PET). The combination of these with a cross-sectional modality (i.e., CT and lately even MRI) results in the so-called hybrid imaging.

Scintigraphy

In scintigraphy, a gamma (γ) camera detects γ rays emitted from the radionuclides used. The resulting images are either 2D whole-body (planar imaging) or 3D SPECT (single photon emission computed tomography) axial images of the abdominal area. In planar imaging, the acquisition is at 4 and 24 h after injection of the radioisotope while in SPECT at 24 h.

For the workup of PNETs, the vast majority of radiotracers used are somatostatin analogs (SSA) based on the expression of somatostatin receptors (SSR) in the majority of PNETs [17]. Octreotide is the most commonly used analog for somatostatin receptor scintigraphy (SRS) and is commercially widely available as ^{111}In-pentetreotide (^{111}In-DTPA-octreotide, Octreoscan™). Apart from the SSA, other analogs for imaging a subclass of PNETs based on their expression of the glucagon-like peptide 1 (GLP-1) receptor (i.e., benign insulinomas) have been developed. Their use is limited for research purposes and they are not yet clinically available.

Positron Emission Tomography

In PET, the radionuclides used emit positrons. When an emitted positron encounters an electron, they annihilate and emit two photons in opposite directions and are, consequently, detected by the PET camera at the same moment. Compared to scintigraphy, image acquisition can be completed within much shorter time intervals, resulting in images of higher spatial resolution and tissue contrast. Drawbacks include the short half-life of the radionuclides and the relatively complicated process of the labeling procedure. Two major types of radiotracers are used: those reflecting tumor activity and those related to receptor expression [18].

The first category comprises amine precursors such as ^{11}C-5-hydroxytryptophan (^{11}C-5-HTP), ^{18}F-DOPA, and ^{11}C-L-DOPA as well as the glucose analog ^{18}F-fluorodeoxyglucose (FDG). ^{18}F-FDG is by far the most widely available and well-studied radiotracer in PET imaging, while amine precursors are less widely available but can be valuable in cases where the suspected tumors are expected to have low SSR expression (in cases of PNET). For the production of all these radiotracers, a cyclotron is required.

The second category includes all available SSAs labeled with a positron emitter, mainly ^{68}Ga, and is therefore suited only for the imaging

evaluation of PNETs. In practice, the most often used preparations are ^{68}Ga-DOTATOC, ^{68}Ga-DOTANOC, and ^{68}Ga-DOTATATE (collectively termed ^{68}Ga-DOTA-SSA). These three exhibit some differences in the affinity to the SSR-subtypes 2, 3, and 5, which, however, are not significant for clinical practice. The production of ^{68}Ga does not need a cyclotron but can easily be generated in standard equipment available at nuclear medicine departments. Image acquisition can be done within an hour from injection of the radiotracer. Compared to the SSAs used in scintigraphy, ^{68}Ga-SSAs for PET imaging still have less availability.

Hybrid Imaging

In modernscanners, nuclear medicine modalities such as PET and SPECT are combined with a cross-sectional counterpart such as CT or, lately, even MRI [18, 19]. In that way, anatomical and functional images can be viewed simultaneously and findings in one modality can be directly correlated to the other. Furthermore, "fusion" images, where one image set is overlaid to the other, are available for easier evaluation. The cross-sectional examination can be performed according to dedicated contrast-enhanced protocols, as mentioned earlier in the corresponding section, for not compromising the diagnostic quality. Furthermore, data from CT are available for attenuation correction of the PET images, making the procedure more time-efficient compared to PET.

Diagnostic Imaging Algorithm

In case there is suspicion of a pancreatic cancer or the presence of a dilated MPD or/and CBD (in the latter case, the so called "double-duct" sign), a dedicated pancreatic protocol CT or MRI is indicated, as these are considered equivalent in determining engagement of vessel and lymph nodes, according to the recommendations by NCCN [1]. On the one hand, if a mass is then detected on CT (at most institutions, CT is the first-line modality) and there are no signs of metastatic disease, CT of the thorax and liver function tests should be performed and the patient discussed at a multidisciplinary tumor board as a potential surgical candidate. EUS should also be considered. On the other hand, if a mass is not detected, then besides CT of the thorax and liver function tests, EUS or ERCP or MRI/MRCP are indicated [1]. If the initial CT examination of the patient is high-quality, no further examination is considered necessary. For the detection of small liver and peritoneal metastases, it has been shown that MRI is superior to CT [20, 21]; thus, it may be considered a complement to CT in patients with a high risk for liver metastases when the initial examination failed to demonstrate them. The role of PET/CT is yet not clear; it was not shown beneficial for detecting early cancer but may prove useful for identifying extrapancreatic distant disease in "high-risk" patients [1].

In case there is suspicion of PNETs, the European Neuroendocrine Tumor Society's (ENETS) suggested workup algorithm includes pancreatic protocol CT or MRI and an additional SRS (or ^{68}Ga-DOTA-SSA PET/CT, when available) for the selection of patients eligible for treatment with radiolabeled SSA (peptide receptor radionuclide therapy; PRRT) [17]. When major surgery is an option and CT/MRI or SRS does not confirm the presence of tumor, then the next steps are ^{68}Ga-DOTA-SSA PET/CT and/or ^{18}F-DOPA and ^{11}C-5-HTP (if available); ^{18}F-FDG PET/CT may also be considered. In all PNET cases where the proliferation index Ki-67 is greater than 10 %, ^{18}F-FDG PET/CT should be considered.

When a cystic lesion is detected and further characterization is required, dedicated pancreatic protocol CT and MRI are considered particularly valuable [22]. For incidentally detected cystic lesions, MRI is the method of choice proposed by the Incidental Findings Committee of the American College of Radiology due to its superior contrast resolution [23]. ^{18}F-FDG PET/CT is potentially advantageous for detecting distant disease in cases of invasive carcinoma, but its role for the characterization of cystic masses is unclear, as data are not sufficient [22]. For their

cross-sectional imaging follow-up, the currently most widely established management guidelines favor the use of contrast-enhanced MRI [24, 25]. However, some preliminary reports have shown that—for the purpose of follow-up—unenhanced MRI may be adequate [26, 27].

Imaging Features

The imaging features of the most common solid and cystic masses of the pancreas as well as their differential diagnosis will be presented in the following section. Further details of each of these lesions are discussed separately in other chapters in this book.

Solid Masses

Pancreatic ductal adenocarcinoma (PDAC) and neuroendocrine tumors (PNETs) comprise together about 90–95 % of all malignant pancreatic neoplasms [28, 29].

Adenocarcinoma: PDAC, being a predominantly hypovascular fibrotic tumor, is usually depicted as a mass of lower density (on CT) or lower SI (on MRI) compared to the adjacent, avidly enhancing parenchyma during the late arterial phase of the dynamic contrast imaging (Figs. 7.1, 7.2a–d and 7.3) [30, 31]. Additional imaging features on MRI include hypointensity on unenhanced T1-weighted and variable appearance on

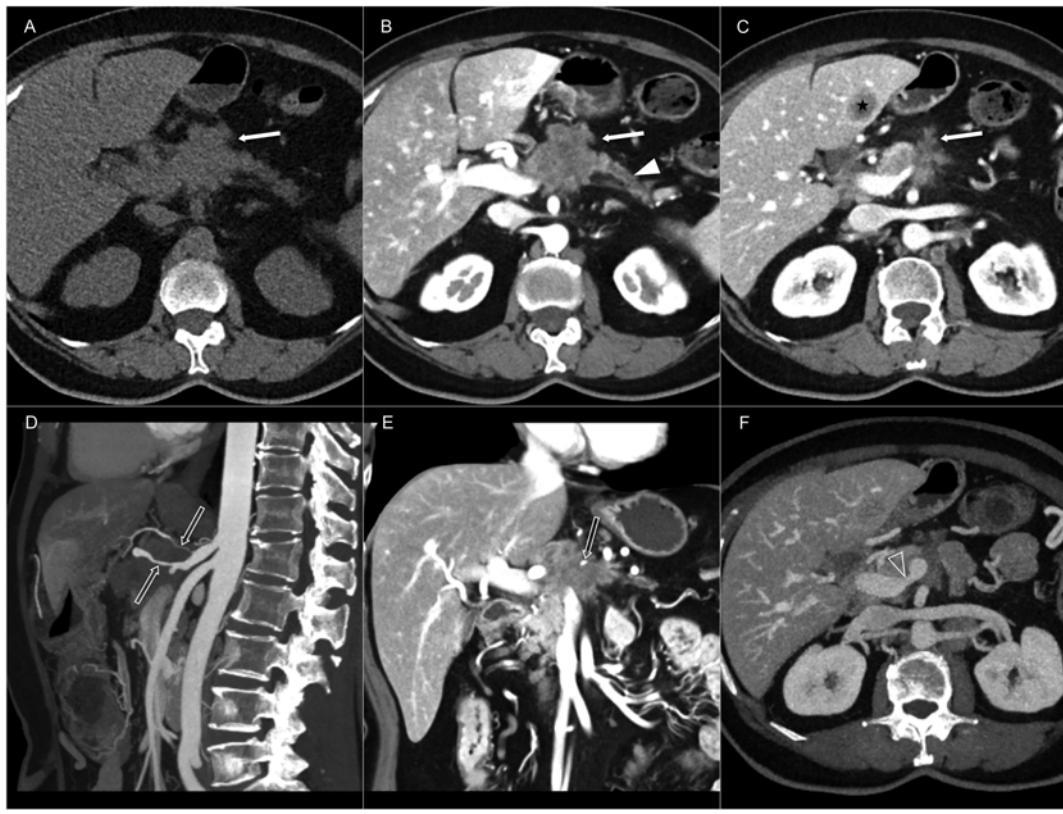

Fig. 7.1 Dedicated pancreatic protocol CT examination of a patient with a pancreatic ductal adenocarcinoma. In the dynamic contrast-enhanced (DCE) axial images [unenhanced (**a**), late arterial (**b**), and portal venous (**c**) phases], there are an ill-defined, hypovascular mass at the pancreatic body (*arrow*) with upstream parenchymal atrophy (*arrowhead*) and a hypovascular solid lesion in the left hepatic lobe (*asterisk*), compatible with a metastasis. In the sagittal MIP image (**d**) and coronal projection (**e**) (both at the late arterial phase), there are tumor encasement and stricturing of all branches of the celiac trunk (*open arrows*). In the axial MIP image of the portal venous phase (**f**), the stenosis of portomesenteric confluence (*open arrowhead*) is readily identified

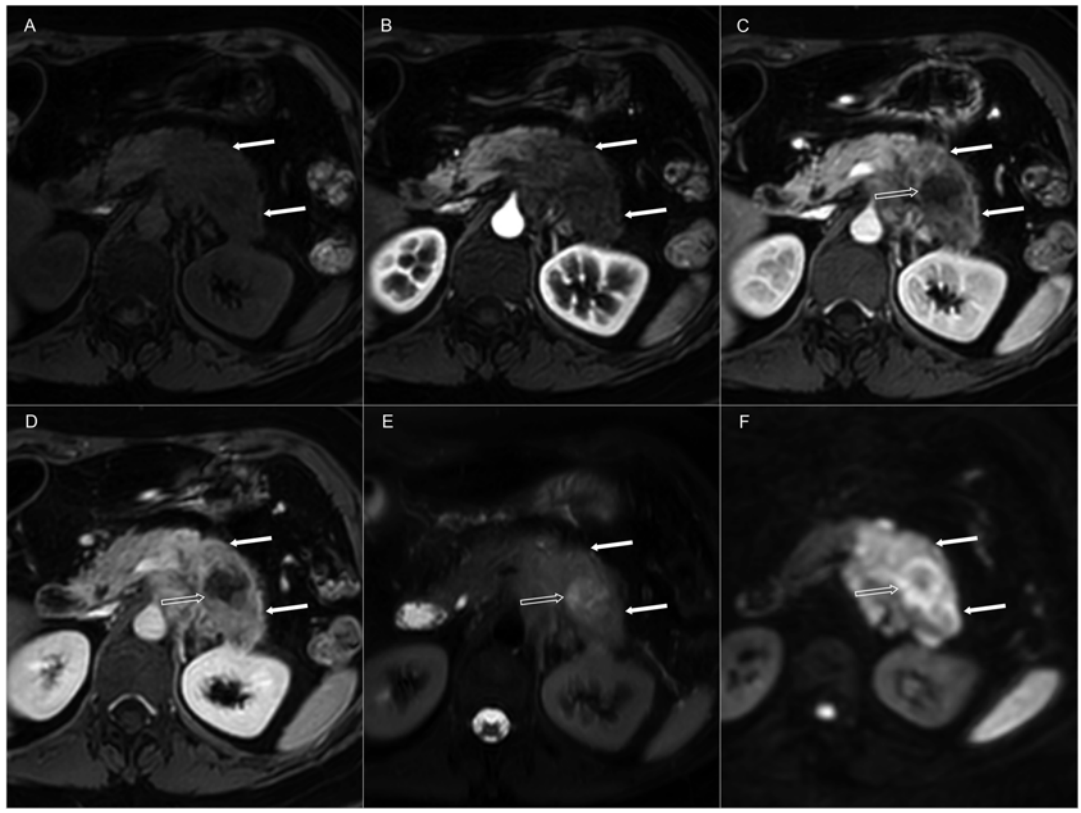

Fig. 7.2 Dedicated pancreatic protocol MRI examination of a patient with a pancreatic ductal adenocarcinoma. In the unenhanced image (**a**), the mass located at the proximal tail (arrows) has a lower signal intensity (SI) compared to the downstream normal parenchyma. The mass is hypovascular compared to the avidly enhancing parenchyma in the late arterial phase (**b**) of the DCE series and shows progressive enhancement in the portal venous (**c**) and equilibrium (**d**) phases, where even a central necrotic area (*open arrow*) is observed. Compared to the normal parenchyma, the mass has a slightly higher SI on the T2-weighted image (**e**) and a much higher SI on DWI with a high *b*-value (**f**), indicating restricted diffusion

T2-weighted sequences. On visual assessment of DWI, the lesion usually exhibits high SI on images with high *b*-values and low SI on ADC maps representing restricted diffusion (Fig. 7.2). The margins of the lesion are often not well defined and, in many cases, there are secondary signs indicating the presence of a tumor, such as main pancreatic or/and common bile duct dilation and/or abrupt cutoff, upstream obstructive pancreatitis with parenchymal atrophy or focally abnormal parenchymal contour. In about 5 % of cases, the tumor may not be distinguished from the adjacent parenchyma on CT, even when dedicated protocols are applied (Fig. 7.4) [32, 33]. In such cases, the presence of secondary tumor signs combined with a further evaluation with other methods (EUS/MRI/PET-CT) may prove helpful. For the evaluation of engagement of vessels and lymph nodes, dedicated pancreatic CT and MRI are considered equivalent [1]. However, size as a criterion of lymph node engagement has been shown not to be specific [34].

In the differential diagnosis, PDAC has to be distinguished from other solid hypovascular lesions (Table 7.1) [35]. A major diagnostic challenge is to correctly differentiate adenocarcinoma from an inflammatory pseudotumor, such as in cases of mass-forming chronic pancreatitis (CP), focal autoimmune pancreatitis (AIP), and groove pancreatitis (Fig. 7.5). In cases of mass-forming CP, MRCP is of great value when it depicts the pancreatic duct passing through the suspicious

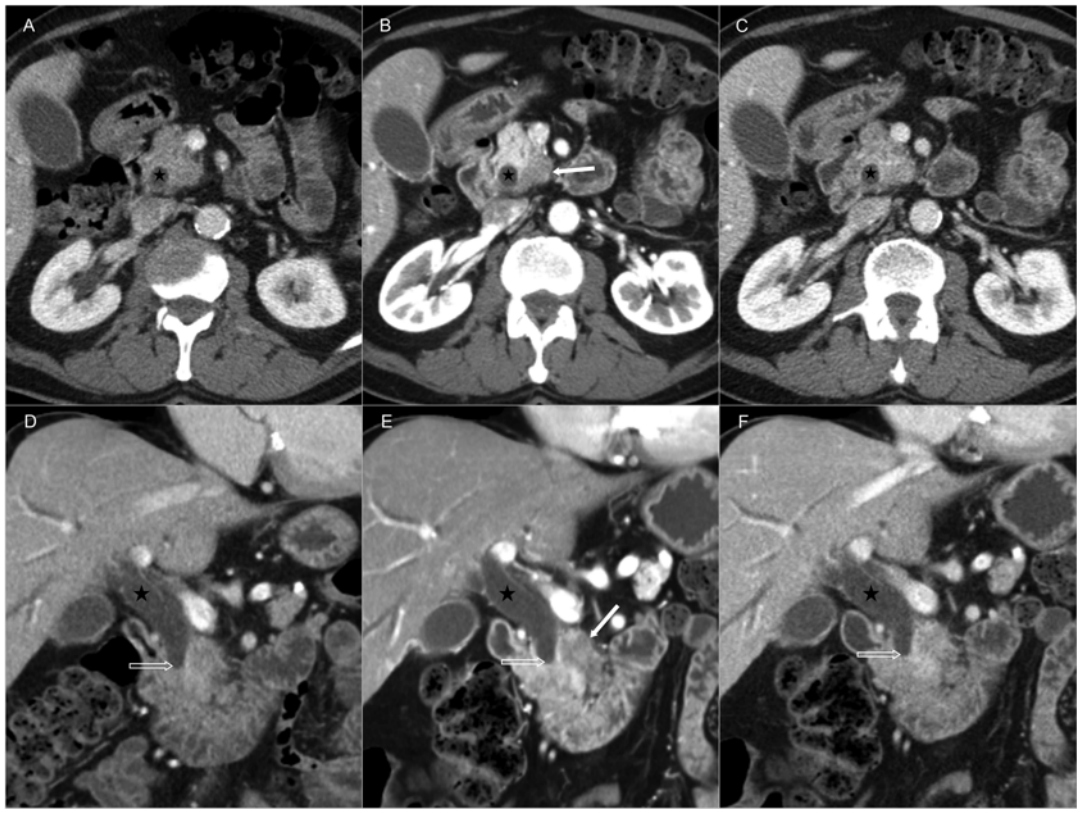

Fig. 7.3 Axial (**a**–**c**) and coronal (**d**–**f**) CT images of a patient presenting with mild pain in the upper abdomen, fatigue, and itching. The nondedicated contrast-enhanced CT protocol (**a**, **d**) performed at the emergency setting shows dilation of the common bile duct (*asterisk*) with abrupt cutoff at the level of the pancreatic head (*open arrow*) but fails to demonstrate any mass. Two days later, the patient undergoes a dedicated pancreatic protocol CT and the hypovascular mass (*arrow*) is readily identified at the pancreatic head/uncinate process in the late arterial (**b**, **e**) but not in the portal venous phase (**c**, **f**) of the DCE imaging. The lesion was a ductal adenocarcinoma, verified histopathologically after surgery (pancreatico-duodenectomy)

area, the so-called duct-penetrating sign, favoring nonmalignancy [36]. In cases of AIP, there might be a long compression of the MPD without a prominent upstream dilatation, a sausage-like appearance of the gland, and an enhancing soft-tissue halo in the peripancreatic fat as well as signs of extrapancreatic manifestation of autoimmune disease, such as in the bile duct, gallbladder, retroperitoneum, and more [37]. After appropriate cortisone therapy, there should be a partial or complete response of the radiological findings. Recently developed techniques such as CT perfusion, MRI perfusion, and DWI have shown promising results [38–41]. Particularly for DWI, the IVIM-derived parameter perfusion fraction (*f*) was shown to be significantly lower in cases of PDAC compared to CP and thus helpful for their differentiation [42, 43]. Furthermore, ^{18}F-FDG PET/CT has been reported to be able to differentiate mass-forming pancreatitis from adenocarcinoma by showing standardized uptake value (SUV) between 3 and 4 for chronic pancreatitis and >4 for PADC [44] and AIP from PDAC by demonstrating different patterns of radiotracer uptake (more commonly diffuse uptake in the pancreatic parenchyma and salivary glands observed in cases of AIP, while in cases of PDAC, there is focal accumulation in the tumor but not in the rest of the parenchyma) [45, 46].

Neuroendocrine tumors: Contrary to adenocarcinomas, PNETs are often highly vascularized

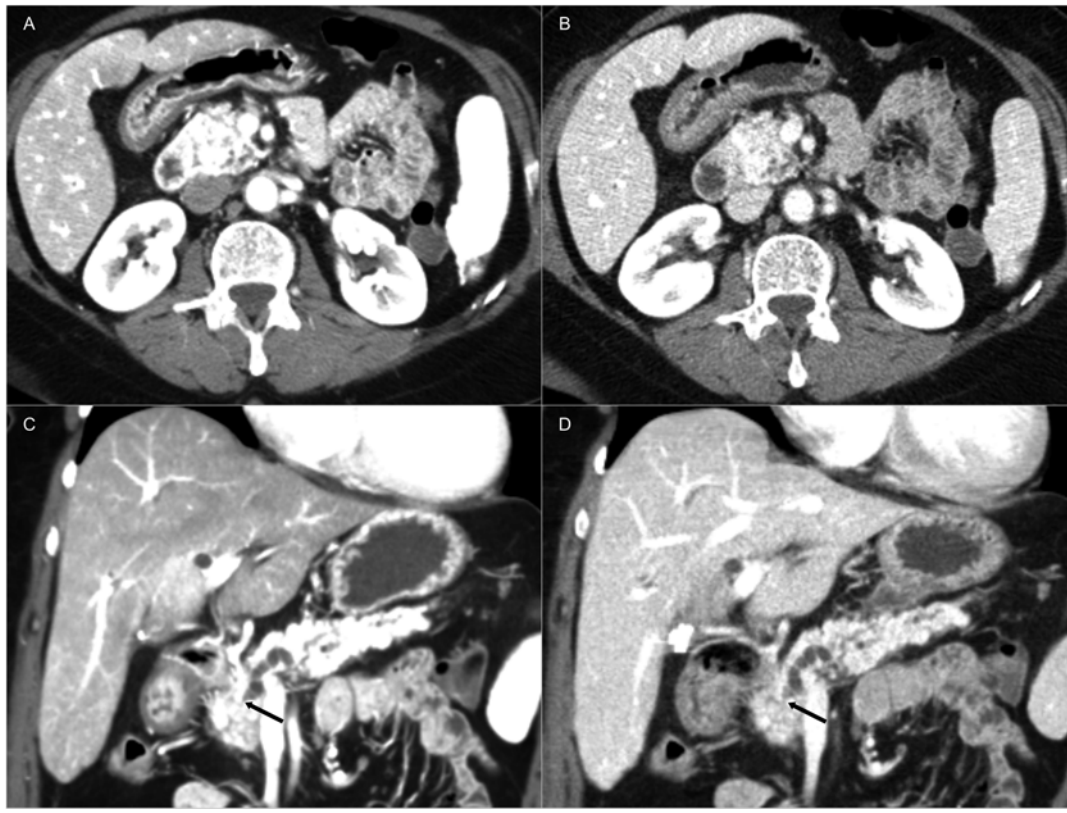

Fig. 7.4 Axial (**a**, **b**) and coronal (**c**, **d**) images of a dedicated pancreatic protocol CT of a patient presenting with fever, leukocytosis, elevated CRP, and liver function tests one month after endoscopic removal of CBD stent. The nondedicated CT protocol (not shown) performed two days earlier was not conclusive. No tumor can be visualized in the late arterial (**a**, **c**) or portal venous (**b**, **d**) phase of the DCE imaging despite the application of the dedicated protocol. However, secondary signs such as dilated main pancreatic duct in the upper part of the pancreatic head with abrupt cutoff in the upper part of the pancreatic head (*arrow*) may indicate the presence of a tumor. At histopathology after surgery, the presence of a small ductal adenocarcinoma was verified

Table 7.1 Differential diagnosis of pancreatic ductal adenocarcinoma (PDAC)

Inflammatory pseudotumors
Mass-forming chronic pancreatitis
Focal autoimmune pancreatitis
Groove pancreatitis
Nonhypervascular neuroendocrine tumors
Hypovascular metastases (e.g., lung cancer)
Lymphoma

Source: From [35]

tumors, which lead to the classical appearance of a hyperdense (on CT) or hyperintense (on MRI) mass during the late arterial phase of the dynamic contrast imaging (Fig. 7.6a–c) [47]. Nevertheless, there are exceptions with some PNETs—more often nonfunctioning—not showing hypervascularity but a rather heterogeneous contrast enhancement (Fig. 7.7) [47]. Calcifications are present in every sixth to eighth patient and are readily identified on unenhanced CT (Fig. 7.6a) [48, 49]. Additional typical imaging features on MRI include low SI on T1-weighted and high SI on T2-weighted sequences and restricted diffusion on DWI (Fig. 7.7a,e,f). Unlike adenocarcinomas, PNETs are usually well circumscribed and dilation of the MPD and/or CBD is less commonly present [50]; duct dilation, however, may be present, more often in cases of small serotonin-producing tumors [51]. Recently, it was reported that for the detection of highly differentiated PNETs, the visual assessment of DWI had the same detection rate as the

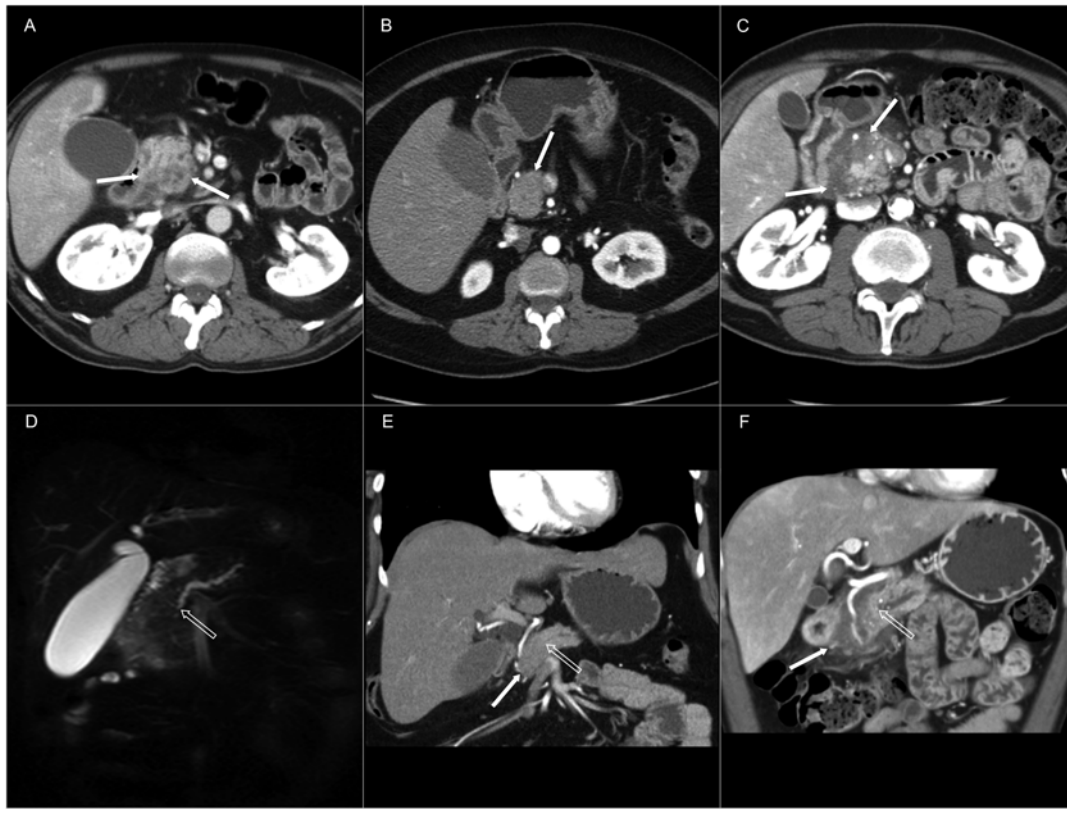

Fig. 7.5 Axial (**a**–**c**) and coronal (**d**–**f**) images of three different patients with solid hypovascular lesions (*arrows*) at the pancreatic head with secondary mild to moderate dilation of the main pancreatic duct and abrupt cutoff, simulating pancreatic ductal adenocarcinoma. The histopathological analysis after surgery showed mass-forming chronic pancreatitis in the first patient (**a**, **d**) and focal autoimmune pancreatitis in the second (**b**, **e**). In the third patient (**c**, **f**), changes of groove pancreatitis are identified radiologically (at 3-year control CT examination, no signs of malignancy had developed in the area)

contrast-enhanced MRI, in a lesion- and patient-based analysis [52]. This may prove to be of great value in cases where the intravenous injection of MRI contrast agents is contraindicated (e.g., in patients with low GFR or previous allergic reactions to gadolinium chelates).

At Octreoscan and ^{68}Ga-DOTA-SSA PET/PET-CT, PNETs exhibit, in general, high radiotracer uptake (Fig. 7.6d, e). ^{68}Ga-DOTA-SSA imaging performs better than Octreoscan [17]; however, both have lower detections rates for insulinomas compared to other PNETs [53]. Interestingly, for benign insulinomas, scintigraphy with GLP-1 analogs has shown promising initial results [54].

For the staging of PNETs, both the CT perfusion-extracted parameter blood flow and the monoexponential-based ADC calculations were shown to be significantly higher for G1 compared to G2 and G3 tumors [55–57]. In the latter report, G1 tumors were also significantly more often hypervascular, showing contrast enhancement after the intravenous injection of gadoxetic acid, compared to G2 and G3 tumors. Furthermore, the MRI perfusion-extracted parameter K^{trans} was reported to be significantly higher in G1 and G2 and could, thus, differentiate them from G3 PNETs [39]. In the differential diagnosis, PNETs have to be distinguished from other hypervascular lesions (Table 7.2) [58].

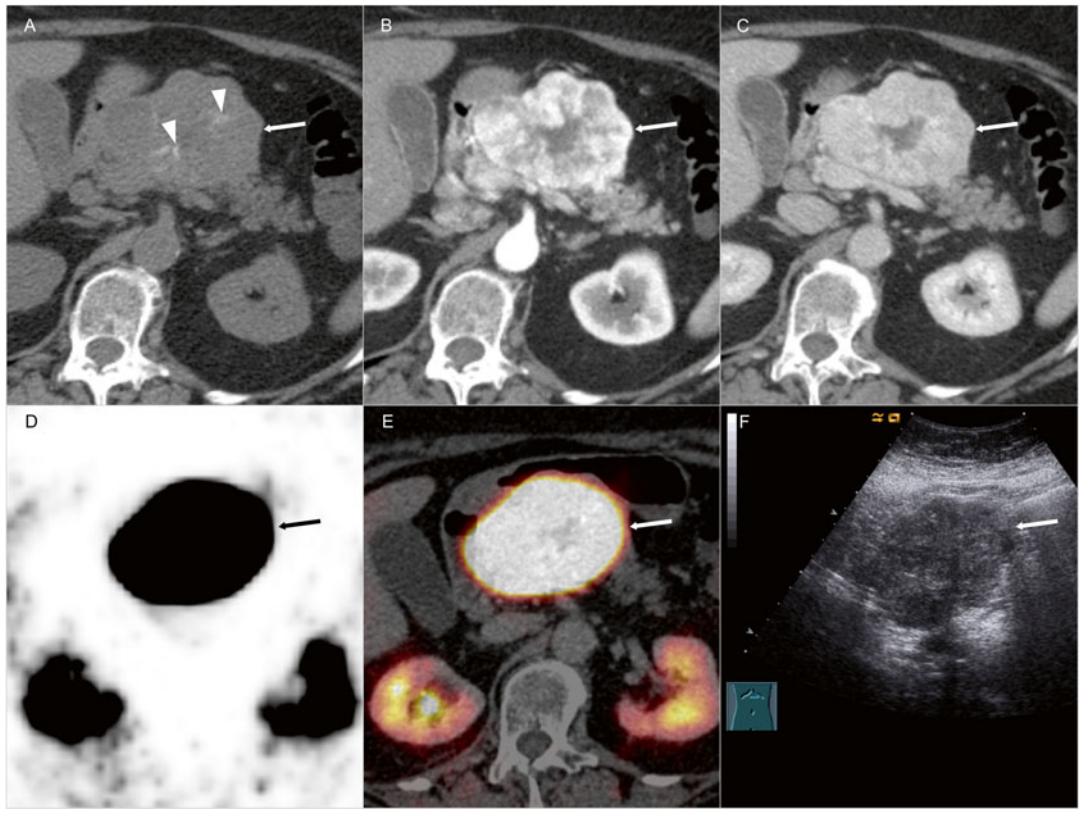

Fig. 7.6 Typical imaging findings of a patient with a neuroendocrine tumor in the pancreatic body. In the axial unenhanced CT image (**a**), the lobulated, well-defined mass (*arrow*) has central calcifications (*arrowheads*) and in the DCE imaging [late arterial (**b**) and portal venous (**c**) phase] it exhibits rapid, relatively inhomogeneous contrast enhancement. There is no upstream dilation of the main pancreatic duct. In the axial 68Ga-DOTATOC PET (**d**) and fusion 68Ga-DOTATOC PET/CT image (**e**), the lesion has very strong radiotracer uptake while at transabdominal ultrasound (**f**), it is relatively inhomogeneous and with low echogeneity

Cystic Masses

Serous cystic adenomas (SCAs), mucinous cystic neoplasms (MCNs), and intraductal papillary mucinous neoplasms (IPMNs) comprise about 90 % of all primary cystic lesions [59].

Serous Cystic Adenoma: The radiological appearance of an SCA depends on the histopathological type; it is usually classified in the microcystic (also known as polycystic) and the, much less frequent, macrocystic (also known as oligocystic) variants [60–62].

Microcystic SCAs, due to the presence of multiple, fluid-filled cysts <2 cm, separated from each other by thin septae, with the smaller cysts located centrally around fibrous tissue (central scar) and the larger ones in the periphery, have a multilobular shape with well-defined margins. The fibrous central scar can be partially calcified in up to one third of patients [63]. In about 20 % of cases, the comprising cysts are very small and the lesion can resemble a solid tumor (honeycomb pattern) [61]. More specifically on US, the cystic parts are hypoechoic while the septa and central scar are hyperechoic; in case of a honeycomb pattern, the tumor may appear entirely solid, that is, homogeneously hypoechoic with no posterior acoustic enhancement. The calcifications are depicted as centrally located

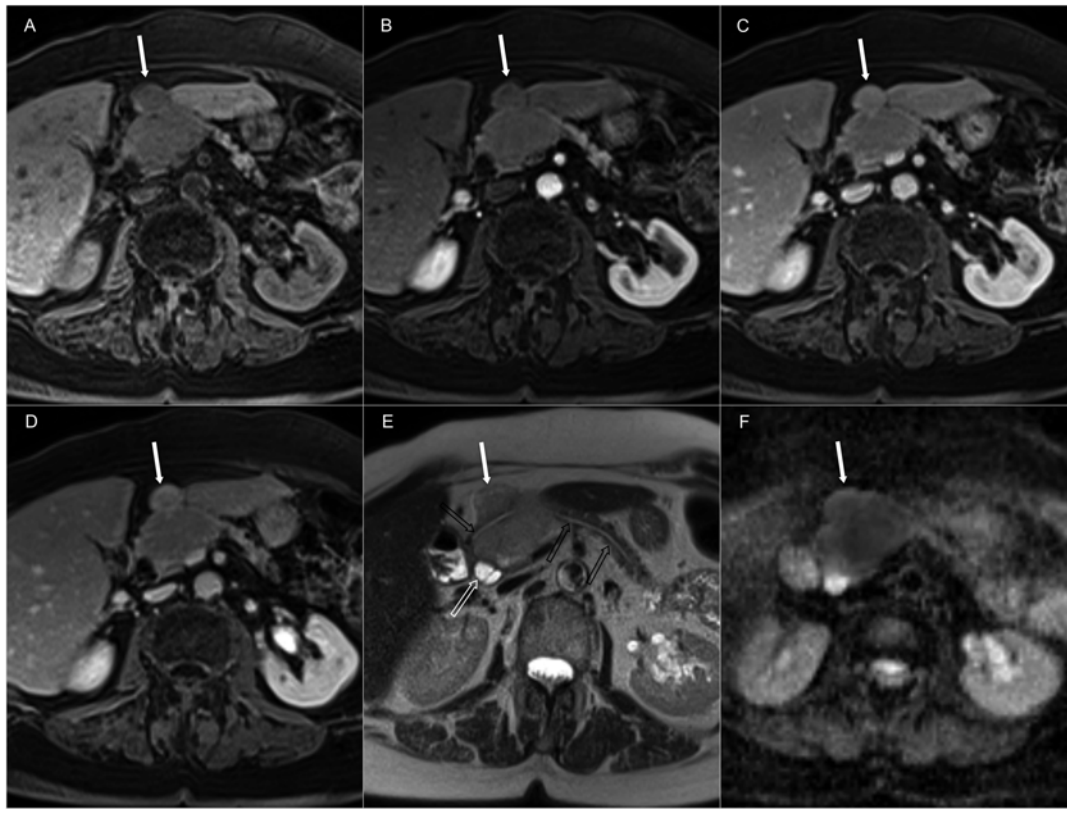

Fig. 7.7 MRI examination of a patient with a nonhypervascular neuroendocrine tumor in the proximal body of the pancreas. On fat-saturated T1-weighted images before (**a**) and post contrast (**b–d**), the tumor (*white arrow*) does not show hypervascularity, a finding more common in nonfunctioning PNETs. On the T2-weighted HASTE image (**e**), the tumor shows relatively high signal intensity and its relation to the common bile duct (*open white arrow*) and the main pancreatic duct (*open black arrows*) can easily be appreciated. On the ADC map (**f**), the lesion has markedly low signal intensity, indicating restricted diffusion

Table 7.2 Differential diagnosis of pancreatic neuroendocrine tumors (PNETs)

Exocrine tumors
Cystic: Serous cystic adenoma
Solid: Solid pseudopapillary neoplasia, acinar cell carcinoma
Hypervascular metastases
Renal cell carcinoma
Carcinoid
Medullary thyroid carcinoma
Multiple myeloma
Neurogenic
Schwannoma
Vascular
Aneurysm
Pseudoaneurysm
Arteriovenous malformation, AVM
Developmental
Intrapancreatic splenule (accessory spleen)

Source: Modified from Bhosale et al. [58]

hyperechoic structures with acoustic shadowing. On unenhanced CT, the lesion has low density and the calcifications are readily identified as central hyperdensities. On postcontrast CT, there is relatively rapid enhancement of the septa while the cystic portions remain hypodense due to the presence of nonenhancing fluid (Fig. 7.8a–c). In cases of lesions exhibiting a honeycomb pattern, the enhancement can be fairly homogeneous and, thus, closely resemble a solid tumor [64]. On T2-weighted images, the cystic portions of the lesions have a distinctly high SI while the septae

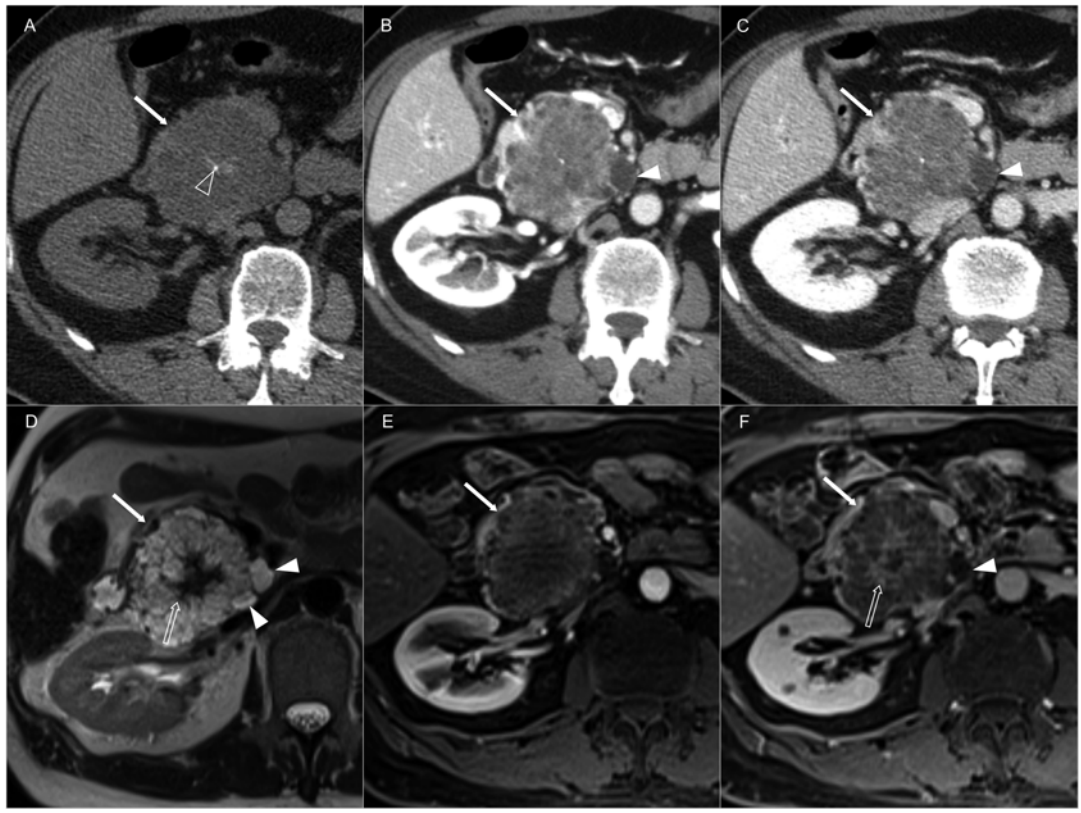

Fig. 7.8 Typical imaging findings of a patient with microcystic serous cystic adenoma. In the axial unenhanced CT image (**a**), the lesion (*arrow*) has central calcifications (*open arrowhead*) and in the DCE imaging [late arterial (**b**) and portal venous (**c**) phases], it shows relatively early, mild contrast enhancement. It is composed of multiple very small cysts in the central part and a few larger cysts in the periphery (*arrowheads*); the internal structure is much easier to appreciate in the axial T2-weighted MRI image (**d**). The central scar (*open arrow*) has a low signal intensity and in the fat-saturated T1-weighted images shows no enhancement in the later arterial phase (**e**); however, there is obvious, late enhancement in the equilibrium phase (**f**)

and fibrous scar have a low SI (Fig. 7.8d). T2-weigthed images depict fluid content, even in cases of a honeycomb pattern, due to the superb contrast resolution of T2-weighted MRI compared to CT. On unenhanced T1-weighted MRI, both the cystic and the noncystic parts have a low SI, and in cases of intralesional hemorrhage, there might be hyperintense areas. On postcontrast images, there is enhancement of the septa, in an analogous manner to postcontrast CT, and additionally, in the later phases of the dynamic imaging, the central scar may retain contrast (Fig. 7.8e, f). Compared to CT, calcifications are more difficult to detect on T1- and T2-weighted images; if present, they are depicted as areas of signal void. The lesion does not show restricted diffusion [65]. The differentiation of microcystic serous adenoma includes other solid enhancing lesions, such as PNETs and solid pseudopapillary neoplasia (SPNs) [58].

The macrocystic SCA, due to the presence of only a few number of cysts that are usually >1 cm or, sometimes, even up to several cm in size, is also multilobulated and well circumscribed [61, 66]. They do not have a central scar, calcifications, or mural nodules. On US and CT, the

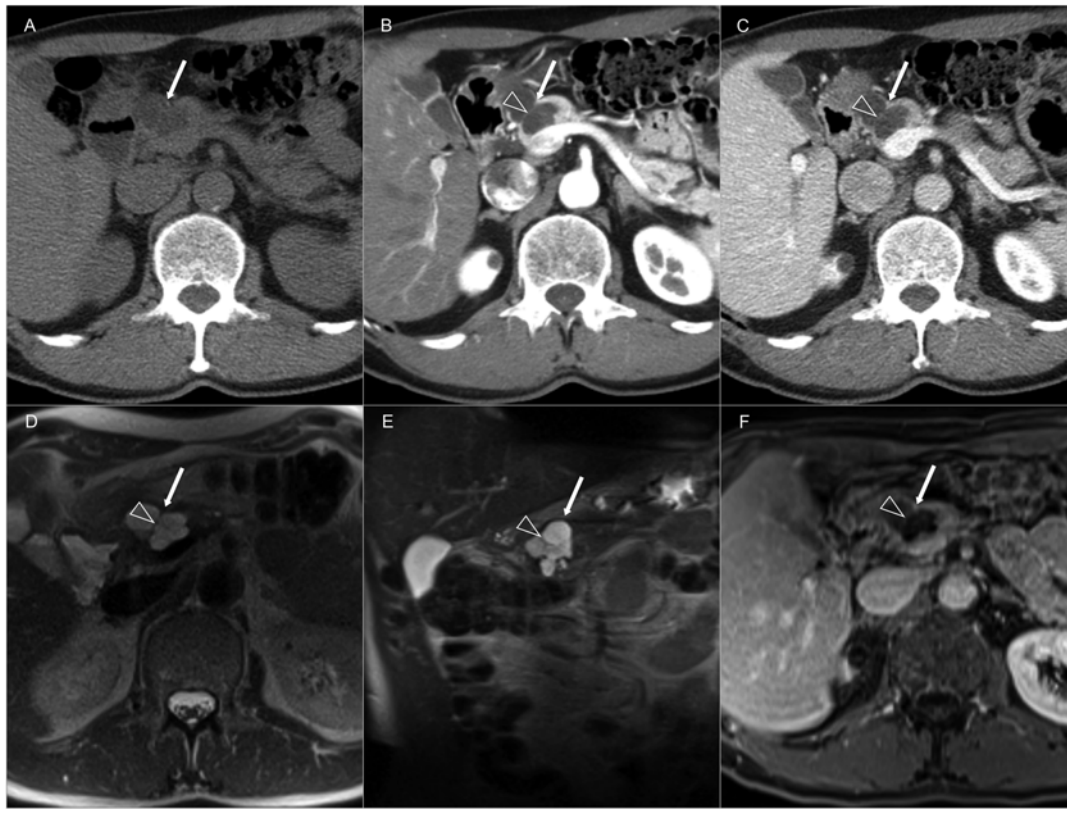

Fig. 7.9 Typical imaging findings of a patient with an oligocystic serous cystic adenoma. In the axial unenhanced CT image (**a**), the lesion in the pancreatic neck (*arrow*) has no calcifications. In the axial DCE imaging [late arterial (**b**) and portal venous (**c**) phases], there are few, very thin internal septations (*arrowhead*), which are more easily appreciated on T2-weighted sequences [axial (**d**) and coronal (**e**) T2-weighted images]. The lesion is comprised of a few cysts, larger in size compared to microcystic SCAs (Fig. 7.8) and there is no upstream dilation of the main pancreatic duct. In the postcontrast fat-saturated T1-weighted image (**f**), there are no signs of cyst wall thickening, nodularity, or abnormal enhancement

lesions have a fairly homogeneous cystic appearance with low echogeneity (respectively, density) and high SI on T2- and low SI on unenhanced T1-weighted MRI (Fig. 7.9). The few septa may be recognizable on US or postcontrast CT but are more readily visible on T2- and postcontrast T1-weighted images, due to the superb contrast resolution (Fig. 7.9d–f). In contrast to their microcystic counterparts, macrocystic SCAs may resemble MCNs or side-branch IPMNs, and their differentiation based on imaging features is not always possible, sometimes necessitating further workup (Fig. 7.10) [67, 68]. Furthermore, they need to be differentiated from pseudocysts and SPNs [61].

None of the two types of SCAs show communication with the MPD.

Mucinous Cystic Neoplasm: MCNs comprise a group of mucin-producing, cystic lesions with a varying grade of malignant potential, that is, from completely benign to invasive carcinoma [69–72]. The lesions are located in 75 % of cases in the body and tail of the pancreas [73]. They are

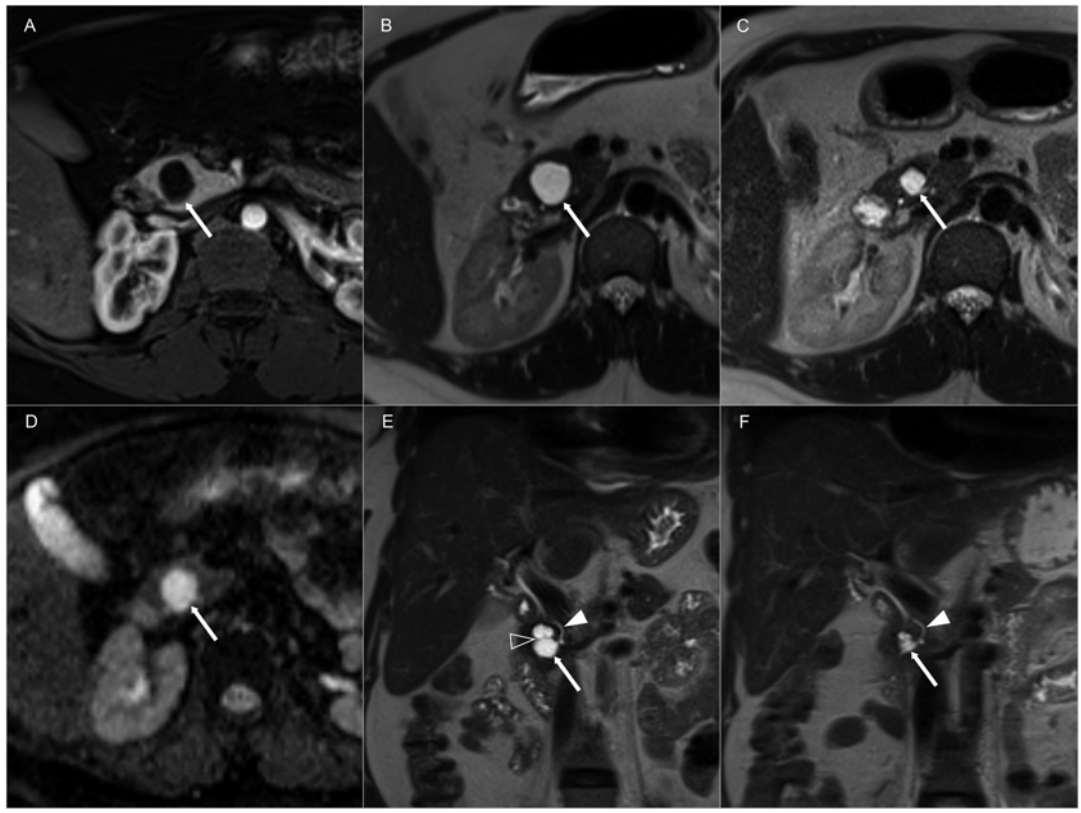

Fig. 7.10 MRI images of a patient with a cystic lesion at the pancreatic head at two different occasions. The lesion (*arrow*) shows no contrast enhancement (**a**), unrestricted diffusion on the ADC map (**d**), and one very thin internal septation (*open arrowhead*), easily identified on T2-weighted sequences [axial (**b**) and coronal (**e**) T2-weighted images]. The normal main pancreatic duct (*arrowhead*) is very close to the lesion, giving the impression of communicating with the cystic lesion. The lesion size increased from 1.2 (**c**, **f**) to 2.5 cm (**b**, **e**) during an interval of 18 months and, as there was suspicion of communication with the main pancreatic duct, it was considered a rapidly growing side-brunch IPMN. At histopathology after surgery, the lesion was shown to be an oligocystic serous cystic adenoma

encapsulated, well circumscribed, usually unilocular or, less commonly, multilocular (20 %) [60]. The presence of a thick capsule, internal septa, and solid components as well as peripheral or septal calcifications increases the risk of underlying malignancy [69, 74]. Relatively rarely, there might be intralesional hemorrhage. The lesion does not communicate with the MPD.

On US, the lesion has low echogeneity with posterior acoustic enhancement and can be homogeneous or heterogeneous, depending on the nature of its contents. A thickened capsule, the presence of septa, solid components, and, rarely, hemorrhagic products can be visualized as echogenic structures. Accordingly, calcifications can also be detected as echogenic structures with posterior acoustic shadow. On unenhanced CT, the lesion is usually hypodense and the internal architecture is not easy to delineate in detail. Calcifications in the periphery and/or in the central parts are readily identified (Fig. 7.11) [75]. On MRI, the internal architecture is easier to

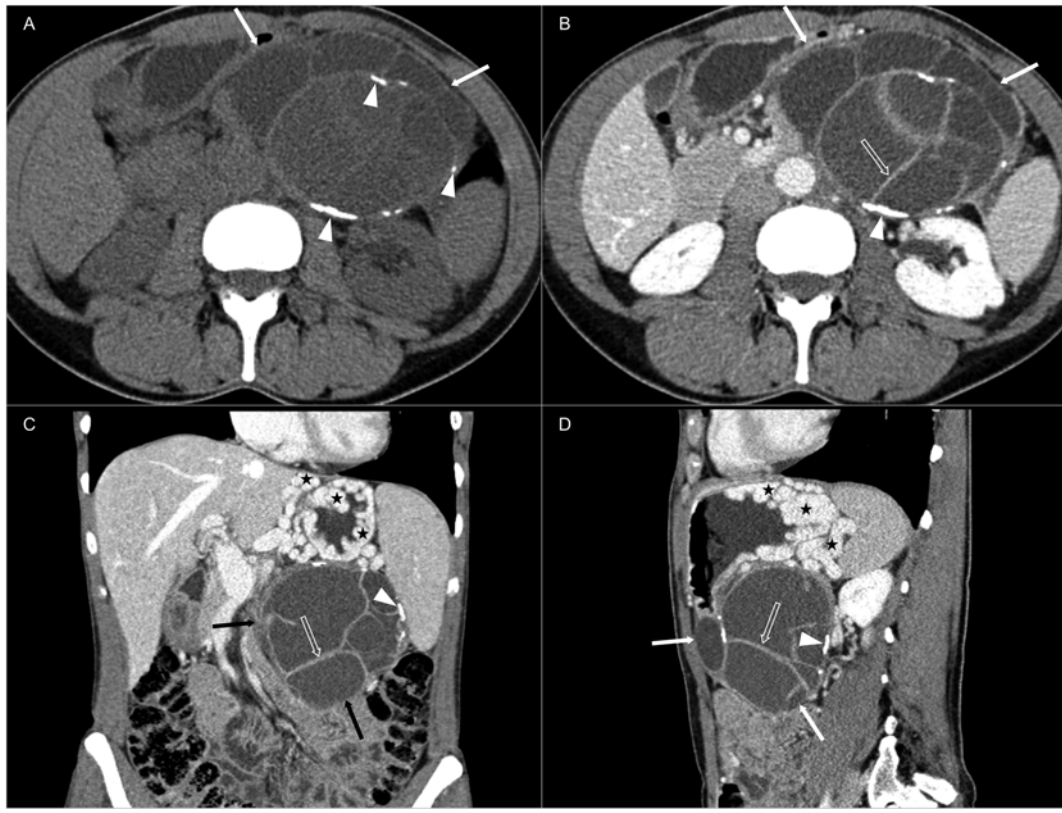

Fig. 7.11 Imaging features of a female patient with a large mucinous cystic neoplasm at the pancreatic body and tail on unenhanced (**a**) and contrast-enhanced (**b**–**d**) CT. The lesion (*arrows*) is multilocular, has peripheral and septal calcifications (*arrowheads*), and has relatively thick, contrast-enhancing internal septations (*open arrow*). Due to compression of the splenic vein, an extended network of varices (*asterisks*) has developed in the stomach and abdomen's left upper quadrant. On histopathology after surgery, there was up to high-grade dysplasia but no signs of invasive carcinoma

depict. On T2-weighted images, the lesion has markedly high SI, while the capsule, septations, mural nodule, and possible hemorrhagic components have low SI (Fig. 7.12). On unenhanced T1-weighted images, the lesion is of variable SI depending on the contents. On postcontrast CT and MRI images, there is enhancement of the capsule as well as of internal septations and/or solid components, when present, making the internal architecture of the lesion better delineated (Figs. 7.11 and 7.12). In general, the lesions do not show restricted diffusion, except when there are thickened septations and/or mural nodularity/solid components.

The major differential diagnosis of MCN includes side-branch IPMN, oligocystic SCA, and pseudocyst. Other much more uncommon lesions are cystic lymphangioma, lymphoepithelial cysts, retention cysts, as well as cystic-degenerated PDACs or PNETs.

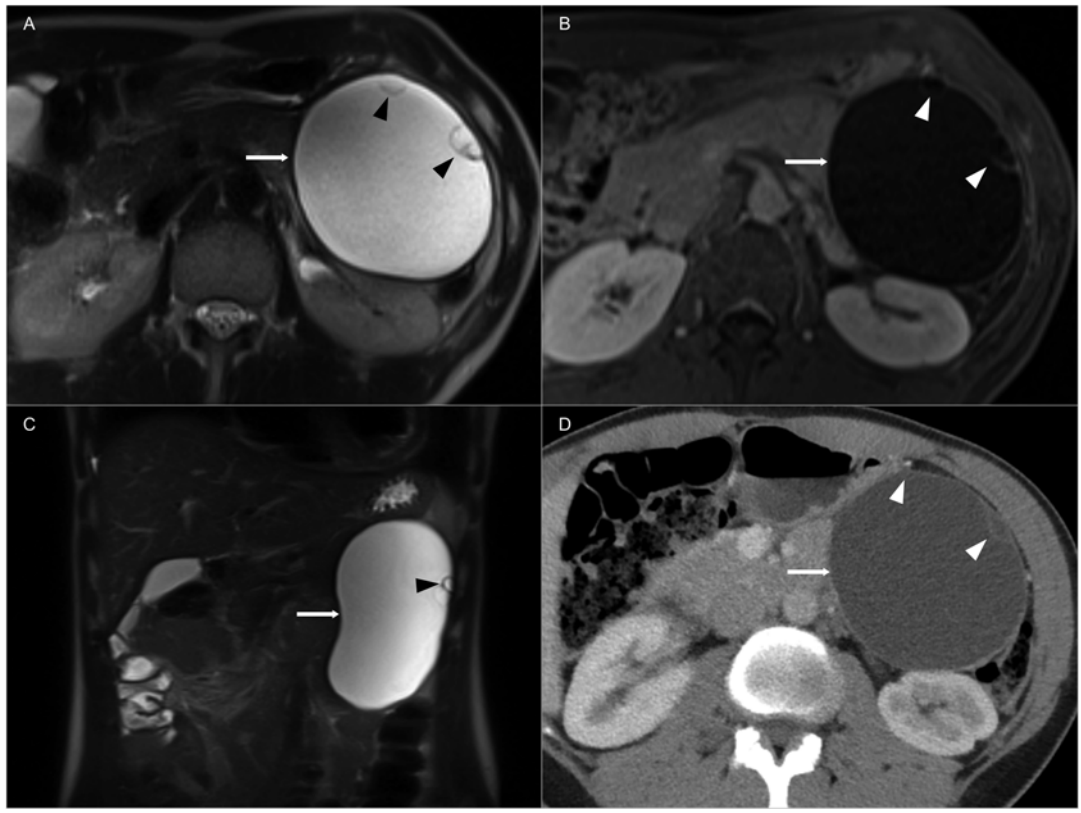

Fig. 7.12 Typical imaging findings of a female patient with a large mucinous cystic neoplasm at the pancreatic tail on MRI (**a**–**c**) and CT (**d**). The lesion (*arrow*) is unilocular with homogeneous content and two mural nodules (*arrowheads*), more easily appreciated on T2-weighted sequences [axial (**a**) and coronal (**c**) T2-weighted images]. No signs of malignancy were identified on histopathology after surgery

Intraductal Papillary Mucinous Neoplasms

These lesions are classified into the main-duct (MD) type, which can be diffuse or segmental, side-branch duct (SB) type, or mixed-type IPMN [76]. There is a varying degree of dysplasia (from mild to moderate to high dysplasia/carcinoma in situ) or even invasive carcinoma. Many authors have described various findings that increase the risk of malignancy in cases of IPMNs. Among these are the degree of MPD widening (when the diameter is 5–9 mm, it is reported to be a worrisome feature and when ≥10 mm is a high-risk finding), the existence of mural nodules/solid components, wall thickening, enhancement of the ductal wall, invasion of adjacent structures, and dilation of the CBD as well as—only in cases of SB type—progressively increasing size or size >3 cm [24, 25, 77–83]. All of the above-

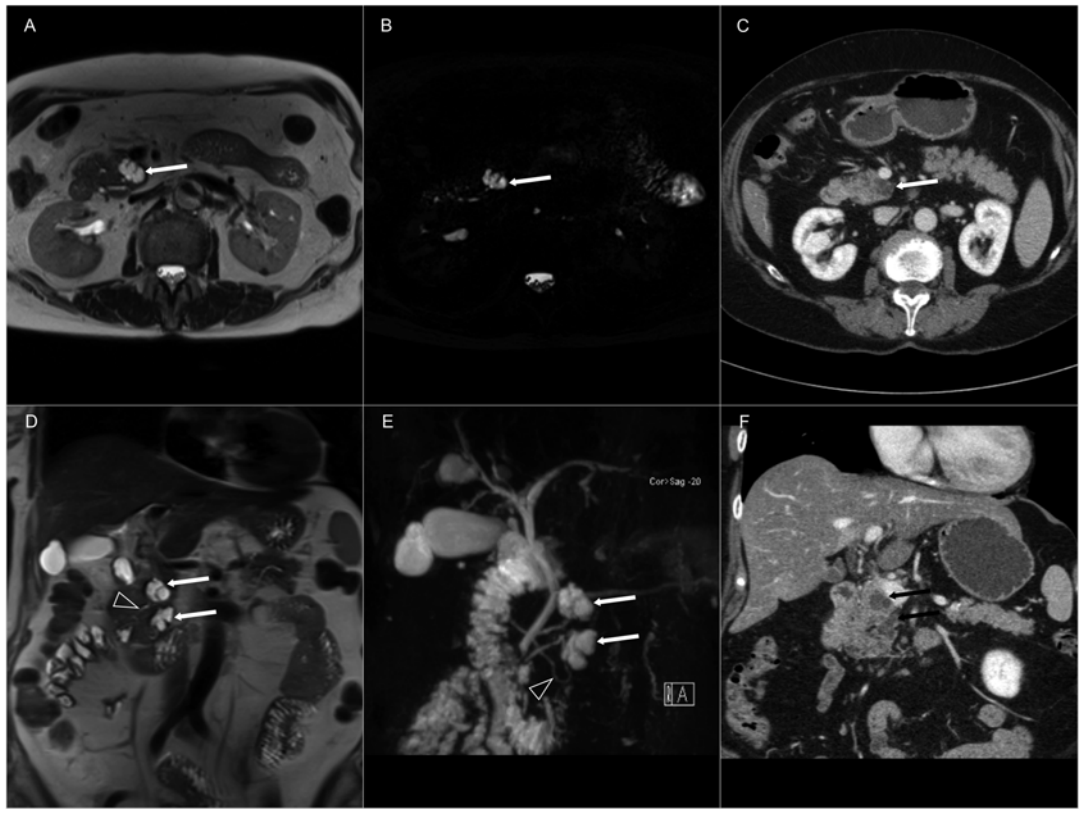

Fig. 7.13 Typical imaging findings of a patient with two side-branch IPMN lesions at the pancreatic head and uncinate process, respectively. Both lesions (*arrows*) are multilocular and lobulated, have thin internal septations, and communicate with the pancreatic ductal system (*arrowhead*), which is easier to demonstrate on the T2-weighted sequences [axial (**a**) and coronal (**d**) images) and especially on MRCP [axial thin-slice (**b**) and coronal MIP (**e**) images] compared to postcontrast CT [axial (**c**) and coronal (**f**) images]

described findings have to be carefully evaluated and taken into account, but it is advisable to avoid relying dogmatically on these predicting factors on an individual basis, as there exists no universally applicable rule [67]. SB- and mixed-type IPMNs communicate with the MPD, a key feature for their differentiation from all other cystic neoplasms.

On US, there is dilation of the MPD or a well-defined hypoechoic lesion with posterior acoustic enhancement near the MPD, in cases of MD- or SB-IPMN, respectively. The communication of the SB-IPMN with the MPD is difficult to demonstrate. On both CT and MRI, SB-IPMN is depicted as a well-defined lesion of low density (CT) or intensity (MRI) communicating or lying

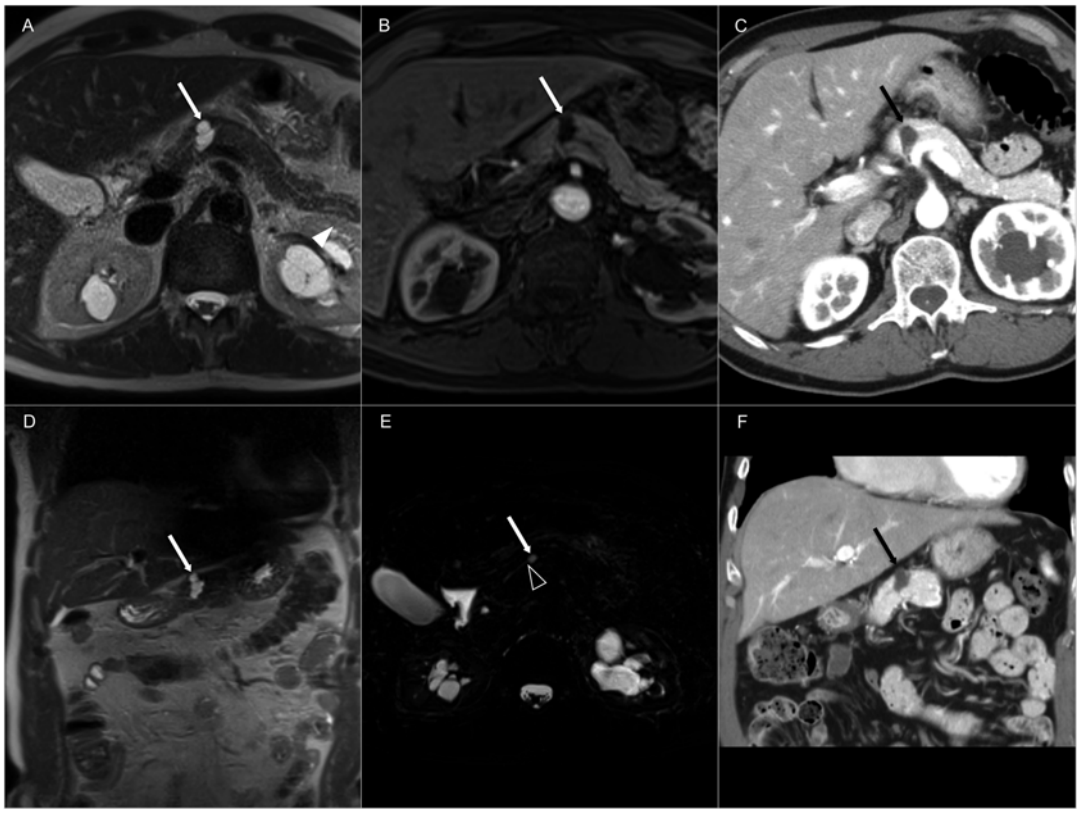

Fig. 7.14 Typical imaging findings of a patient with a side-branch IPMN at the pancreatic body on MRI (**a**, **b**, **d**, **e**) and CT (**c**, **f**). The lesion (*arrow*) has a slightly lobular contour, has a couple of thin internal septations, and shows communication with the pancreatic ductal system (*arrowhead*), nicely depicted on the thin-slice axial MRCP image (**e**). No pathological cyst wall enhancement or nodularity is seen on postcontrast images (**b**, **c**, **f**)

very near the MPD, sometimes with a typical appearance of a "cluster of grapes" (Figs. 7.13 and 7.14). MRI, and especially MRCP, is more reliable in demonstrating the communication to MPD compared to CT (Fig. 7.14e) [84]. Accordingly on both CT and MRI, MD-IPMN is depicted as a dilation of the duct, either diffusely or segmentally. Mixed-type has imaging findings of both MD- and SB-IPMN (Fig. 7.15). For all types, signs suspicious of malignancy, as described earlier in the same section, can be shown on pre- and/or postcontrast image series. The differential diagnosis of SB-IPMN includes, mainly, MCN, oligocystic SCA, and pseudocyst, while for MD-IPMN chronic pancreatitis, which may also present with diffuse or segmental dilation of the MPD [85]. For the differentiation of benign from malignant IPMNs, the DWI-based

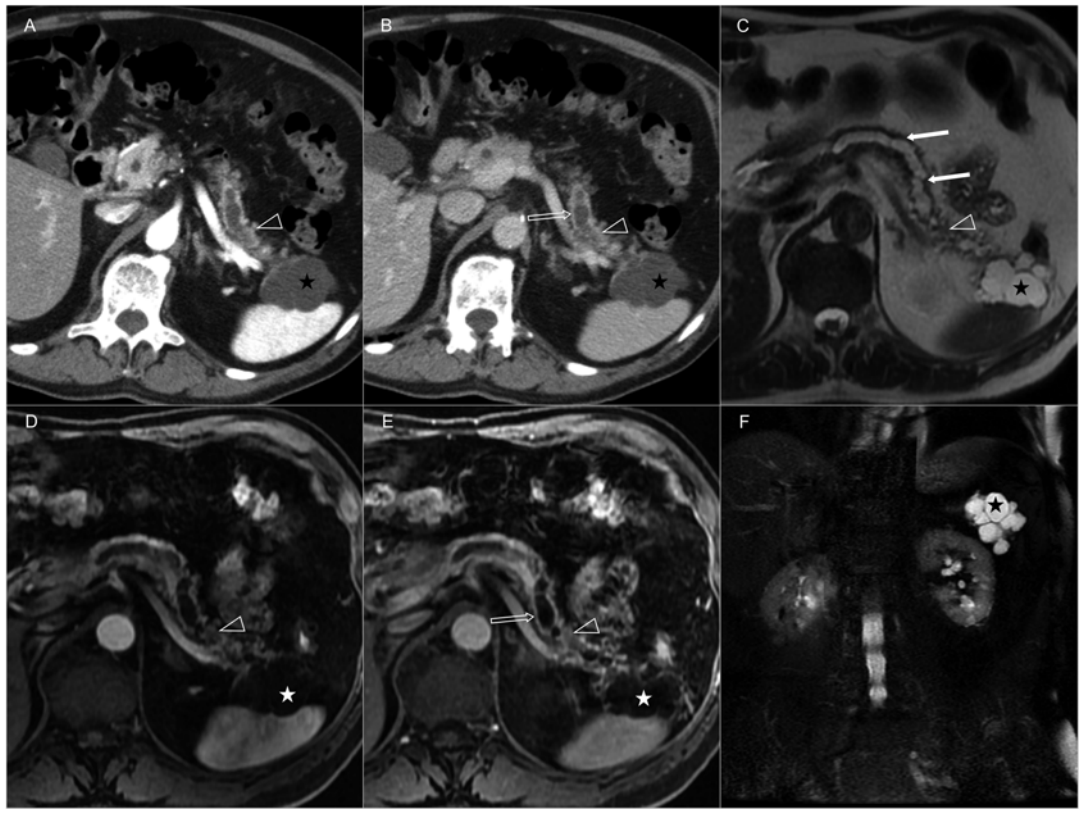

Fig. 7.15 Imaging features of a patient with mixed-type IPMN on axial CT (**a**, **b**) and MRI (**c**–**f**) images. There is a relatively smooth dilation of the main pancreatic duct (*arrow*) and a multilocular, lobulated cystic lesion (*asterisk*) at the tip of the pancreatic tail. In the tail, the wall of the main pancreatic duct shows contrast enhancement (*open arrow*) and a solid component (*arrowhead*), findings suspicious of malignancy. At histopathology after surgery, there was a varying degree of dysplasia and focal areas of invasive carcinoma

IVIM model and ^{18}F-FDG PET/CT have been reported to have promising results [43, 86].

References

1. Tempero MA, Arnoletti JP, Behrman SW, Ben-Josef E, Benson 3rd AB, Casper ES, et al. National Comprehensive Cancer Networks. Pancreatic Adenocarcinoma, version 2.2012: featured updates to the NCCN guidelines. J Natl Compr Canc Netw. 2012;10:703–13.
2. Schueller G, Schima W, Schueller-Weidekamm C, Weber M, Stift A, Gnant M, et al. Multidetector CT of pancreas: effects of contrast material flow rate and individualized scan delay on enhancement of pancreas and tumor contrast. Radiology. 2006;241:441–8.
3. Prokesch RW, Chow LC, Beaulieu CF, Nino-Murcia M, Mindelzun RE, Bammer R, et al. Local staging of pancreatic carcinoma with multi-detector row CT: use of curved planar reformations initial experience. Radiology. 2002;225:759–65.
4. Horton KM, Fishman EK. Volume-rendered 3D CT of the mesenteric vasculature: normal anatomy, anatomic variants, and pathologic conditions. Radiographics. 2002;22:161–72.
5. Horton KM. Multidetector CT, and three-dimensional imaging of the pancreas: state of the art. J Gastrointest Surg. 2002;6:126–8.
6. Horton KM, Fishman EK. Multidetector CT angiography of pancreatic carcinoma: part 2, evaluation of venous involvement. AJR Am J Roentgenol. 2002;178:833–6.
7. Horton KM, Fishman EK. Multidetector CT angiography of pancreatic carcinoma: part I, evaluation of arterial involvement. AJR Am J Roentgenol. 2002;178:827–31.
8. Kambadakone AR, Sahani DV. Body perfusion CT: technique, clinical applications, and advances. Radiol Clin North Am. 2009;47:161–78. doi:10.1016/j.rcl.2008.11.003.

9. Tirkes T, Menias CO, Sandrasegaran K. MR imaging techniques for pancreas. Radiol Clin North Am. 2012;50:379–93. doi:10.1016/j.rcl.2012.03.003.
10. Le Bihan D. Molecular diffusion, tissue microdynamics and microstructure. NMR Biomed. 1995;8: 375–86.
11. Koh DM, Collins DJ, Orton MR. Intravoxel incoherent motion in body diffusion-weighted MRI: reality and challenges. AJR Am J Roentgenol. 2011;196:1351–61. doi:10.2214/AJR.10.5515.
12. Song HK, Dougherty L. Dynamic MRI with projection reconstruction and KWIC processing for simultaneous high spatial and temporal resolution. Magn Reson Med. 2004;52:815–24.
13. Tofts PS, Brix G, Buckley DL, Evelhoch JL, Henderson E, Knopp MV, et al. Estimating kinetic parameters from dynamic contrast-enhanced T(1)-weighted MRI of a diffusable tracer: standardized quantities and symbols. J Magn Reson Imaging. 1999;10:223–32.
14. Sandrasegaran K. Functional MR, imaging of the abdomen. Radiol Clin North Am. 2014;52:883–903. doi:10.1016/j.rcl.2014.02.018.
15. Badea R, Seicean A, Diaconu B, Stan-Iuga R, Sparchez Z, Tantau M, et al. Contrast-enhanced ultrasound of the pancreas—a method beyond its potential or a new diagnostic standard? J Gastrointestin Liver Dis. 2009;18:237–42.
16. Kitano M, Kudo M, Sakamoto H, Komaki T. Endoscopic ultrasonography and contrast-enhanced endoscopic ultrasonography. Pancreatology. 2011;11 Suppl 2:28–33. doi:10.1159/000323493.
17. van Essen M, Sundin A, Krenning EP, Kwekkeboom DJ. Neuroendocrine tumours: the role of imaging for diagnosis and therapy. Nat Rev Endocrinol. 2014;10:102–14. doi:10.1038/nrendo.2013.246.
18. Rufini V, Baum RP, Castaldi P, Treglia G, De Gaetano AM, Carreras C, et al. Role of PET/CT in the functional imaging of endocrine pancreatic tumors. Abdom Imaging. 2012;37:1004–20. doi:10.1007/s00261-012-9871-9.
19. Nensa F, Beiderwellen K, Heusch P, Wetter A. Clinical applications of PET/MR: current status and future perspectives. Diagn Interv Radiol. 2014;20(5):438–47. doi:10.5152/dir.14008.
20. Schima W, Függer R, Schober E, Oettl C, Wamser P, Grabenwöger F, et al. Diagnosis and staging of pancreatic cancer: comparison of mangafodipir trisodium-enhanced MR imaging and contrast-enhanced helical hydro-CT. AJR Am J Roentgenol. 2002;179:717–24.
21. Schima W, Ba-Ssalamah A, Goetzinger P, Scharitzer M, Koelblinger C. State-of-the-art magnetic resonance imaging of pancreatic cancer. Top Magn Reson Imaging. 2007;18:421–9. doi:10.1097/rmr.0b013e31816459e0.
22. Sahani DV, Kambadakone A, Macari M, Takahashi N, Chari S, Fernandez-del Castillo C. Diagnosis and management of cystic pancreatic lesions. AJR Am J Roentgenol. 2013;200:343–54. doi:10.2214/AJR.12.8862.
23. Berland LL, Silverman SG, Gore RM, Mayo-Smith WW, Megibow AJ, Yee J, et al. Managing incidental findings on abdominal CT: white paper of the ACR Incidental Findings Committee. J Am Coll Radiol. 2010;7:754–73. doi:10.1016/j.jacr.2010.06.013.
24. Tanaka M, Fernández-del Castillo C, Adsay V, Chari S, Falconi M, Jang JY, et al. International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas. Pancreatology. 2012;12:183–97. doi:10.1016/j.pan.2012.04.004.
25. Del Chiaro M, Verbeke C, Salvia R, Klöppel G, Werner J, McKay C, et al. European experts' consensus statement on cystic tumours of the pancreas. Dig Liver Dis. 2013;45:703–11. doi:10.1016/j.dld.2013.01.010.
26. Macari M, Lee T, Kim S, Jacobs S, Megibow AJ, Hajdu C, et al. Is gadolinium necessary for MRI follow-up evaluation of cystic lesions in the pancreas? Preliminary results. AJR Am J Roentgenol. 2009;192:159–64. doi:10.2214/AJR.08.1068.
27. Nougaret S, Reinhold C, Chong J, Escal L, Mercier G, Fabre JM, et al. Incidental pancreatic cysts: natural history and diagnostic accuracy of a limited serial pancreatic cyst MRI protocol. Eur Radiol. 2014;24:1020–9. doi:10.1007/s00330-014-3112-2.
28. Saif MW. Pancreatic neoplasm in 2011: an update. JOP. 2011;12:316–21.
29. Oberg K. Pancreatic endocrine tumors. Semin Oncol. 2010;37:594–618. doi:10.1053/j.seminoncol.2010.10.014.
30. Horton KM, Fishman EK. Adenocarcinoma of the pancreas: CT imaging. Radiol Clin North Am. 2002;40:1263–72.
31. Miller FH, Rini NJ, Keppke AL. MRI of adenocarcinoma of the pancreas. AJR Am J Roentgenol. 2006;187:W365–74.
32. Kim JH, Park SH, Yu ES, Kim MH, Kim J, Byun JH, et al. Visually isoattenuating pancreatic adenocarcinoma at dynamic-enhanced CT: frequency, clinical and pathologic characteristics, and diagnosis at imaging examinations. Radiology. 2010;257:87–96. doi:10.1148/radiol.10100015.
33. Prokesch RW, Schima W, Chow LC, Jeffrey RB. Multidetector CT of pancreatic adenocarcinoma: diagnostic advances and therapeutic relevance. Eur Radiol. 2003;13:2147–54.
34. Valls C, Andía E, Sanchez A, Fabregat J, Pozuelo O, Quintero JC, et al. Dual-phase helical CT of pancreatic adenocarcinoma: assessment of resectability before surgery. AJR Am J Roentgenol. 2002;178:821–6.
35. Coakley FV, Hanley-Knutson K, Mongan J, Barajas R, Bucknor M, Qayyum A. Pancreatic imaging mimics: part 1, imaging mimics of pancreatic adenocarcinoma. AJR Am J Roentgenol. 2012;199:301–8. doi:10.2214/AJR.11.7907.
36. Ichikawa T, Sou H, Araki T, Arbab AS, Yoshikawa T, Ishigame K, et al. Duct-penetrating sign at MRCP: usefulness for differentiating inflammatory pancreatic mass from pancreatic carcinomas. Radiology. 2001;221:107–16.
37. Sahani DV, Sainani NI, Deshpande V, Shaikh MS, Frinkelberg DL, Fernandez-del Castillo C. Autoimmune pancreatitis: disease evolution, stag-

ing, response assessment, and CT features that predict response to corticosteroid therapy. Radiology. 2009;250:118–29. doi:10.1148/radiol.2493080279.
38. Lu N, Feng XY, Hao SJ, Liang ZH, Jin C, Qiang JW, et al. 64-slice CT perfusion imaging of pancreatic adenocarcinoma and mass-forming chronic pancreatitis. Acad Radiol. 2011;18:81–8. doi:10.1016/j.acra.2010.07.012.
39. Kim JH, Lee JM, Park JH, Kim SC, Joo I, Han JK, et al. Solid pancreatic lesions: characterization by using timing bolus dynamic contrast-enhanced MR imaging assessment—a preliminary study. Radiology. 2013;266:185–96. doi:10.1148/radiol.12120111.
40. Fattahi R, Balci NC, Perman WH, Hsueh EC, Alkaade S, Havlioglu N, et al. Pancreatic diffusion-weighted imaging (DWI): comparison between mass-forming focal pancreatitis (FP), pancreatic cancer (PC), and normal pancreas. J Magn Reson Imaging. 2009;29:350–6. doi:10.1002/jmri.21651.
41. Lee SS, Byun JH, Park BJ, Park SH, Kim N, Park B, et al. Quantitative analysis of diffusion-weighted magnetic resonance imaging of the pancreas: usefulness in characterizing solid pancreatic masses. J Magn Reson Imaging. 2008;28:928–36. doi:10.1002/jmri.21508.
42. Klauss M, Lemke A, Grünberg K, Simon D, Re TJ, Wente MN, et al. Intravoxel incoherent motion MRI for the differentiation between mass forming chronic pancreatitis and pancreatic carcinoma. Invest Radiol. 2011;46:57–63. doi:10.1097/RLI.0b013e3181fb3bf2.
43. Kang KM, Lee JM, Yoon JH, Kiefer B, Han JK, Choi BI. Intravoxel incoherent motion diffusion-weighted MR imaging for characterization of focal pancreatic lesions. Radiology. 2014;270:444–53. doi:10.1148/radiol.13122712.
44. Imdahl A, Nitzsche E, Krautmann F, Högerle S, Boos S, Einert A, et al. Evaluation of positron emission tomography with 2-[18F]fluoro-2-deoxy-D-glucose for the differentiation of chronic pancreatitis and pancreatic cancer. Br J Surg. 1999;86:194–9.
45. Lee TY, Kim MH, do Park H, Seo DW, Lee SK, Kim JS, et al. Utility of 18F-FDG PET/CT for differentiation of autoimmune pancreatitis with atypical pancreatic imaging findings from pancreatic cancer. AJR Am J Roentgenol. 2009;193:343–8. doi:10.2214/AJR.08.2297.
46. Ozaki Y, Oguchi K, Hamano H, Arakura N, Muraki T, Kiyosawa K, et al. Differentiation of autoimmune pancreatitis from suspected pancreatic cancer by fluorine-18 fluorodeoxyglucose positron emission tomography. J Gastroenterol. 2008;43:144–51. doi:10.1007/s00535-007-2132-y.
47. Herwick S, Miller FH, Keppke AL. MRI of islet cell tumors of the pancreas. AJR Am J Roentgenol. 2006;187:W472–80.
48. Gallotti A, Johnston RP, Bonaffini PA, Ingkakul T, Deshpande V, Fernández-del Castillo C, et al. Incidental neuroendocrine tumors of the pancreas: MDCT findings and features of malignancy. AJR Am J Roentgenol. 2013;200:355–62. doi:10.2214/AJR.11.8037.
49. Poultsides GA, Huang LC, Chen Y, Visser BC, Pai RK, Jeffrey RB, et al. Pancreatic neuroendocrine tumors: radiographic calcifications correlate with grade and metastasis. Ann Surg Oncol. 2012;19:2295–303. doi:10.1245/s10434-012-2305-7.
50. Sheth S, Hruban RK, Fishman EK. Helical CT of islet cell tumors of the pancreas: typical and atypical manifestations. AJR Am J Roentgenol. 2002;179:725–30.
51. Kawamoto S, Shi C, Hruban RH, Choti MA, Schulick RD, Fishman EK, et al. Small serotonin-producing neuroendocrine tumor of the pancreas associated with pancreatic duct obstruction. AJR Am J Roentgenol. 2011;197:W482–8. doi:10.2214/AJR.10.5428.
52. Schmid-Tannwald C, Schmid-Tannwald CM, Morelli JN, Neumann R, Haug AR, Jansen N, et al. Comparison of abdominal MRI with diffusion-weighted imaging to 68Ga-DOTATATE PET/CT in detection of neuroendocrine tumors of the pancreas. Eur J Nucl Med Mol Imaging. 2013;40:897–907. doi:10.1007/s00259-013-2371-5.
53. de Herder WW, Kwekkeboom DJ, Valkema R, Feelders RA, van Aken MO, Lamberts SW, et al. Neuroendocrine tumors and somatostatin: imaging techniques. J Endocrinol Invest. 2005;28(11 Suppl International):132–6.
54. Christ E, Wild D, Forrer F, Brändle M, Sahli R, Clerici T, et al. Glucagon-like peptide-1 receptor imaging for localization of insulinomas. J Clin Endocrinol Metab. 2009;94:4398–405. doi:10.1210/jc.2009-1082.
55. d'Assignies G, Couvelard A, Bahrami S, Vullierme MP, Hammel P, Hentic O, et al. Pancreatic endocrine tumors: tumor blood flow assessed with perfusion CT reflects angiogenesis and correlates with prognostic factors. Radiology. 2009;250:407–16. doi:10.1148/radiol.2501080291.
56. Wang Y, Chen ZE, Yaghmai V, Nikolaidis P, McCarthy RJ, Merrick L, et al. Diffusion-weighted MR imaging in pancreatic endocrine tumors correlated with histopathologic characteristics. J Magn Reson Imaging. 2011;33(5):1071–9. doi:10.1002/jmri.22541.
57. Jang KM, Kim SH, Lee SJ, Choi D. The value of gadoxetic acid-enhanced and diffusion-weighted MRI for prediction of grading of pancreatic neuroendocrine tumors. Acta Radiol. 2014;55:140–8. doi:10.1177/0284185113494982.
58. Bhosale PR, Menias CO, Balachandran A, Tamm EP, Charnsangavej C, Francis IR, et al. Vascular pancreatic lesions: spectrum of imaging findings of malignant masses and mimics with pathologic correlation. Abdom Imaging. 2013;38:802–17. doi:10.1007/s00261-012-9954-7.
59. Fernández-del Castillo C, Warshaw AL. Cystic tumors of the pancreas. Surg Clin North Am. 1995;75:1001–16.
60. Sarr MG, Murr M, Smyrk TC, Yeo CJ, Fernandez-del-Castillo C, Hawes RH, et al. Primary cystic neoplasms of the pancreas. Neoplastic disorders of emerging importance—current state-of-the-art and unanswered questions. J Gastrointest Surg. 2003;7:417–28.
61. Choi JY, Kim MJ, Lee JY, Lim JS, Chung JJ, Kim KW, et al. Typical and atypical manifestations of

serous cystadenoma of the pancreas: imaging findings with pathologic correlation. AJR Am J Roentgenol. 2009;193:136–42. doi:10.2214/AJR.08.1309.
62. Barral M, Soyer P, Dohan A, Laurent V, Hoeffel C, Fishman EK, et al. Magnetic resonance imaging of cystic pancreatic lesions in adults: an update in current diagnostic features and management. Abdom Imaging. 2014;39:48–65. doi:10.1007/s00261-013-0048-y.
63. Chu LC, Singhi AD, Hruban RH, Fishman EK. Characterization of pancreatic serous cystadenoma on dual-phase multidetector computed tomography. J Comput Assist Tomogr. 2014;38:258–63. doi:10.1097/RCT.10.1097/RCT.0b013e3182ab1556.
64. Takeshita K, Kutomi K, Takada K, Kohtake H, Furui S, Takada T, et al. Unusual imaging appearances of pancreatic serous cystadenoma: correlation with surgery and pathologic analysis. Abdom Imaging. 2005;30:610–5.
65. Mottola JC, Sahni VA, Erturk SM, Swanson R, Banks PA, Mortele KJ. Diffusion-weighted MRI of focal cystic pancreatic lesions at 3.0-Tesla: preliminary results. Abdom Imaging. 2012;37:110–7. doi:10.1007/s00261-011-9737-6.
66. Khurana B, Mortelé KJ, Glickman J, Silverman SG, Ros PR. Macrocystic serous adenoma of the pancreas: radiologic-pathologic correlation. AJR Am J Roentgenol. 2003;181:119–23.
67. Dewhurst CE, Mortele KJ. Cystic tumors of the pancreas: imaging and management. Radiol Clin North Am. 2012;50:467–86. doi:10.1016/j.rcl.2012.03.001.
68. Visser BC, Yeh BM, Qayyum A, Way LW, McCulloch CE, Coakley FV. Characterization of cystic pancreatic masses: relative accuracy of CT and MRI. AJR Am J Roentgenol. 2007;189:648–56.
69. Procacci C, Carbognin G, Accordini S, Biasiutti C, Guarise A, Lombardo F, et al. CT features of malignant mucinous cystic tumors of the pancreas. Eur Radiol. 2001;11:1626–30.
70. Crippa S, Salvia R, Warshaw AL, Domínguez I, Bassi C, Falconi M, et al. Mucinous cystic neoplasm of the pancreas is not an aggressive entity: lessons from 163 resected patients. Ann Surg. 2008;247:571–9. doi:10.1097/SLA.0b013e31811f4449.
71. Goh BK, Tan YM, Chung YF, Chow PK, Cheow PC, Wong WK, et al. A review of mucinous cystic neoplasms of the pancreas defined by ovarian-type stroma: clinicopathological features of 344 patients. World J Surg. 2006;30:2236–45.
72. Nadig SN, Pedrosa I, Goldsmith JD, Callery MP, Vollmer CM. Clinical implications of mucinous nonneoplastic cysts of the pancreas. Pancreas. 2012;41:441–6. doi:10.1097/MPA.0b013e318229b9b8.
73. Sarr MG, Kendrick ML, Nagorney DM, Thompson GB, Farley DR, Farnell MB. Cystic neoplasms of the pancreas: benign to malignant epithelial neoplasms. Surg Clin North Am. 2001;81:497–509.
74. Balci NC, Semelka RC. Radiologic features of cystic, endocrine and other pancreatic neoplasms. Eur J Radiol. 2001;38:113–9.
75. Chalian H, Töre HG, Miller FH, Yaghmai V. CT attenuation of unilocular pancreatic cystic lesions to differentiate pseudocysts from mucin-containing cysts. JOP. 2011;12:384–8.
76. Procacci C, Megibow AJ, Carbognin G, Guarise A, Spoto E, Biasiutti C, et al. Intraductal papillary mucinous tumor of the pancreas: a pictorial essay. Radiographics. 1999;19:1447–63.
77. Pedrosa I, Boparai D. Imaging considerations in intraductal papillary mucinous neoplasms of the pancreas. World J Gastrointest Surg. 2010;2:324–30. doi:10.4240/wjgs.v2.i10.324.
78. Arakawa A, Yamashita Y, Namimoto T, Tang Y, Tsuruta J, Kanemitsu K, et al. Intraductal papillary tumors of the pancreas. Histopathologic correlation of MR cholangiopancreatography findings. Acta Radiol. 2000;41:343–7.
79. Irie H, Honda H, Aibe H, Kuroiwa T, Yoshimitsu K, Shinozaki K, et al. MR cholangiopancreatographic differentiation of benign and malignant intraductal mucin-producing tumors of the pancreas. AJR Am J Roentgenol. 2000;174:1403–8.
80. Choi BS, Kim TK, Kim AY, Kim KW, Park SW, Kim PN, et al. Differential diagnosis of benign and malignant intraductal papillary mucinous tumors of the pancreas: MR cholangiopancreatography and MR angiography. Korean J Radiol. 2003;4:157–62.
81. Maire F, Voitot H, Aubert A, Palazzo L, O'Toole D, Couvelard A, et al. Intraductal papillary mucinous neoplasms of the pancreas: performance of pancreatic fluid analysis for positive diagnosis and the prediction of malignancy. Am J Gastroenterol. 2008;103:2871–7. doi:10.1111/j.1572-0241.2008.02114.x.
82. Werner JB, Bartosch-Härlid A, Andersson R. Cystic pancreatic lesions: current evidence for diagnosis and treatment. Scand J Gastroenterol. 2011;46:773–88. doi:10.3109/00365521.2011.551892.
83. Manfredi R, Graziani R, Motton M, Mantovani W, Baltieri S, Tognolini A, et al. Main pancreatic duct intraductal papillary mucinous neoplasms: accuracy of MR imaging in differentiation between benign and malignant tumors compared with histopathologic analysis. Radiology. 2009;253:106–15. doi:10.1148/radiol.2531080604.
84. Waters JA, Schmidt CM, Pinchot JW, White PB, Cummings OW, Pitt HA, et al. CT vs MRCP: optimal classification of IPMN type and extent. J Gastrointest Surg. 2008;12:101–9.
85. Akisik MF, Sandrasegaran K, Aisen AA, Maglinte DD, Sherman S, Lehman GA. Dynamic secretin-enhanced MR cholangiopancreatography. Radiographics. 2006;26:665–77.
86. Sperti C, Bissoli S, Pasquali C, Frison L, Liessi G, Chierichetti F, et al. 18-fluorodeoxyglucose positron emission tomography enhances computed tomography diagnosis of malignant intraductal papillary mucinous neoplasms of the pancreas. Ann Surg. 2007;246:932–7; discussion 937–9.

EUS Imaging in the Diagnosis of Pancreatic Masses

8

Pradermchai Kongkam and Rungsun Rerknimitr

EUS Imaging Features of Solid Pancreatic Lesions

Pancreatic Adenocarcinoma

Pancreatic adenocarcinoma, an aggressive form of cancer, usually presents at an advanced stage, resulting in a very disappointing prognosis for these patients. Typically, a 5-year survival rate is less than 5 % [1]. Surgical removal is currently the only curative treatment. Only small pancreatic tumors without significant invasion into surrounding organs are suitable for a complete surgical resection [2]. Unfortunately, the majority of pancreatic cancer presents at an advanced stage and cannot be treated curatively.

Given that operable pancreatic cancers are small in diameter and that they tend to be asymptomatic, the current noninvasive techniques, including computed tomography (CT) and magnetic resonance imaging (MRI), cannot provide sufficient resolution to reliably detect these small lesions [3]. Hence, endoscopic ultrasound (EUS), which has a significantly higher resolution, plays a significant role in the identification of these small pancreatic lesions [4]. Moreover, EUS also enables tumor staging together with a capacity for fine-needle aspiration (FNA); thus, it is commonly used for the evaluation of pancreatic adenocarcinoma [5]. Therefore, to provide the best management for patients, the abilities to recognize and to be familiar with EUS imaging features of pancreatic adenocarcinoma are valuable although EUS-FNA is needed to make a definite diagnosis of pancreatic adenocarcinoma.

A normal pancreas typically shows endosonographic features with a homogeneous "salt–and-pepper" appearance (Fig. 8.1). Pancreatic adenocarcinoma commonly displays as a heterogeneous hypoechoic mass with an irregular border during EUS examination, and it may be readily differentiated from the normal surrounding pancreatic parenchyma (Fig. 8.2). Solid pancreatic masses with these endosonographic features are suspected as pancreatic adenocarcinoma. However, results from a prospective study that used EUS images to diagnose 115 pancreatic lesions showed sensitivity and specificity rates for diagnosing malignant pancreatic masses that were 95 % and 53 %, respectively. Thus, EUS imaging alone is nonspecific for pancreatic cancer [6]. Upon retrospective analysis of results

P. Kongkam, M.D. (✉) • R. Rerknimitr, M.D.
Department of Medicine, Gastrointestinal Endoscopy Excellent Center, King Chulalongkorn Memorial Hospital, Thai Red Cross Society, Chulalongkorn University, 1873, Rama 4 Road, Patumwan, Bangkok 10500, Thailand
e-mail: kongkam@hotmail.com

M.S. Wagh, P.V. Draganov (eds.), *Pancreatic Masses*, DOI 10.1007/978-3-319-19677-0_8

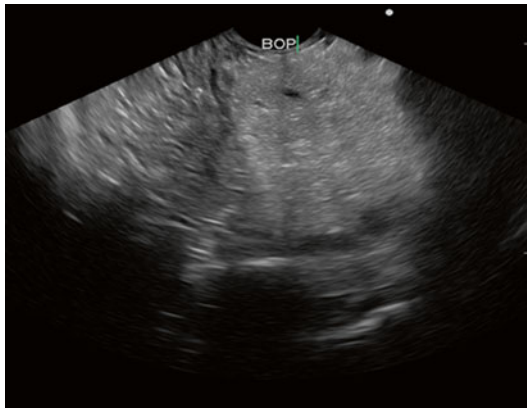

Fig. 8.1 A normal pancreas typically shows a homogeneous "salt-and-pepper" appearance

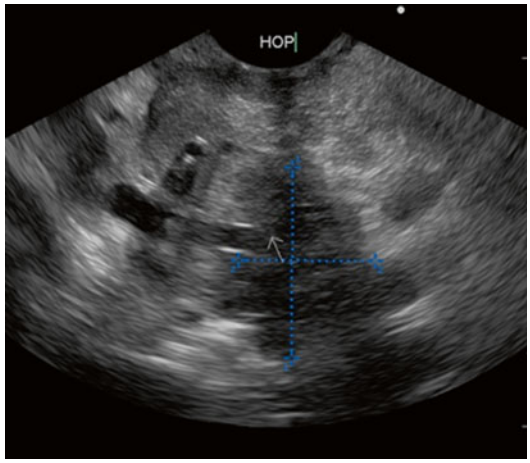

Fig. 8.2 A hypoechoic mass measuring 26 mm × 18 mm at its maximal diameter is demonstrated in the head of the pancreas

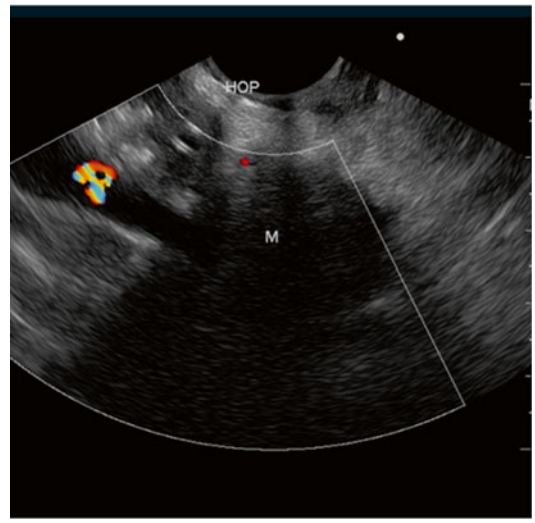

Fig. 8.3 A hypoechoic mass at the head of the pancreas with invasion into the main portal vein is demonstrated. A plastic biliary stent was endosonographically demonstrated by the couple of linear echogenic lines in the left upper corner of the figure

from that study, features associated with pancreatic cancer were lesions larger than 2 cm in diameter, vessel ingrowth, an absence of cystic spaces, and an absence of diffuse pancreatitis [6].

As discussed above, the only curative treatment for pancreatic cancer is complete surgical resection. If preoperative tumor staging suggests that the patient is a potential candidate for resectable pancreatic cancer, most surgeons would not hesitate to perform an exploratory laparotomy to remove the tumor completely. One of the critical points involved in making the decision is vascular invasion. To demonstrate invasion, either CT or MRI is used in practice. Unfortunately, a recent meta-analysis of eight studies ($n = 296$) reported that the pooled sensitivity rates of CT vs. MRI for the staging of pancreatic cancer were 71 % vs. 67 %, respectively, although their specificity rates were higher than 90 % [7]. In comparison, EUS was reported highly sensitive for detecting portal vein and confluence invasion [8, 9]. When three EUS parameters (visualization of tumor in the lumen, complete obstruction, or collateral vessels) were used, the overall sensitivity and specificity of EUS for diagnosing venous invasion were 43 % and 91 %, respectively; however, when another parameter of irregular tumor–vessel relationships was added to the criteria listed above, the sensitivity rate increased to 62 %, but the specificity rate dropped to 79 % [9]. EUS imaging features of portal vein invasion and celiac artery involvement are demonstrated in this chapter (Figs. 8.3, 8.4, 8.5 and 8.6). However, currently, the accuracy rate of EUS vs. CT for the staging of pancreatic cancer cannot be directly compared due to heterogeneity of design, quality, and results in relevant studies [10].

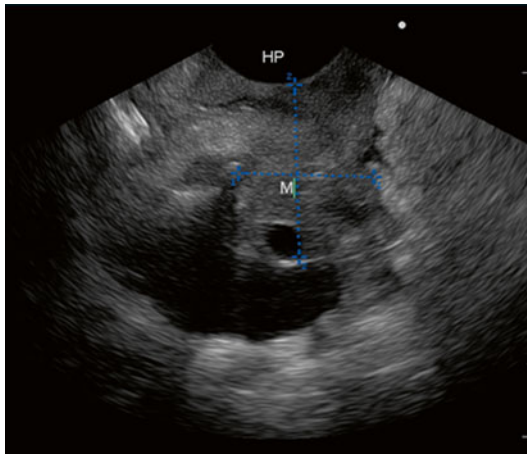

Fig. 8.4 The irregular relationship between the solid mass of pancreatic adenocarcinoma (M) and the portal vein is endosonographically demonstrated

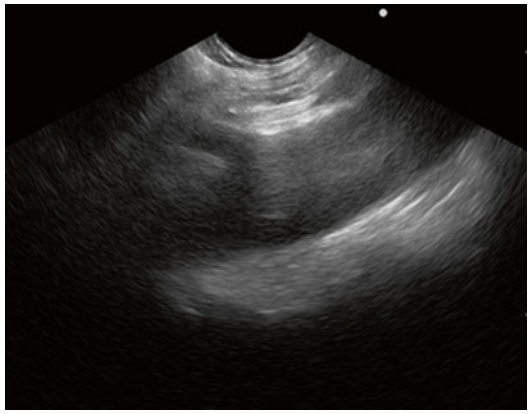

Fig. 8.5 The abdominal aorta demonstrated as a long tubular anechoic structure with the celiac artery originating from the aorta

Pancreatic Neuroendocrine Tumors

Pancreatic neuroendocrine tumors (PNETs) are rare pancreatic neoplasms that account for less than 10 % of all pancreatic cancers [11]. In general,)prognoses for PNETs are more favorable than for pancreatic adenocarcinoma, given that they show a more indolent course and thus a slower rate of growth. Nonetheless, these tumors have the potential to be aggressive; therefore, when identified, they must be removed.)Currently, surgical removal is the only curative treatment. Early detection, when the tumor is relatively small, is the only method of ensuring complete surgical removal. EUS plays a significant role in both the diagnostic management and, more recently, the therapeutic management of PNETs.

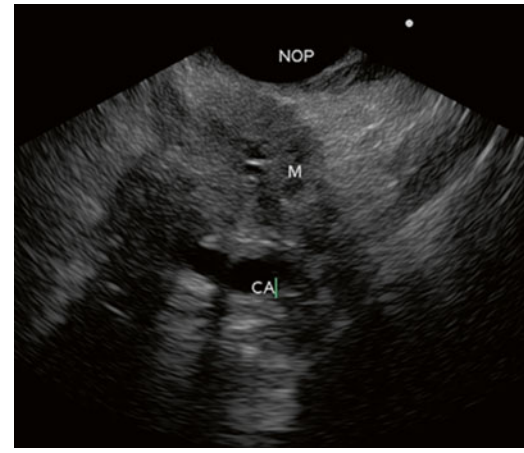

Fig. 8.6 A hypoechoic solid pancreatic mass (M) encases the celiac artery (CA). This mass was subsequently diagnosed as pancreatic adenocarcinoma

The management of)PNETs requires a multidisciplinary approach including expertise from endosonographers, radiologists, and surgeons. This section will focus on the EUS imaging features of PNETs.

Diagnostic Role of EUS

Functioning)PNETs generally present with hormonal symptoms; hence, they mostly present with small-diameter masses. It is generally recognized that any pancreatic mass smaller than 20 mm in diameter is at risk of being overlooked when using noninvasive imaging, particularly CT, which is the most widely available imaging technique [12]. EUS has the ability of enabling the detection of functioning PNETs lesions that are not identifiable using CT [13]. In studies comparing the sensitivity of EUS vs. CT scans to identify insulinomas, result showed that the former had a sensitivity rate of 79–87 % for the detection of fPNETs whereas the latter shows only 14–30 % sensitivity [14–17]. A recent large retrospective study reported an accuracy rate of 90.1 % (73/81) for EUS-FNA for the diagnosis of PNETs [18]. Other large series reported a sensitivity rate of 87 % in 89 patients [19] and 90 % in 86 patients [20]. In general, the use of EUS-FNA to confirm a diagnosis of PNETs

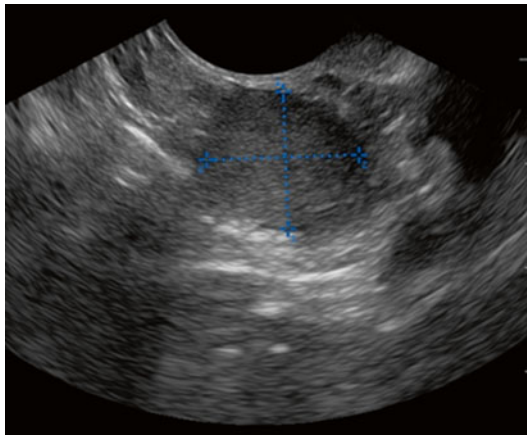

Fig. 8.7 A well-defined border of a homogeneous hypoechoic mass was identified in the tail of the pancreas. The final diagnosis was insulinoma

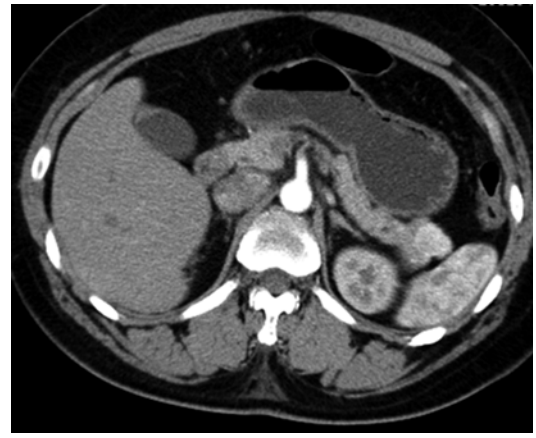

Fig. 8.8 A 2.1-cm × 1.8-cm early and late arterial-enhancing lesion at the tail of pancreas is shown

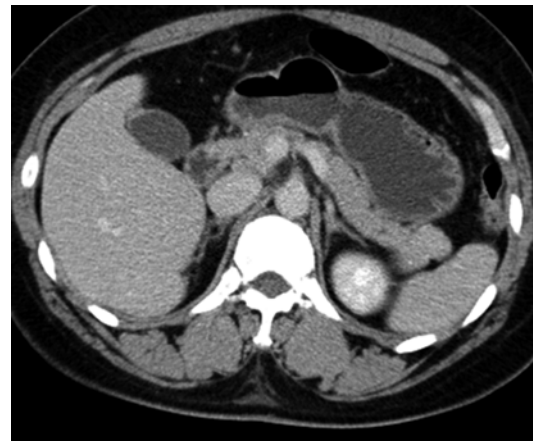

Fig. 8.9 An isodense lesion at the tail of the pancreas was identified. It was difficult to identify the lesion without information from a CT scan in arterial phase

is strongly recommended due to its high accuracy rate. Specific immunohistochemical staining is required for the diagnosis. Because a small pancreatic lesion is a well-known risk factor for inadequate sampling when using EUS-FNA [21], if tissue from the EUS-FNA of a small pancreatic lesion is insufficient to make a diagnosis of PNET but other clinical and laboratory parameters, including obtaining typical endosonographic lesion features, support the diagnosis, definite treatment may be considered. Typical endosonographic features of a small PNET are a homogeneous, slightly hypoechoic mass with a well-defined border (Fig. 8.7). One of the reasons that CT misses diagnoses of fPNETs is that CT shows enhanced lesions only during the arterial phase, whereas the lesion shows an isodensity during the venous phase (Figs. 8.8 and 8.9). Despite studies reporting this impressive capability of identifying fPNETs, in practice, EUS requires a high degree of technical expertise and experience because the echogenicity of fPNETs is generally slightly hypoechoic or even isoechoic compared with surrounding parenchyma. Not only the expertise and experience of endosonographers determine the efficacy of EUS but also other important factors, including the resolution of the ultrasonographic images and, in particular, the period of prediagnostic time that has elapsed prior to the point of clinical presentation of the patient.

Because approximately 90 % of PNETs present as solid lesions, it is often falsely presumed that any cystic lesions are not PNETs. This fact underscores the need to perform FNA for any cases clinically suspected of PNETs where cystic lesions have been identified by EUS. Based on the few existing studies reporting on cystic PNETs, these lesions do not display the typical characteristics of cystic tumors because they may present as simple cysts, mixed solid–cystic lesions, or cysts with septation; thus, endosonographic images are not recommended as the sole means of diagnosis (Fig. 8.10). FNA should

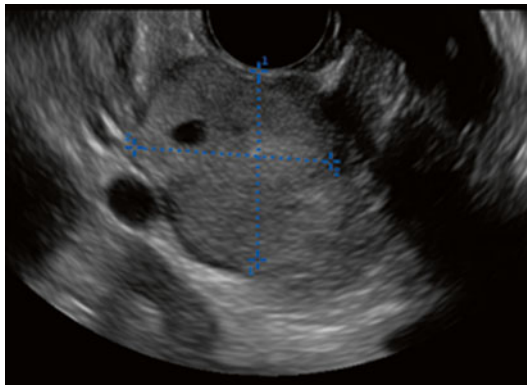

Fig. 8.10 A well-defined homogeneous hypoechoic solid pancreatic mass with a small cystic area inside the mass is shown. The final diagnosis was a cystic pancreatic neuroendocrine tumor

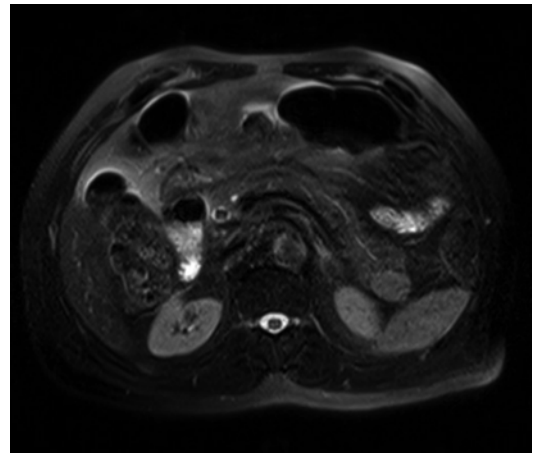

Fig. 8.11 Magnetic resonance imaging (MRI) showed a solid, well-defined, hypervascular lesion in the tail of the pancreas. The lesion was located close to the spleen. It showed a similar enhancing pattern to the adjacent spleen. All these features are typical when diagnosing an intrapancreatic accessory spleen

always be performed for the definitive identification of PNETs [22–26].

In summary, for fPNETs displaying typical endosonographic features, a presumptive diagnosis of PNETs may be made based on the endosonographic features alone. Nonetheless, to confirm the diagnosis preoperatively, EUS-FNA should be performed whenever possible because, together with its relatively low complication rate, the efficacy of FNA has been reported in several studies as being approximately 80 %. However, in atypical lesions, such as mixed solid–cystic lesions, preoperative diagnosis is required, and it is readily performed via EUS-FNA).

Accessory Spleen

The accessory spleen is a congenital anomaly caused by failure of the splenic anlage to fuse with the spleen during embryogenesis. It is found in 10–15 % of the general population and mostly shows no symptoms. Anatomically, it may either be a lesion connecting the main spleen or a separate nodule. In general, lesions are typically smaller than 2 cm; however, they can be as large as the spleen itself [27]. Approximately 80 % of accessory spleens are located adjacent to the splenic hilum, with the majority of the remaining located at the tail of the pancreas. However, occasionally, they may locate along the length of the splenic artery or anywhere in the abdominal cavity. Lesions are solitary or multiple in 80 % and 10 % of cases, respectively [28].

Intrapancreatic accessory spleens are solid, well-defined, hypervascular lesions in CT and MRI images (Fig. 8.11). These lesions should be differentiated from well-differentiated adenocarcinoma, mucinous cystic neoplasm, solid pseudopapillary neoplasm of the pancreas, neuroendocrine tumor, and metastases [29]. Endosonographically, the accessory spleens are generally round or oval-shaped lesions with a regular and sharp margin. They are usually homogeneous hypoechoic lesions with similar echogenic patterns to the major spleen (Fig. 8.12). It is difficult to differentiate from a splenic lobule. In equivocal cases, EUS-FNA may provide a definite diagnosis [30]. Classic cytopathological features include a heterogeneous population of lymphocytes, traversing small vascular structures, and a background of mixed inflammatory cells and blood [29].

Mass-Forming Chronic Pancreatitis

Chronic pancreatitis is a well-known risk factor for pancreatic cancer. A large prospective study following 373 patients with chronic pancreatitis

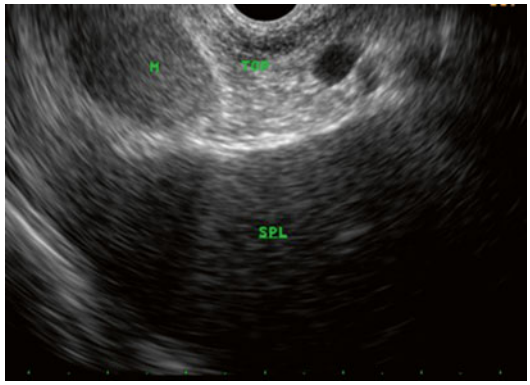

Fig. 8.12 A homogeneous hypoechoic solid mass (M) with an echogenic pattern similar to the major spleen (SPL) was identified in the tail of the pancreas (TOP). Endosonographically, the accessory spleens are usually round or oval-shaped lesions with regular and sharp margins

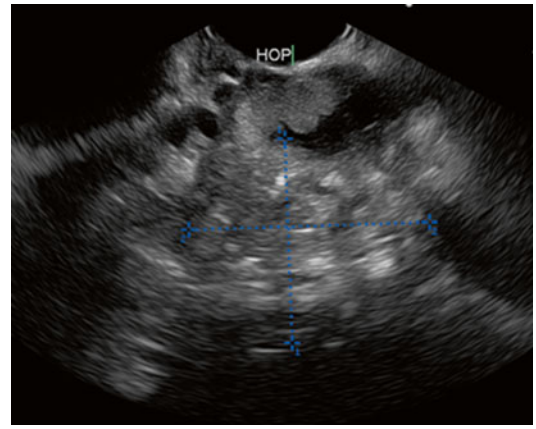

Fig. 8.13 An ill-defined heterogeneous hypoechoic calcified solid pancreatic mass is identified in the head of the pancreas. The final diagnosis of the mass was a mass-forming chronic pancreatitis

for at least 2 years observed four cases of pancreatic adenocarcinoma (1.1 %). The authors concluded that patients with chronic pancreatitis are at a markedly increased risk of pancreatic cancer compared with the general population [31]. Thus, when patients with baseline chronic pancreatitis develop a solid pancreatic mass, it is very challenging to differentiate between a mass-forming chronic pancreatitis or a de novo pancreatic cancer in addition to chronic pancreatitis.

Several technologies have been developed to assist the physician to diagnose solid pancreatic masses in the context of chronic pancreatitis. To date, the gold standard is EUS-FNA. Currently, EUS-FNA is recognized as the best test for diagnosing solid pancreatic masses, with reported sensitivity and specificity rates of 91 % and 94 %, respectively [5]. However, in the context of a solid mass with baseline chronic pancreatitis, the sensitivity of EUS-FNA drops from 89–91 % to 54–73 %, respectively [32, 33]. Thus, with this significant limitation, it is valuable for clinicians to recognize and be familiar with the typical EUS imaging features of mass-forming chronic pancreatitis; perhaps these data may assist in managing patients with solid pancreatic masses.

Radiographically, compared with pancreatic cancer, mass-forming chronic pancreatitis shows less severe main pancreatic ductal dilation, a more irregular main pancreatic duct contour, and more dilated side branches [34]. Endosonographically, a diagnosis of chronic pancreatitis is conventionally based on five parenchymal criteria (calcification with shadowing, echogenic foci without shadowing, echogenic strands, lobulation, and cystic change) and four ductal criteria (main pancreatic ductal stone, dilation or irregular contour of the main pancreatic duct, increased echogenicity of the main pancreatic ductal wall, and side-branch dilation). An international consensus has weighted each EUS criterion of chronic pancreatitis as being major or minor for the diagnosis of more solid lesions and to help standardize terminology. Major criteria include (1) echogenic foci with shadowing and main pancreatic duct calculi and (2) lobularity with honeycombing. Minor criteria include cystic changes, a dilated main pancreatic duct (≥3 mm), an irregular pancreatic duct contour, dilated side branches (≥1 mm), a hyperechoic ductal wall, strands, nonshadowing hyperechoic foci, and lobularity with noncontiguous lobules. This consensus is known as the Rosemont classification and is used for the diagnosis of chronic pancreatitis in several institutions [35]. Therefore, classically, mass-forming chronic pancreatitis shows imaging features including an inhomogeneous echogenic pattern, calcification, peripancreatic echorich stranding, and cysts (Fig. 8.13) [36, 37].

Autoimmune Pancreatitis

Autoimmune pancreatitis may present as either diffuse enlargement of the pancreas or focal pancreatic mass or enlargement [38]. In practice, differentiation between the focal mass of autoimmune pancreatitis and pancreatic adenocarcinoma is a challenging issue. Certainly, pathological diagnosis remains the gold-standard criterion; unfortunately, obtaining adequate tissue for a diagnosis is not straightforward. Therefore, clinically, the combination of various clinical findings is used to differentiate these two conditions. A recent review from Japan proposed that the following clinical parameters may suggest autoimmune pancreatitis rather than pancreatic adenocarcinoma. These findings include fluctuating obstructive jaundice; elevated serum IgG4 levels; diffuse enlargement of the pancreas; delayed enhancement of the enlarged pancreas and the presence of a capsule-like rim on dynamic CT; low apparent diffusion coefficient values on diffusion-weighted MRI images; irregular narrowing of the main pancreatic duct upon endoscopic retrograde cholangiopancreatography (ERCP); less upstream dilation of the main pancreatic duct upon magnetic resonance cholangiopancreatography (MRCP); the presence of other organ involvement, such as bilateral salivary gland swelling, retroperitoneal fibrosis, and hilar or intrahepatic sclerosing cholangitis; negative workup for malignancy, including EUS-guided FNA; and steroid responsiveness [39].

As discussed above, the diagnosis of autoimmune pancreatitis cannot rely solely on EUS findings; however, it is valuable to learn the typical endosonographic imaging features of autoimmune pancreatitis. Endosonographically, both diffuse and focal forms of autoimmune pancreatitis show echo-poor pancreatic parenchyma with echogenic interlobular septa (Fig. 8.14) [40]. In the diffuse form, a thickened gland border may be noted. These changes may vary based on the degree of pancreatitis as shown in a study that

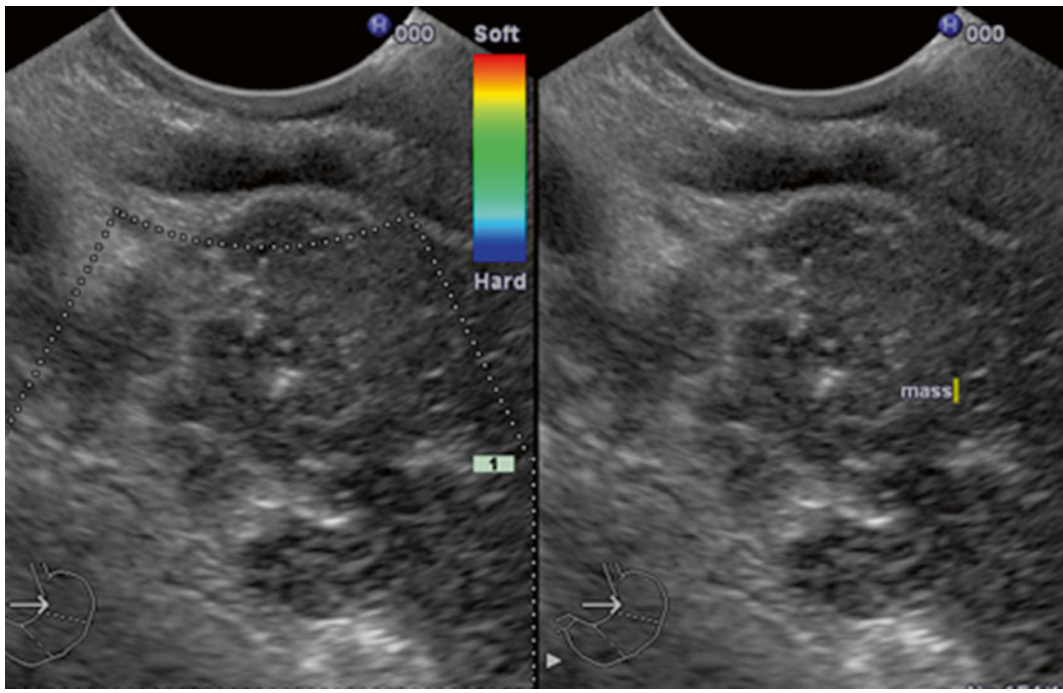

Fig. 8.14 A hypoechoic pancreatic mass in a patient with a final diagnosis of a focal form of autoimmune pancreatitis is shown. Endosonographic findings of echo-poor pancreatic parenchyma with echogenic interlobular septa are demonstrated

compared endosonographic findings in nine patients with early-stage and ten patients with advanced-stage autoimmune pancreatitis who were classified based on the Cambridge classification. Endosonographic findings of lobularity and a hyperechoic pancreatic duct margin were detected at a significantly higher frequency in early-stage compared with advanced-stage autoimmune pancreatitis [41].

Pancreatic Lymphoma

Primary pancreatic lymphoma is rare. From a retrospective review of 2397 patients with solid pancreatic masses over a 10-year period, only 12 patients (0.5 %) with pancreatic lymphoma were finally identified [42]. Based on results from this study, at the time of diagnosis, masses of primary pancreatic lymphoma were large and more than 80 % were located in the head of the pancreas. Heterogeneous versus homogeneous hypoechoic masses were found in 75 % and 25 % of patients, respectively (Fig. 8.15). The margins of all masses were ill defined, with vascular invasions in 41.7 %. Peripancreatic lymphadenopathy was noted in 58.3 % of patients. Neither EUS imaging features of chronic pancreatitis nor main pancreatic ductal dilation was noted [42]. However, to the best of our knowledge, EUS imaging features of pancreatic lymphoma have only been reported on a few series; thus, it is difficult to conclude the characteristic endosonographic findings [43, 44].

Pancreatic Metastases

Pancreatic metastases are relatively rare. Of these types of metastases, renal cell carcinoma is the most common primary cancer that metastasizes to the pancreas. It is difficult to differentiate pancreatic metastases from pancreatic adenocarcinoma based on EUS imaging alone. Nevertheless, a few studies have reported on the EUS imaging features of pancreatic metastases. Most lesions are solid, are likely to have well-defined margins, and are mostly present in patients with a known history of primary malignancy (Fig. 8.16) [45, 46]. Another retrospective study of 28 and 60 patients with pancreatic metastases and primary pancreatic adenocarcinoma, respectively, reported that the presence of regular borders, the absence of retention cysts, and the presence of a nondilated main pancreatic duct detected by EUS indicated the former rather than the latter disease [47]. However, because pancreatic metastases may present with other features, including solid pancreatic masses with irregular margins or _cys-

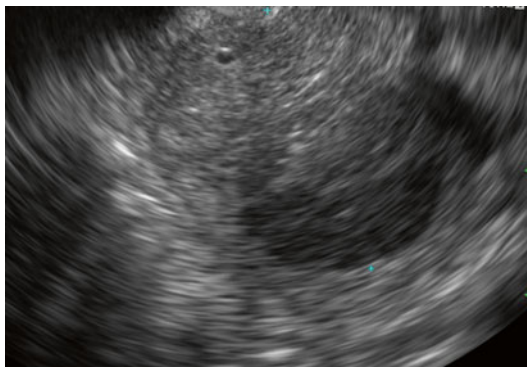

Fig. 8.15 A well-defined heterogeneous hypoechoic pancreatic mass was identified in the pancreas with a final diagnosis of primary pancreatic lymphoma

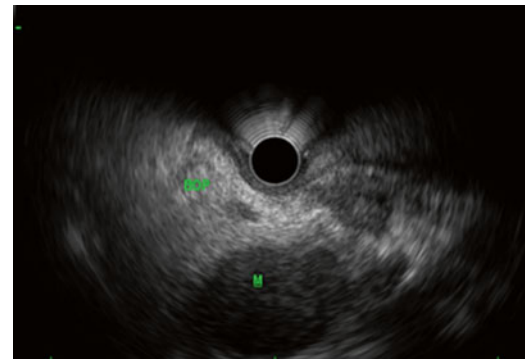

Fig. 8.16 A well-defined homogeneous hypoechoic pancreatic metastatic solid mass (M) from gastric adenocarcinoma is located in the body of the pancreas (BOP)

tic lesions, it is recommended that accurate diagnoses should be made based on pathology rather than EUS imaging features alone.

EUS Imaging Features of Cystic Pancreatic Lesions

Cystic pancreatic lesions are being increasingly identified worldwide due to the increased use of radiological imaging, including CT scans and MRI.

In comparison with other cross-sectional imaging including CT and MRI, EUS is considered a more invasive technique. Advantages of EUS include higher magnification of pancreatic cysts and the ability to perform EUS-guided diagnostic procedures. Those procedures include cystic fluid analysis for tumor markers and pancreatic enzymes, cytology, and direct visualization of the cystic wall.

Pseudocyst

Diagnosis of a pseudocyst should be made only when the clinical course and imaging features are compatible. Clinical and radiological evidence of either acute or chronic pancreatitis supports a diagnosis of pseudocyst although they are not entirely specific. Imaging features alone are not sufficient to confirm a diagnosis of a pseudocyst because it can mimic cystic neoplasms of the pancreas (Fig. 8.17). In questionable cases of pseudocysts, cystic fluid features and analysis help in differentiating pseudocysts from cystic neoplasms of the pancreas [48]. Cystic fluid may be obtained using transabdominal ultrasound or CT or EUS guidance. EUS is the most preferable due to its proximity to the pancreas. Low-viscosity, low-cystic-fluid CEA levels and significantly higher cystic-fluid amylase levels are suggestive of a pseudocyst [49].

Serous Cystadenoma

Serous cystadenoma may present with either a microcystic or honeycomb appearance or an oligocystic appearance, the latter of which is less common. A microcystic serous cystadenoma

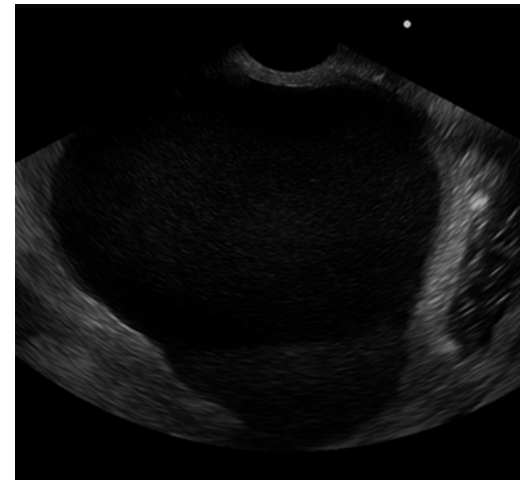

Fig. 8.17 A large pancreatic cyst with a regular border and echogenic content at the bottom of the lesion was identified in the tail of the pancreas. The lesion was finally diagnosed as a pseudocyst

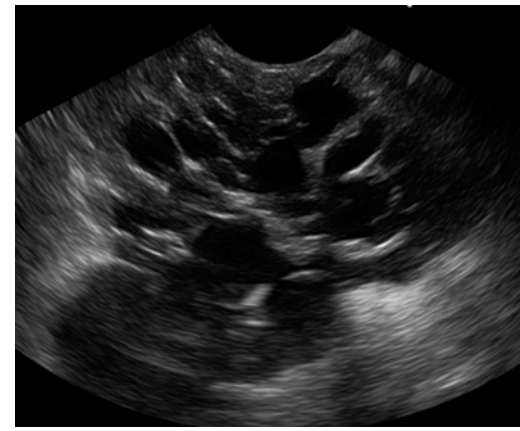

Fig. 8.18 This figure demonstrates a multilocular pancreatic cyst with a characteristic microcystic and honeycomb appearance. These features are characteristic of a serous cystadenoma. A 10-month follow-up period demonstrated a stable pancreatic cyst

comprises multiple small cysts (less than 2–3 mm each) that aggregate (typically more than six cysts) and that are separated by thin-wall septa (Fig. 8.18) [50]. EUS imaging features of a microcystic or honeycomb appearance are strongly suggestive of serous cystadenoma [51]. The microcystic feature is noted in more than 80 % of serous cystadenoma and is very specific when making a diagnosis of this lesion [50]. It is better diagnosed by EUS than other imaging

modalities. However, an oligocystic appearance, which comprises fewer and larger cysts, is difficult to differentiate from a mucinous cystadenoma or an intraductal papillary mucinous neoplasm (IPMN) [52].

Mucinous Cystadenoma

Histologically, a diagnosis of mucinous cystadenoma should be made when a specific finding of ovarian type of stroma has occurred; however, epithelial cells of the cyst may produce mucin, similar to IPMN [53, 54]. Endosonographically, a mucinous cystadenoma may either be unilocular or septated cysts with or without wall calcification. If solid components are identified, they may suggest malignancy (Fig. 8.19) [55]. Diagnosis of mucinous cystadenoma was made based on the criteria elevated cystic fluid CEA and a typical wall thickening and irregularity [56]. Whipple's operation was subsequently performed. A surgical biopsy confirmed mucinous cystadenoma with in situ carcinoma foci.

Pathologically, a malignant mucinous cystadenoma correlates with multilocularity and the presence of a papillary projection or mural nodules, the loss of ovarian-like stroma, and p53 immunoreactivity [54]. Endosonographically, endosonographic signs suggestive of malignancy include intracystic solid lesions, an adjacent solid mass, and an increasing diameter. A mucinous cystadenoma requires surgical resection in all surgically fit patients due to its malignant potential [57]. Unlike IPMN, communication with the pancreatic duct is rarely observed. Therefore, if the communication is clearly demonstrated, IPMN is a more likely diagnosis.

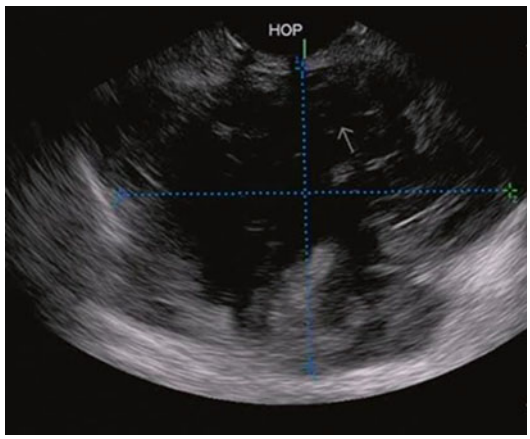

Fig. 8.19 This figure demonstrates a multilocular pancreatic cyst with papillary projection. A large multiloculated pancreatic cyst measuring 55 mm×42 mm in diameter is demonstrated at the head of the pancreas. A papillary projection was demonstrated from the cystic wall. EUS-FNA was performed. The aspirated fluid was a thick mucin

Intraductal Papillary Mucinous Neoplasm

Precancerous lesions of invasive pancreatic ductal adenocarcinoma include pancreatic intraepithelial neoplasms (PanINs), mucinous cystadenomas, and IPMNs. IPMNs are histologically classified as one of three types: main-duct type, branch-duct type, and mixed type [58]. Surgical resection is recommended for the majority of IPMNs. Radiographically, IPMNs are classified as branch-duct IPMN (BD-IPMN), main-duct IPMN (MD-IPMN), or mixed type. From the perspective of imaging, BD-IPMNs and MD-IPMNs are differential diagnoses of cystic pancreatic lesions and obstructive chronic pancreatitis, respectively.

Three classic EUS imaging features of BD-IPMNs have been described: multiloculated lesions or bunch-of-grapes; finger-like; and clubbed features (Fig. 8.20) [51]. The first is the most common type and shows irregular contours and a "cyst-by-cyst" appearance rather that the "cyst-in-cyst" and multi-loculated appearance of a mucinous cystadenoma [53].

Solid Pseudopapillary Neoplasms

Solid pseudopapillary neoplasms of the pancreas SPNs can be either benign or low grade potential tumor of the pancreas [59, 60]. These tumors occur predominantly in women as shown by Buetow and colleagues in a study of 96 patients that recruited 56 patients with SPNs of the pancreas [61]. The study reported that more than 90 % of patients

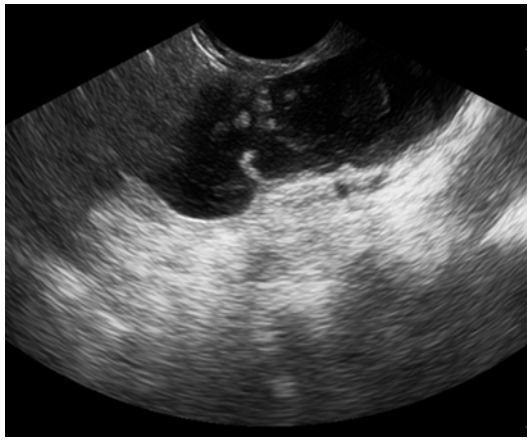

Fig. 8.20 This figure demonstrates a dilated side branch of the pancreatic duct at the body of the pancreas. These dilated side branches communicated with the main pancreatic duct. The final diagnosis was a side-branch intraductal papillary mucinous neoplasm of the pancreas (IPMN)

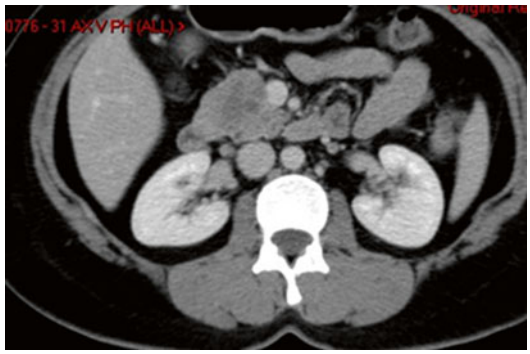

Fig. 8.21 An abdominal CT demonstrated a hypodense solid mass in the head of the pancreas. The mass measured approximately 3.1 cm × 3.9 cm × 4.1 cm. It was a heterogeneous enhancing mass. No vessel invasion was observed. No peri-lesional lymph node was observed

were female. The mean age of the patients was approximately 30 years [59, 60]. In general, the tumors were larger than 30 mm in diameter at the time of presentation. Radiographically, the tumor was an encapsulated mass with heterogeneous enhancement that included some cystic space and a solid component (Figs. 8.21, 8.22, 8.23, 8.24 and 8.25). EUS-FNA is an effective method to make a preoperative diagnosis of the SPNs [62].

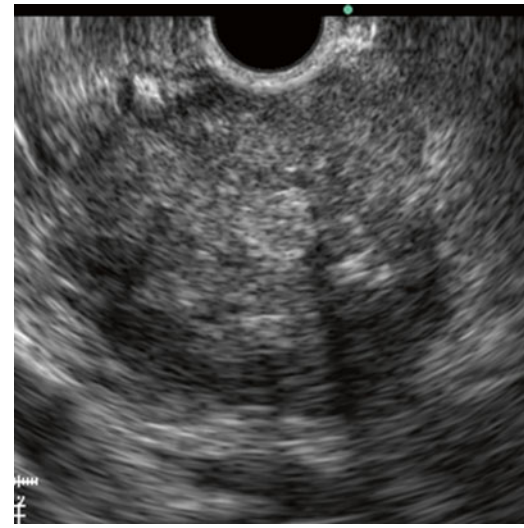

Fig. 8.22 An EUS examination demonstrated a well-defined, irregular border and a heterogeneous hypoechoic mass measuring 34 mm × 30 mm in diameter. A few tiny calcified spots were observed inside the mass

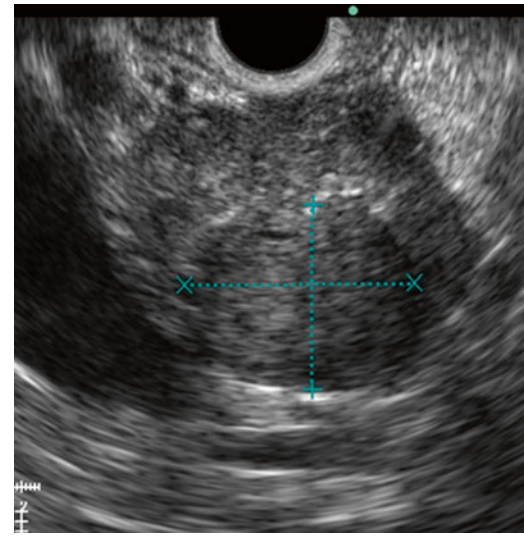

Fig. 8.23 There was a hypoechoic area measuring approximately 20 mm × 17 mm inside the mass. Endosonographically, it showed a well-defined border, it was encapsulated, and hypoechoic solid lesions showed an irregular margin. A deep hypoechoic area was observed inside the mass, likely the beginning of cystic degeneration of the mass. This area was not detected in a CT scan, reflecting the superiority of EUS over CT. No vessel invasion was observed. No lymph node was observed

Fig. 8.24 Gross surgical biopsy of the mass

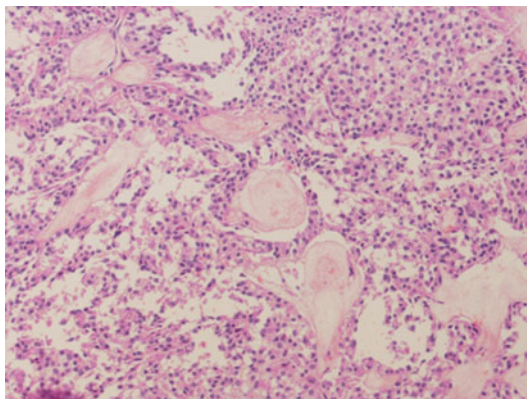

Fig. 8.25 Surgical histopathological examination following a Whipple procedure showed a circumscribed mass composed of solid sheets of uniform bland-looking cells admixed with delicate blood vessels that are surrounded by myxoid material. These findings were consistent with a solid pseudopapillary neoplasm of the pancreas

EUS-Guided Needle-Based Confocal Laser Endomicroscopy

Confocal laser endomicroscopy (CLE) is an endoscope-integrated or probe-based miniprobe that can provide real-time magnified endoscopic images at the cellular level. It has been applied for making real-time diagnoses of gastrointestinal tract mucosal lesions. Results from a recent meta-analysis were impressive [63]. Subsequently, the probe-based CLE has progressed into the submillimeter needle-based CLE (nCLE), which may be

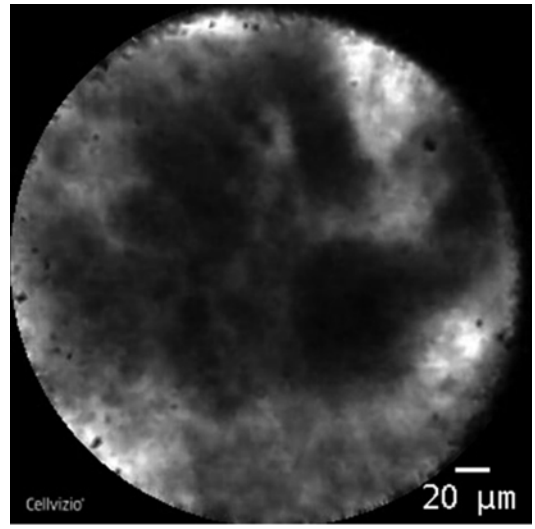

Fig. 8.26 Dark clumps of cells were demonstrated by EUS-guided needle-based confocal laser endomicroscopy of a solid pancreatic lesion with a final diagnosis of pancreatic adenocarcinoma

inserted into a 19-G EUS-FNA needle. Since this development, EUS-guided needle-based confocal laser endomicroscopy (EUS-nCLE) has been applied for the evaluation of both cystic and solid pancreatic lesions.

In the case of pancreatic lesions, EUS-nCLE has been evaluated in a feasibility trial that recruited patients with 16 cystic and 2 solid pancreatic lesions [64]. The trial reported a complication of acute pancreatitis in 2 of the 16 patients with pancreatic cysts. Subsequently, EUS-nCLE was used in 66 patients with pancreatic cysts in a multicenter study, known as the In vivo nCLE Study in the Pancreas with Endosonography of Cystic Tumors (INSPECT). The sensitivity and specificity rates of the finding of epithelial villous structure for the diagnosis of cystic pancreatic neoplasms using an nCLE miniprobe were 59 % and 100 %, respectively [65]. Characteristic nCLE signs for serous cystadenoma and IPMN were a superficial vascular network and finger-like projections, respectively [65, 66].

For solid pancreatic lesions, at the time of writing, to the best of our knowledge, there have only been two trials that have systematically reported on results of EUS-nCLE for solid pancreatic lesions. The first was a multicenter trial,

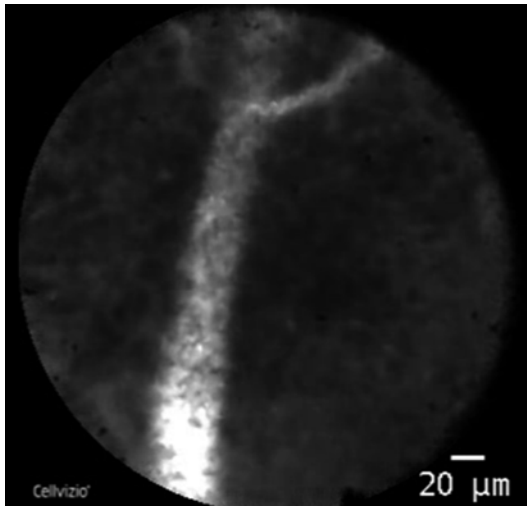

Fig. 8.27 A dilated vessel larger than 20 µm was demonstrated by EUS-guided needle-based confocal laser endomicroscopy of a solid pancreatic lesion with a final diagnosis of pancreatic adenocarcinoma

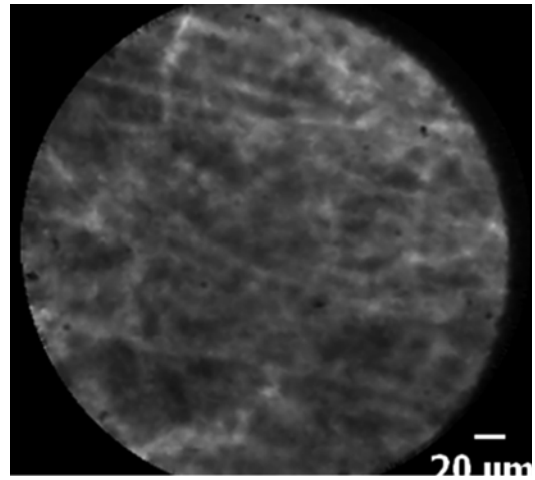

Fig. 8.28 A fine reticular network was demonstrated by EUS-guided needle-based confocal laser endomicroscopy of a solid pancreatic lesion with a final diagnosis of mass-forming chronic pancreatitis

the Clinical Evaluation of Needle-Based Confocal LASER Endomicroscopy (nCLE) for the Diagnosis of Pancreatic Masses (Contact Study), which thus far has been reported only in abstract form. In this retrospective study, nCLE images were reviewed by experts who knew the clinical information and diagnosis of all lesions. The criteria for malignant lesions, dark-cell aggregates with pseudo-glandular aspects and straight hyperdense elements, were described. [66] The second study, the Endoscopic Ultrasound Guided Needle Confocal Laser Endomicroscopy to Distinguish Between Benign and Malignant Lesions in Solid Pancreatic Masses (ENES Study), is a prospective blind study from our group that evaluated the efficacy of EUS-nCLE for solid pancreatic lesions. Preliminary results from the ENES study concluded that the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy rate were 100 %, 66.7 %, 90.9%, 100 %, and 92.3 %, respectively. From this study, the criteria of EUS-nCLE for malignant lesions included dark clumping with or without dilated vessels (>20 µm) (Figs. 8.26 and 8.27). For benign lesions, the criteria included a fibrous band, small black-cell movement, and normal acini (Fig. 8.28) [67]. Interestingly, of 33 patients from the three available studies listed above, no procedure-related complications have thus far been reported.

EUS-nCLE for both solid and cystic pancreatic lesions appears to be a promising technique for providing real-time histology. However, with data available from only a few studies, it is still too early to draw conclusions regarding its efficacy in actual clinical practice. More studies are required to clarify several unclear questions, such as interobserver variations, standard criteria, and correlations with histopathology, among others.

References

1. Gong Z, Holly EA, Bracci PM. Survival in population-based pancreatic cancer patients: San Francisco Bay area, 1995–1999. Am J Epidemiol. 2011;174(12):1373–81.
2. Cheng CT, Tsai CY, Hsu JT, Vinayak R, Liu KH, Yeh CN, et al. Aggressive surgical approach for patients with T4 gastric carcinoma: promise or myth? Ann Surg Oncol. 2011;18(6):1606–14.
3. Kongkam P, Ang TL, Vu CK, Dy FT, Yasuda K, Rerknimitr R, et al. Current status on the diagnosis and evaluation of pancreatic tumor in Asia with particular emphasis on the role of endoscopic ultrasound. J Gastroenterol Hepatol. 2013;28(6):924–30.
4. DeWitt J, Devereaux B, Chriswell M, McGreevy K, Howard T, Imperiale TF, et al. Comparison of

endoscopic ultrasonography and multidetector computed tomography for detecting and staging pancreatic cancer. Ann Intern Med. 2004;141(10):753–63.
5. Hewitt MJ, McPhail MJ, Possamai L, Dhar A, Vlavianos P, Monahan KJ. EUS-guided FNA for diagnosis of solid pancreatic neoplasms: a meta-analysis. Gastrointest Endosc. 2012;75(2):319–31.
6. Brand B, Pfaff T, Binmoeller KF, Sriram PV, Fritscher-Ravens A, Knofel WT, et al. Endoscopic ultrasound for differential diagnosis of focal pancreatic lesions, confirmed by surgery. Scand J Gastroenterol. 2000;35(11):1221–8.
7. Zhang Y, Huang J, Chen M, Jiao LR. Preoperative vascular evaluation with computed tomography and magnetic resonance imaging for pancreatic cancer: a meta-analysis. Pancreatology. 2012;12(3):227–33.
8. Brugge WR, Lee MJ, Kelsey PB, Schapiro RH, Warshaw AL. The use of EUS to diagnose malignant portal venous system invasion by pancreatic cancer. Gastrointest Endosc. 1996;43(6):561–7.
9. Rosch T, Dittler HJ, Strobel K, Meining A, Schusdziarra V, Lorenz R, et al. Endoscopic ultrasound criteria for vascular invasion in the staging of cancer of the head of the pancreas: a blind reevaluation of videotapes. Gastrointest Endosc. 2000;52(4):469–77.
10. Dewitt J, Devereaux BM, Lehman GA, Sherman S, Imperiale TF. Comparison of endoscopic ultrasound and computed tomography for the preoperative evaluation of pancreatic cancer: a systematic review. Clin Gastroenterol Hepatol. 2006;4(6):717–25; quiz 664.
11. Lam KY, Lo CY. Pancreatic endocrine tumour: a 22-year clinico-pathological experience with morphological, immunohistochemical observation and a review of the literature. Eur J Surg Oncol. 1997;23(1):36–42.
12. Aniwan S, Kongkam P, Ridtitid W, Amornsawadwattana S, Sriuranpong V, Ponauthai Y, et al. Su1390 predicting factors of pancreatic lesions missed by CT but diagnosed by EUS. Gastrointest Endosc. 2011;73(4 Supplement):AB251–2.
13. Anderson MA, Carpenter S, Thompson NW, Nostrant TT, Elta GH, Scheiman JM. Endoscopic ultrasound is highly accurate and directs management in patients with neuroendocrine tumors of the pancreas. Am J Gastroenterol. 2000;95(9):2271–7.
14. Zimmer T, Stolzel U, Bader M, Koppenhagen K, Hamm B, Buhr H, et al. Endoscopic ultrasonography and somatostatin receptor scintigraphy in the preoperative localisation of insulinomas and gastrinomas. Gut. 1996;39(4):562–8.
15. Ardengh JC, Rosenbaum P, Ganc AJ, Goldenberg A, Lobo EJ, Malheiros CA, et al. Role of EUS in the preoperative localization of insulinomas compared with spiral CT. Gastrointest Endosc. 2000;51(5):552–5.
16. Palazzo L, Roseau G, Chaussade S, Salmeron M, Gaudric M, Paolaggi JA. Pancreatic endocrine tumors: contribution of ultrasound endoscopy in the diagnosis of localization. Ann Chir. 1993;47(5):419–24.
17. De Angelis C, Carucci P, Repici A, Rizzetto M. Endosonography in decision making and management of gastrointestinal endocrine tumors. Eur J Ultrasound. 1999;10(2–3):139–50.
18. Atiq M, Bhutani MS, Bektas M, Lee JE, Gong Y, Tamm EP, et al. EUS-FNA for pancreatic neuroendocrine tumors: a tertiary cancer center experience. Dig Dis Sci. 2012;57(3):791–800.
19. Pais SA, Al-Haddad M, Mohamadnejad M, Leblanc JK, Sherman S, McHenry L, et al. EUS for pancreatic neuroendocrine tumors: a single-center, 11-year experience. Gastrointest Endosc. 2010;71(7):1185–93.
20. Figueiredo FA, Giovannini M, Monges G, Charfi S, Bories E, Pesenti C, et al. Pancreatic endocrine tumors: a large single-center experience. Pancreas. 2009;38(8):936–40.
21. Siddiqui AA, Brown LJ, Hong SK, Draganova-Tacheva RA, Korenblit J, Loren DE, et al. Relationship of pancreatic mass size and diagnostic yield of endoscopic ultrasound-guided fine needle aspiration. Dig Dis Sci. 2011;56(11):3370–5.
22. Charfi S, Marcy M, Bories E, Pesanti C, Caillol F, Giovannini M, et al. Cystic pancreatic endocrine tumors: an endoscopic ultrasound-guided fine-needle aspiration biopsy study with histologic correlation. Cancer. 2009;117(3):203–10.
23. Kongkam P, Al-Haddad M, Attasaranya S, O'Neil J, Pais S, Sherman S, et al. EUS and clinical characteristics of cystic pancreatic neuroendocrine tumors. Endoscopy. 2008;40(7):602–5.
24. Ahrendt SA, Komorowski RA, Demeure MJ, Wilson SD, Pitt HA. Cystic pancreatic neuroendocrine tumors: is preoperative diagnosis possible? J Gastrointest Surg. 2002;6(1):66–74.
25. Weissmann D, Lewandrowski K, Godine J, Centeno B, Warshaw A. Pancreatic cystic islet-cell tumors. Clinical and pathologic features in two cases with cyst fluid analysis. Int J Pancreatol. 1994;15(1):75–9.
26. Maletta F, Pacchioni D, Carucci P, Accinelli G, Bruno M, Brizzi F, et al. Analysis of cyst fluid obtained by endoscopic ultrasound-guided fine-needle aspiration supporting the diagnosis of a pancreatic neuroendocrine neoplasm. Endoscopy. 2011;43 Suppl 2:E34–5.
27. Curtis GM, Movitz D. The surgical significance of the accessory spleen. Ann Surg. 1946;123:276–98.
28. Halpert B, Gyorkey F. Lesions observed in accessory spleens of 311 patients. Am J Clin Pathol. 1959; 32(2):165–8.
29. Rodriguez E, Netto G, Li QK. Intrapancreatic accessory spleen: a case report and review of literature. Diagn Cytopathol. 2013;41(5):466–9.
30. Barawi M, Bekal P, Gress F. Accessory spleen: a potential cause of misdiagnosis at EUS. Gastrointest Endosc. 2000;52(6):769–72.
31. Malka D, Hammel P, Maire F, Rufat P, Madeira I, Pessione F, et al. Risk of pancreatic adenocarcinoma in chronic pancreatitis. Gut. 2002;51(6):849–52.
32. Varadarajulu S, Tamhane A, Eloubeidi MA. Yield of EUS-guided FNA of pancreatic masses in the presence or the absence of chronic pancreatitis. Gastrointest Endosc. 2005;62(5):728–36; quiz 51, 53.

33. Fritscher-Ravens A, Brand L, Knofel WT, Bobrowski C, Topalidis T, Thonke F, et al. Comparison of endoscopic ultrasound-guided fine needle aspiration for focal pancreatic lesions in patients with normal parenchyma and chronic pancreatitis. Am J Gastroenterol. 2002;97(11):2768–75.
34. Perez-Johnston R, Sainani NI, Sahani DV. Imaging of chronic pancreatitis (including groove and autoimmune pancreatitis). Radiol Clin North Am. 2012;50(3):447–66.
35. Catalano MF, Sahai A, Levy M, Romagnuolo J, Wiersema M, Brugge W, et al. EUS-based criteria for the diagnosis of chronic pancreatitis: the Rosemont classification. Gastrointest Endosc. 2009;69(7): 1251–61.
36. Rosch T, Lorenz R, Braig C, Feuerbach S, Siewert JR, Schusdziarra V, et al. Endoscopic ultrasound in pancreatic tumor diagnosis. Gastrointest Endosc. 1991;37(3):347–52.
37. Glasbrenner B, Schwarz M, Pauls S, Preclik G, Beger HG, Adler G. Prospective comparison of endoscopic ultrasound and endoscopic retrograde cholangiopancreatography in the preoperative assessment of masses in the pancreatic head. Dig Surg. 2000;17(5):468–74.
38. Chari ST, Smyrk TC, Levy MJ, Topazian MD, Takahashi N, Zhang L, et al. Diagnosis of autoimmune pancreatitis: the Mayo Clinic experience. Clin Gastroenterol Hepatol. 2006;4(8):1010–6; quiz 934.
39. Takuma K, Kamisawa T, Gopalakrishna R, Hara S, Tabata T, Inaba Y, et al. Strategy to differentiate autoimmune pancreatitis from pancreas cancer. World J Gastroenterol. 2012;18(10):1015–20.
40. Buscarini E, De Lisi S, Arcidiacono PG, Petrone MC, Fuini A, Conigliaro R, et al. Endoscopic ultrasonography findings in autoimmune pancreatitis. World J Gastroenterol. 2011;17(16):2080–5.
41. Kubota K, Kato S, Akiyama T, Fujita K, Yoneda M, Takahashi H, et al. A proposal for differentiation between early- and advanced-stage autoimmune pancreatitis by endoscopic ultrasonography. Dig Endosc. 2009;21(3):162–9.
42. Ramesh J, Hebert-Magee S, Kim H, Trevino J, Varadarajulu S. Frequency of occurrence and characteristics of primary pancreatic lymphoma during endoscopic ultrasound guided fine needle aspiration: a retrospective study. Dig Liver Dis. 2014;46(5):470–3.
43. Khashab M, Mokadem M, DeWitt J, Emerson R, Sherman S, LeBlanc J, et al. Endoscopic ultrasound-guided fine-needle aspiration with or without flow cytometry for the diagnosis of primary pancreatic lymphoma—a case series. Endoscopy. 2010;42(3):228–31.
44. Li Z, Zhang S, Vasdani N, Castillo E. Clues for diagnosing primary pancreatic lymphoma. Case Rep Gastroenterol. 2012;6(2):438–45.
45. El II H, LeBlanc JK, Sherman S, Al-Haddad MA, Cote GA, McHenry L, et al. Endoscopic ultrasound-guided biopsy of pancreatic metastases: a large single-center experience. Pancreas. 2013;42(3):524–30.
46. DeWitt J, Jowell P, Leblanc J, McHenry L, McGreevy K, Cramer H, et al. EUS-guided FNA of pancreatic metastases: a multicenter experience. Gastrointest Endosc. 2005;61(6):689–96.
47. Hijioka S, Matsuo K, Mizuno N, Hara K, Mekky MA, Vikram B, et al. Role of endoscopic ultrasound and endoscopic ultrasound-guided fine-needle aspiration in diagnosing metastasis to the pancreas: a tertiary center experience. Pancreatology. 2011;11(4):390–8.
48. Lewandrowski KB, Southern JF, Pins MR, Compton CC, Warshaw AL. Cyst fluid analysis in the differential diagnosis of pancreatic cysts. A comparison of pseudocysts, serous cystadenomas, mucinous cystic neoplasms, and mucinous cystadenocarcinoma. Ann Surg. 1993;217(1):41–7.
49. Linder JD, Geenen JE, Catalano MF. Cyst fluid analysis obtained by EUS-guided FNA in the evaluation of discrete cystic neoplasms of the pancreas: a prospective single-center experience. Gastrointest Endosc. 2006;64(5):697–702.
50. Kubo H, Nakamura K, Itaba S, Yoshinaga S, Kinukawa N, Sadamoto Y, et al. Differential diagnosis of cystic tumors of the pancreas by endoscopic ultrasonography. Endoscopy. 2009;41(8):684–9.
51. Barresi L, Tarantino I, Granata A, Curcio G, Traina M. Pancreatic cystic lesions: how endoscopic ultrasound morphology and endoscopic ultrasound fine needle aspiration help unlock the diagnostic puzzle. World J Gastrointest Endosc. 2012;4(6):247–59.
52. Gouhiri M, Soyer P, Barbagelatta M, Rymer R. Macrocystic serous cystadenoma of the pancreas: CT and endosonographic features. Abdom Imaging. 1999;24(1):72–4.
53. Tanaka M, Chari S, Adsay V, Fernandez-del Castillo C, Falconi M, Shimizu M, et al. International consensus guidelines for management of intraductal papillary mucinous neoplasms and mucinous cystic neoplasms of the pancreas. Pancreatology. 2006;6(1–2):17–32.
54. Zamboni G, Scarpa A, Bogina G, Iacono C, Bassi C, Talamini G, et al. Mucinous cystic tumors of the pancreas: clinicopathological features, prognosis, and relationship to other mucinous cystic tumors. Am J Surg Pathol. 1999;23(4):410–22.
55. Khalid A, Brugge W. ACG practice guidelines for the diagnosis and management of neoplastic pancreatic cysts. Am J Gastroenterol. 2007;102(10):2339–49.
56. Levy MJ. Pancreatic cysts. Gastrointest Endosc. 2009;69(2 Suppl):S110–6.
57. Tanaka M, Fernandez-del Castillo C, Adsay V, Chari S, Falconi M, Jang JY, et al. International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas. Pancreatology. 2012;12(3): 183–97.
58. Hruban RH, Takaori K, Klimstra DS, Adsay NV, Albores-Saavedra J, Biankin AV, et al. An illustrated consensus on the classification of pancreatic intraepithelial neoplasia and intraductal papillary mucinous neoplasms. Am J Surg Pathol. 2004;28(8):977–87.
59. Butte JM, Brennan MF, Gonen M, Tang LH, D'Angelica MI, Fong Y, et al. Solid pseudopapillary tumors of the pancreas. Clinical features, surgical outcomes, and long-term survival in 45 consecutive

patients from a single center. J Gastrointest Surg. 2011;15(2):350–7.
60. Martin RC, Klimstra DS, Brennan MF, Conlon KC. Solid-pseudopapillary tumor of the pancreas: a surgical enigma? Ann Surg Oncol. 2002;9(1):35–40.
61. Buetow PC, Buck JL, Pantongrag-Brown L, Beck KG, Ros PR, Adair CF. Solid and papillary epithelial neoplasm of the pancreas: imaging-pathologic correlation on 56 cases. Radiology. 1996;199(3):707–11.
62. Park HY, Lee YJ, Lee JH, Lee MJ, Lee JK, Lee KT, et al. Endoscopic ultrasound-guided fine needle aspiration of solid pseudopapillary tumors of the pancreas: a report of three cases. Korean J Intern Med. 2013;28(5):599–604.
63. Wanders LK, East JE, Uitentuis SE, Leeflang MM, Dekker E. Diagnostic performance of narrowed spectrum endoscopy, autofluorescence imaging, and confocal laser endomicroscopy for optical diagnosis of colonic polyps: a meta-analysis. Lancet Oncol. 2013;14(13):1337–47.
64. Konda VJ, Aslanian HR, Wallace MB, Siddiqui UD, Hart J, Waxman I. First assessment of needle-based confocal laser endomicroscopy during EUS-FNA procedures of the pancreas (with videos). Gastrointest Endosc. 2011;74(5):1049–60.
65. Konda VJ, Meining A, Jamil LH, Giovannini M, Hwang JH, Wallace MB, et al. A pilot study of in vivo identification of pancreatic cystic neoplasms with needle-based confocal laser endomicroscopy under endosonographic guidance. Endoscopy. 2013;45(12):1006–13.
66. Giovannini M, Caillol F, Bories E, Filoche B, Napoleon B. Mo1557 Clinical Evaluation of Needle-Based Confocal LASER Endomicroscopy (nCLE) for the Diagnosis of Pancreatic Masses (Contact Study). Gastrointest Endosc. 2013;77(5):AB425.
67. Pittayanon R, Kongkam P, Sampatanukul P, Aniwan S, Angsuwatcharakon P, Treeprasertsuk S, et al. 1043 EUS Guided Needle-Based Confocal LASER Endomicroscopy (nCLE) to distinguish between benign and malignant lesions in solid pancreatic masses: preliminary results of a prospective single-blind study. Gastrointest Endosc. 2014;79(5 Supplement):AB190–1.

Contrast-Enhanced EUS

9

Masayuki Kitano

Introduction

Ductal carcinoma of the pancreas is one of the solid carcinomas which have the worst prognosis. Despite better diagnostic methods, it is still rare to detect pancreatic ductal carcinoma in an early stage. Although most solid pancreatic masses are ductal carcinomas, it is essential to distinguish them from noncarcinoma lesions, such as focal pancreatitis and neuroendocrine tumors, which have a different prognosis and require different therapeutic approaches. Endoscopic ultrasonography (EUS) is thought to be one of the most reliable and efficient modalities for diagnosing pancreatic tumors as it can detect pancreatic carcinomas with a sensitivity of >90 % [1–6]. Its spatial resolution is superior to that of other modalities such as CT and magnetic resonance imaging (MRI). Thus, EUS is more accurate than transabdominal US, CT, and MRI in terms of detecting and staging pancreatic diseases [1–17]. However, the ability of EUS to characterize pancreatic masses is limited.

M. Kitano (✉)
Department of Gastroenterology and Hepatology,
Kinki University Faculty of Medicine,
377-2 Ohno-Higashi, Osaka-Sayama, Osaka
589-8511, Japan
e-mail: m-kitano@med.kindai.ac.jp

On EUS, pancreatic carcinomas typically appear as hypoechoic masses with irregular contours or heterogeneous regions. However, it is difficult to diagnose some pancreatic lesions by EUS because, like most carcinomas, neuroendocrine tumors and inflammatory pseudotumors also typically appear as hypoechoic masses. One way to characterize such hypoechoic masses, thus allowing them to be distinguished from carcinomas, is by using contrast enhancement. Contrast enhancement in CT and MRI during imaging of the pancreas has been shown to provide important supplementary information. There have also been recent advances in contrast enhancement in the field of EUS that have facilitated the characterization of conventional EUS-detected pancreatic lesions.

Technological Advances in Contrast-Enhanced EUS

Contrast-Enhanced EUS Using Fundamental B Mode

Contrast-enhanced EUS was introduced in the early 1990s. The first method was to infuse carbon dioxide (CO_2) microbubbles into the hepatic artery through a catheter during angiography [18]. Fundamental B-mode EUS sufficiently depicts the signals from the CO_2 microbubbles in a real-time manner and thus intraarterial CO_2 infusion combined with ultrasonography yields

M.S. Wagh, P.V. Draganov (eds.), *Pancreatic Masses*, DOI 10.1007/978-3-319-19677-0_9

images with very high spatial and time resolution. However, this method is hampered by the fact that the ultrasonographic scanning must be performed during angiography.

Contrast-Enhanced Doppler EUS

In the 1990s, the first-generation intravenous ultrasound contrast agent called Levovist appeared. Such contrast agents are more convenient compared to CO_2 microbubbles for contrast-enhanced ultrasonography because only a bolus infusion of the agent from a peripheral vein is required. Contrast-enhanced Doppler sonography has been proposed to be a valuable technique for the diagnosis of pancreatic tumors because phase shift of the returned signals from the ultrasound contrast agent produces pseudo-Doppler signals that enhance the Doppler signals from the vessels [19–25]. Thus, infusing an ultrasound contrast agent increases the sensitivity with which color and power Doppler imaging depicts the Doppler signals from vessels, which in turn aids the characterization of pancreatic lesions (Fig. 9.1). However, this technique is hampered by artifacts such as blooming, which limit vessel imaging. Moreover, using a Doppler technique can only lead to a contrast-enhancing effect in vessels. Recently, a novel type of directional power Doppler method called Directional eFLOW (Aloka Co., Ltd, Tokyo, Japan) was developed [26]. This method permits the blood flow in minute vessels to be detected in more detail than can be achieved with conventional power or color Doppler. In directional eFLOW mode, fewer blooming artifacts are observed because broadband transmission is optimized and the real repeating frequency is increased (Fig. 9.2) [26].

Contrast-Enhanced Harmonic EUS

Another sonographic technique is contrast-enhanced harmonic imaging. By employing a microbubble contrast agent, contrast-enhanced harmonic US depicts signals from microbubbles in very slow flow without Doppler-related artifacts, thereby enabling the slow flow in microscopic vessels to be visualized [27, 28]. However, when only the first-generation ultrasound contrast agent Levovist was available, the contrast harmonic imaging technique could not be used for EUS examination because the echoendoscope transducer has a limited frequency bandwidth and is too small to produce enough acoustic power. However, second-generation ultrasound contrast agents, such as SonoVue (Bracco Imaging, Milan, Italy), Sonazoid (Daiichi-Sankyo, Tokyo, Japan; GE Health Care, Milwaukee, WI, USA), and Definity (Lantheus Medical Imaging, North Billerica, MA, USA) produce harmonic signals at lower acoustic power and are therefore suitable for EUS imaging with low acoustic power [29–31]. Contrast-enhanced harmonic EUS could thus be performed

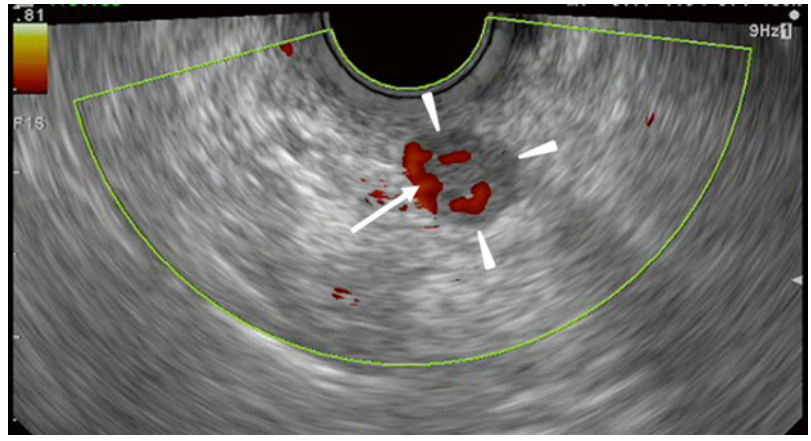

Fig. 9.1 Typical image of the pancreatic neuroendocrine tumor on contrast-enhanced Doppler EUS. Contrast-enhanced power Doppler imaging shows a tumor of 7 mm in diameter (*arrowheads*), which includes abundant vessels (*arrow*). The vessels are depicted wider than themselves

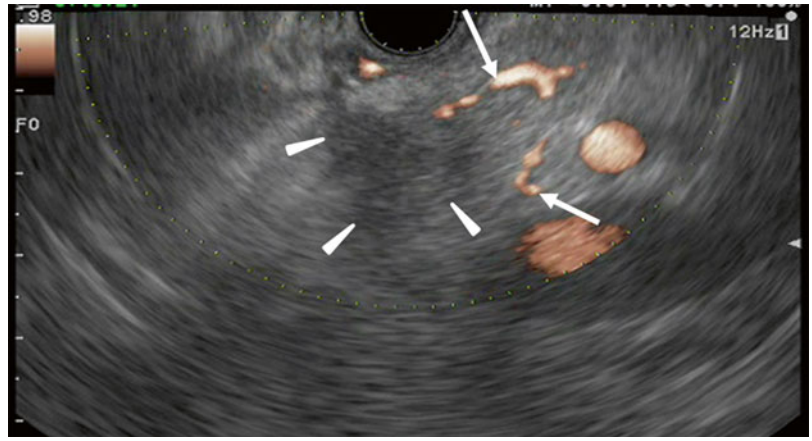

Fig. 9.2 Typical image of the pancreatic ductal carcinoma on contrast-enhanced directional eFLOW EUS. Contrast-enhanced directional eFLOW imaging shows a tumor of 14 mm in diameter (*arrowheads*). The tumor does not have color signals, while the fine vessel structure can be depicted in the surrounding tissue (*arrows*)

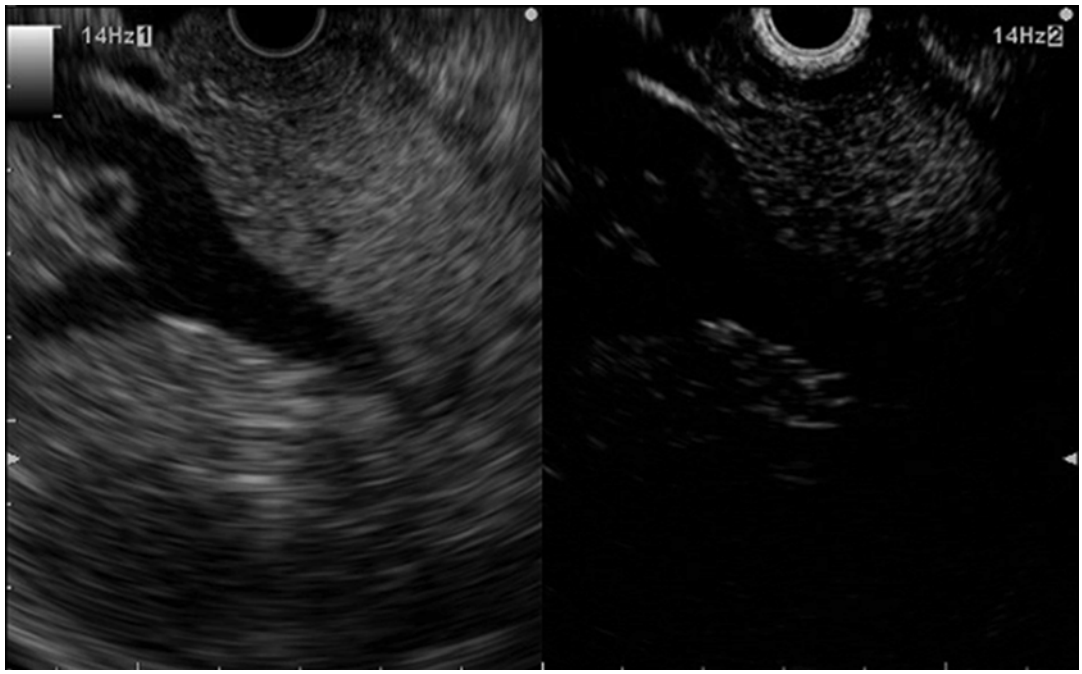

Fig. 9.3 Time course of contrast-enhanced harmonic EUS images of the normal pancreas before and after infusion of an ultrasound contrast agent (Sonazoid). *Left*: conventional EUS image (monitor mode). *Right*: contrast-enhanced harmonic EUS image (extended pure harmonic detection mode). (**a**) Images before infusion. Contrast-enhanced harmonic EUS (*right*) shows no signals from the pancreas. (**b**) Images 10 s after infusion. Contrast-enhanced harmonic EUS (*right*) shows strong signal from common hepatic artery (*arrow*) and branching microvessels in the pancreas (*arrowheads*). (**c**) Images 22 s after infusion. Contrast-enhanced harmonic EUS (*right*) shows diffuse signals in the pancreatic parenchyma and strong signals in the portal vein (*arrowheads*). Pancreatic duct (PD) and bile duct (BD) are depicted as avascular ductal structures

with these second-generation ultrasound contrast agents and a wide-band transducer equipped with EUS (Fig. 9.3). This technique is likely to improve the differential diagnosis of pancreatic disease (Figs. 9.4 and 9.5). Two groups first reported this new technology with different

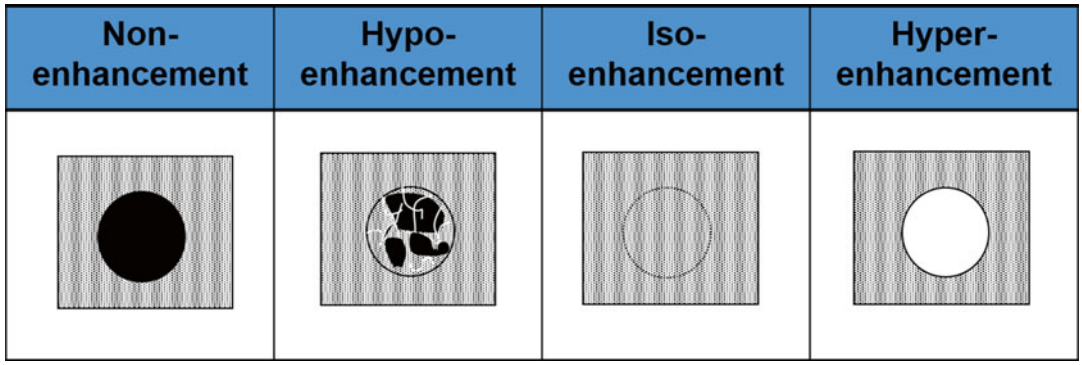

Fig. 9.4 Vascular patterns that can be depicted by contrast-enhanced harmonic EUS. Solid pancreatic lesions can be categorized into four patterns, namely, nonenhancement, hypoenhancement, isoenhancement, and hyperenhancement

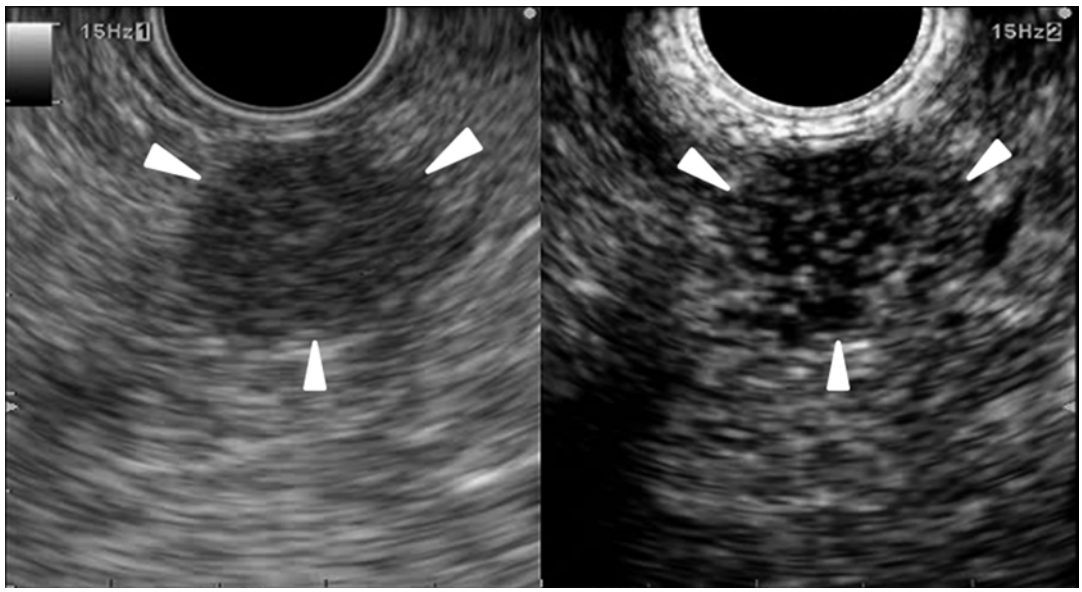

Fig. 9.5 Typical images of pancreatic solid tumors on contrast-enhanced harmonic EUS. *Left*: conventional EUS image (monitor mode). *Right*: contrast-enhanced harmonic EUS image (extended pure harmonic detection mode). (**a**) Ductal carcinoma with hypoenhancement. Conventional EUS (*left*) shows a hypoechoic area (*arrowheads*) of 10 mm in diameter at the pancreas body. CH-EUS (*right*) indicates that the area has hypoenhancement (*arrowheads*) compared with the surrounding tissue. (**b**) Autoimmune pancreatitis with isoenhancement. Conventional EUS (*left*) shows a hypoechoic area (*arrowheads*) of 23 mm in diameter at the pancreas body. CH-EUS (*right*) indicates that the area has homogeneous enhancement similar to the surrounding tissue; a margin is not observed. (**c**) Neuroendocrine tumor with hyperenhancement. Conventional EUS (*left*) shows a hypoechoic area (*arrowheads*) of 19 mm in diameter at the pancreas body. CH-EUS (*right*) indicates that the area has hyperenhancement (*arrowheads*) compared with the surrounding tissue

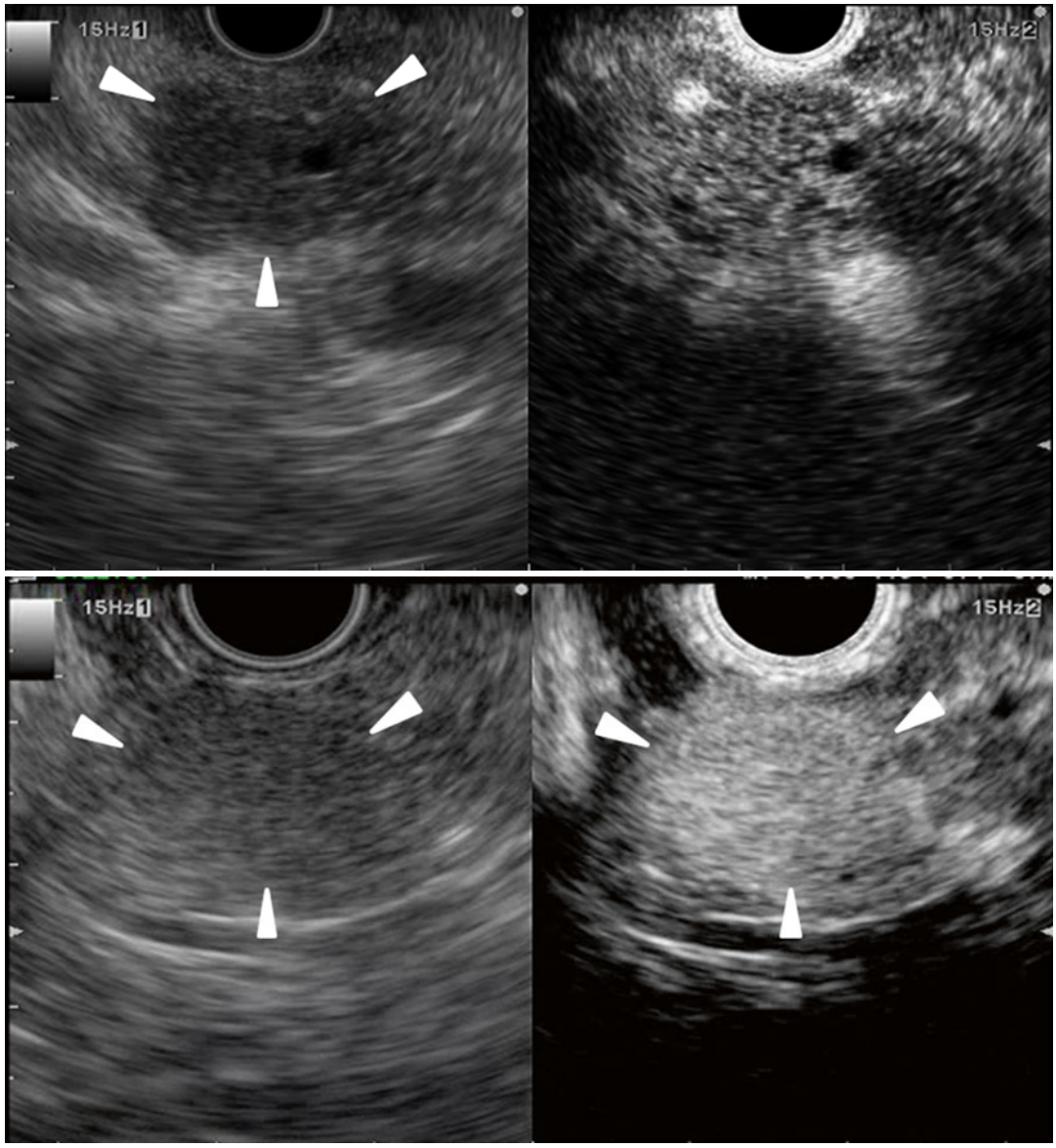

Fig. 9.5 (continued)

high-end EUS systems. In 2005, Dietrich et al. described contrast-enhanced, low-mechanical index, real-time EUS that employed adapted dynamic-contrast harmonic wide-band pulsed inversion software [29]. This method was used to identify the celiac trunk, the common hepatic artery, the splenic artery, and the portal vein and its branches and collaterals in patients with portal vein thrombosis [29]. In 2008, the authors of the present chapter described the development of another EUS system that was equipped with an echoendoscope with a broadband transducer and a specific mode for contrast harmonic imaging [30, 31]. This system allowed depiction of the microcirculation and parenchymal perfusion in patients with pancreatobiliary diseases, gastrointestinal stromal tumors, and lymph node metastases [30, 31]. Unlike contrast-enhanced Doppler

EUS, contrast-enhanced harmonic EUS depicts large vessels without blooming artifacts; fine vessels are also detected, which allows parenchymal perfusion imaging [30]. A recent report also described the quantitative assessment of pancreatic lesions with contrast-enhanced harmonic EUS by using a time–intensity curve. This reproducible and objective analysis may aid the diagnosis of pancreatic lesions [32–35].

Principle and Ultrasound Contrast Agents of Contrast-Enhanced Harmonic EUS

Principle

Ultrasound contrast agents are microbubbles consisting of gas covered with a lipid or phospholipid membrane. A certain range of acoustic power induces microbubble oscillation or breakage. When microbubbles are oscillated or broken, harmonic components that are integer multiples of the fundamental frequency are produced [27, 28]. The harmonic content derived from microbubbles is higher than that from tissues. Contrast harmonic imaging more intensively depicts signals from the microbubbles than those from the tissue by selectively detecting the second harmonic components [27, 28]. Phase-shift output, which more greatly occurs in ultrasound contrast agents than in the other part, also enhances the signals from the ultrasound contrast agent. Phase-shift signal outputs are synthesized with second harmonic signals to reinforce the harmonic signals [30, 31].

Ultrasound Contrast Agents

The first ultrasound contrast agent, Levovist, consists of air-filled galactose microbubbles [36]. However, high acoustic power is needed to oscillate or break these microbubbles. To overcome this disadvantage, second-generation ultrasound contrast agents, including SonoVue (Bracco Imaging, Milan, Italy), Sonazoid (Daiichi-Sankyo, Tokyo, Japan; GE Health Care, Milwaukee, WI, USA), and Definity (Lantheus Medical Imaging, North Billerica, MA, USA), were created. These agents are composed of microbubbles of gases, not room air, that are covered with a lipid or phospholipid membrane [36]. They can be oscillated by low acoustic power, which is suitable for EUS. Immediately before performing contrast enhancement, these ultrasound contrast agents are constituted by shaking powder with water and gas and then infused intravenously as a bolus.

Contrast-Enhanced Doppler EUS for Pancreatic Masses

Doppler Mode EUS Without Ultrasound Contrast Agents

While waiting for the second-generation ultrasound contrast agents to be developed, color and power Doppler with and without ultrasound contrast agents were used for vessel imaging. The development of electronic EUS led to color and power Doppler EUS, which are powerful and simple methods for detecting blood vessels and can be of great advantage in difficult cases. Most pancreatic carcinomas, neuroendocrine tumors, and inflammatory pseudotumors are simply depicted as hypoechoic masses by Doppler mode EUS. When contrast agents are not used for vessel imaging, pancreatic cancer can be diagnosed on the basis of their lack of power Doppler signals with an accuracy of 34–88 % [21, 22, 25].

Doppler Mode EUS with Ultrasound Contrast Agents

The use of contrast improves the characterization of the vasculature inside the organ of interest and better delineates hypoechoic masses. Indeed, on the basis of contrast-enhanced Doppler EUS images, pancreatic tumors can be classified according to their vessel density relative to that in the surrounding pancreatic tissue. Well-designed

prospective studies have shown that contrast-enhanced Doppler EUS diagnoses pancreatic carcinomas with a sensitivity ranging from 85 to 94 % and a specificity ranging from 71 to 100 % [20–26].

When Dietrich et al. used contrast-enhanced (color Doppler) EUS to investigate patients with undetermined pancreatic tumors, they found that 92 % of the adenocarcinomas of the pancreas exhibited hypovascularity (Fig. 9.3) [23]. By contrast, all other pancreatic lesions had an isovascular or hypervascular pattern (Fig. 9.2). In their experience, hypovascularity in contrast-enhanced Doppler EUS indicated pancreatic malignancy with 92 % sensitivity and 100 % specificity [23]. Regarding the usefulness of contrast-enhanced EUS in terms of differentiating inflammation from pancreatic carcinoma, Hocke et al. reported that Sonovue increased the sensitivity of EUS from 73 to 91 % [21]. Moreover, when Sakamoto et al. compared the abilities of contrast-enhanced CT and contrast-enhanced Doppler EUS by power Doppler mode using Levovist to detect and differentially diagnose the pancreatic tumors in 156 consecutive patients with suspected pancreatic tumors, they found that EUS detected small (2 cm or less) pancreatic carcinomas with a significantly higher sensitivity (94 %) than contrast-enhanced CT (50 %) [22]. Moreover, contrast-enhanced CT, Doppler mode EUS without contrast, and contrast-enhanced Doppler EUS could distinguish small (≤2 cm) ductal carcinomas from other small (≤2 cm) pancreatic tumors with sensitivities of 50.0 %, 11.0 %, and 83.3 %, respectively. Thus, contrast-enhanced Doppler EUS was significantly more sensitive than Doppler mode EUS and contrast-enhanced CT [22].

With respect to pancreatic neuroendocrine tumors, most heterogeneous hypoechoic areas and anechoic areas correspond to hemorrhage or necrosis on pathological examination, which was the most significant factor suggestive of malignancy [24]. These areas are identified as filling defects in contrast-enhanced Doppler EUS and thus are depicted more clearly by contrast-enhanced Doppler EUS than by conventional EUS [24].

Contrast-Enhanced Harmonic EUS for Pancreatic Masses

Enhancement Patterns

Compared to contrast-enhanced Doppler EUS, contrast-enhanced harmonic EUS more clearly depicts microvessels and parenchymal perfusion in the pancreas. Pancreatic solid lesions can be characterized on the basis of their contrast-enhanced harmonic EUS enhancement patterns, namely, nonenhancement, hypoenhancement, isoenhancement, or hyperenhancement (Figs. 9.4 and 9.5) [32–35, 37–41]. Pancreatic ductal carcinomas are depicted as nodules with hypoenhancement that mostly have irregular network-like vessels (Fig. 9.5a) [30]. When we use Sonazoid, which is the most sensitive of the ultrasound contrast agents, all ductal carcinomas exhibit signals from the ultrasound contrast agent. However, in most lesions, the signals are lower than those in their surrounding tissues (Fig. 9.5a). By contrast, in most patients with autoimmune pancreatitis and inflammatory tumors, the whole pancreatic organ shows homogeneous iso-enhancement on contrast-enhanced harmonic EUS (Fig. 9.5b). Moreover, most neuroendocrine tumors exhibit hyperenhancement on contrast-enhanced harmonic EUS (Fig. 9.5c). This supports the underlying theory that different kinds of masses in the pancreas have different microvasculatures. A recently published meta-analysis showed that when pancreatic adenocarcinomas were defined as lesions with hypoenhancement on contrast-enhanced harmonic EUS, these tumors were diagnosed with a pooled sensitivity and specificity of 94 % and 89 %, respectively, although it should be noted that this meta-analysis included articles using both contrast-enhanced Doppler and contrast-enhanced harmonic imaging [42].

Quantitative Analysis

Recent articles on quantitative analyses using a time–intensity curve with contrast-enhanced harmonic EUS revealed that several variables

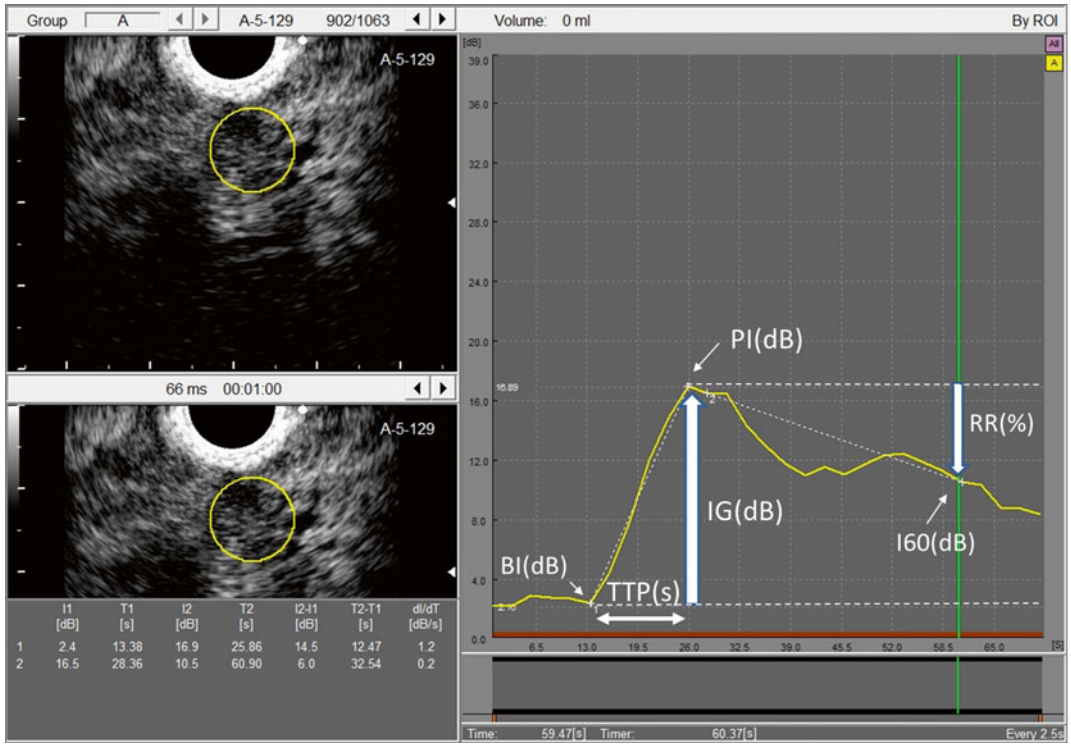

Fig. 9.6 Time–intensity curve of echo intensity in a pancreatic carcinoma. Time-course of the echo intensity in the *yellow circle* is measured. *BI,* base intensity; *PI,* peak intensity; *IG,* intensity gain; *TTP,* time to peak; *I60,* intensity at 60 s; *RR,* reduction rate of the echo intensity

measured by the time–intensity curve can be used to differentially diagnose conventional EUS-detected pancreatic masses. Most neuroendocrine tumors exhibit hyperenhancement on contrast-enhanced harmonic EUS (Fig. 9.6) [32–35]. Seicean et al. reported that the ratio between the uptake inside the mass and the uptake of the surrounding parenchyma was useful for differentiating adenocarcinomas from mass-forming chronic pancreatitis [32]. Adenocarcinomas and pseudotumoral pancreatitis also differed significantly in terms of median intensity, maximum intensity, time to peak, and area under the curve [34]. Contrast-enhanced EUS using such time–intensity curve analysis diagnosed pancreatic adenocarcinomas with a sensitivity and specificity of 94 % and 89 %, respectively [34]. Imazu et al. also reported that adenocarcinomas and autoimmune pancreatitis differed significantly in terms of peak intensity and maximum intensity gain [33]. Receiver operating characteristics analysis yielded an optimal maximum intensity gain cutoff value of 12.5 that was associated with a high sensitivity and specificity (both 100 %) [33]. Matsubara et al. reported that of all pancreatic lesions, adenocarcinomas had the greatest echo intensity reduction rate from the peak at 1 min ($P<0.05$) [35]. In their report, adenocarcinomas were diagnosed more accurately by using the contrast imaging pattern (84.0 %) and time–intensity curve analysis (88.0 %) than by using fundamental B-mode imaging (82.6 %) or dynamic CT (81.3 %) [35]. So far, which quantitative analysis valuable is most sensitive remains unclear. This may reflect the fact that all reports on quantitative analysis are based on a limited number of patients in a single institute. A multicenter study with a large number of patients would reveal which variable should be used for diagnosing pancreatic masses.

Comparison to Other Imaging Methods

When Fusaroli et al. compared contrast-enhanced harmonic EUS with conventional EUS, they found that the former detects hypoenhanced lesions with a higher sensitivity and specificity (96 % and 64 %, respectively) than conventional EUS detects hypoechoic lesions (86 % and 18 %, respectively) [37]. They also reported that contrast-enhanced harmonic EUS improves the depiction of pancreatic tumors compared to conventional EUS. Indeed, in some ductal carcinomas with uncertain conventional EUS findings, an outline was detected by contrast-enhanced harmonic EUS [37].

When the authors of the present review compared contrast-enhanced harmonic EUS to contrast-enhanced CT, they found they were generally comparable in terms of differentiating ductal carcinomas from other masses [39]. However, contrast-enhanced harmonic EUS (91 % sensitivity and 94 % specificity) was superior to contrast-enhanced CT (71 % sensitivity and 92 % specificity) for diagnosing small (≤2 cm) carcinomas. In particular, contrast-enhanced harmonic EUS was useful for characterizing 12 neoplasms that contrast-enhanced CT failed to detect [39].

EUS elastography is another new image enhancement technology. Two reports have compared contrast-enhanced EUS and EUS elastography. When Săftoiu et al. compared the diagnostic accuracy of contrast-enhanced Doppler EUS and/or EUS elastography in pancreatic solid masses, they found that the two techniques had comparably high sensitivities (91 % and 85 %, respectively) [25]. Although their individual specificities were less than 70 %, combining the two methods improved the specificity: When ductal carcinomas were defined as lesions with hypoenhancement on contrast-enhanced Doppler EUS and hard elasticity on EUS elastography, the specificity was 95 %. Thus, the combination method reduces the number of false-positive cases [25]. By contrast, Hocke et al. concluded that the combination of fundamental B mode, elastography, and contrast-enhanced Doppler EUS imaging (the sensitivity and specificity were 90 % and 64 %, respectively) was not superior to contrast-enhanced Doppler EUS alone (90 % sensitivity and 92 % specificity) [43]. The different conclusions of these two reports may depend on the diagnostic accuracy of EUS elastography and contrast-enhanced EUS. Further study is needed to establish the contrast-enhanced harmonic EUS and EUS elastography criteria that can be used to diagnose pancreatic tumors.

Relationship to EUS-FNA

Conventional EUS fails to depict pancreatic tumors in cases with chronic pancreatitis, diffusely infiltrating carcinoma, or a recent episode of acute pancreatitis. In such cases, the target of EUS-FNA cannot be identified. Since contrast-enhanced harmonic EUS clearly depicts subtle lesions that conventional EUS cannot identify, it can be used to identify the target of EUS-FNA [37, 39, 44]. It can also be used to identify a specific site within an otherwise clearly visible lesion that would be more suitable for EUS-FNA than other sites (Fig. 9.7) [45]. Identification and avoidance of the avascular sites in a lesion may help avoid sampling necrotic areas (Fig. 9.7) [45].

Three studies reported that contrast-enhanced harmonic EUS is as sensitive as EUS-FNA in detecting pancreatic adenocarcinomas [38, 39, 41]. Thus, contrast-enhanced harmonic EUS may be complementary to EUS-FNA, particularly for identifying adenocarcinomas with false-negative EUS-FNA findings [38, 39, 41]. The authors of the present review have reported that when contrast-enhanced harmonic EUS is combined with EUS-FNA, the sensitivity of EUS-FNA increases from 92 to 100 % [39]. Similarly, in a French multicenter study, five EUS-FNA false-negative cases were correctly classified by contrast-enhanced harmonic EUS [41].

EUS-FNA is also sometimes difficult to perform because of intervening vessels or anticoagulation treatment. In such cases, contrast-enhanced EUS may be a useful substitute [46]. Contrast-enhanced EUS may also be useful for assessing lymph nodes that cannot be accessed by EUS-FNA because of an intervening tumor; it can also eliminate the time and risk associated with performing EUS-FNA at a second site [46].

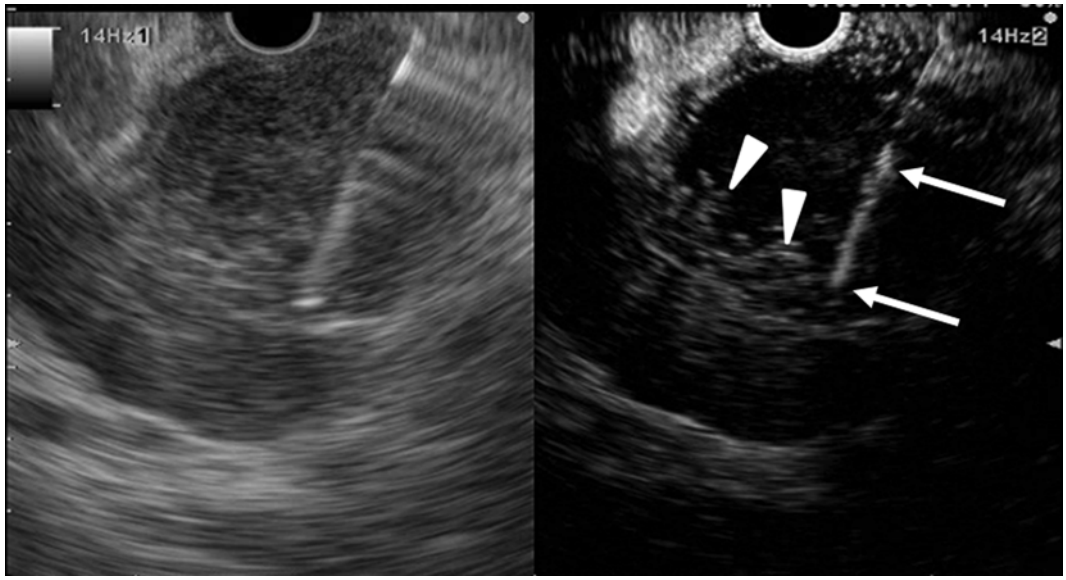

Fig. 9.7 EUS-guided fine-needle aspiration under simultaneous guidance of conventional EUS and contrast-enhanced harmonic EUS. *Left*: conventional EUS image (monitor mode). *Right*: contrast-enhanced harmonic EUS image (extended pure harmonic detection mode). Conventional EUS (*left*) shows a hypoechoic tumor of 38 mm in diameter. Contrast-enhanced harmonic EUS shows nonenhancement, indicating necrotic tissue in most parts of the tumor, except a part with enhancement (*arrowheads*) which is punctured with a needle (*arrows*)

Contrast-Enhanced EUS for Staging

T-Staging

When Imazu et al. compared conventional EUS and contrast-enhanced harmonic EUS in terms of preoperative T-staging of pancreatobiliary tumors, they found that contrast-enhanced harmonic EUS correctly T-staged 24 of 26 pancreatobiliary tumors, six of which were misstaged by conventional EUS [47]. In particular, contrast-enhanced harmonic EUS depicted the wall of the portal vein more clearly than conventional EUS, which means that it is superior in terms of diagnosing portal invasion by pancreatobiliary adenocarcinomas [47].

N-Staging

With respect to lymph node metastases, Kanamori et al. evaluated the utility of contrast-enhanced Doppler EUS for differentiating malignant from benign lymph nodes [48]. Contrast-enhanced Doppler EUS using Levovist was significantly more sensitive (100 %) and specific (86 %) than plain EUS (88 % and 77 %), respectively [48]. When Xia et al. used contrast-enhanced harmonic EUS to diagnose intraabdominal lesions of undetermined origin, 96.3 % of the malignant lesions exhibited heterogeneous enhancement on contrast-enhanced harmonic EUS (Fig. 9.8a) [49]. By contrast, 75 % of the benign lesions exhibited homogeneous enhancement (Fig. 9.8b). Thus, contrast-enhanced EUS can be used for N-staging of digestive tract tumors [49].

Future Perspectives for Contrast-Enhanced EUS

To date, the contrast-enhanced EUS technique has largely been used to evaluate vascularity. However, recent studies revealed that this technique can also be used to evaluate response to treatment, for molecular imaging, and to provide local therapy [50–55]. Recently, there has been interest in the possibility of using EUS-guided ablation to treat focal pancreatic lesions.

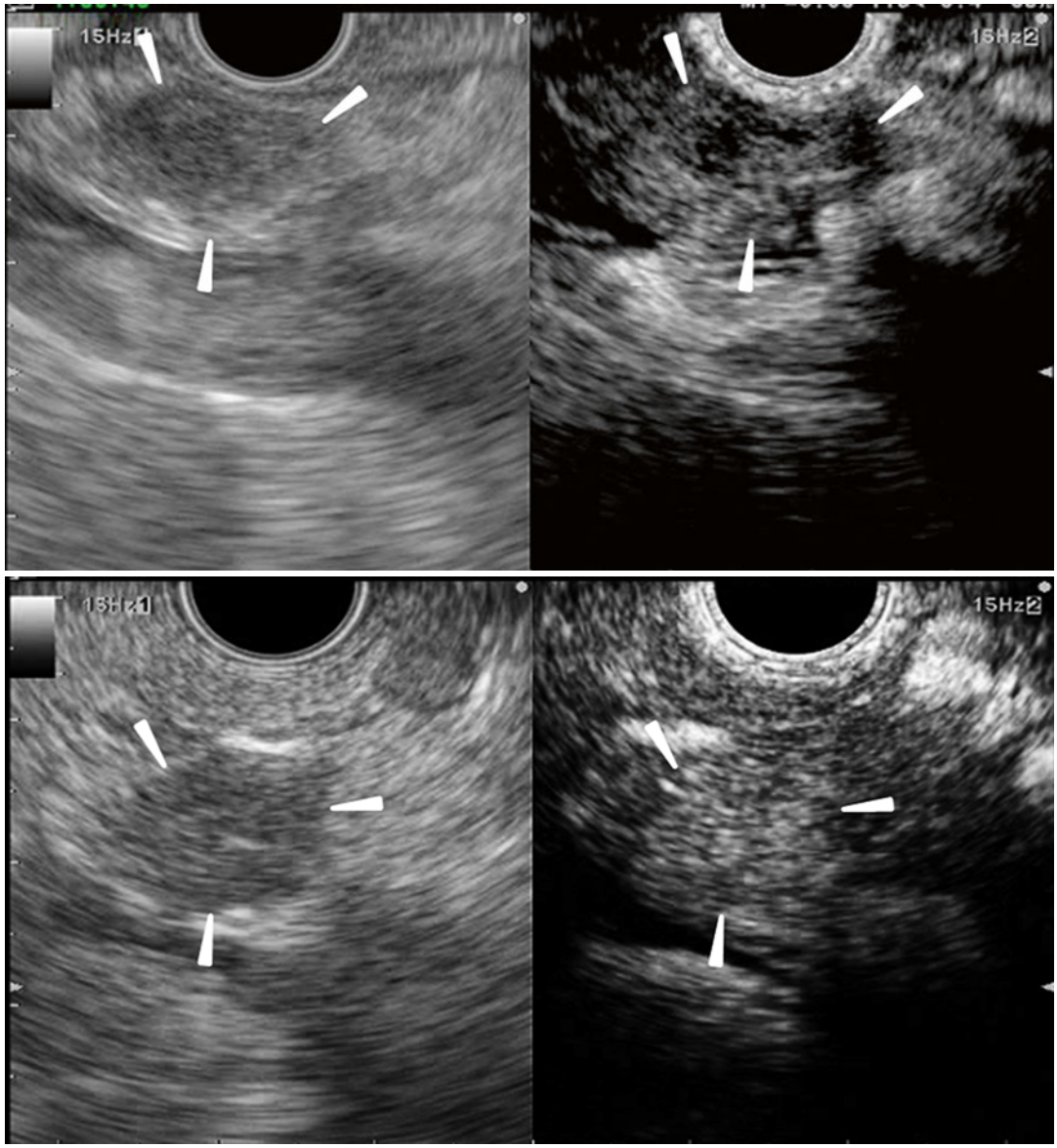

Fig. 9.8 Typical images of lymph nodes with contrast-enhanced harmonic EUS. *Left*: conventional EUS image (monitor mode). *Right*: contrast-enhanced harmonic EUS image (extended pure harmonic detection mode). (**a**) Malignant lymph node with heterogeneous enhancement. Conventional EUS (*left*) shows a lymph node of 14 mm in diameter (*arrowheads*). Contrast-enhanced harmonic EUS (*right*) indicates that the lymph node has heterogeneous enhancement (*arrowheads*). (**b**) Benign lymph node with homogeneous enhancement. Conventional EUS (*left*) shows a lymph node of 13 mm in diameter (*arrowheads*). Contrast-enhanced harmonic EUS (*right*) indicates that the lymph node has homogeneous enhancement (*arrowheads*)

Experiments in pigs showed that contrast-enhanced EUS improved the visualization of altered pancreatic vascular perfusion after a local injection of ethanol, which indicates that contrast-enhanced EUS can be used to follow up the ablated lesion [53]. Moreover, an ultrasound contrast agent that was covalently coupled to a recombinant single-chain vascular endothelial growth factor (VEGF) succeeded in depicting the tumor in a murine model of colon adenocarcinoma [50–52]. This suggests that ultrasonic depiction of VEGF may facilitate the molecular

profiling of angiogenesis in the tumor and the early assessment of antiangiogenic therapy effects.

The development of contrast-enhanced EUS will also be beneficial for targeted drug delivery applications in pancreatic tumors. Drug substances, including plasmid DNA, can be delivered within the microbubbles. High-intensity ultrasound beams can potentially destroy these microbubbles so that the drug is only released in the pancreas [54]. This targeted drug delivery treatment is likely to enhance drug action and reduce undesirable adverse effects. A recently developed microbubble precursor called phase change nanodroplets (PCNDs) becomes microbubbles and produces high energy that can destroy tissues when it receives high-intensity ultrasound beams [55]. In addition, the spatial distribution of locally injected PCNDs can be manipulated using ultrasound pulses [55], suggesting that EUS-guided injection of this microbubble precursor and high-intensity focused ultrasound may lead to cancer ablation. Thus, contrast-enhanced EUS technology will expand to these promising applications in the near future.

Conclusions

Contrast-enhanced harmonic EUS is a promising method that promotes the identification and differentiation of pancreatic masses, particularly small lesions that cannot be identified by other imaging methods. Moreover, contrast-enhanced harmonic EUS-detected hypoenhancement in a lesion is a sensitive and accurate predictor of pancreatic adenocarcinoma. Contrast-enhanced harmonic EUS can also supplement EUS-FNA in terms of characterizing pancreatic lesions. Moreover, it can be used to identify the target of EUS-FNA.

References

1. Yasuda K, Mukai H, Fujimoto S, Nakajima M, Kawai K. The diagnosis of pancreatic cancer by endoscopic ultrasonography. Gastrointest Endosc. 1989;35:214–9.
2. Kaufman AR, Sivak Jr MV. Endoscopic ultrasonography in the differential diagnosis of pancreatic disease. Gastrointest Endosc. 1989;35:214–9.
3. Rösch T, Lorenz R, Braig C, et al. Endoscopic ultrasound in pancreatic tumor diagnosis. Gastrointest Endosc. 1991;37:347–52.
4. Palazzo L, Roseau G, Gayet B, et al. Endoscopic ultrasonography in the diagnosis and staging of pancreatic adenocarcinoma. Results of a prospective study with comparison to ultrasonography and CT scan. Endoscopy. 1993;25:143–50.
5. DeWitt J, Devereaux B, Chriswell M, et al. Comparison of endoscopic ultrasonography and multidetector computed tomography for detecting and staging pancreatic cancer. Ann Intern Med. 2004;141:753–63.
6. Ngamruengphong S, Zhou Y, Chak A, et al. EUS and survival in patients with pancreatic cancer: a population-based study. Gastrointest Endosc. 2010; 72:78–83.
7. Tio TL, Tytgat GN, Cikot RJ, et al. Ampullopancreatic carcinoma: preoperative TNM classification with endosonography. Radiology. 1990;175:455–61.
8. Yasuda K, Mukai H, Nakajima M, et al. Staging of pancreatic carcinoma by endoscopic ultrasonography. Endoscopy. 1993;25:151–5.
9. Rösch T, Lightdale CJ, Botet JF, et al. Localization of pancreatic endocrine tumors by endoscopic ultrasonography. N Engl J Med. 1992;326:1721–6.
10. Palazzo L, Roseau G, Salmeron M. Endoscopic ultrasonography in the preoperative localization of pancreatic endocrine tumors. Endoscopy. 1992;24 suppl 1:350–3.
11. Glover JR, Sover PJ, Lees WR. Endoscopic ultrasound for localization of islet cell tumors. Gut. 1992;33:108–10.
12. Baron PL, Aabakken LE, Cole DJ. Differentiation of benign from malignant pancreatic masses by endoscopic ultrasound. Ann Surg Oncol. 1997;4:639–43.
13. Buscail L, Pages P, Berthelemy P, et al. Role of EUS in the management of pancreatic and ampullary carcinoma: a prospective study assessing resectability and prognosis. Gastrointest Endosc. 1999;50: 34–40.
14. Gress FG, Hawes RH, Savides TJ, et al. Role of EUS in the preoperative staging of pancreatic cancer: a large single-center experience. Gastrointest Endosc. 1999;50:786–91.
15. Ahmad NA, Lewis JD, Ginsberg GG, et al. EUS in preoperative staging of pancreatic cancer. Gastrointest Endosc. 2000;52:463–8.
16. Soriano A, Castells A, Ayuso C, et al. Preoperative staging and tumor resectability assessment of pancreatic cancer: prospective study comparing endoscopic ultrasonography, helical computed tomography, magnetic resonance imaging, and angiography. Am J Gastroenterol. 2004;99:492–501.
17. Khashab MA, Yong E, Lennon AM, et al. EUS is still superior to multidetector computed tomography for detection of pancreatic neuroendocrine tumors. Gastrointest Endosc. 2011;73:691–6.
18. Kato T, Tsukamoto Y, Naitoh Y, et al. Ultrasonographic and endoscopic ultrasonographic angiography in pancreatic mass lesions. Acta Radiol. 1995;36:381–7.

19. Bhutani MS, Hoffman BJ, van Velse A, et al. Contrast-enhanced endoscopic ultrasonography with galactose microparticles: SHU508A (Levovist). Endoscopy. 1997;29:635–9.
20. Becker D, Strobel D, Bernatik T, et al. Echo-enhanced color and power-Doppler EUS for the discrimination between focal pancreatitis and pancreatic carcinoma. Gastrointest Endosc. 2001;53:784–9.
21. Hocke M, Schulze E, Gottschalk P, et al. Contrast-enhanced endoscopic ultrasound in discrimination between focal pancreatitis and pancreatic cancer. World J Gastroenterol. 2006;12:246–50.
22. Sakamoto H, Kitano M, Suetomi Y, et al. Utility of contrast enhanced endoscopic ultrasonography for diagnosis of small pancreatic carcinomas. Ultrasound Med Biol. 2008;34:525–32.
23. Dietrich CF, Ignee A, Braden B, et al. Improved differentiation of pancreatic tumors using contrast-enhanced endoscopic ultrasound. Clin Gastroenterol Hepatol. 2008;6:590–7.
24. Ishikawa T, Itoh A, Kawashima H, et al. Usefulness of EUS combined with contrast-enhancement in the differential diagnosis of malignant versus benign and preoperative localization of pancreatic endocrine tumors. Gastrointest Endosc. 2010;71:951–9.
25. Săftoiu A, Iordache SA, Gheonea DI, et al. Combined contrast-enhanced power Doppler and real-time sonoelastography performed during EUS, used in the differential diagnosis of focal pancreatic masses (with videos). Gastrointest Endosc. 2010;72:739–47.
26. Das K, Kudo M, Kitano M, et al. Diagnostic value of endoscopic ultrasound-guided directional eFLOW in solid pancreatic lesions. J Med Ultrason. 2013;40: 211–8.
27. Kudo M. Various contrast-enhanced imaging modes after administration of Levovist. In: Kudo M, editor. Contrast harmonic imaging in the diagnosis and treatment of hepatic tumors. Tokyo: Springer; 2003. p. 22–30.
28. Whittingham TA. Contrast-specific imaging techniques; technical perspective. In: Quaia E, editor. Contrast media in ultrasonography. Basic principles and clinical applications. Berlin: Springer; 2005. p. 43–84.
29. Dietrich CF, Ignee A, Frey H. Contrast-enhanced endoscopic ultrasound with low mechanical index: a new technique. Z Gastroenterol. 2005;43:1219–23.
30. Kitano M, Sakamoto H, Matsui U, et al. A novel perfusion imaging technique of the pancreas: contrast-enhanced harmonic EUS (with video). Gastrointest Endosc. 2008;67:141–50.
31. Kitano M, Kudo M, Sakamoto H, et al. Preliminary study of contrastenhanced harmonic endosonography with second-generation contrast agents. J Med Ultrasonics. 2008;35:11–8.
32. Seicean A, Badea R, Stan-Iuga R, Mocan T, Gulei I, Pascu O. Quantitative contrast-enhanced harmonic endoscopic ultrasonography for the discrimination of solid pancreatic masses. Ultraschall Med. 2010;31: 571–6.
33. Imazu H, Kanazawa K, Mori N, et al. Novel quantitative perfusion analysis with contrast-enhanced harmonic EUS for differentiation of autoimmune pancreatitis from pancreatic carcinoma. Scand J Gastroenterol. 2012;47:853–60.
34. Gheonea DI, Streba CT, Ciurea T, Săftoiu A. Quantitative low mechanical index contrast enhanced endoscopic ultrasound for the differential diagnosis of chronic pseudotumoral pancreatitis and pancreatic cancer. BMC Gastroenterol. 2013;13:2.
35. Matsubara H, Itoh A, Kawashima H, et al. Dynamic quantitative evaluation of contrast enhanced endoscopic ultrasonography in the diagnosis of pancreatic diseases. Pancreas. 2011;40:1073–9.
36. Quaia E. Classification and safety of microbubble-based contrast agents. In: Quaia E, editor. Contrast media in ultrasonography. Basic principles and clinical applications. Berlin: Springer; 2005. p. 1–14.
37. Fusaroli P, Spada A, Mancino MG, et al. Contrast harmonic echo-endoscopic ultrasound improves accuracy in diagnosis of solid pancreatic masses. Clin Gastroenterol Hepatol. 2010;8:629–34.
38. Napoleon B, Alvarez-Sanchez MV, Gincoul R, et al. Contrast enhanced harmonic endoscopic ultrasound in solid lesions of the pancreas: results of a pilot study. Endoscopy. 2010;42:564–70.
39. Kitano M, Kudo M, Yamao K, et al. Characterization of small solid tumors in the pancreas: contrast: the value of contrast enhanced harmonic endoscopic ultrasonography. Am J Gastroenterol. 2012;107: 303–10.
40. Fusaroli P, Kypraios D, Mancino MG, et al. Interobserver agreement in contrast harmonic endoscopic ultrasound. J Gastroenterol Hepatol. 2012;27: 1063–9.
41. Gincul R, Palazzo M, Pujol B, et al. Contrast-harmonic endoscopic ultrasound for the diagnosis of pancreatic adenocarcinoma: a prospective multicenter trial. Endoscopy. 2014;46:373–9.
42. Gong TT, Hu DM, Zhu Q. Contrast-enhanced EUS for differential diagnosis of pancreatic mass lesions: A meta-analysis. Gastrointest Endosc. 2012;76: 301–9.
43. Hocke M, Ignee A, Dietrich CF. Advanced endosonographic diagnostic tools for discrimination of focal chronic pancreatitis and pancreatic carcinoma—elastography, contrast enhanced high mechanical index (CEHMI) and low mechanical index (CELMI) endosonography in direct comparison. Z Gastroenterol. 2012;50:199–203.
44. Romagnuolo J, Hoffman B, Vela S, et al. Accuracy of contrast enhanced harmonic EUS with a second-generation perflutren lipid microsphere contrast agent (with video). Gastrointest Endosc. 2011;73:52–63.
45. Kitano M, Sakamoto H, Komaki T, et al. FNA guided by contrast-enhanced harmonic EUS in pancreatic tumors. Gastrointest Endosc. 2009;69:A328–9.
46. Romagnuolo J. Flow, firmness, or FNA? Is enhanced EUS fantastic or just fancy? Gastrointest Endosc. 2012;76:310–2.

47. Imazu H, Uchiyama Y, Matsunaga K, et al. Contrast-enhanced harmonic EUS with novel ultrasonographic contrast (Sonazoid) in the preoperative T-staging for pancreaticobiliary malignancies. Scand J Gastroenterol. 2010;45:732–8.
48. Kanamori A, Hirooka Y, Itoh A, et al. Usefulness of contrast enhanced endoscopic ultrasonography in the differentiation between malignant and benign lymphadenopathy. Am J Gastroenterol. 2006;101:45–51.
49. Xia Y, Kitano M, Kudo M, et al. Characterization of intra-abdominal lesions of undetermined origin by contrast-enhanced harmonic EUS (with video). Gastrointest Endosc. 2010;72:637–42.
50. Willmann JK, Lutz AM, Paulmurugan R, et al. Dual-targeted contrast agent for US assessment of tumor angiogenesis in vivo. Radiology. 2008;248:936–44.
51. Anderson CR, Rychak JJ, Backer M, Backer J, Ley K, Klibanov AL. scVEGF microbubble ultrasound contrast agents: a novel probe for ultrasound molecular imaging of tumor angiogenesis. Invest Radiol. 2010;45:579–85.
52. Palmowski M, Huppert J, Ladewig G, et al. Molecular profiling of angiogenesis with targeted ultrasound imaging: early assessment of antiangiogenic therapy effects. Mol Cancer Ther. 2008;7:101–9.
53. Giday SA, Magno P, Gabrielson KL, et al. The utility of contrast enhanced endoscopic ultrasound in monitoring ethanol-induced pancreatic tissue ablation: a pilot study in a porcine model. Endoscopy. 2007;39:525–9.
54. Hermot S, Klibanov AL. Microbubbles in ultrasound-triggered drug and gene delivery. Adv Drug Deliv Rev. 2008;60:1153–66.
55. Kawabata K, Maruoka T, Asami R, Ashida R. Acousto-chemical manipulation of drug distribution: in vitro study of new drug delivery system. Jpn J Appl Phys. 2014;53:52.

Endoscopic Ultrasonography: Role of EUS Sampling in Solid Pancreas Lesions

10

James L. Buxbaum and Mohamad A. Eloubeidi

In 1992 Peter Vilmann first reported the technique of endoscopic ultrasound-guided biopsy of the pancreas [1]. Similar to transrectal prostate biopsy, this technique minimizes potential injury to intervening structures and has become the dominant approach to the gland. In this chapter the powerful advantages, limitations, and techniques of EUS-FNA of pancreas masses will be explored.

Advantages

Prior to the introduction of EUS, the diagnostic evaluation of pancreas masses was done by bile duct brushings at the time of endoscopic retrograde cholangiopancreatography (ERCP) and percutaneous biopsies. The former approach had a sensitivity of 22–71 % [2]. During the mid- to late 1990s, prospective series demonstrated the feasibility and favorable performance of EUS-FNA for the diagnosis of pancreas masses. Initial work reported a sensitivity of 64–94 % and specificity of 94–100 % [3–6]. Two large recent meta-analyses integrating the more recent literature have shown an impressive pooled sensitivity of 85–87 % and a specificity of 96–98 % [7, 8]. Investigation has shown that the strengths of EUS-FNA for the evaluation of pancreas masses are its high yield in the face of nondiagnostic biopsy by other modalities, ability to detect small subtle lesions, low risk of seeding, and cost-effectiveness.

Performance Where Other Methods Fail

Gress et al. prospectively evaluated 102 patients with suspected pancreas cancer who had previously undergone nondiagnostic computed tomography (CT)-guided biopsy or ERCP with cytologic brushings. Based on pathologic diagnosis or long-term follow-up, EUS-FNA had a sensitivity of 93 % and a specificity of 83 %. These findings were corroborated by Harewood et al., who found that EUS could be used to determine the origin of >90 % of lesions which had a nondiagnostic prior CT-guided biopsy or brushings [9]. In 1997 Horwat et al. initiated a randomized trial of EUS versus percutaneous FNA for pancreas masses [10]. Preference for EUS by referring physicians limited enrollment such that the sample size requirement was not met at 5 years. Though statistical significance was not reached likely secondary to anemic enrollment, the sensitivity of EUS-FNA, 84 %, exceeded that of CT-guided FNA, 62 %. Additionally, FNA agreement with final pathology was significantly better for the FNA-acquired specimen (kappa = 0.76) than percutaneous aspirates (kappa = 0.47).

J.L. Buxbaum, M.D.
Division of Gastroenterology, University of Southern California, Los Angeles, CA, USA

M.A. Eloubeidi, M.D., M.H.S. (✉)
Division of Gastroenterology and Hepatology, American University of Beirut School of Medicine, Riad El Solh 110, Beirut 72020, Lebanon
e-mail: me75@aub.edu.lb

M.S. Wagh, P.V. Draganov (eds.), *Pancreatic Masses*, DOI 10.1007/978-3-319-19677-0_10

Small Lesions and Seeding

The theoretical advantage of EUS in the evaluation of pancreas masses is that imaging can be performed in close (0.5–2.0 cm) proximity to the pancreas. This optimizes resolution and enables detection and targeting of very small lesions. Volmar et al. compared the performance of CT or transabdominal ultrasound (TUS)-guided FNA compared to EUS-FNA in 1050 patients with pancreas masses [11]. The accuracy of EUS (86 %) vs. CT (86 %) and US (85 %) was comparable for lesions >3 cm. However, the accuracy of lesions <3 cm was superior for EUS compared to TUS and CT. For example, the accuracy of EUS-FNA for lesions 2–3 cm in size was 86 % compared to 62 % for TUS and CT-guided biopsy. EUS-FNA has a favorable sensitivity (87 %) and specificity (98 %) for the confirmation of pancreas masses, which cannot even be definitively detected (and thus targeted) by multidetector CT [12].

A longstanding concern of percutaneous biopsy of pancreas lesions has been malignant seeding of the skin, fascia, peritoneal lining, and other intervening structures, which must be crossed. EUS offer the advantage of a shorter needle tract and the needle pathway is included in the resection specimen. Micamenes et al. compared the risk of seeding for percutaneous versus endoscopic biopsy [13]. Patients underwent laparoscopic staging to exclude metastatic disease at the outset as part of a neoadjuvant chemoradiotherapy protocol. Peritoneal failure occurred more frequently, in 16.3 % of patients who had undergone percutaneous biopsy compared to 2.2 % for EUS-FNA.

Cost-Effectiveness and Safety

The ability to more accurately detect and confirm pancreas lesions appears to result in less invasive and more cost-effective management. Chang et al. demonstrated in a prospective series that EUS-FNA of pancreas masses and associated lymph nodes avoided surgery and additional procedures in 57 % of patients and results in a saving of US$3300 per patient in the series [14]. Modeling indicates that EUS followed by laparoscopy minimizes the rate of unnecessary staging surgical explorations to 5 % [15].

Cost-minimization analysis suggests that EUS-FNA is the best initial method to evaluate suspected pancreas cancer [16]. EUS-FNA was of lower cost and greater efficacy than ERCP or percutaneous biopsy. While surgical biopsy had a slightly higher yield, the cost for a successful diagnosis of pancreas cancer was US$1405 compared to US$17,711 for surgery. Similarly, decision analysis models demonstrate that for staging purposes EUS-FNA is a less costly strategy than CT-guided FNA or surgery [17].

EUS-FNA is also a relatively safe modality to evaluate pancreas masses. A pooled analysis of 4909 EUS-FNA procedures from 19 centers suggested a pancreatitis risk of 0.3 % for biopsy of the pancreas mass. However, a higher rate (0.6 %) in the limited number of centers which prospectively collected data suggested recall bias [18]. In the largest prospective series of complications of EUS-FNA for pancreas mass, the rate of pancreatitis was 0.9 % and the overall rate of complications was 2.5 % [19]. These results compare favorably with rates of pancreatitis of 4 % following percutaneous pancreatic biopsy [20]. ERCP enables sampling via cytologic brushings but is associated with a much higher pancreatitis rate of 5–15 % [21, 22].

Challenges and Solutions

Despite its significant advantages, a number of challenges have faced the community of endosonographers. An early problem was lack of available practitioners and the need to establish training programs. An ongoing problem has been decreased sensitivity in the setting of pancreatic inflammation and in the workup of pancreas masses of unusual origin.

Training and the EUS Workforce

Early barriers preventing widespread EUS-FNA for the assessment of pancreas mass lesions were that there were few endoscopists with EUS experience, it was not part of the standard gastroenterology fellowship curriculum, and there were

no training guidelines [23]. Mertz and Gautam reported a significant learning curve in which the sensitivity of EUS-FNA for pancreas masses was <50 % initially but increased to >80 % after 30–50 cases [24]. While many early endosonographers learned by observing cases and studying textbooks and video materials, hands-on performance in the presence of a mentor is critical for improved results [25]. Thus, guidelines for credentialing and granting privileges for endoscopic ultrasound were developed recommending that endoscopists have at least 150 supervised cases, 75 of which should be pancreaticobiliary cases [26].

The development of third-tier fellowship of 1–2 years' length following the standard 3-year gastroenterology fellowship has helped to expand this technique. Prospective assessment of the yield of EUS-FNA immediately following a fourth year of training exceeded 90 % and was comparable to that in large centers, though the number of passes and minor complications did decrease over time [27]. Currently, there are more than 70 third-tier programs which train advanced fellows in endoscopic ultrasonography.

However, it is not unusual for endoscopists who have performed 200 or more supervised procedures to require additional training [28]. Ongoing efforts aim to define quality measures and more rigorous ways to track trainee and practitioner performance. As a quality indicator, the yield of malignancy in patients referred for EUS-FNA of pancreas masses was found to be 71 % on average [29]. Those with a yield of <52 % are encouraged to review their techniques.

Sampling Error and Rapid on-Site Cytology (ROSE)

While EUS has emerged as the dominant strategy to sample the pancreas, its performance is somewhat limited by sampling error. In part this is related to the desmoplasia and necrosis associated with this aggressive malignancy. The accuracy of EUS-FNA is improved if a pathologist is present in the procedure to assess the needle passes for adequacy and diagnosis [30]. In addition to improved accuracy, rapid on-site cytology (ROSE) results in fewer needle passes and its complications in the evaluation of pancreas masses [31]. This concept has been elaborated elsewhere (see Chap. 14 in this book).

Decreased Sensitivity in Pancreatitis

The evaluation of pancreas masses in the setting of chronic pancreatitis and the differentiation of focal pancreatitis (i.e., pseudotumor) from pancreas cancer are difficult. Pancreatic malignancy is unusual in that it results in intensive desmoplasia, which makes needle passage difficult and diminishes yield as malignant cells may be widely dispersed in a collagen network. Calcifications and hyperechoic foci also make visualization to target these passes difficult. Chronic pancreatitis similarly results in extensive fibrosis and may mimic pancreas cancer; however, given their increased risk of pancreas cancer, comprehensive assessment is required [38–40].

Fritscher-Ravens et al. compared the performance of EUS-FNA in the evaluation of focal pancreatic lesions in the setting of chronic pancreatitis versus normal parenchyma. While the sensitivity of EUS-FNA was 85 % overall and 89 % in normal-appearing parenchyma, it was 53 % in the setting of chronic pancreatitis [41]. Performance may be improved in this setting if additional passes are performed at the behest of an on-site cytopathologist whose interpretation may guide targeting [42]. However, while this approach improves the sensitivity of EUS-FNA in the setting of pancreatitis, it still remains lower, 74 %, compared to biopsies of masses in an otherwise normal pancreas, 91 % [42].

In addition to the utilization of ROSE and performance of additional passes, several new technologies may facilitate EUS-FNA of pancreas masses as discussed elsewhere in this book (see Chap. 14).

Neuroendocrine and Other Unusual Pancreas Masses

Another challenge in EUS evaluation of pancreas masses has been the assessment of unusual pancreas tumors. Nonepithelial tumors, including

neuroendocrine lesions, lymphomas, and metastasis, account for 5–23 % of pancreas masses evaluated by EUS-FNA [53, 54]. Aspirates of neuroendocrine tumors reveal small, round uniform cells [55]. Special stains including synaptophysin, chromogramin, and neuron-specific enolase must be considered and used to make the correct diagnosis [56, 57]. Pancreatic lymphoma typically requires confirmatory flow cytometry of aspirates [58]. Voss et al. reported that the performance of EUS-FNA in the evaluation of NET and other unusual tumors was inferior to its use in the evaluation of epithelial tumors. In this series of 99 patients with pancreas masses, EUS-FNA was 81 % sensitive for adenocarcinoma but 47 % for neuroendocrine tumors.

However, several subsequent studies have demonstrated that EUS-FNA has a sensitivity of >80 % for neuroendocrine lesions [59, 60]. Recent series also indicate that the detection of metastasis to the pancreas, lymphomas, and other unusual lesions by EUS-FNA is also comparable to its performance in adenocarcinoma [57, 58, 61, 62]. Potential differences in the latter reports are the utilization of rapid on-site cytologic assessment and special stains for critical cell surface markers. In contrast, Voss et al. did not have these advantages and nearly half of the specimens acquires were found to be bloody and inadequate for evaluation after the procedure was finished. Adequate material is critical to enable special stains [56].

The evolving technique of contrast-enhanced harmonic endoscopic ultrasound (CH-EUS) holds particular promise in the evaluation of the vascular neuroendocrine lesions. In this technique intravenous contrast containing microbubbles are injected which oscillate upon exposure to the ultrasound pulse [63]. Enhanced detection of the microvascular pattern is enabled by the selective analysis of high-frequency multiples (harmonics) of insonating frequency. Neuroendocrine tumors are hypervascular and demonstrate hyperenhancement on CH-EUS [64]. The technique demonstrates a sensitivity of 79% and 98% for these lesions [64]. CH-EUS also enables the accurate characterization of lesions, both neuroendocrine and adenocarcinoma, that are too small to be detected by multidetector CT and following false-negative EUS-FNA [64, 65]. CH-EUS likely has a role in the more accurate targeting of EUS-FNA both for unusual pancreas masses as well as for adenocarcinoma.

Evolving Techniques and Tools

The introduction of the linear array echoendoscope enables the aspiration needle to be passed under direct Doppler ultrasonic guidance into the pancreas. Significant work has gone into perfection of the techniques and technology for this procedure.

Techniques

A number of endoscopic and needle-handling techniques may help improve yield of pancreatic EUS-FNA. Apposition of the echoendoscope is directly against the duodenal or gastric mucosa and continuous luminal suction is applied to minimize interference of air [14]. Continuous endoscopic suction helps prevent intervening air from impacting visualization. Targeting of FNA passage near transition points in the size of the pancreatic and bile ducts optimizes yield of FNA even when the lesion may be very difficult to differentiate from adjacent tissue [12, 66]. As there can be sampling error, necrosis, and fibrosis, it is advantageous to change the angulation of the needle while passing through the lesion using the echoendoscope elevator. Experts recommend that fanning through at least four different areas is ideal to sample most pancreas masses [67, 68].

Stylet and Suction

EUS needles have a central stylet designed for removal upon entry of lesions to minimize the risk of contamination by the intervening lining of the gastrointestinal tract. Following aspiration of the lesion it may be used to expel the contents of the needle. A luer-lock suction tube is provided to apply negative pressure to the needle following

stylet removal. The use of stylet and suction has been the topic of considerable debate.

A prospective trial by Sahai demonstrated that there was no significant difference in yield when equivalent numbers of passes with and without stylet were performed [69]. The results suggested that specimens obtained using the stylet were more likely to be bloody and inadequate on a pass-for-pass basis. Two subsequent prospective randomized trials have demonstrated that the yield of EUS-FNA with and without stylet did not differ [70, 71]. These studies did not demonstrate any significant differences in specimen quality or adequacy.

The use of suction has been similarly debated. An early randomized trial of suction for lymph nodes that suggested no difference in yield with suction was extrapolated to pancreas masses [72]. Suction did increase the cellularity of specimen but also increased bloodiness. However, when pancreatic masses were specifically studied in subsequent randomized trials, suction was demonstrated to increase sensitivity of EUS-FNA [73, 74]. Expression of the aspirate using air flush instead of stylet did not impact yield but decreased blood contamination [74]. Recently, investigators have proposed that slowly withdrawing the stylet is a good alternative to suction [75, 76]. In a large retrospective study, slow withdrawal of the stylet enabled adequate tissue to be obtained in 90 % of cases compared to 68 % for suction with the 25-gauge needle [75]. No difference between the two approaches was seen for the 22-gauge needle. The authors propose that the slow withdrawal minimizes blood contamination and enables detection of useful tissue in the aspirate, particularly small white cores which may be useful for cytology. This difference was enhanced for the 25-gauge needle as there are fewer cells to work with overall.

Needle Size

Most of the first generation of endosonographers used 22-gauge needles though 25- and 19-gauge are now widely utilized. It is proposed that larger needles—while increasing cellularity—may also increase blood contamination and possibly complications. A retrospective analysis of 842 solid pancreas mass FNA suggested that the 25-gauge needle has a greater sensitivity, 92 %, than the 22-gauge needle, 84 %, in the evaluation of pancreas masses [77]. It was proposed that more trauma and bleeding with the 22-gauge needle were associated with both findings. Additionally, the 25-gauge needle was associated with a lower complication rate, 0 %, than the 22-gauge needle, 2 %. Subsequently, needle size has been the topic of a number of randomized trials. In the first randomized clinical trial (RCT) of 131 patients with pancreas mass, Siddiqui et al. demonstrated the yield of the two needles as equivalent, 96 % for the 25-gauge needle versus 88 % for the 22-gauge needle. A meta-analysis of retrospective and randomized trials suggested that while the two needles have comparable specificity, the sensitivity of the 25-gauge needle was higher in the evaluation of solid pancreatic lesions [78]. However, when the Yusuf trial, which accounted for two thirds of the patients in the analysis, was excluded, this trend remained but lost statistical significance. Prospective work suggests that while the 22-gauge needle is better visualized and enables more precise targeting, the 25-gauge needle may pass more easily through desmoplastic pancreas masses and induce less bleeding [78, 79].

Core Biopsy for Histology

While cytology enables assessment of cellular details such as nuclear size and shape, it does not provide information about tissue architecture which may be vital to differentiate well-differentiated malignancy from normal tissue and to assess for pancreatic lymphoma and autoimmune pancreatitis. Thus the development of tools to acquire histology has been of paramount interest. The first device to acquire histologic specimen was the Trucut (Cook Medical; Winston-Salem, NC) needle. The needle is first passed into the lesion of interest to guide an inner tissue tray of 2-cm length. At the appropriate time a spring-loaded mechanism fires an outer cutting sheath over the tray to generate a core

specimen [80]. Initial work with transgastric biopsy showed that Trucut biopsy of pancreas masses was feasible and increased diagnostic accuracy to 88–100 % [81, 82]. However, subsequent work revealed that when transduodenal biopsy was attempted, torque in the scope prevented firing of the device and tissue acquisition was not successful [83, 84]. This problem worsened with more distal duodenal lesions, Sakamoto et al. reported 0 % success for uncinate pancreas lesions with this device [85].

A new technology for pancreas biopsy is the Procore (Cook Medical; Winston-Salem, NC) needle. This needle has a reverse bevel which shears tissue into the needle upon withdrawl [78]. In a multicenter study a variety of lesions, among which pancreas masses were most common, were sampled using the 19-gauge reverse-bevel orientation needle [76]. The problems with misfiring due to echoendoscope torque were not encountered and histology could be obtained in 89 %, for an overall accuracy of 93 % [76]. Smaller-size reverse-bevel core needles have also been introduced. A prospective study of 25-gauge core needles in pancreas masses revealed a cumulative sensitivity (four passes) and specificity of 96 % [76]. Nonetheless, a histologic core was obtained in only 32 % of patients. The slow pull technique was found to be critical to the performance of the core needle in this study.

There is growing interest in whether histology may be obtained from a variety of needles if the appropriate technique, such as slow pull, is used and appropriate processing techniques are used. In assessing studies in which conventional needles are used for histology, it is important to assess the definitions of histologic specimens. In Japan aspirates are carefully evaluated to identify clear or whitish aspirates which are then transferred to filter paper, placed in formalin, and subsequently sectioned as a true histologic specimen [86]. Other groups report "histologic" results when aspirates are combined and centrifuged to form a pellet which is then sectioned, i.e., the cell block approach.

The ability to obtain histology expands the role of FNA into the frontier where cytology has limitations. Oncologists have been very skeptical about the role of FNA in the diagnosis of lymphoma. Yasuda et al. used a conventional 19-gauge FNA needle to obtain specimen in a cohort of 152 patients with lymphoma of the pancreas and other intraabdominal sites [87]. By using meticulous specimen preparation techniques, they were able to obtain histology in 89 % of cases, which enabled immunohistochemical staining to characterize the lymphoma. In this cohort EUS-guided FNA had a sensitivity of 93 % for the diagnosis of lymphoma compared to 52 % for cytology alone.

However, the approach has limitations. Iwashita et al. used a 19-gauge needle to obtain histological specimen in patients with suspected autoimmune pancreatitis. Though adequate sample was obtained in 93 % of patients, lymphoplasmacytic sclerosing pancreatitis and infiltration with IgG4-positive plasma cells to confirm the diagnosis was only possible in 43 % [86]. The 19-gauge needles may have some limitations for pancreas histology for technical reasons. In their comparison of 19- and 22-gauge aspiration needles, Song et al. found that the 19-gauge needle could be used to obtain more cytologic material but the overall yields were comparable given that it was difficult to aim the needle around oblique angles in the duodenum, resulting in failure in 5 (8 %) of cases [88]. Varadarajulu et al. recently reported the use of a more flexible nitinol (as opposed to stainless steel) 19-gauge (Boston Scientific; Natick, MA) needle to obtain specimens and perform interventions. The authors were able to biopsy head and uncinate pancreas masses which required a transuodenal approach and obtained histology in 95 % of cases [68]. Nonetheless, cell block was used for histologic analysis, not a true core specimen.

Thus, in regards to technical considerations, it appears that the use of the stylet does not impact the yield of EUS-FNA for pancreas masses though suction may be helpful. The slow withdrawal of the stylet is under investigation. While 25-gauge needles may acquire less pancreatic tissue than larger counterparts, their ability to pass around tighter angles, through more desmoplastic regions, and cause less bleeding (and thus contamination) more than compensates.

They are at least as useful, if not more so, than the 22- and 19-gauge needles in the EUS-FNA of solid pancreas lesions. Finally, the acquisition of tissue for histology is a primary interest of endosonographers, though the definitions of histologic specimen and the best needles to achieve this aim are under active development.

Conclusions

Endoscopic ultrasound–guided fine-needle aspiration has emerged as the paramount approach to evaluate solid pancreas masses. It has a high yield even when other methods of tissue sampling have failed. It is also less likely to result in seeding and procedural complications. However, EUS-guided FNA has limitations, including false negatives in the setting of inflammation and possibly in the assessment of nonadenocarcinomas. Rapid on-site cytology (ROSE), special stains, and molecular methods to analyze aspirates are helping to address these challenges. Newer imaging modalities to target biopsy, perfected techniques, and improved needles will further improve the performance of this method.

Acknowledgment The authors have no conflict of interest to disclose.

References

1. Vilmann P, Jacobsen GK, Henriksen FW, Hancke S. Endoscopic ultrasonography with guided fine needle aspiration biopsy in pancreatic disease. Gastrointest Endosc. 1992;38(2):172–3.
2. Lee JG, Leung J. Tissue sampling at ERCP in suspected pancreatic cancer. Gastrointest Endosc Clin N Am. 1998;8(1):221–35.
3. Wiersema MJ, Vilmann P, Giovannini M, Chang KJ, Wiersema LM. Endosonography-guided fine-needle aspiration biopsy: diagnostic accuracy and complication assessment. Gastroenterology. 1997;112(4):1087–95.
4. Giovannini M, Seitz JF, Monges G, Perrier H, Rabbia I. Fine-needle aspiration cytology guided by endoscopic ultrasonography: results in 141 patients. Endoscopy. 1995;27(2):171–7.
5. Faigel DO, Ginsberg GG, Bentz JS, Gupta PK, Smith DB, Kochman ML. Endoscopic ultrasound-guided real-time fine-needle aspiration biopsy of the pancreas in cancer patients with pancreatic lesions. J Clin Oncol. 1997;15(4):1439–43.
6. Bhutani MS, Hawes RH, Baron PL, Sanders-Cliette A, van Velse A, Osborne JF, et al. Endoscopic ultrasound guided fine needle aspiration of malignant pancreatic lesions. Endoscopy. 1997;29(9):854–8.
7. Hewitt MJ, McPhail MJ, Possamai L, Dhar A, Vlavianos P, Monahan KJ. EUS-guided FNA for diagnosis of solid pancreatic neoplasms: a meta-analysis. Gastrointest Endosc. 2012;75(2):319–31.
8. Puli SR, Bechtold ML, Buxbaum JL, Eloubeidi MA. How good is endoscopic ultrasound-guided fine-needle aspiration in diagnosing the correct etiology for a solid pancreatic mass?: A meta-analysis and systematic review. Pancreas. 2013;42(1):20–6.
9. Harewood GC, Wiersema MJ. Endosonography-guided fine needle aspiration biopsy in the evaluation of pancreatic masses. Am J Gastroenterol. 2002;97(6):1386–91.
10. Horwhat JD, Paulson EK, McGrath K, Branch MS, Baillie J, Tyler D, et al. A randomized comparison of EUS-guided FNA versus CT or US-guided FNA for the evaluation of pancreatic mass lesions. Gastrointest Endosc. 2006;63(7):966–75.
11. Volmar KE, Vollmer RT, Jowell PS, Nelson RC, Xie HB. Pancreatic FNA in 1000 cases: a comparison of imaging modalities. Gastrointest Endosc. 2005;61(7):854–61.
12. Wang W, Shpaner A, Krishna SG, Ross WA, Bhutani MS, Tamm EP, et al. Use of EUS-FNA in diagnosing pancreatic neoplasm without a definitive mass on CT. Gastrointest Endosc. 2013;78(1):73–80.
13. Micames C, Jowell PS, White R, Paulson E, Nelson R, Morse M. Lower frequency of peritoneal carcinomatosis in patients with pancreatic cancer diagnosed by EUS-guided FNA vs percutaneous FNA. Gastrointest Endosc. 2003;58(5):690–5.
14. Chang KJ, Nguyen P, Erickson RA, Durbin TE, Katz KD. The clinical utility of endoscopic ultrasound-guided fine-needle aspiration in the diagnosis and staging of pancreatic carcinoma. Gastrointest Endosc. 1997;45(5):387–93.
15. Tierney WM, Fendrick AM, Hirth RA, Scheiman JM. The clinical and economic impact of alternative staging strategies for adenocarcinoma of the pancreas. Am J Gastroenterol. 2000;95(7):1708–13.
16. Chen VK, Arguedas MR, Kilgore ML, Eloubeidi MA. A cost-minimization analysis of alternative strategies in diagnosing pancreatic cancer. Am J Gastroenterol. 2004;99(11):2223–34.
17. Harewood GC, Wiersema MJ. A cost analysis of endoscopic ultrasound in the evaluation of pancreatic head adenocarcinoma. Am J Gastroenterol. 2001;96(9):2651–6.
18. Eloubeidi MA, Gress FG, Savides TJ, Wiersema MJ, Kochman ML, Ahmad NA, et al. Acute pancreatitis after EUS-guided FNA of solid pancreatic masses: a pooled analysis from EUS centers in the United States. Gastrointest Endosc. 2004;60(3):385–9.
19. Eloubeidi MA, Tamhane A, Varadarajulu S, Wilcox CM. Frequency of major complications after EUS-guided FNA of solid pancreatic masses: a prospective evaluation. Gastrointest Endosc. 2006;63(4):622–9.

20. Evans WK, Ho CS, McLoughlin MJ, Tao LC. Fatal necrotizing pancreatitis following fine-needle aspiration biopsy of the pancreas. Radiology. 1981;141(1): 61–2.
21. Sherman S, Blaut U, Watkins JL, Barnett J, Freeman M, Geenen J, et al. Does prophylactic administration of corticosteroid reduce the risk and severity of post-ERCP pancreatitis: a randomized, prospective, multicenter study. Gastrointest Endosc. 2003;58(1):23–9.
22. Buxbaum J, Yan A, Yeh K, Lane C, Nguyen N, Laine L. Aggressive hydration with lactated ringer's solution reduces pancreatitis after endoscopic retrograde cholangiopancreatography. Clin Gastroenterol Hepatol. 2014;12(2):303–7. 2.
23. Boyce Jr HW. Training in endoscopic ultrasonography. Gastrointest Endosc. 1996;43(2 Pt 2):S12–5.
24. Mertz H, Gautam S. The learning curve for EUS-guided FNA of pancreatic cancer. Gastrointest Endosc. 2004;59(1):33–7.
25. Harewood GC, Wiersema LM, Halling AC, Keeney GL, Salamao DR, Wiersema MJ. Influence of EUS training and pathology interpretation on accuracy of EUS-guided fine needle aspiration of pancreatic masses. Gastrointest Endosc. 2002;55(6):669–73.
26. Eisen GM, Dominitz JA, Faigel DO, Goldstein JA, Petersen BT, Raddawi HM, et al. Guidelines for credentialing and granting privileges for endoscopic ultrasound. Gastrointest Endosc. 2001;54(6):811–4.
27. Eloubeidi MA, Tamhane A. EUS-guided FNA of solid pancreatic masses: a learning curve with 300 consecutive procedures. Gastrointest Endosc. 2005; 61(6):700–8.
28. Wani S, Cote GA, Keswani R, Mullady D, Azar R, Murad F, et al. Learning curves for EUS by using cumulative sum analysis: implications for American Society for Gastrointestinal Endoscopy recommendations for training. Gastrointest Endosc. 2013;77(4):558–65.
29. Savides TJ, Donohue M, Hunt G, Al-Haddad M, Aslanian H, Ben-Menachem T, et al. EUS-guided FNA diagnostic yield of malignancy in solid pancreatic masses: a benchmark for quality performance measurement. Gastrointest Endosc. 2007;66(2):277–82.
30. Klapman JB, Logrono R, Dye CE, Waxman I. Clinical impact of on-site cytopathology interpretation on endoscopic ultrasound-guided fine needle aspiration. Am J Gastroenterol. 2003;98(6):1289–94.
31. Iglesias-Garcia J, Dominguez-Munoz JE, Abdulkader I, Larino-Noia J, Eugenyeva E, Lozano-Leon A, et al. Influence of on-site cytopathology evaluation on the diagnostic accuracy of endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) of solid pancreatic masses. Am J Gastroenterol. 2011;106(9):1705–10.
32. Nasuti JF, Gupta PK, Baloch ZW. Diagnostic value and cost-effectiveness of on-site evaluation of fine-needle aspiration specimens: review of 5,688 cases. Diagn Cytopathol. 2002;27(1):1–4.
33. Buxbaum JL, Eloubeidi MA, Lane CJ, Varadarajulu S, Linder A, Crowe AE, et al. Dynamic telecytology compares favorably to rapid onsite evaluation of endoscopic ultrasound fine needle aspirates. Dig Dis Sci. 2012;57(12):3092–7.
34. Nguyen YP, Maple JT, Zhang Q, Ylagan LR, Zhai J, Kohlmeier C, et al. Reliability of gross visual assessment of specimen adequacy during EUS-guided FNA of pancreatic masses. Gastrointest Endosc. 2009; 69(7):1264–70.
35. Buxbaum J, Yan A, Visrodia K, Lane C, Quarto B, Chan M, et al. The performance of pathology trainees compared to non-physician cytotechnologists in the assessment of EUS-FNA specimen adequacy. Gastrointest Endosc. 2012;75(3):AB447.
36. Eloubeidi MA, Buxbaum JL. Improving endoscopic ultrasound-guided fine needle aspiration specimens in the absence of rapid onsite evaluation: does cytotechnologist training provide the solution? Dig Liver Dis. 2012;44(4):273–4.
37. Petrone MC, Arcidiacono PG, Carrara S, Mezzi G, Doglioni C, Testoni PA. Does cytotechnician training influence the accuracy of EUS-guided fine-needle aspiration of pancreatic masses? Dig Liver Dis. 2012;44(4):311–4.
38. Lowenfels AB, Maisonneuve P, Cavallini G, Ammann RW, Lankisch PG, Andersen JR, et al. Pancreatitis and the risk of pancreatic cancer. International Pancreatitis Study Group. N Engl J Med. 1993;328(20):1433–7.
39. Barthet M, Portal I, Boujaoude J, Bernard JP, Sahel J. Endoscopic ultrasonographic diagnosis of pancreatic cancer complicating chronic pancreatitis. Endoscopy. 1996;28(6):487–91.
40. Bhutani MS, Gress FG, Giovannini M, Erickson RA, Catalano MF, Chak A, et al. The No Endosonographic Detection of Tumor (NEST) Study: a case series of pancreatic cancers missed on endoscopic ultrasonography. Endoscopy. 2004;36(5):385–9.
41. Fritscher-Ravens A, Brand L, Knofel WT, Bobrowski C, Topalidis T, Thonke F, et al. Comparison of endoscopic ultrasound-guided fine needle aspiration for focal pancreatic lesions in patients with normal parenchyma and chronic pancreatitis. Am J Gastroenterol. 2002;97(11):2768–75.
42. Varadarajulu S, Tamhane A, Eloubeidi MA. Yield of EUS-guided FNA of pancreatic masses in the presence or the absence of chronic pancreatitis. Gastrointest Endosc. 2005;62(5):728–36; quiz 51, 53.
43. Saftoiu A, Vilmann P, Gorunescu F, Gheonea DI, Gorunescu M, Ciurea T, et al. Neural network analysis of dynamic sequences of EUS elastography used for the differential diagnosis of chronic pancreatitis and pancreatic cancer. Gastrointest Endosc. 2008;68(6):1086–94.
44. Fusaroli P, Saftoiu A, Mancino MG, Caletti G, Eloubeidi MA. Techniques of image enhancement in EUS (with videos). Gastrointest Endosc. 2011;74(3):645–55.
45. Iglesias-Garcia J, Larino-Noia J, Abdulkader I, Forteza J, Dominguez-Munoz JE. Quantitative endoscopic ultrasound elastography: an accurate method for the differentiation of solid pancreatic masses. Gastroenterology. 2010;139(4):1172–80.
46. Iglesias-Garcia J, Dominguez-Munoz JE, Castineira-Alvarino M, Luaces-Regueira M, Larino-Noia J. Quantitative elastography associated with endoscopic ultrasound for the diagnosis of chronic pancreatitis. Endoscopy. 2013;45(10):781–8.

47. Dawwas MF, Taha H, Leeds JS, Nayar MK, Oppong KW. Diagnostic accuracy of quantitative EUS elastography for discriminating malignant from benign solid pancreatic masses: a prospective, single-center study. Gastrointest Endosc. 2012;76(5):953–61.
48. Janssen J, Schlorer E, Greiner L. EUS elastography of the pancreas: feasibility and pattern description of the normal pancreas, chronic pancreatitis, and focal pancreatic lesions. Gastrointest Endosc. 2007;65(7):971–8.
49. Fusaroli P, Eloubeidi MA. Pancreatic cancer: image enhancement by endoscopic ultrasonography-elastography. Nat Rev Gastroenterol Hepatol. 2012; 9(11):623–4.
50. Fuccio L, Hassan C, Laterza L, Correale L, Pagano N, Bocus P, et al. The role of K-ras gene mutation analysis in EUS-guided FNA cytology specimens for the differential diagnosis of pancreatic solid masses: a meta-analysis of prospective studies. Gastrointest Endosc. 2013;78(4):596–608.
51. Takahashi K, Yamao K, Okubo K, Sawaki A, Mizuno N, Ashida R, et al. Differential diagnosis of pancreatic cancer and focal pancreatitis by using EUS-guided FNA. Gastrointest Endosc. 2005;61(1):76–9.
52. Khalid A, Nodit L, Zahid M, Bauer K, Brody D, Finkelstein SD, et al. Endoscopic ultrasound fine needle aspirate DNA analysis to differentiate malignant and benign pancreatic masses. Am J Gastroenterol. 2006;101(11):2493–500.
53. Eloubeidi MA, Jhala D, Chhieng DC, Chen VK, Eltoum I, Vickers S, et al. Yield of endoscopic ultrasound-guided fine-needle aspiration biopsy in patients with suspected pancreatic carcinoma. Cancer. 2003;99(5):285–92.
54. Voss M, Hammel P, Molas G, Palazzo L, Dancour A, O'Toole D, et al. Value of endoscopic ultrasound guided fine needle aspiration biopsy in the diagnosis of solid pancreatic masses. Gut. 2000;46(2):244–9.
55. Chang F, Chandra A, Culora G, Mahadeva U, Meenan J, Herbert A. Cytologic diagnosis of pancreatic endocrine tumors by endoscopic ultrasound-guided fine-needle aspiration: a review. Diagn Cytopathol. 2006;34(9):649–58.
56. Jhala D, Eloubeidi M, Chhieng DC, Frost A, Eltoum IA, Roberson J, et al. Fine needle aspiration biopsy of the islet cell tumor of pancreas: a comparison between computerized axial tomography and endoscopic ultrasound-guided fine needle aspiration biopsy. Ann Diagn Pathol. 2002;6(2):106–12.
57. Eloubeidi MA, Tamhane AR, Buxbaum JL. Unusual, metastatic, or neuroendocrine tumor of the pancreas: a diagnosis with endoscopic ultrasound-guided fine-needle aspiration and immunohistochemistry. Saudi J Gastroenterol. 2012;18(2):99–105.
58. Ramesh J, Hebert-Magee S, Kim H, Trevino J, Varadarajulu S. Frequency of occurrence and characteristics of primary pancreatic lymphoma during endoscopic ultrasound guided fine needle aspiration: a retrospective study. Dig Liver Dis. 2014;46(5):470–3.
59. Chatzipantelis P, Konstantinou P, Kaklamanos M, Apostolou G, Salla C. The role of cytomorphology and proliferative activity in predicting biologic behavior of pancreatic neuroendocrine tumors: a study by endoscopic ultrasound-guided fine-needle aspiration cytology. Cancer. 2009;117(3):211–6.
60. Ardengh JC, de Paulo GA, Ferrari AP. EUS-guided FNA in the diagnosis of pancreatic neuroendocrine tumors before surgery. Gastrointest Endosc. 2004; 60(3):378–84.
61. Atiq M, Bhutani MS, Ross WA, Raju GS, Gong Y, Tamm EP, et al. Role of endoscopic ultrasonography in evaluation of metastatic lesions to the pancreas: a tertiary cancer center experience. Pancreas. 2013; 42(3):516–23.
62. DeWitt J, Jowell P, Leblanc J, McHenry L, McGreevy K, Cramer H, et al. EUS-guided FNA of pancreatic metastases: a multicenter experience. Gastrointest Endosc. 2005;61(6):689–96.
63. Napoleon B, Alvarez-Sanchez MV, Gincoul R, Pujol B, Lefort C, Lepilliez V, et al. Contrast-enhanced harmonic endoscopic ultrasound in solid lesions of the pancreas: results of a pilot study. Endoscopy. 2010;42(7):564–70.
64. Kitano M, Kudo M, Yamao K, Takagi T, Sakamoto H, Komaki T, et al. Characterization of small solid tumors in the pancreas: the value of contrast-enhanced harmonic endoscopic ultrasonography. Am J Gastroenterol. 2012;107(2):303–10.
65. Gincul R, Palazzo M, Pujol B, Tubach F, Palazzo L, Lefort C, et al. Contrast-harmonic endoscopic ultrasound for the diagnosis of pancreatic adenocarcinoma: a prospective multicenter trial. Endoscopy. 2014;46(5):373–9.
66. Eloubeidi MA, Luz LP, Tamhane A, Khan M, Buxbaum JL. Ratio of pancreatic duct caliber to width of pancreatic gland by endosonography is predictive of pancreatic cancer. Pancreas. 2013;42(4):670–9.
67. Savides TJ. Tricks for improving EUS-FNA accuracy and maximizing cellular yield. Gastrointest Endosc. 2009;69(2 Suppl):S130–3.
68. Varadarajulu S, Bang JY, Hebert-Magee S. Assessment of the technical performance of the flexible 19-gauge EUS-FNA needle. Gastrointest Endosc. 2012;76(2):336–43.
69. Sahai AV, Paquin SC, Gariepy G. A prospective comparison of endoscopic ultrasound-guided fine needle aspiration results obtained in the same lesion, with and without the needle stylet. Endoscopy. 2010; 42(11):900–3.
70. Rastogi A, Wani S, Gupta N, Singh V, Gaddam S, Reddymasu S, et al. A prospective, single-blind, randomized, controlled trial of EUS-guided FNA with and without a stylet. Gastrointest Endosc. 2011;74(1):58–64.
71. Wani S, Early D, Kunkel J, Leathersich A, Hovis CE, Hollander TG, et al. Diagnostic yield of malignancy during EUS-guided FNA of solid lesions with and without a stylet: a prospective, single blind, randomized, controlled trial. Gastrointest Endosc. 2012;76(2): 328–35.
72. Wallace MB, Kennedy T, Durkalski V, Eloubeidi MA, Etamad R, Matsuda K, et al. Randomized controlled trial of EUS-guided fine needle aspiration techniques for the detection of malignant lymphadenopathy. Gastrointest Endosc. 2001;54(4):441–7.

73. Puri R, Vilmann P, Saftoiu A, Skov BG, Linnemann D, Hassan H, et al. Randomized controlled trial of endoscopic ultrasound-guided fine-needle sampling with or without suction for better cytological diagnosis. Scand J Gastroenterol. 2009;44(4):499–504.
74. Lee JK, Choi JH, Lee KH, Kim KM, Shin JU, Lee KT, et al. A prospective, comparative trial to optimize sampling techniques in EUS-guided FNA of solid pancreatic masses. Gastrointest Endosc. 2013;77(5): 745–51.
75. Nakai Y, Isayama H, Chang KJ, Yamamoto N, Hamada T, Uchino R, et al. Slow pull versus suction in endoscopic ultrasound-guided fine-needle aspiration of pancreatic solid masses. Dig Dis Sci. 2014;59(7):1578–85.
76. Iwashita T, Nakai Y, Samarasena JB, do Park H, Zhang Z, Gu M, et al. High single-pass diagnostic yield of a new 25-gauge core biopsy needle for EUS-guided FNA biopsy in solid pancreatic lesions. Gastrointest Endosc. 2013;77(6):909–15.
77. Yusuf TE, Ho S, Pavey DA, Michael H, Gress FG. Retrospective analysis of the utility of endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) in pancreatic masses, using a 22-gauge or 25-gauge needle system: a multicenter experience. Endoscopy. 2009;41(5):445–8.
78. Madhoun MF, Wani SB, Rastogi A, Early D, Gaddam S, Tierney WM, et al. The diagnostic accuracy of 22-gauge and 25-gauge needles in endoscopic ultrasound-guided fine needle aspiration of solid pancreatic lesions: a meta-analysis. Endoscopy. 2013;45(2):86–92.
79. Vilmann P, Saftoiu A, Hollerbach S, Skov BG, Linnemann D, Popescu CF, et al. Multicenter randomized controlled trial comparing the performance of 22 gauge versus 25 gauge EUS-FNA needles in solid masses. Scand J Gastroenterol. 2013;48(7):877–83.
80. Levy MJ, Jondal ML, Clain J, Wiersema MJ. Preliminary experience with an EUS-guided Trucut biopsy needle compared with EUS-guided FNA. Gastrointest Endosc. 2003;57(1):101–6.
81. Larghi A, Verna EC, Stavropoulos SN, Rotterdam H, Lightdale CJ, Stevens PD. EUS-guided Trucut needle biopsies in patients with solid pancreatic masses: a prospective study. Gastrointest Endosc. 2004;59(2): 185–90.
82. Storch I, Jorda M, Thurer R, Raez L, Rocha-Lima C, Vernon S, et al. Advantage of EUS Trucut biopsy combined with fine-needle aspiration without immediate on-site cytopathologic examination. Gastrointest Endosc. 2006;64(4):505–11.
83. Itoi T, Itokawa F, Sofuni A, Nakamura K, Tsuchida A, Yamao K, et al. Puncture of solid pancreatic tumors guided by endoscopic ultrasonography: a pilot study series comparing Trucut and 19-gauge and 22-gauge aspiration needles. Endoscopy. 2005;37(4): 362–6.
84. Varadarajulu S, Fraig M, Schmulewitz N, Roberts S, Wildi S, Hawes RH, et al. Comparison of EUS-guided 19-gauge Trucut needle biopsy with EUS-guided fine-needle aspiration. Endoscopy. 2004;36(5): 397–401.
85. Sakamoto H, Kitano M, Komaki T, Noda K, Chikugo T, Dote K, et al. Prospective comparative study of the EUS guided 25-gauge FNA needle with the 19-gauge Trucut needle and 22-gauge FNA needle in patients with solid pancreatic masses. J Gastroenterol Hepatol. 2009;24(3):384–90.
86. Iwashita T, Yasuda I, Doi S, Ando N, Nakashima M, Adachi S, et al. Use of samples from endoscopic ultrasound-guided 19-gauge fine-needle aspiration in diagnosis of autoimmune pancreatitis. Clin Gastroenterol Hepatol. 2012;10(3):316–22.
87. Yasuda I, Goto N, Tsurumi H, Nakashima M, Doi S, Iwashita T, et al. Endoscopic ultrasound-guided fine needle aspiration biopsy for diagnosis of lymphoproliferative disorders: feasibility of immunohistological, flow cytometric, and cytogenetic assessments. Am J Gastroenterol. 2012;107(3):397–404.
88. Song TJ, Kim JH, Lee SS, Eum JB, Moon SH, do Park H, et al. The prospective randomized, controlled trial of endoscopic ultrasound-guided fine-needle aspiration using 22G and 19G aspiration needles for solid pancreatic or peripancreatic masses. Am J Gastroenterol. 2010;105(8):1739–45.

Endoscopic Ultrasonography: Role of EUS sampling in Cystic Lesions

11

Abdurrahman Kadayifci and William R. Brugge

Introduction

Pancreatic cystic lesions (PCLs) show a wide spectrum of demographical, morphological, and histological characteristics. The diagnosis and discrimination of these lesions are very important because of the risk for concurrent or later development of malignancy. From the clinical standpoint, the distinction is mostly needed between mucinous [intraductal papillary mucinous neoplasms (IPMNs) and mucinous cystic neoplasms (MCNs)] and nonmucinous [pseudocysts and serous cystic neoplasms (SCNs)] cysts. Cross-sectional imaging tests and endoscopic ultrasound (EUS) alone are sometimes ineffective for accurately distinguishing between benign/malignant or mucinous/nonmucinous cystic lesions. In fact, none of the diagnostic modalities are uniformly effective in all cases. Nevertheless, EUS–fine-needle aspiration (FNA) is currently the most helpful procedure for distinguishing the type of cysts and, thus, managing the patient (Fig. 11.1). International consensus guidelines from 2012 for the management of IPMNs and MCNs of the pancreas recommended cyst fluid analysis for evaluation of small branch-duct (BD) IPMNs without "worrisome features" in centers with expertise in EUS-FNA and cytological interpretation [1] (Table 11.1). The diagnostic success of EUS-FNA cyst aspiration depends on the preparation of patients and instruments, technical and procedural factors, and the expertise of a dedicated team as well as the location, size, and characteristics of the target lesion. Therefore, each step of the procedure should be carefully planned and executed with the entire team.

EUS-FNA of PCLs requires extra care compared to solid lesions. Before proceeding with EUS-FNA, a complete diagnostic EUS should be performed to evaluate the lesion and adjacent structures for selection of the optimal needle tract. The procedure itself is generally safe with a low complication rate, but the possible risks and benefits should always be evaluated carefully before the intervention. The expectations for the result of the FNA should be a change in diagnostic algorithm, a decision for a specific treatment and follow-up, or to dispense from invasive treatments. Including sedation, the patient is prepared for the procedure similarly to other endoscopic interventions. EUS-FNA complications such as

A. Kadayifci, M.D.
Medicine and Gastrointestinal Unit, Pancreas Biliary Center, Massachusetts General Hospital,
55 Fruit Street, Blake 4, Boston, MA 02114, USA

Division of Gastroenterology, University of Gaziantep, Gaziantep, Turkey
e-mail: akadayifci@mgh.harvard.edu

W.R. Brugge, M.D. (✉)
Medicine and Gastrointestinal Unit, Pancreas Biliary Center, Massachusetts General Hospital,
55 Fruit Street, Blake 4, Boston, MA 02114, USA
e-mail: wbrugge@partners.org

M.S. Wagh, P.V. Draganov (eds.), *Pancreatic Masses*, DOI 10.1007/978-3-319-19677-0_11

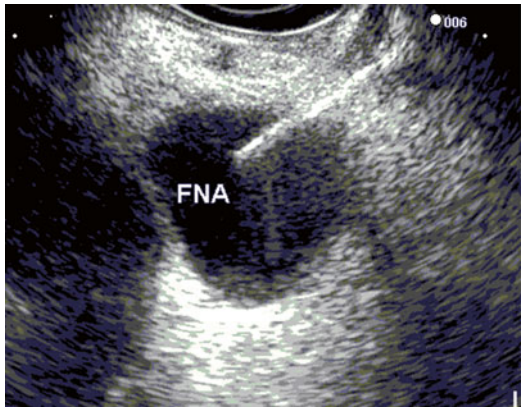

Fig. 11.1 A 25-mm-diameter, thin-walled, anechoic, unilocular, nonseptated, cystic lesion in the tail of the pancreas. The needle is inside the cyst for aspiration

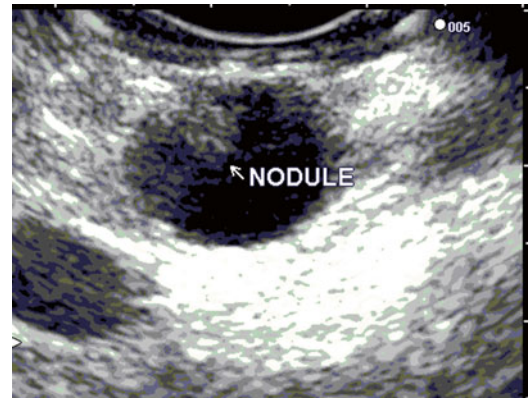

Fig. 11.2 A 20-mm-diameter anechoic cystic lesion with an internal nodule in the pancreas body. The interpretation of this cyst is a side-branch IPMN. The aspiration of the nodule is suggested for cytological evaluation

Table 11.1 "High-risk stigmata" and "worrisome features" of IPMN on cross-sectional imaging

High-risk stigmata	Worrisome features
Obstructive jaundice in a patient with cystic lesion of the head of the pancreas	Cyst > 3 cm
	Thickened/enhancing cyst walls
Enhancing solid component within cyst	Nonenhancing mural nodule
Main pancreatic duct >10 mm in size	Main pancreatic duct size of 5–9 mm
	Abrupt change in caliber of pancreatic duct with distal pancreatic atrophy
	Lymphadenopathy

infection, bleeding, and pancreatitis have been reported more frequently with cystic lesions compared to solid masses. Multiple passes into the cyst may also increase the risk of infection. The aspiration of all cyst contents may minimize the risk of infection and maximize the diagnostic yield. A prophylactic antibiotic is usually recommended for patients undergoing FNA of pancreatic cysts. Tumor seeding has been reported in mucinous cystic lesions located in the body and tail of the pancreas after EUS-FNA [2]. However, a recent comparative study could not find any difference in the frequency of peritoneal seeding in patients undergoing resection of IPMN after EUS-FNA [3]. If there is a solid component inside the cyst which increases the suspicion of malignancy, it should be aspirated for cytological analyses (Fig. 11.2). Usually a 22-gauge (G) needle is most appropriate for cyst aspiration; however, a 25-G needle may also be used for small (<2 cm) nonmucinous cysts or for cases requiring a transduodenal approach. The minimum size of cyst to obtain an adequate sample for analysis is not certain and might be dependent on the location, viscosity of fluid, and size of each component in multilobular cysts. The aspirated cyst fluid volume correlates significantly with cyst size and a minimum size of 1.5 cm is needed for successful analysis [4].

After EUS-FNA, cyst fluid is routinely evaluated for gross appearance, amylase and carcinoembryonic antigen (CEA) levels, and cytology [5]. *KRAS* and *GNAS* genetic mutation analyses have been shown recently to help distinguish mucinous lesions and IPMNs in selected cases. Recently, some metabolomic-derived novel cyst fluid biomarkers have also been identified which have potential clinical utility for differentiating mucinous from nonmucinous pancreatic cysts. No single test diagnoses PCLs with 100 % accuracy, and different EUS-FNA–based tests are combined to obtain the best result. The combination of EUS-FNA test results with clinical findings and imaging features may determine the cyst type in a majority of the patients. This chapter will review the role of EUS sampling in PCLs based on the recent advances in diagnostic tests.

Gross Appearance of Fluid

The aspirated cyst fluid can be visually inspected for its color and viscosity. A highly viscous, thick fluid is the first clue that the cyst is likely IPMN or MCN. The viscosity of cyst fluid may be tested simply at the bedside by a string test. A drop of fluid is stretched slowly between the thumb and index finger until its disruption. A string length of more than 3.5 mm is a strong finding for a mucinous cyst [6]. The fluid is usually thin and clear in SCNs. Because of the vascular nature, aspirants may sometimes be bloody in SCNs. However, this is not a specific finding since all aspirates might be bloody due to traumatic puncture of the cyst wall. Pseudocyst fluid is usually thin, opaque, sometimes hemorrhagic, and may contain inflammatory debris.

Biochemical Analyses of Pancreatic Fluid

Carcinoembryonic Antigen

The epithelium of the cyst wall may produce a variety of tumor markers and chemical substances which are often used in diagnostic testing. Cyst fluids have been evaluated to date for different tumor antigens including CA 19-9, CA 72-4, CA 15-3, CA 125, and CEA [7]. These markers were found elevated in some cases of malignant or mucinous cystic lesions, but only CEA was determined as a useful marker to distinguish mucinous from nonmucinous PCLs. A high concentration of CEA reflects the presence of a mucinous epithelium and is observed in both IPMNs and MCNs. Nonmucinous cysts including pseudocysts and serous cystic neoplasms do not include a mucinous epithelium and should have relatively low levels of CEA. Particularly, low cyst fluid CEA is seen in SCNs. A cutoff CEA level of 192 ng/mL has a sensitivity of 73 %, specificity of 84 %, and accuracy of 79 % for differentiating mucinous from nonmucinous pancreatic cystic lesions in a multicenter series consisting of patients who underwent surgical resection [8]. Among all the cyst fluid diagnostic parameters, CEA concentration alone was the most accurate test for the diagnosis of cystic mucinous neoplasms in the same study. Depending on the assay method, 0.5–1 mL of fluid is needed for the CEA analyses. American College of Gastroenterologists' Guidelines recommended CEA as the first test to do if minimal fluid is acquired during aspiration [5].

Despite considerable overlap, CEA is useful in order to distinguish mucinous from nonmucinous cysts. A meta-analysis of 450 patients from 12 studies reported that a CEA level > 800 ng/mL was 98 % specific but only 48 % sensitive for the diagnosis of mucinous cyst [9]. A CEA level < 5 ng/mL was 98 % specific for a serous cystadenoma but the sensitivity was only 19 %. This study clearly showed that increasing the cutoff value of CEA for support of a mucinous cyst or decreasing it to support a nonmucinous cyst will have a negative effect on sensitivity. Another meta-analysis of 12 published studies showed that the pooled sensitivity and specificity of CEA for differentiate mucinous versus nonmucinous cystic lesions was 63 % and 88 %, respectively [10]. Table 11.2 summarizes the diagnostic results of fluid CEA analyses in various published studies [8, 11–24].

The reported CEA cutoff levels are assay-specific and may change according to manufacturer. Besides, different cutoff values were used in clinical studies which affect the sensitivity, specificity, and diagnostic accuracy rate of CEA for differentiation of a mucinous cyst. Clinical studies are often carried out in groups of patients who underwent surgical resection since there is not a gold standard for diagnosis of mucinous cyst in a clinical setting. As a result, these published series usually consist of patients with MCNs and BD-IPMNs with high-risk stigmata or worrisome features. Cyst fluid CEA levels do not differentiate IPMNs from MCNs or benign IPMNs from malignant; however, some studies demonstrate that higher CEA levels are more likely in high-grade MCNs and IPMNs. Fluid CEA levels correlated with low-, moderate-, and high-grade IPMNs as well as degrees of dysplasia (1261 ng/mL vs. 7171 ng/mL vs. 10,807 ng/mL, respectively) [25]. However, CEA levels were signifi-

Table 11.2 The diagnostic value of fluid CEA for differentiation of mucinous cysts in several studies

Author (year)	Patient (*n*)	Cyst diagnosis	Cutoff (ng/mL)	Sensitivity (%)	Specificity (%)	Diagnostic accuracy (%)
Brugge (2004)	111	SP	192	75	83	79
Shami (2007)	43	SP	300	64	92	76
Sreenarasimhaiah (2009)	20	Cx and SP	192	66	78	75
Khalid (2009)	76	SP	192	64	83	68
Snozek (2009)	442	Cx and SP	30	79	73	77
Sawhney (2009)	84	Cx and SP	192	82	100	84
Morris-Stiff (2010)	47	SP	192	93	43	N/A
Nagula (2010)	97	SP	192	73	65	70
Cizginer (2011)	154	SP	109.9	81	98	85
Park (2011)	124	SP	200	60	93	72
Rogart (2011)	75	Cx	192	55	97	74
De Jong (2012)	18	SP	192	44	100	72
Chai (2013)	52	Cx and SP	192	62	89	76
Talar-Wojnarowska (2013)	52	Cx and SP	45	92	64	71
Al-Haddad (2014)	48	SP	192	63	62	62
Kadayifci and Brugge[a] (2014)	243	Cx and SP	192	49	97	65
Kadayifci and Brugge[a] (2014)	243	Cx and SP	50	77	87	80

SP surgical pathology, *Cx* clinical diagnosis
[a]Unpublished data

cantly lower (462 ng/mL) in cysts with invasive carcinoma; the possible explanation was that fewer cells with intact tight-junctions and less CEA were available at the luminal surface for release into the cyst fluid. In another study including 66 patients, the median CEA level was significantly higher in patients with MCNs than IPMNs (2844 ng/mL vs. 574 ng/mL) [17].

In clinical practice, the most common cysts encountered are those that do not meet criteria for a surgical resection; these cysts are the greatest challenge for early diagnosis and follow-up. Therefore, the lower cutoff level of CEA (less than 192 ng/dL) may be more helpful to increase sensitivity and diagnostic accuracy of fluid CEA level without a significant decrease in specificity. The sensitivity, specificity, and diagnostic accuracy of fluid CEA (>192 ng/mL) level for mucinous differentiation was 49 %, 97 %, and 65 %, respectively, in the evaluation of 243 cyst patients in our database (Table 11.2). A lower CEA cutoff level (>50 ng/mL) increased the sensitivity to 77 % and the diagnostic accuracy to 80 %, but decreased the specificity to only 87 %. The median CEA level of mucinous cysts was 400 ng/mL in patients who underwent surgical resection but only 160 ng/mL for those who followed up without surgery. The lower CEA cutoff level improved the sensitivity and diagnostic accuracy of CEA, especially in IPMN patients who did not have a surgical indication. On the basis of these data, we think a lower fluid CEA cutoff level than 192 ng/mL might be more helpful for the diagnosis of IPMN in a clinical setting.

Amylase

Cyst fluid amylase level is also a useful marker for the differential diagnosis of pancreatic cysts. Its presence in cyst fluid is often used as an indicator of a communication between a cystic lesion and the ductal system. Amylase-rich fluid is uniformly found in pancreatic pseudocysts and the concentration is not expected to be less than 250 U/mL. Due to connectivity to the pancreatic ductal system, amylase levels may also be elevated in IPMNs. It is always low in serous cysts and in the majority of MCNs. The sensitivity of fluid amylase (>250 U/mL) for differentiation of a pseudocyst is very

high (96–100 %); however, the specificity is not good since it is also elevated frequently in IPMNs. In a recent analysis of 139 patients with IPMN, we have detected that fluid amylase was elevated (>250 U/mL) in 76 % of cases. Even MCNs, which have no connection with the pancreatic ductal system, have an elevated amylase level, and the utility of fluid amylase to differentiate IPMNs from MCNs is not clear [26].

Cytology

Cytological examination of cyst fluid alone is often nondiagnostic to characterize cyst type due to the low cellularity of the aspirated fluid [27]. However, a multimodal approach combining the patient's history, clinical findings, imaging features, cytology, special stains, and cyst fluid analyses can improve the overall cytological interpretation. The collaboration between the endoscopist and cytopathologist is one of the main factors that may determine the outcome of EUS-FNA. The aspirated fluid during EUS-FNA is examined cytologically for degenerative debris, inflammatory cells, epithelial cells, granolocytes, histiocytes, extra-cellular mucin, mucinous epithelium with cytoplasmic mucin and atypical/malignant cells. The aim of cytological analyses is to differentiate between serous and mucinous cysts, to distinguish pseudocysts from neoplastic cysts, and to detect malignancy in patients with mucinous cysts.

Cytological findings of a pseudocyst may be affected by infectious complications. An uncomplicated pseudocyst fluid is generally thin, nonmucoid, and discolored and may consist of only scattered histiocytes. However, an infected cyst may be purulent, mucoid-appearing fluid and contain acute and chronic inflammatory cells, histiocytes, and hemosiderin-laden or foamy macrophages [26]. The presence of granulocytes in the aspirated fluid is suggestive of an acute infection. Pseudocysts do not have an epithelial lining and are surrounded by inflammatory cells and histiocytes. If there is any cytological evidence of epithelial cells within the cyst fluid, this should raise the suspicion of a cystic neoplasm rather than a pseudocyst [26].

The fluid aspirated from SCNs is usually very scant in volume and includes few intact cells. Many cases are interpreted as nondiagnostic because of insufficient cellularity. Intact cell clusters are composed of bland cuboidal cells with round central to slightly eccentric nuclei and scant finely vacuolated but nonmucinous cytoplasm [26]. The cells from SCNs can be stained with periodic acid–Schiff (PAS) without diastase for the presence of glycogen. Because there is no mucin in serous cysts, mucicarmine staining should be negative. The yield of cytology with EUS-FNA is poor for SCNs.

Mucinous lesions may be diagnosed with the presence of mucin-producing epithelial cells on cytologic analysis. Mucin can be demonstrated by mucicarmine staining and PAS with diastase in nearly half of mucinous cysts. Direct smears of thick and viscous cyst fluid may be reflected on the slide as thick sheets of colloid-like mucin that covers much of the slide [26]. If mucin is present, it is important to assess if the mucin originates from the cyst lining or represents a contaminant (gastric/duodenal secretions). Degenerated inflammatory cells and histiocytes within the mucin provide added support that the mucin is from the cyst. Cyst fluid cytology is rarely sufficiently diagnostic to distinguish IPMN from MCN, and it is usually reported as "mucinous cyst." The accuracy of cytology alone in differentiating mucinous from nonmucinous cysts was 58 % in a multicenter cooperative pancreatic cyst study [8]. The cytological findings detected in common pancreatic cysts are summarized with other EUS-FNA tests (Table 11.3).

Cytology is the most accurate test for the detection of malignancy in patients with mucinous cysts, and a "positive" or "malignant" diagnosis is generally 100 % specific [26]. In addition, the presence of high-grade epithelial atypia in the cyst fluid analysis has an accuracy of 80 % to predict malignancy and detects 30 % more cancers in small BD-IPMN than the presence of "worrisome features" [28]. Based on these results, new high-risk factors proposed for BD-IPMN include a rapidly increasing cyst size and high-grade atypia rather than "positive" cytology [1]. The reported sensitivity and diagnostic accuracy of cyst fluid cytology for malignant IPMNs is

Table 11.3 Endosonography–fine needle aspiration findings of common pancreatic cysts

Parameters	Pseudocyst	SCNs	MCNs	IPMNs (MD and BD)
Gross examination	Thin, clear or brown to green, nonmucinous, sometimes hemorrhagic	Clear and thin, may be hemorrhagic	Thick, viscous mucus	Thick, viscous mucus
Biochemistry	CEA concentration very low, amylase and lipase concentrations usually high	CEA and amylase concentrations very low	CEA concentration usually high	CEA concentration usually high, amylase concentration may be high
Cytology	Degenerative debris, inflammatory cells, histiocytes, no epithelial cells	Usually acellular and nondiagnostic, small cluster of cells with bland cuboidal morphology, glycogen stain positive, mucin negative	Mucinous epithelial cells with varying degrees of atypia, colloid-like mucin, mucin stains positive	Colloid-like mucin, mucin stains positive mucinous epithelial cells with varying degrees of atypia, sparsely cellular
DNA analyses			*KRAS* mutation (+) (14 %)	*GNAS* mutation (+) (60 %) *KRAS* mutation (+) (60 %)

approximately 75 % and 86 %, respectively [26]. EUS-guided FNA of mural nodules was superior to EUS alone (75 % vs. 61 %) for the diagnosis of malignancy in IPMNs [29]. The reported diagnostic accuracy for a solid pseudopapillary neoplasm (SPN) based on cytology and immunohistochemistry is 65 % [30]. Aspirated cyst fluid may display necrotic debris for SPNs.

DNA Analysis

Certain DNA mutations may serve as molecular markers for the diagnosis of mucinous cysts. DNA is extracted and amplified from epithelial cells that have been exfoliated into the cyst cavity. A multicenter trial, which is referred to as the PANDA study, showed that pancreatic cyst fluid *KRAS* mutation is highly specific (96 %) for mucinous cysts but the sensitivity is only 45 % [13]. *KRAS* is an early oncogenic mutation in the adenoma–carcinoma sequence and can be detected in patients with low-grade pancreatic intraepithelial neoplasia and pancreatic ductal adenocarcinoma. The presence of a *KRAS* mutation cannot distinguish a benign from malignant mucinous cyst. However, the PANDA study demonstrated that high-amplitude *KRAS* mutation followed by allelic loss was the most specific marker (96 %) for malignancy. DNA analysis diagnosed malignancy in all cases where cytology with FNA was negative [13]. *KRAS* mutation had a specificity of 100 % and a sensitivity of 54 % in a more recent study of the same group [31]. *KRAS* mutation was detected in 43 of 63 mucinous cysts (68.3 %), in which diameters were equal or less than 3 cm, in another series [32].

The *KRAS* mutation added value to cytology and CEA in the same series and a diagnosis was made by molecular analysis in 20 patients (31.7 %) when either cytology was unsatisfactory, or CEA was not elevated. The sensitivity of *KRAS* mutation to detect mucinous cysts has been found between 8 and 50 % in some other studies and the value of *KRAS* mutation and CEA combination to differentiate a mucinous cyst was inconsistent among these studies [12, 15, 22, 24]. We have found the sensitivity, specificity, and diagnostic accuracy of *KRAS* mutation to be 58 %, 100 %, and 70 %, respectively, in the analysis of 281 patients with pancreatic cysts (unpublished data). The *KRAS* mutation alone did not offer a more diagnostic test than cyst fluid CEA; however, the combination of both tests improved

the diagnostic accuracy significantly. The role of *KRAS* mutation for a malignant transformation in mucinous cysts, or to predict patients with a high risk of malignancy, is not clear and needs further prospective studies with long-term follow-up.

A recent study demonstrated that the *GNAS* mutation detected in cyst fluid can separate IPMN from MCN but, similar to *KRAS* mutations, does not predict malignancy [33]. The absence of a *GNAS* mutation also does not correlate with a diagnosis of MCN because not all IPMNs will demonstrate a *GNAS* mutation. A *GNAS* mutation was present in 66 % of IPMNs and either *KRAS* or *GNAS* mutations were identified in 96 % of IPMNs [33]. Furukawa et al. performed whole-exome sequencing for primary IPMN tissue and analyzed 17 somatic mutations [34]. They found *GNAS* mutation in 48 of 118 patients (40.7 %) but none of the 32 patients with pancreatic ductal adenocarcinoma. We analyzed *GNAS* mutation in 80 patients with PCLs, including 49 IPMNs, and found the sensitivity, specificity, and diagnostic accuracy as 61 %, 100 %, and 75 %, respectively (unpublished data). The combination of *GNAS* with CEA has also improved the diagnostic accuracy in this series.

The DNA analysis, overall, provides a new insight into the molecular pathogenesis, diagnosis, and management of mucinous cysts. However, most of the studies have been done with a limited number of patients and by a retrospective analysis of cyst databases. Moreover, there are still many queries awaiting a response. The role of molecular analysis to identify high-risk or malignant cysts, the association of IPMN histological subtype with mutational frequency, the importance of type of mutation, and the clonality in the diagnosis and management are not clear yet. Cyst fluid DNA analysis recently has been commercially available (Pathfinder TG; RedPath Integrated Pathology, Inc, Pittsburgh, PA). However, the routine use of DNA analyses does not have strong evidence yet and high cost may be a limitation for widespread usage. Nevertheless, it has the potential to improve the diagnosis in cases in which imaging modalities, the cyst fluid CEA level, and cytology are indeterminate for type differentiation. Future studies will better define the impact of DNA analysis on the diagnostic and prognostic stratification of mucinous cysts and especially in IPMNs.

Novel Tests for Cyst-Type Differentiation

To identify the novel cyst fluid biomarkers, a recent study used a metabolomics approach to identify uniquely expressed metabolites in different pancreatic cyst types [35]. A total of 506 metabolites were detected in the cyst fluids and compared between nonmucinous and mucinous cysts. They identified glucose and kynurenine to be differentially expressed between nonmucinous and mucinous pancreatic cysts. Metabolomic abundances for both were significantly lower in mucinous cysts compared with nonmucinous cysts and the ROC curves for glucose and kynurenine was 0.92 and 0.94, respectively. Neither metabolite could differentiate premalignant from malignant cysts. The clinical utility of these biomarkers will be addressed in future studies.

The cyst fluid's interleukin-1β concentration has been shown to be higher in malignant IPMN than in benign IPMN in a preliminary study including 40 patients with IPMN [36]. It has been proposed as a potential biomarker for differential diagnosis of benign and malignant cysts; however, confirmation is needed in larger clinical studies.

Several microRNA expressions, protein-based biomarkers, proteomic analyses, and glycoproteomics in cyst fluid are under investigation to develop new biomarkers for differentiation of mucinous or malignant cysts in some pilot studies [37].

Combination of Tests for Mucinous Differentiation

Cyst fluid CEA level and *KRAS*/*GNAS* mutations have a very good specificity but low sensitivity in differentiating mucinous from nonmucinous cystic lesions. The cytology alone is also highly specific in describing high-grade atypia and malignant cysts but insensitive for benign/malignant and cyst

type differentiation. Therefore, there is no single test accurate enough for characterization of cyst type in every case. A combination of tests to improve the sensitivity and diagnostic accuracy of mucinous differentiation has been investigated in different studies. The combination of cytology and fluid CEA did not provide additional diagnostic accuracy in the cooperative cyst study, and CEA alone was more accurate than combining tests [8]. The combination of fluid CEA and cyst mucin obtained the best sensitivity to determine mucinous lesions in a retrospective data analysis [38].

The combination of the presence of atypical (not malignant) epithelial cells on cytological evaluation or with a CEA value of >2500 ng/mL improved the sensitivity and accuracy for the detection of malignancy and invasion in patients with small BD-IPMNs [39]. This approach was even better than the recommended management algorithm including evaluation of patient symptoms, positive cytology, dilated main pancreatic duct > 6 mm, or the presence of a mural nodule in the cyst wall as detected by radiological studies [40].

The combination of DNA mutation analysis with CEA and cytology may potentially improve the sensitivity and diagnostic accuracy for mucinous differentiation. Sawhney et al. found a 100 % sensitivity for diagnosing mucinous cysts with the combination of CEA and *KRAS* mutation [15]. Their study was limited to 19 patients and the CEA level did not correlate well with the quantity of DNA. The combination of molecular analysis with cyst fluid CEA and cytology resulted in higher mucinous cyst diagnostic performance than either one of its individual components in another recent study [24]. A volume-based protocol using different components of the specimen has been proposed to be able to optimize diagnostic yield in pancreatic cyst fluids [22]. The protocol used minimal cyst fluid volumes for the analysis of CEA, *KRAS* analyses, and cytology, thus optimizing the use of the often scant cyst fluid volumes obtained during aspiration. They demonstrated that the supernatant is comparable to the neat fluid and cell block material for CEA and KRAS testing. *KRAS* mutation testing increased the diagnostic yield when combined with cytology and CEA analysis. As mentioned above, the combination of *GNAS* or *KRAS* with CEA has also improved the diagnostic accuracy of CEA in our series. These studies shows that, in practice, a combined approach of molecular tests with CEA level has potential to improve the sensitivity and diagnostic accuracy of cyst fluid analysis.

Limitations of EUS-FNA and New Methods to Improve the Diagnostic Yield

Even though EUS-FNA is technically an easier procedure for the experienced endoscopist, the puncture of the cyst wall may not be possible due to an unfavorable location or an unavoidable intervening blood vessel. In a prospective study of 143 patients who underwent EUS for a cyst aspiration, FNA could be performed in 128 (90 %) of them [41]. Cyst fluid sent for cytology provided adequate cellular material in 31 % of patients and sufficient fluid for biochemical analysis was obtained in 49 % of the cases in the same study. Complications occurred in three patients (2.4 %). Several studies have also reported the accuracy of EUS-FNA cytology between 20 and 50 % in PCLs [8, 42, 43]. These results showed that overall diagnostic value of EUS-FNA of PCLs is still limited and new methods are needed to improve the yield of FNA.

A through-the-needle (19-G) new cytologic brush system was compared with standard FNA cytology in ten consecutive patients with PCLs in a preliminary study [44]. In seven of ten patients, brush cytology was superior to conventional FNA cytology in terms of cellularity and detection of diagnostic cells. However, there were one major and one minor intracystic bleeding in this study. The same authors, recently, reported the result of EUS brush cytology to assess intracellular mucin on cytobrushing specimens in 37 patients and compared it with EUS-FNA for the diagnosis of suspected mucinous PCLs [45]. Cytobrushings were more likely to detect intracellular mucin than the EUS-FNA, but complications occurred in three patients. The same method was applied in

30 patients in another prospective study and failed technically in eight cases [46]. Brush cytology provided a cellular diagnosis in 20 of 22 cases (91 %). The EUS brushing was superior to the aspirated fluid for detecting diagnostic cells (73 % vs. 36 %) and mucinous cells (50 % vs. 18 %), but again complications occurred in three patients. The EUS brushing showed promising results to improve the diagnostic yield of cytology in preliminary studies; however, the usage of 19-G needle might be a problem in some cases and more studies are needed to demonstrate safety.

To improve the diagnostic yield of material obtained from FNA, cyst wall puncture with a 22-G needle after fluid aspiration was evaluated in 69 PCLs [47]. Cellular material from cyst wall puncture was adequate for cytological assessment in 56 cysts (81 %), and 4 malignant cysts were diagnosed using this technique. Cytology showed a mucinous epithelium in one third of cysts whose CEA level was <192 ng/mL. Only one episode of mild and self-limited pancreatitis was detected as a complication.

Confocal laser endomicroscopy (CLE) is a novel imaging technology that uses low-power laser to obtain in vivo histology of the gastrointestinal mucosa. Recently, a CLE miniprobe has been developed for use during EUS-FNA to visualize the cyst wall and epithelium directly through a 19-G FNA needle. The technical feasibility of this probe was shown and the preliminary studies of pancreatic cystic lesions revealed some important cyst wall findings to differentiate mucinous and nonmucinous cysts. The presence of epithelial villous structures was associated with IPMNs, with 59 % sensitivity and 100 % specificity, in a recent study [48]. The superficial vascular network criterion, which corresponded to a dense and subepithelial capillary vascularization in pathological specimens, was associated with a serous cystadenoma with 100 % specificity and 63 % sensitivity. In spite of these promising findings, further studies are needed to ascertain the contribution of CLE for the differential diagnosis of IPMNs. In a preliminary study, we successfully visualized the cyst wall with miniprobe CLE during EUS-FNA in 17 cases and confirmed IPMN in 9 and SCN in 2 patients (Fig. 11.3).

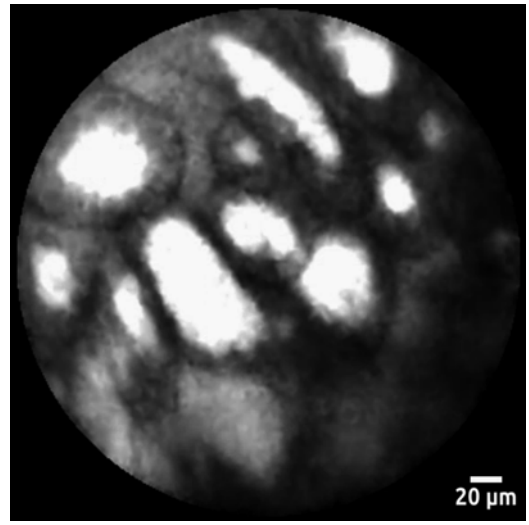

Fig. 11.3 Confocal laser endomicroscopy of a patient with IPMN. Epithelial villous structures were detected on cyst wall consistent with IPMN

Optical coherence tomography (OCT) is an interferometric technique that typically uses near-infrared light and allows noninvasive micron-scale cross-sectional imaging of biological tissues by measuring their optical reflections. Ex vivo OCT of freshly resected pancreatectomy specimens demonstrated that mucinous cysts could be differentiated from nonmucinous cysts with high sensitivity (>95 %), specificity (>95 %), and almost perfect interobserver agreement. A special OCT probe designed for placement through a 19-G FNA needle has been developed for cyst wall imaging [49].

Direct pancreatic cystoscopy and intracystic biopsy through a 19-G needle with a SpyGlass fiber optic catheter was feasible in a pilot study including two patients [50]. Both cysts were considered to be mucinous cystoadenomas, because mucinous-like cylindric epithelium without cellular atypia was observed. Histological examination of biopsies obtained from the cyst wall confirmed the diagnosis.

The diagnostic value of these novel methods have not been confirmed with adequately powered studies yet, but preliminary results show that they have a significant potential to improve the diagnostic yield of EUS-FNA and may be predictive for the malignant potential of PCLs.

References

1. Tanaka M, Fernandez-del Castillo C, Adsay V, et al. International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas. Pancreatology. 2012;12:183–97.
2. Hirooka Y, Goto H, Itoh A, et al. Case of intraductal papillary mucinous tumor in which endosonography-guided fine-needle aspiration biopsy caused dissemination. J Gastroenterol Hepatol. 2003;18:1323–4.
3. Yoon WJ, Daglilar ES, Castillo CF, et al. Peritoneal seeding in intraductal papillary mucinous neoplasm of the pancreas patients who underwent endoscopic ultrasound-guided fine-needle aspiration: the PIPE study. Endoscopy. 2014;46:382–7.
4. Walsh RM, Zuccaro G, Dumot JA, et al. Predicting success of endoscopic aspiration for suspected pancreatic cystic neoplasms. JOP. 2008;9:612–7.
5. Khalid A, Brugge W. ACG practice guidelines for the diagnosis and management of neoplastic pancreatic cysts. Am J Gastroenterol. 2007;102:2339–49.
6. Leung KK, Ross WA, Evans D, et al. Pancreatic cystic neoplasm: the role of cyst morphology, cyst fluid analysis, and expectant management. Ann Surg Oncol. 2009;16:2818–24.
7. Brugge WR, Lauwers GY, Sahani D, et al. Cystic neoplasms of the pancreas. N Engl J Med. 2004;351:1218–26.
8. Brugge WR, Lewandrowski K, Lee-Lewandrowski E, et al. Diagnosis of pancreatic cystic neoplasms: a report of the cooperative pancreatic cyst study. Gastroenterology. 2004;126:1330–6.
9. van der Waaij LA, van Dullemen HM, Porte RJ. Cyst fluid analysis in the differential diagnosis of pancreatic cystic lesions: a pooled analysis. Gastrointest Endosc. 2005;62:383–9.
10. Thornton GD, McPhail MJ, Nayagam S, et al. Endoscopic ultrasound guided fine needle aspiration for the diagnosis of pancreatic cystic neoplasms: a meta-analysis. Pancreatology. 2013;13:48–57.
11. Shami VM, Sundaram V, Stelow EB, et al. The level of carcinoembryonic antigen and the presence of mucin as predictors of cystic pancreatic mucinous neoplasia. Pancreas. 2007;34:466–9.
12. Sreenarasimhaiah J, Lara LF, Jazrawi SF, et al. A comparative analysis of pancreas cyst fluid CEA and histology with DNA mutational analysis in the detection of mucin producing or malignant cysts. JOP. 2009;10:163–8.
13. Khalid A, Zahid M, Finkelstein SD, et al. Pancreatic cyst fluid DNA analysis in evaluating pancreatic cysts: a report of the PANDA study. Gastrointest Endosc. 2009;69:1095–102.
14. Snozek CL, Mascarenhas RC, O'Kane DJ. Use of cyst fluid CEA, CA19-9, and amylase for evaluation of pancreatic lesions. Clin Biochem. 2009;42:1585–8.
15. Sawhney MS, Devarajan S, O'Farrel P, et al. Comparison of carcinoembryonic antigen and molecular analysis in pancreatic cyst fluid. Gastrointest Endosc. 2009;69:1106–10.
16. Morris-Stiff G, Lentz G, Chalikonda S, et al. Pancreatic cyst aspiration analysis for cystic neoplasms: mucin or carcinoembryonic antigen—which is better? Surgery. 2010;148:638–44; discussion 644–5.
17. Nagula S, Kennedy T, Schattner MA, et al. Evaluation of cyst fluid CEA analysis in the diagnosis of mucinous cysts of the pancreas. J Gastrointest Surg. 2010;14:1997–2003.
18. Cizginer S, Turner BG, Bilge AR, et al. Cyst fluid carcinoembryonic antigen is an accurate diagnostic marker of pancreatic mucinous cysts. Pancreas. 2011;40:1024–8.
19. Park WG, Mascarenhas R, Palaez-Luna M, et al. Diagnostic performance of cyst fluid carcinoembryonic antigen and amylase in histologically confirmed pancreatic cysts. Pancreas. 2011;40:42–5.
20. Rogart JN, Loren DE, Singu BS, Kowalski TE. Cyst wall puncture and aspiration during EUS-guided fine needle aspiration may increase the diagnostic yield of mucinous cysts of the pancreas. J Clin Gastroenterol. 2011;45:164–9.
21. de Jong K, van Hooft JE, Nio CY, et al. Accuracy of preoperative workup in a prospective series of surgically resected cystic pancreatic lesions. Scand J Gastroenterol. 2012;47:1056–63.
22. Chai SM, Herba K, Kumarasinghe MP, et al. Optimizing the multimodal approach to pancreatic cyst fluid diagnosis: developing a volume-based triage protocol. Cancer Cytopathol. 2013;121:86–100.
23. Talar-Wojnarowska R, Pazurek M, Durko L, et al. Pancreatic cyst fluid analysis for differential diagnosis between benign and malignant lesions. Oncol Lett. 2013;5:613–6.
24. Al-Haddad M, DeWitt J, Sherman S, et al. Performance characteristics of molecular (DNA) analysis for the diagnosis of mucinous pancreatic cysts. Gastrointest Endosc. 2014;79:79–87.
25. Kucera S, Centeno BA, Springett G, et al. Cyst fluid carcinoembryonic antigen level is not predictive of invasive cancer in patients with intraductal papillary mucinous neoplasm of the pancreas. JOP. 2012;13:409–13.
26. Pitman MB, Lewandrowski K, Shen J, et al. Pancreatic cysts: preoperative diagnosis and clinical management. Cancer Cytopathol. 2010;118:1–13.
27. Frossard JL, Amouyal P, Amouyal G, et al. Performance of endosonography-guided fine needle aspiration and biopsy in the diagnosis of pancreatic cystic lesions. Am J Gastroenterol. 2003;98:1516–24.
28. Pitman MB, Genevay M, Yaeger K, et al. High-grade atypical epithelial cells in pancreatic mucinous cysts are a more accurate predictor of malignancy than "positive" cytology. Cancer Cytopathol. 2010;118:434–40.
29. Brandwein SL, Farrell JJ, Centeno BA, Brugge WR. Detection and tumor staging of malignancy in cystic, intraductal, and solid tumors of the pancreas by EUS. Gastrointest Endosc. 2001;53:722–7.
30. Yoon WJ, Brugge WR. Pancreatic cystic neoplasms: diagnosis and management. Gastroenterol Clin North Am. 2012;41:103–18.

31. Nikiforova MN, Khalid A, Fasanella KE, et al. Integration of KRAS testing in the diagnosis of pancreatic cystic lesions: a clinical experience of 618 pancreatic cysts. Mod Pathol. 2013;26:1478–87.
32. Toll AD, Kowalski T, Loren D, Bibbo M. The added value of molecular testing in small pancreatic cysts. JOP. 2010;11:582–6.
33. Wu J, Matthaei H, Maitra A, et al. Recurrent GNAS mutations define an unexpected pathway for pancreatic cyst development. Sci Transl Med. 2011;3:92ra66.
34. Furukawa T, Kuboki Y, Tanji E, et al. Whole-exome sequencing uncovers frequent GNAS mutations in intraductal papillary mucinous neoplasms of the pancreas. Sci Rep. 2011;1:161.
35. Park WG, Wu M, Bowen R, et al. Metabolomic-derived novel cyst fluid biomarkers for pancreatic cysts: glucose and kynurenine. Gastrointest Endosc. 2013;78:295–302.
36. Maker AV, Katabi N, Qin LX, et al. Cyst fluid interleukin-1beta (IL1beta) levels predict the risk of carcinoma in intraductal papillary mucinous neoplasms of the pancreas. Clin Cancer Res. 2011;17:1502–8.
37. Kwon RS, Simeone DM. The use of protein-based biomarkers for the diagnosis of cystic tumors of the pancreas. Int J Proteomics. 2011;2011:413646.
38. Morris-Stiff G, Lentz G, Chalikonda S, et al. Pancreatic cyst aspiration analysis for cystic neoplasms: mucin or carcinoembryonic antigen—which is better? Surgery. 2010;148:638–45.
39. Pitman MB, Michaels PJ, Deshpande V, et al. Cytological and cyst fluid analysis of small (< or =3 cm) branch duct intraductal papillary mucinous neoplasms adds value to patient management decisions. Pancreatology. 2008;8:277–84.
40. Tanaka M, Chari S, Adsay V, et al. International consensus guidelines for management of intraductal papillary mucinous neoplasms and mucinous cystic neoplasms of the pancreas. Pancreatology. 2006;6:17–32.
41. de Jong K, Poley JW, van Hooft JE, et al. Endoscopic ultrasound-guided fine-needle aspiration of pancreatic cystic lesions provides inadequate material for cytology and laboratory analysis: initial results from a prospective study. Endoscopy. 2011;43:585–90.
42. Stelow EB, Stanley MW, Bardales RH, et al. Intraductal papillary-mucinous neoplasm of the pancreas. The findings and limitations of cytologic samples obtained by endoscopic ultrasound-guided fine-needle aspiration. Am J Clin Pathol. 2003;120:398–404.
43. Maire F, Couvelard A, Hammel P, et al. Intraductal papillary mucinous tumors of the pancreas: the preoperative value of cytologic and histopathologic diagnosis. Gastrointest Endosc. 2003;58:701–6.
44. Al-Haddad M, Raimondo M, Woodward T, et al. Safety and efficacy of cytology brushings versus standard FNA in evaluating cystic lesions of the pancreas: a pilot study. Gastrointest Endosc. 2007;65:894–8.
45. Al-Haddad M, Gill KR, Raimondo M, et al. Safety and efficacy of cytology brushings versus standard fine-needle aspiration in evaluating cystic pancreatic lesions: a controlled study. Endoscopy. 2010;42:127–32.
46. Sendino O, Fernandez-Esparrach G, Sole M, et al. Endoscopic ultrasonography-guided brushing increases cellular diagnosis of pancreatic cysts: a prospective study. Dig Liver Dis. 2010;42:877–81.
47. Hong SK, Loren DE, Rogart JN, et al. Targeted cyst wall puncture and aspiration during EUS-FNA increases the diagnostic yield of premalignant and malignant pancreatic cysts. Gastrointest Endosc. 2012;75:775–82.
48. Konda VJ, Meining A, Jamil LH, et al. A pilot study of in vivo identification of pancreatic cystic neoplasms with needle-based confocal laser endomicroscopy under endosonographic guidance. Endoscopy. 2013;45:1006–13.
49. Iftimia N, Cizginer S, Deshpande V, et al. Differentiation of pancreatic cysts with optical coherence tomography (OCT) imaging: an ex vivo pilot study. Biomed Opt Express. 2011;2:2372–82.
50. Aparicio JR, Martinez J, Niveiro M, et al. Direct intracystic biopsy and pancreatic cystoscopy through a 19-gauge needle EUS (with videos). Gastrointest Endosc. 2010;72:1285–8.

The Role of ERCP in Diagnosing Pancreatic Masses

12

Ioana Smith and Michel Kahaleh

Introduction

With the advent of endoscopic ultrasound (EUS), there has been a steady decrease in diagnostic endoscopic retrograde cholangiopancreatography (ERCP) for pancreatic malignancies. Though ERCP provides extremely accurate delineation of the pancreatobiliary system, EUS-guided fine-needle aspiration (FNA) has a diagnostic accuracy that can reach 90 % and has been shown to reduce overall costs given ERCP-related complications such as pancreatitis and cholangitis [1]. In contrast to EUS, which visualizes the pancreatic parenchyma, ERCP serves an important role in the detection of hepatobiliary and pancreatic ductal dilation. Given that pancreaticobiliary malignancies often present as biliary strictures, biliary brush cytology via ERCP is an established diagnostic technique in further investigating these strictures [2]. Pancreatic masses can cause obstructive jaundice; ERCP has both diagnostic and therapeutic roles in patients with obstructive jaundice [3]. Additionally, ERCP is indicated in obtaining tissue material for diagnosis in patients with atypical pancreatic head masses and to differentiate pancreatic cancer from chronic pancreatitis [4].

I. Smith
Division of Gastroenterology and Hepatology, University of Alabama, Birmingham, AL, USA

M. Kahaleh, MD, AGAF, FACG, FASGE (✉)
Division of Gastroenterology and Hepatology, Weill Cornell Medical College, New York, NY, USA
e-mail: mkahaleh@gmail.com

Indications for ERCP in Patients with Pancreatic Masses

A definitive diagnosis of pancreatic cancer requires examination of cellular material obtained from bile or pancreatic juice collection, brushing, FNA, or biopsy. Effective screening techniques are lacking, but ERCP, EUS, and EUS-FNA are considered the most sensitive procedures to detect small pancreatic cancers [5]. EUS had an average rate of pancreatic tumor detection of 97 % while that of ERCP was 91 % [6]. The difference lies in EUS having the ability to diagnose abnormalities of the pancreatic parenchyma while ERCP catches the state of the pancreatic duct [6]. In one study, ERCP was beneficial when computed tomography (CT) and/or ultrasound (US) detected a minor dilation of the main pancreatic duct or cystic lesion in the pancreas [5].

Clinical indications for ERCP in patients include obtaining tissue material with atypical masses in the pancreatic head, particularly in the periampullary area, suspicion of intraductal neoplasm, and difficulty differentiating between pancreatic cancer and chronic pancreatitis [4]. ERCP can also play a role in diagnosing pancreatic cancer in the setting of underlying chronic pancreatitis [7]. One study revealed ERCP's sensitivity and specificity in separating malignant

M.S. Wagh, P.V. Draganov (eds.), *Pancreatic Masses*, DOI 10.1007/978-3-319-19677-0_12

from benign masses in the pancreatic head are 81 % and 88 %, respectively [8].

ERCP capable of cytological sampling via brush cytology, forceps biopsy, and/or needle aspiration should be the preferred primary modality when suspected pancreatic cancer presents with obstructive jaundice or intractable pruritis [9]. The sensitivity of combining all three cytological sampling methods is 62 % with a negative predictive value of 39 % [10]. Given that pancreatic masses can cause obstructive jaundice, ERCP has both diagnostic and therapeutic roles in patients with obstructive jaundice [3].

ERCP with brushings is a valuable diagnostic tool when pancreatic cancer is suspected despite unrevealing US or CT and may be used as an additional method to differentiate between chronic pancreatitis and cancer [11]. If the patient's history and blood test abnormalities suggest pancreatic cancer but no mass is visualized on helical CT, a diagnostic ERCP is recommended [12]. Given that pancreaticobiliary malignancies often present as biliary strictures, biliary brush cytology via ERCP is an established diagnostic technique in further investigating these strictures [2].

In a selected patient population with a higher likelihood of pancreatic cancer (jaundice or pancreatic mass on radiological imaging), up to 85 % of patients do indeed have pancreatic cancer [13]. This degree of risk would certainly warrant more aggressive workup via ERCP. ERCP's deficiency lies in missing uncinate process pancreatic malignancy and malignancies too small to impinge on the pancreatic duct [14]. That being said, ERCP's diagnostic accuracy in one study was 91 % and in another was 95 % and allows for the visualization of the main pancreatic duct and its side branches with their morphological alterations [6, 15], which are present in most cases of pancreatic cancer [15].

Description/Features of Cholangiograms and Pancreatograms in Pancreatic Masses

The most common finding in pancreatic cancer is the stricture of the pancreatic duct, the bile duct, or both [15]. In one study, the common bile duct (CBD) was the site of brushing within the biliary tree most associated with malignant outcome (76 %) [16]. Ductal adenocarcinoma is usually associated with ductal stricture or amputation [17]. On occasion, it may appear as an intraductal filling defect either as a polypoid mass, similar to the intraductal papilloma, or as a large, irregular growth expanding the main pancreatic duct [17].

Mucinous cystic neoplasms and rarely adenocarcinoma can be seen with mucinous hypersecretion [17]. The mucin can cause dilation of the main pancreatic duct with extension into the ampullary portion of the distal portion of the common bile duct [17]. Though a pancreatic mass may not be apparent during pancreatography, a cystic mass may be apparent as a result of draping, narrowing, or total obstruction of the main pancreatic duct [17].

In one study, all patients with pancreatic head cancer showed a pattern of smooth or irregular duct dilation on ultrasonographic pancreatograms that corresponded to the dilation patterns seen with endoscopic opacification of the duct [18]. In the same study, 15 of 16 patients with cancer of the head of the pancreas had an obstructing lesion of the duct visualized [18]. Also, the arbitrarily assigned "normal" inner diameter (<0.8 mm) of the pancreatic duct measured in the body was not seen in any of the patients with carcinoma of the pancreatic head but was seen in one patient with body and tail pancreatic cancer and in one patient with chronic pancreatitis [18].

The upper range of normal pancreatic duct width was 8.0 mm, 4 mm, and 2.4 mm in the head, body, and tail of the pancreas, respectively [19]. Abnormal ductograms were wider than the normal ranges in the head, body, and tail of the pancreas in 14 %, 49 %, and 59 % ($p < 0.001$) of the patients [19]. In another study, most ductal pancreatic cancers showed stenosis of the main pancreatic duct and/or obstruction of the main pancreatic duct and they were easy to detect in early stages [20].

Regardless of presenting symptoms, a double-duct sign on ERCP is caused by pancreatic malignancy in 58 % of patients [13]. The sensitivity and specificity of the double-duct sign observed by ERCP for pancreatic cancer varies between 50–76 % and 63–80 %, respectively [13].

In one study, the length of the pancreatic duct stricture as measured on ERCP correlated with the size and the stage of cancer [21]. Patients with pancreatic head strictures with either a pancreatitis history or side-branch changes (but not both) or an isolated body or tail stricture with neither feature have malignancy risks of 12 %, 41 %, or 26 %, respectively [7]. Surprisingly, patients with isolated pancreatic head or neck strictures and no history of pancreatitis or side-branch changes of chronic pancreatitis have a 94 % chance of their stricture being malignant [7].

Role of ERCP Brushings and Biopsies

Pancreaticobiliary malignancies often present with biliary strictures; attaining biliary brush cytology is a common practice to investigate such strictures [2]. Biliary duct lesions are often not amenable to biopsy; thus, brushing with cytological evaluation offers a method to obtain tissue [16]. Despite the low sensitivity of biliary brush itself, when the findings are combined with clinical factors such as increasing age, higher serum bilirubin levels, and the presence of a mass, there is an increased identification of malignancy [2, 16].

Ductal brush cytology and K-ras mutation analysis can also be performed during ERCP [15]. Pugliese et al. performed ERCP with pancreatic brush cytology, salvage cytology, and collection of pancreatic juice prospectively in patients with pancreatic cancer and chronic pancreatitis [22]. Brush cytology coupled with salvage cytology had a sensitivity of 74 %, but the addition of cytological analysis of pancreatic juice did not substantially improve the sensitivity [22]. Combining cytology with K-ras-2 mutation analysis increased the sensitivity to 93 % but reduced the positive predictive value [22]. In another study, endoscopic retrograde brush cytology had a 65 % sensitivity for detecting pancreatic cancer, an overall sensitivity of 63 %, and a specificity of 96 % [23]. Similarly, endoscopic retrograde brush cytology had a 56.1 % sensitivity and a 90.5 % specificity for detecting pancreatic cancer [24]. The sensitivity and specificity for ERCP-guided cytology when using conventional and spiral suction brushes were 46 % and 100 %, respectively [25].

Some have suggested that ERCP may distinguish malignant from nonmalignant intraductal papillary mucinous neoplasm (IPMN) and delineate the ductal involvement before pancreatectomy when performed with EUS or pancreatoscopy [26]. Others have proposed that histological or cytological preoperative diagnosis of IPMN can be obtained from ERCP with transpapillary brushings or pancreatic juice [26].

In the study by Ross et al., biopsies of bile duct strictures were performed during an ERCP in 20 patients and results were positive in 3 cases, suspicious in 1, and negative in 16 [27]. Of the 16 with negative results, 7 were found to have cancer by other means (surgery, endoscopic biopsy, and EUS-FNA) [27]. In the same study, 73 patients with a final cancer diagnosis had a biopsy, a brushing, and/or FNA during combined EUS and ERCP, and the sensitivity was 82.6 % [27]. In another study, the sensitivity and specificity for ERCP-guided biopsy were 36 % and 100 %, respectively [25].

In a prospective study of 26 patients, the sensitivity, accuracy, and negative predictive values were 5.9 %, 38.5 %, and 36 % for standard cytology brushings, 29.4 %, 53.8 %, and 42.8 % for standard forceps biopsies, and 76.5 %, 84.6 %, and 69.2 % for cholangioscopy-guided mini-forceps biopsies, respectively [28].

Importantly, despite biliary brushings obtained during ERCP having a sensitivity no higher than 70 % when combined with factors predictive of malignancy, there is an increased identification of malignancy. These factors include, but are not limited to, suspicious or malignant endoscopic impression, older age, stricture location within the common bile duct, indications including jaundice and/or dilated bile ducts, and the presence of a pancreatic mass [16]. Of 71 % of patients with "atypical" brushings the endoscopist specifically recorded, 75 % were found to harbor a true malignancy [16]. In a similar study by Stewart et al., 70.7 % of patients with atypical results on biliary brushings via ERCP had pancreaticobiliary malignancies [29]. In Volmar et al., 10.4 % had atypical biliary brushings and 43.6 % of those patients had malignancy [30].

Cost-Effectiveness of ERCP in Diagnosis of PMasses

There is a paucity of cost-minimization studies comparing modalities for diagnosing pancreatic cancer. The preferred initial modality for the diagnosis of pancreatic cancer was EUS-FNA. The resultant expected costs and strategies in decreasing optimality include (1) EUS-FNA ($1405), (2) ERCP with brushings ($1432), (3) CT-US-FNA ($3682), and (4) surgery ($17,711) [9]. In an older study, EUS was the preferred initial diagnostic test, yielding an average cost of $1111 per patient, while the cost of MRCP was $1145 and that of ERCP was $1346 [31].

Future of ERCP in Diagnosing Pancreatic Masses

High-definition cholangioscopy by providing excellent views of the pancreaticobiliary ductal system is a useful adjunct to ERCP in the diagnosis of pancreatobiliary disorders [32]. Fragility of the cholangioscope remains a problem, but changes in its design have made it more durable [32]. A novel, ultrathin (5 Fr) scanning fiber endoscope (SFE) with two-axis tip-bending capability has been developed specifically for high-resolution imaging as a pancreatoscope during ERCP [33]. This 1.7-mm-diameter SFE that produces significantly less average force during insertion has the potential to dramatically improve diagnostic capabilities during ERCP by providing direct video feedback and tool guidance to physicians [33]. Further evaluation of SFE's effectiveness in humans should be pursued [33].

References

1. Mesenas SJ. Does the advent of endoscopic ultrasound (EUS) sound the death knell for endoscopic retrograde cholangiopancreatography (ERCP)? Ann Acad Med Singapore. 2006;35:89–95.
2. Parsi MA, Deepinder F, Lopez R, et al. Factors affecting the yield of brush cytology for the diagnosis of pancreatic and biliary cancers. Pancreas. 2011;40(1):52–4.
3. Khurram M, Durrani AA, Hasan Z, et al. Endoscopic retrograde cholangiopancreatographic evaluation of patients with obstructive jaundice. J Coll Physicians Surg Pak. 2003;13(6):325–8.
4. Licender L, Vrcic D, Sadagic E, et al. Magnetic resonance cholangiopancreatography (MRCP): correlation with diagnosis using ERCP. Med Arh. 2002; 56(1 Suppl 1):25–8.
5. Nakamura T, Masuda K, Harada S, et al. Pancreatic cancer: slow progression in the early stages. Int J Surg Case Rep. 2013;4(8):693–6.
6. Tanaka K, Kida M. Role of endoscopy in screening of early pancreatic cancer and bile duct cancer. Dig Endosc. 2009;21 Suppl 1:S97–100.
7. Erickson RA. Editorial ERCP and pancreatic cancer. Ann Surg Oncol. 2004;11(6):555–7.
8. Glasbrenner B, Schwarz M, Pauls S, et al. Prospective comparison of endoscopic ultrasound and endoscopic retrograde cholangiopancreatography in the preoperative assessment of masses in the pancreatic head. Dig Surg. 2000;17(5):468–74.
9. Chen VK, Arguedas MR, Kilgore ML. A cost-minimization analysis of alternative strategies in diagnosing pancreatic cancer. Am J Gastroenterol. 2004;99:2223–34.
10. Jaiwala J, Fogel EL, Sherman S, et al. Triple-tissue sampling at ERCP in malignant biliary obstruction. Gastrointest Endosc. 2000;51(4 Pt 1):383–90.
11. Miller BA, Kolonel LN, Berstein L, et al. Racial/ethnic patterns of cancer in the United States 1988–1992. Bethesda: National Cancer Institute; 1996.
12. Gloor B, Todd KE, Reber HA. Diagnostic workup of patients with suspected pancreatic carcinoma: the University of California–Los Angeles approach. Cancer. 1997;79(9):1780–6.
13. Oterdoom LH, Van Weyenberg SJ, De Boer NK. Double-duct sign: do not forget the gallstones. J Gastrointestin Liver Dis. 2013;22(4):447–50.
14. Miura F, Takada T, Amano H, et al. Diagnosis of pancreatic cancer. HPB (Oxford). 2006;8(5):337–42.
15. Spinell P, Schiavo M, Schicchi AA. Endoscopy in the diagnosis and staging of pancreatic cancer. Tumori. 1999;85(1 Suppl):S14–8.
16. Witt BL, Hilden K, Scaife C, et al. Identification of factors predictive of malignancy in patients with atypical biliary brushing results obtained via ERCP. Diagn Cytopathol. 2013;41(8):682–8.
17. Taylor AJ, Carmody TJ, Schmalz MJ, et al. Filling defects in the pancreatic duct on endoscopic retrograde pancreatography. AJR Am J Roentgenol. 1992; 159:1203–8.
18. Ohto M, Saotome N, Saisho H, et al. Real-time sonography of the pancreatic duct: application to percutaneous pancreatic ductography. AJR Am J Roentgenol. 1980;134:647–52.
19. Ladas SD, Tassios PS, Giorgiotis K, et al. Pancreatic duct width: its significance as a diagnostic criterion for pancreatic disease. Hepatogastroenterology. 1993; 40(1):52–5.
20. Yamao K, Kajikawa M. Early diagnosis of pancreatic cancer: re-evaluation of endoscopic retrograde cholangiopancreatography. Gan No Rinsho. 1983;29(10): 1097–103.

21. Lim JE, Chien MW, Earle CC. Prognostic factors following curative resection for pancreatic adenocarcinoma: a population-based, linked database analysis of 396 patients. Ann Surg. 2003;237:74–85.
22. Pugliese V, Pujic N, Saccomanno S, et al. Pancreatic intraductal sampling during ERCP in patients with chronic pancreatitis and pancreatic cancer: cytologic studies and K-ras-2 codon 12 molecular analysis in 47 cases. Gastrointest Endosc. 2001;54(5):595–9.
23. Macken E, Drijikoningen M, Van Aken E, et al. Brush cytology of ductal strictures during ERCP. Acta Gastroenterol Belg. 2000;63(3):254–9.
24. Glasbrenner B, Ardan M, Boeck W, et al. Prospective evaluation of brush cytology of biliary strictures during endoscopic retrograde cholangiopancreatography. Endoscopy. 1999;31(9):712–7.
25. Rosch T, Hofrichter K, Frimberger E, et al. ERCP and EUS for tissue diagnosis of biliary strictures? A prospective comparative study. Gastrointest Endosc. 2004;60(3):390–6.
26. Canto MI, Goggins M, Hruban RH, et al. Screening for early pancreatic neoplasia in high-risk individuals: a prospective controlled study. Clin Gastroenterol Hepatol. 2006;4:766–81.
27. Ross WA, Wasan SM, Evans DB, et al. Combined EUS with FNA and ERCP for the evaluation of patients with obstructive jaundice from presumed pancreatic malignancy. Gastrointest Endosc. 2008; 68(3):461–6.
28. Draganov PV, Chauhan S, Wagh MS, et al. Diagnostic accuracy of conventional and cholangioscopy-guided sampling of indeterminate biliary lesions at the time of ERCP: a prospective, long-term follow-up study. Gastrointest Endosc. 2012;75:347–53.
29. Stewart CJ, Mills PR, Carter R, et al. Brush cytology in the assessment of pancreatico-biliary strictures: a review of 406 cases. J Clin Pathol. 2001;54:449–55.
30. Volmar KE, Vollmer RT, Routbort MJ, et al. Pancreatic and bile duct brushing cytology in 1000 cases: review of findings and comparison of preparation methods. Cancer. 2006;108:231–8.
31. Scheiman JM, Carlos RC, Barnett JL, et al. Can endoscopic ultrasound or magnetic resonance cholangiopancreatography replace ERCP in patients with suspected biliary disease? A prospective trial and cost analysis. Am J Gastroenterol. 2001;96(10):2900–4.
32. Parsi MA, Jang S, Sanaka M, Stevens T, et al. Diagnostic and therapeutic cholangiopancreatoscopy: performance of a new digital cholangioscope. Gastrointest Endosc. 2014;79(6):936–42.
33. Chandler JE, Lee CM, Babchanik AP, et al. Evaluation of a novel, ultrathin, tip-bending endoscope in a synthetic force-sensing pancreas with comparison to medical guide wires. Med Dev. 2012;5:1–12.

13 Endoscopic Retrograde Cholangiopancreatography (ERCP): Pancreatoscopy for the Evaluation of Pancreatic Neoplasia

Ihab I. El Hajj and Raj J. Shah

Peroral Pancreatoscopy Equipment and Technique

Peroral pancreatoscopy was first described in Japan in 1975 [1]. The usefulness of this technique was limited by poor optics and instrument fragility as well as the relatively large diameter of the instrument compared to the main pancreatic duct (MPD) diameter.

Types of Pancreatoscopes

In the United States, pancreatoscopy is currently performed with scopes and catheters designed for inspection of the bile duct. The limitation inherent with pancreatic duct inspection is its relatively narrower caliber compared to the bile duct. Initial iterations of devices specific to the pancreatic duct were primarily developed in East Asia. Prototypes included optical image fiber bundles and ultrathin pancreatoscopes without a working channel or an ability to perform tip deflection. Current prototype and commercially available pancreatoscopes have improved optical resolution and working channels, but limitations of diameter, fragility, and tip deflection to negotiate tortuous ducts and strictures remain. Although slim endoscopes may be used for direct POP, this procedure is primarily performed in conjunction with a duodenoscope. The devices used for pancreatoscopy include prototype video pancreatoscopes with narrow-band imaging (NBI) or autofluorescence imaging (AFI), and commercially available choledochoscopes with two-way tip deflection and a single 1.2-mm working channel for irrigation and biopsy forceps introduction (Olympus, Inc. and Pentax, Inc.). Also, the semidisposable catheter-based SpyGlass Direct visualization™ (Boston Scientific, Inc.) system is FDA-approved for pancreatic duct inspection and has a four-way tip deflection, a dedicated 1.2-mm working channel diameer, two 0.6-mm irrigation ports, and a lumen for the reusable optical probe [2–4]. A detailed review of the available cholangiopancreaotoscopes has been summarized in a technical status evaluation report by the American Society of Gastrointestinal Endoscopy's Technology committee and other technical reviews [5, 6]. It should be noted that to perform pancreatoscopy, significant experience with pancreatic endotherapy is a suggested baseline requirement.

I.I. El Hajj, M.D., M.P.H.
Department of Medicine, University of Colorado School of Medicine, Aurora, CO, USA

R.J. Shah, M.D., F.A.S.G.E., A.G.A.F. (✉)
Department of Medicine, University of Colorado School of Medicine, Aurora, CO, USA

Gastroenterology, Digestive Health Center, University of Colorado Hospital, 1635 Aurora Ct., Mail Stop F735, Rm. AIP 2.031, Aurora, CO 80045, USA
e-mail: raj.shah@ucdenver.edu

M.S. Wagh, P.V. Draganov (eds.), *Pancreatic Masses*, DOI 10.1007/978-3-319-19677-0_13

Patient Preparation and Pancreatic Duct Access

Prophylactic IV antibiotics are administered preprocedurally. We utilize general anesthesia due to the need for saline irrigation during ductal inspection and potential for reflux of fluid into the stomach. These procedures also tend to be longer than conventional pancreatic endotherapy cases. The patient is placed in the semiprone position. Following ductal access with a 0.035-in. coated guidewire advanced typically beyond the target lesion, endoscopic sphincterotomy is performed in preparation for pancreatoscopy. If the pancreatic duct orifice is patulous, as may be seen in patients with main-duct intraductal papillary mucinous neoplasia (IPMN), endoscopic sphincterotomy prior to pancreatoscope introduction may not be necessary. Jung et al. [7] performed endoscopic pancreatic sphincterotomy in 18 patients prior to pancreatoscopy. One complication (bleeding) was reported. Ueno et al. [8] performed endoscopic sphincter dilation in patients with IPMN. This latter technique has the theoretical advantage of preserving the sphincter function of the papilla. The authors observed significant hyperamylasemia after endoscopic sphincter dilation and recommended temporary pancreatic stenting. This, however, may not be necessary in patients with main-duct IPMN. Further, a large mucin burden may rapidly occlude small-diameter stents and result in postprocedural pancreatitis (personal observation). The prototype ultrathin pancreatoscopes have permitted device introduction in nondilated MPD. Kodama et al. [9] reported a series of 36 chronic pancreatitis patients with a technical success of 90 %, but its clinical utility without the ability to perform directed tissue sampling remains to be seen.

Commercially available pancreatoscopes are of larger diameter (approximately 10 F). The angle to the pancreatic orifice from the duodenoscope is more oblique than compared to the bile duct and initial transpapillary advancement is often simpler than traversing the biliary orifice, which is often at a right angle. Difficulty, however, may be encountered when advancing a 10 F device through tortuous segments such as the genu or narrowings that are not always suspected on pancreatography. Dilation with a 4- or 6-mm balloon prior to attempting device introduction may be required.

Technique Description

Pancreatoscopy may be feasible through the major or minor papilla, with the latter being technically challenging because of more acute angulation during device introduction, limited maneuverability, and endoscope stability [10, 11]. The endoscope-based two-operator (e.g., "mother–daughter") system requires an endoscopist and a trained assistant, who may be a nurse, technician, or second endoscopist to control suction and tip deflection at the handle. Further, the assisting provider is also tasked with the important aspect of minimizing angulations and torsion of the exposed shaft along its length from the handle of the pancreatoscope to its entry into the working channel cap of the duodenoscope. The pancreatoscope is advanced over an indwelling guidewire ideally beyond the target, followed by guidewire withdrawal for mucosal inspection and to improve irrigation with sterile saline to aid visualization. During intraductal inspection, due to an inherent acute angulation at the relatively fixed genu, circumferential inspection of this area tends to be limited but may be enhanced by torqueing of the duodenoscope and tip deflection of the pancreatoscope. For the single-operator catheter-based system, the control section knobs should be unlocked and the optical probe is preloaded into the disposable access catheter and advanced to within a few millimeters of the tip of the catheter. Following advancement to the target and guidewire withdrawal, the optical probe is gently advanced beyond the catheter tip for intraductal inspection. The endoscopist has control of the four-way steering dials and may periodically lock the dials for fine movements of the catheter to stabilize visualization of a target during tissue acquisition using miniature forceps biopsy.

Techniques to Improve Visualization

Irrigation rates should be kept as low as possible to permit a sufficient view and to potentially reduce the risk of pancreatitis. Periodic suctioning of duodenal contents in the setting of a sphincterotomy and aspiration using the pancreatoscope is encouraged. For the catheter-based system, a Y-adapter may be connected to the working channel of the control section to permit suctioning, and this preserves other working channel functionality such as biopsy. The endoscope-based system has suction capability. Other techniques used to optimize visualization include the use of mucomyst, which we have not found consistently useful; a "closed circuit" technique of irrigation and suctioning in the catheter-based system to reduce debris obscuring visualization; and the administration of intravenous secretin has been described to stimulate pancreatic juice flow [12].

Sampling Techniques

To facilitate insertion of accessories, such as biopsy forceps or electrohydraulic (EHL) probe, the elevator of the duodenoscope needs to be relaxed and the angulation of both the duodenoscope and the pancreatoscope need to be reduced. If passage of the biopsy forceps is possible through the accessory channel, POP-directed biopsies can be obtained. If the target lesion is closer to the pancreatic orifice (e.g., pancreatic head), then passage of the miniature forceps may not be feasible. In this scenario, or if additional sampling is desired using pediatric or biliary forceps, POP-assisted biopsies can be obtained. With this technique, reference to a fluoroscopic spot film obtained of the position of the pancreatoscope at the target lesion guides tissue sampling through the accessory channel of the duodenoscope [13].

Intraoperative Pancreatoscopy

The selective use of intraoperative pancreatoscopy to evaluate the MPD appears to help to enable the surgeon to guide resection margins. We are unaware, however, of this being routinely utilized in the United States. Kaneko et al. [14] reported a sensitivity, specificity, and overall accuracy of intraoperative pancreatoscopy of 100 % for the diagnosis of IPMN and defining the extent of tumor involvement in the duct. Pucci et al. [15] reported the use of intraoperative pancreatoscopy in 23 pancreatic resections; 18 of these operations were performed for presumed main-duct IPMN, and in 5 (22 %), the surgical resection was extended as a result of the pancreatoscopy findings.

Adverse Events

Adverse events from cholangiopancreatoscopy may be more than double those of endoscopic retrograde cholangiopancreatography (ERCP) alone (7 % vs. 2.9 %). Cholangiopancreatoscopy appears to be associated with similar rates of pancreatitis when compared to ERCP being performed without cholangiopancreatoscopy [16]. It is likely, however, that higher rates of pancreatitis may be seen that is inherent to pancreatic endotherapy, in general, rather than the use of pancreatoscopy itself [10].

Pancreatic Carcinoma in situ

Often, pancreatic cancers are locally advanced or metastatic at the time of diagnosis. Efforts to improve pancreatic cancer survival rates include early-stage detection, such as carcinoma in situ, which are typically difficult to locate by conventional diagnostic methods such as CT, EUS, and ERCP. Limited data exist on this indication, and in general, the literature for detecting adenocarcinoma of the pancreas utilizing pancreatoscopes includes electronic devices that are prototypes or that are not currently under development.

In a small series of 11 patients, POP and pancreatoscopic cytology were utilized to identify pancreatic carcinoma in situ in a select cohort of patients [17]. POP was utilized preoperatively with identification of ten main duct and one side-branch neoplasm. POP mucosal findings included

papillary projections, irregular margins, or a nodular appearance. Using pancreatoscopy-guided aspiration and cytology, malignant cells were obtained from all lesions in the MPD, while conventional pancreatic juice cytology was diagnostic in 60 % of the cases.

Invasive Pancreatic Cancer

EUS has been suggested as the most useful modality for the diagnosis of pancreatic cancer [18]. However, in some patients a discrete mass cannot be delineated within a stenotic ductal segment because of concomitant pancreatitis, for example, and POP with an ultrathin fiberscope may be useful [19]. One issue is that most pancreatic cancers seem to originate within side branches and pancreatoscopy may only observe neoplastic changes when these progress to involve the main duct, limiting its usefulness in the detection of early cancers [20]. In an attempt to overcome this limitation, a prototype 2.2-mm-diameter fiberscope equipped with a shape-memory alloy has been developed. The tip of this fiberscope can be curved freely by heating the alloy with a controller [21]. Tajiri et al. [22] developed a special video converter connected to the head of the pancreatoscope to permit visualization of sequential electronic endoscope images on a monitor. They performed examinations with this system in 52 cases (8 with pancreatic cancer, 19 with chronic pancreatitis, and 25 normal cases); however, we are unaware if current iterations of this technology are available even in the prototype stage.

Peroral Pancreatoscopy Findings in Patients with Pancreatic Cancer

Pancreatoscopy findings in pancreatic cancer include nonspecific descriptors such as coarse mucosa, erythema, and friability and more specific lesions such as protrusions or an infiltrative stricture (e.g., near-occlusion of the lumen) with irregular margins (see Fig. 13.1). Although coarse mucosa and friability are substantially more frequent in pancreatic cancer than in benign ductal stenosis, these are not specific for neoplasia and a lack of standardization of terms has limited widespread applicability when comparing the literature. In a large series of 115 cases of pancreatic diseases, findings specific to pancreatic cancer included protrusion, friability, and tumor vessels, which were particularly associated with small (<2 cm) pancreatic cancers [19].

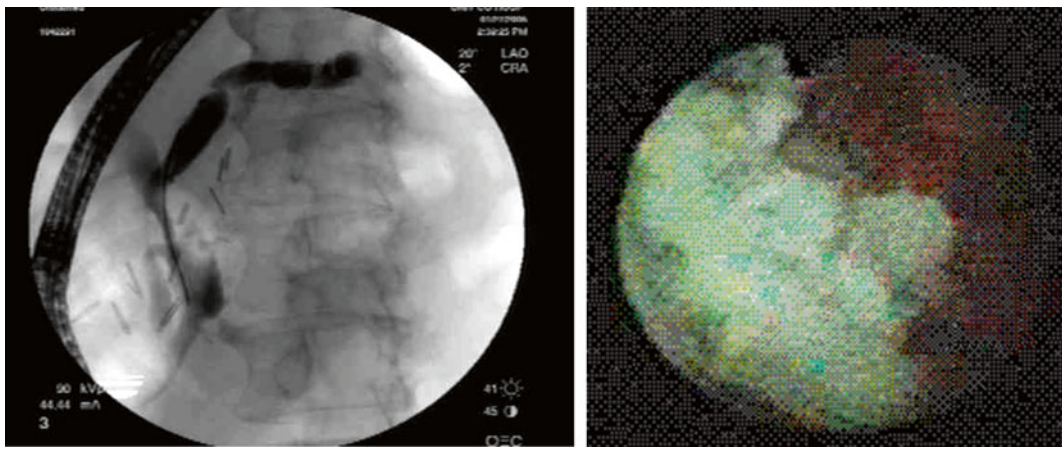

Fig. 13.1 (**a**) Pancreatogram with pancreatic head stricture; (**b**) fiber optic pancreatoscopy of an ulcerated intraductal mass positive for adenocarcinoma

Intraductal Papillary Mucinous Neoplasia

IPMN of the pancreas is an increasingly detected clinical entity characterized by papillary hyperplasia of the pancreatic ductal epithelium, excessive mucin secretion, and cystic dilation of the pancreatic duct. The pathologic abnormalities may involve the entire MPD, a segment of the MPD, multiple segments of the MPD (multifocal IPMN), only the side branches (SB-IPMN), or both MPD and SB (mixed-IPMN) [23].

Because IPMN constitutes a potentially malignant, premalignant, or malignant condition at the time of diagnosis, an accurate definition of disease extent and tissue sampling are paramount to the appropriate management of IPMN [24]. A variety of imaging techniques such as computed tomography (CT scan) of the abdomen, ERCP, endoscopic ultrasound (EUS), and magnetic resonance cholangiopancreatography (MRCP) are currently used. In a small series, when compared to ERCP and MR-virtual pancreatography (MR-VP), computed tomography virtual pancreatoscopy (CT-VP) and three-dimensional (3D) CT pancreatographic images were finer in quality, and the procedures were less invasive, faster, and less expensive [25]. In an early selective series of 47 patients with IPMN who had undergone surgical resection, the overall accuracy of CT, ERCP, and EUS in distinguishing between invasive and noninvasive tumors was 76 %, 79 %, and 76 %, respectively [26]. In an effort to improve the endoscopic detection of IPMN, various analyses of pancreatic juice cytology [27], K-ras gene mutations [28], and telomerase activity [29] have been proposed. Although diagnostic ERCP is often not required in order to secure the diagnosis of IPMN, pancreatic juice cytology may provide a simple method to evaluate IPMN, though it also remains with limited sensitivity. In a series of 103 resection patients with IPMN (29 adenomas, 17 borderline, 25 carcinoma in situ, and 32 invasive carcinoma), pancreatic juice was collected with a catheter in 71 patients and by POP in 32 patients [30]. The sensitivity for the detection of IPMN was 62.2 % when pancreatic juice was collected by POP and was 38.2 % when it was collected using a catheter—and this was despite a highly select group of neoplastic patients. Interestingly, for pancreatic carcinoma, the sensitivity of pancreatic juice cytology was only 25.4 %, which was significantly lower than for POP-assisted collection of pancreatic juice in detecting IPMN (68.2 %). This may be related to the fact that ductal adenocarcinoma strictures are more difficult to traverse and perhaps cytology from juice obtained downstream of the stricture may have limited tumor cells.

Pancreatoscopy Findings in Intraductal Papillary Mucinous Neoplasia

A key study was performed by Hara et al. [31], who performed a retrospective review of their experience in evaluating patients with IPMN by and intraductal ultrasound (IDUS) over a 13-year period. Sixty consecutive IPMN patients were included in this study (Fig. 13.2). The authors assessed tumor type (elevated vs. excavated), morphology per POP (type I: granular; type II: fish-egg-like without vascular images; type III: fish-egg-like with vascular images; type IV: villous type; and type V: vegetative type) (Figs. 13.3, 13.4 and 13.5), maximum tumor height as determined by IDUS, and tumor extent (head vs. body vs. tail; MPD vs. SB). Results obtained with POP and IDUS were correlated and compared with surgical pathology serving as the gold standard. The ability of CT, EUS, and K-ras point mutations in pancreatic juice to distinguish benign (hyperplasia or adenoma) from malignant (carcinoma in situ or invasive carcinoma) IPMN was also studied. A high proportion (40/60, 67 %) had protruding lesions. Most malignant tumors had a POP morphology type III, IV, or V ($p<0.0001$), with a reported sensitivity, specificity, and accuracy of 68 %, 87 %, and 75 % for differentiating benign from malignant IPMN. Maximum tumor height of protruding lesions as measured by IDUS (2.27 ± 1.5 mm in the benign group, and 5.96 ± 4.03 in the malignant group) was also able to discriminate benign from malignant tumors ($p<0.001$). CT and EUS had a sensitivity and accuracy ranging from 32 to 65 %. When a

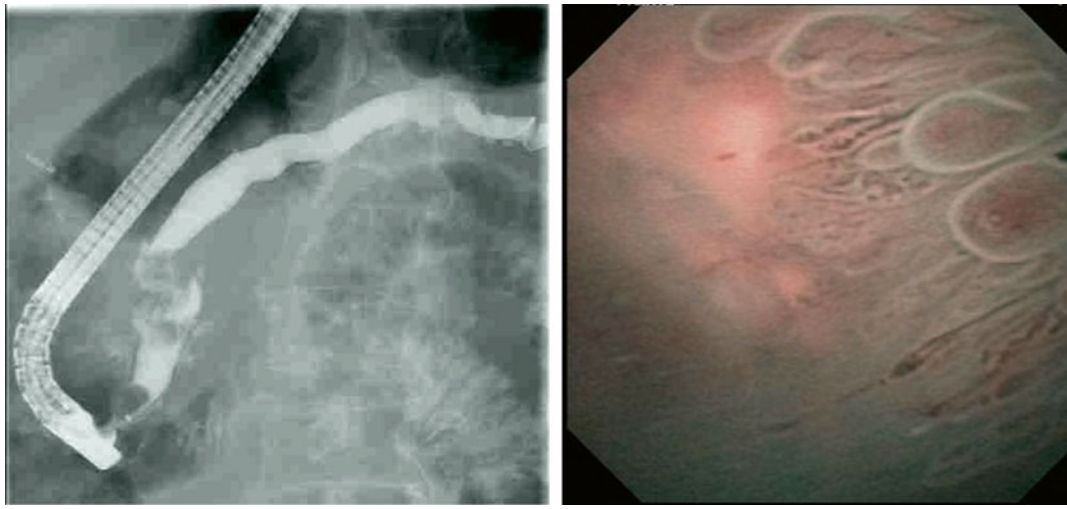

Fig. 13.2 (**a**) Pancreatogram with mucinous filling defects in the pancreatic head; (**b**) video pancreatoscopy image of Type IV villous IPMN

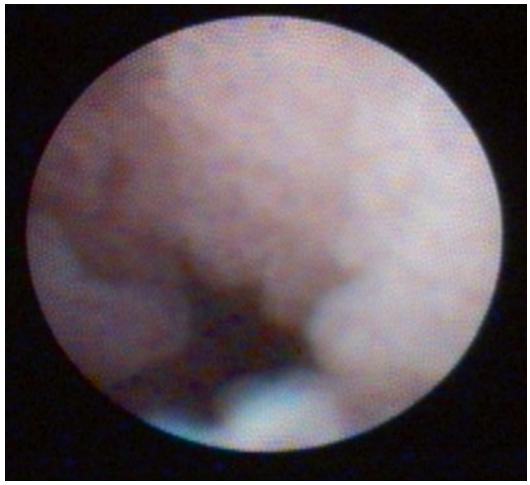

Fig. 13.3 Pancreatoscopy image of a Type 1 granular-type IPMN

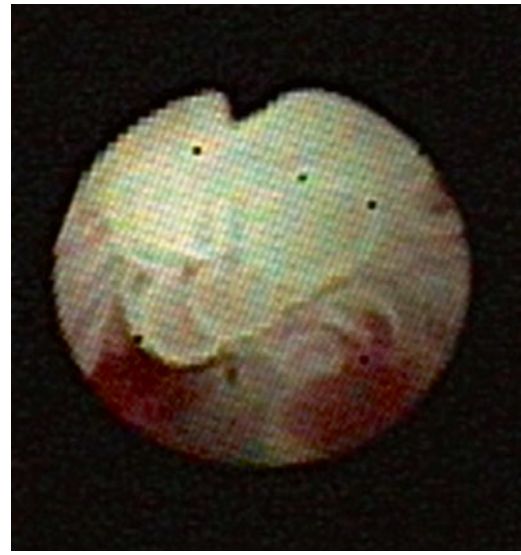

Fig. 13.4 Pancreatoscopy image of Type 2 fish-egg IPMN

positive K-ras point mutation was considered a malignant finding, the sensitivity, specificity, and accuracy reached 87 %, 15 %, and 61 %, respectively. Only one of the 60 patients resected (1.6 %) had positive surgical margins. The 3-year relapse-free and overall survival were 93 % and 95 %, respectively. Thus, POP and IDUS may help to distinguish benign from malignant IPMN, determine tumor extent, and guide therapy. The implication of these data is that these techniques may contribute to the improvement in postoperative results though the follow-up is relatively short. The authors find pancreatoscopy to be of more clinical relevance as directed tissue sampling may be performed at the same time.

Miura et al. [32] reported their experience of diagnosis of IPMN in 21 patients by means of peroral pancreatoscopy using a small-diameter videoscope (2.6-mm OD and 0.5-mm working channel) and NBI. Endoscopically, seven cases were classi-

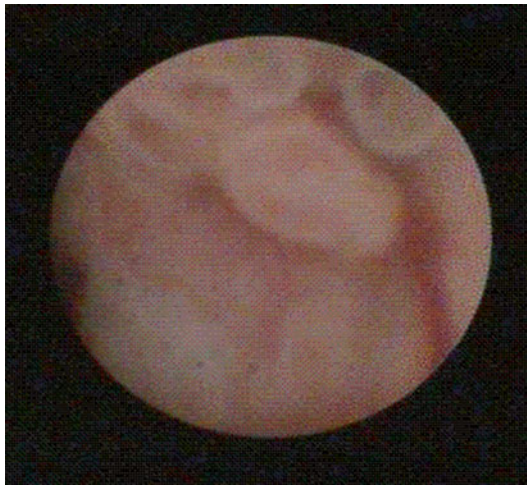

Fig. 13.5 Fiber optic pancreatoscopy image of a Type V vegetative IPMN

fied as villous (Type IV) and two cases as vegetative (Type V), and nine cases were diagnosed as adenocarcinoma. Ten cases with "sessile" type or "semi-pedunculated" type were diagnosed as adenoma or hyperplasia. The distinction between "sessile" and "vegetative" types was not entirely clear. Subjectively, vascular patterns and protrusions were detected more clearly in the NBI images than under white light observation.

In a series of 24 patients with suspected IPMN referred for surgery, intraoperative pancreatoscopy using an ultrathin pancreatoscope detected ten cases of intraductal IPMN lesions that could not be detected by preoperative EUS or ERCP; IPMN is defined in the latter group to include a well-defined filling defect of polypoid tumor by pancreatography. Five of the ten cases were intraductal multicentric lesions [14]. For the diagnosis of IPMN, the sensitivity, specificity, and overall accuracy of intraoperative pancreatoscopy were all 100 %; respective values were 43.8 %, 100 %, and 60.9 % for ERCP without POP and 47 %, 100 %, and 62.5 % for EUS. Intraoperative pancreatoscopy with NBI has been reported also to be a useful adjunct for IPMN management in guiding intraoperative decision making of the resection margins [33].

An additional series of patients undergoing POP included 60 patients with surgically confirmed IPMN of whom 57 (95 %) underwent technically successful POP. POP findings included papillary projections (58 %), mucin only (23 %), granular mucosa (16 %), and coarse mucosa (4 %). As in previous series, papillary projections were more prevalent in patients with advanced histology (23 % of adenoma, 58 % of borderline malignancy, 70 % of noninvasive IPMN, and 89 % of invasive IPMN) [19]. In a smaller series of 12 patients with IPMN (11 MPD, 1 SB), the authors observed oval-shaped "fish-egg" lesions in ten patients and nodular or villous changes in two patients. The patients with invasive IPMN consisted of the oval-shaped tumors with erythema or villous tumors and dilated blood ("tumor") vessels. In the one case of SB-IPMN, POP observed papillary projections spreading from the orifice of the affected side branch [12].

Most recently, our group performed a retrospective review of POP in the evaluation of suspected MPD neoplasia over a 13-year period [34]. Seventy-eight patients underwent 103 POPs. Technical success was 98 %. Twenty-one patients were diagnosed with MD-IPMN (6 dysplastic, and 15 nondysplastic), and five patients with SB-IPMN. POP was useful in localizing MPD-IPMN to guide resection, excluding lesions in the head for anticipated extended pancreatic tail resection, and evaluating for mixed IPMN in patients with established SB-IPMN. Among the 6 dysplastic MPD-IPMN, POP findings included a vegetative mass Type V ($N=1$), and villous projections Type IV ($N=5$). Among the 15 nondysplastic MD-IPMN, POP findings included villous projections ($N=8$), vegetative mass ($N=3$), stricture and mucin ($N=3$), and mucin alone ($N=1$). Overall, the POP visual impression had a sensitivity, specificity, and accuracy of 91 %, 96 %, and 94 %, respectively.

Summary

Commercially available pancreatoscopes are now widely available, though significant baseline experience in not only ERCP but also pancreatic endotherapy is a necessity prior to incorporating this technology into practice. Techniques of tissue sampling include intraductal aspiration of pancreatic juice for cytology, pancreatoscopy-

directed biopsy, and pancreatoscopy-assisted biopsy. POP has a high success rate in appropriate patient populations with dilated pancreatic ducts and carries an acceptable risk profile. It is a useful adjunct to ERCP, EUS, and noninvasive imaging to improve the detection of pancreatic duct neoplasia with specific attention to IPMN. It may also be utilized to discriminate malignant from benign IPMN. Though advancements in fragility have been made, refined optics and ease of accessory device passage through the working channel are still awaiting commercial availability. With this anticipated progress in technology, POP may become more widely adapted, with an improved success and complication profile.

Acknowledgment Disclosures for Raj J. Shah: Medical Advisory Board, Consultant, and Unrestricted Educational Grant from Boston Scientific, Inc. Unrestricted educational grants from Olympus, Inc. and Pentax, Inc.

References

1. Takekoshi T, Maruyama M, Sugiyama N, et al. Retrograde pancreatocholangioscopy. Gastrointest Endosc. 1975;17:678–83.
2. Kodama T, Koshitani T. Pancreatoscopy. In: Baron TH, Kozarek RA, Carr-Locke DL, editors. ERCP. 2nd ed. Philadelphia: Elsevier Saunders; 2013. p. 234–42.
3. Lee J, Kelsey P. Choledochoscopy and pancreatoscopy. In: Cohen J, editor. Successful training in gastrointestinal endoscopy. 1st ed. Malden: Willey-Blackwell; 2011. p. 116–24.
4. Draganov PV, Lin T, Chauhan S, et al. Prospective evaluation of the clinical utility of ERCP-guided cholangiopancreatoscopy with a new direct visualization system. Gastrointest Endosc. 2011;73(5):971–9.
5. Shah RJ, Adler DG, Conway JD, et al. Cholangiopancreatoscopy: ASGE technical committee status evaluation report. Gastrointest Endosc. 2008;68(3):411–21.
6. Nguyen NQ, Binmoeller KF, Shah JN. Cholangioscopy and pancreatoscopy (with videos). Gastrointest Endosc. 2009;70(6):1200–10.
7. Jung M, Zipf A, Schoonbroodt D, et al. Is pancreatoscopy of any benefit in clarifying the diagnosis of pancreatic duct lesions? Endoscopy. 1998;30(3):273–80.
8. Ueno N, Ozawa Y, Aizawa T. Pancreatoscopy assisted by endoscopic sphincter dilation. J Gastroenterol. 2003;38(3):283–7.
9. Kodama T, Imamura Y, Sato H, et al. Feasibility study using a new small electronic pancreatoscope: description of findings in chronic pancreatitis. Endoscopy. 2003;35(4):305–10.
10. Brauer BC, Chen YK, Ringold DA, et al. Peroral pancreatoscopy via the minor papilla for diagnosis and therapy of pancreatic diseases. Gastrointest Endosc. 2013;78(3):545–9.
11. Ringold DA, Shah RJ. Peroral pancreatoscopy in the diagnosis and management of intraductal papillary mucinous neoplasia and indeterminate pancreatic duct pathology. Gastrointest Endosc Clin N Am. 2009;19(4):601–13.
12. Kodama T, Koshitani T, Sato H, et al. Electronic pancreatoscopy for the diagnosis of pancreatic diseases. Am J Gastroenterol. 2002;97(3):617–22.
13. Shah RJ, Langer DA, Antillon MR, et al. Cholangioscopy and cholangioscopic forceps biopsy in patients with indeterminate pancreaticobiliary pathology. Clin Gastroenterol Hepatol. 2006;4(2):219–25.
14. Kaneko T, Nakao A, Nomoto S, et al. Intra-operative pancreatoscopy with the ultra-thin pancreatoscope for mucin-producing tumors of the pancreas. Arch Surg. 1998;133(3):263–7.
15. Pucci MJ, Johnson CM, Punja VP, et al. Intraoperative pancreatoscopy: a valuable tool for pancreatic surgeons? J Gastrointest Surg. 2014;18(6):1100–7.
16. Sethi A, Chen YK, Austin GL, et al. ERCP with cholangiopancreatoscopy may be associated with higher rates of complications than ERCP alone: a single-center experience. Gastrointest Endosc. 2011;73(2):251–6.
17. Uehara H, Nakaizumi A, Tatsuta M, et al. Diagnosis of carcinoma in situ of the pancreas by peroral pancreatoscopy and pancreatoscopic cytology. Cancer. 1997;79(3):454–61.
18. Al-Haddad M, DeWitt J. EUS in pancreatic tumors. In: Hawes RH, Fockens P, Varadarajulu S, editors. Endosonography. 2nd ed. Philadelphia: Elsevier Saunders; 2011. p. 148–65.
19. Yamao K, Ohashi K, Nakamura T, et al. Efficacy of peroral pancreatoscopy in the diagnosis of pancreatic diseases. Gastrointest Endosc. 2003;57(2):205–9.
20. Kawaguchi A, Tajiri H, Niwa H. Visualization of the pancreatic duct through the fine-fiber scope. In: Lygidakis NJ, Makuuchi M, editors. Pitfalls and complications in the diagnosis and management of hepatobiliary and pancreatic diseases. New York: Thieme; 1993. p. 349–51.
21. Tajiri H, Kobayashi M, Niwa H, et al. Clinical application of an ultra-thin pancreatoscope using a sequential video converter. Gastrointest Endosc. 1993;39(3):371–4.
22. Tajiri H, Kobayashi M, Ohtsu A, et al. Peroral pancreatoscopy for the diagnosis of pancreatic diseases. Pancreas. 1998;16(3):408–12.
23. Levy P, Jouannaud V, O'Toole D, et al. Natural history of intraductal papillary mucinous tumors of the pancreas: actuarial risk of malignancy. Clin Gastroenterol Hepatol. 2006;4(4):460–8.

24. Rodriguez JR, Salvia R, Crippa S, et al. Branch-duct intraductal papillary mucinous neoplasms: observations in 145 patients who underwent resection. Gastroenterology. 2007;133(1):72–9; quiz 309–10.
25. Sata N, Kurihara K, Koizumi M, et al. CT virtual pancreaotoscopy: a new method for diagnosing intraductal papillary mucinous neoplasm (IPMN) of the pancreas. Abdom Imaging. 2006;31:326–31.
26. Cellier C, Cuillerier E, Palazzo L, et al. Intraductal papillary and mucinous tumors of the pancreas: accuracy of preoperative computed tomography, endoscopic retrograde pancreatography and endoscopic ultrasonography, and long-term outcome in a large surgical series. Gastrointest Endosc. 1998;47(1):42–9.
27. Uehara H, Nakaizumi A, Iishi H, et al. Cytologic examination of pancreatic juice for differential diagnosis of benign and malignant mucin-producing tumors of the pancreas. Cancer. 1994;74:826–33.
28. Kondo H, Sugano K, Fukayama N, et al. Detection of K-ras gene mutations at codon 12 in the pancreatic juice of patients with intraductal papillary mucinous tumors of the pancreas. Cancer. 1997;79:900–5.
29. Inoue H, Tsuchida A, Kawasaki Y, et al. Preoperative diagnosis of intraductal papillary-mucinous tumors of the pancreas with attention to telomerase activity. Cancer. 2001;91:35–41.
30. Yamaguchi T, Shirai Y, Ishihara T, et al. Pancreatic juice cytology in the diagnosis of intraductal papillary mucinous neoplasm of the pancreas: significance of sampling by peroral pancreatoscopy. Cancer. 2005;104(12):2830–6.
31. Hara T, Yamaguchi T, Ishihara T, et al. Diagnosis and patient management of intraductal papillary-mucinous tumor of the pancreas by using peroral pancreatoscopy and intraductal ultrasonography. Gastroenterology. 2002;122(1):34–43.
32. Miura T, Igarashi Y, Okano N, et al. Endoscopic diagnosis of intraductal papillary-mucinous neoplasm of the pancreas by means of peroral pancreatoscopy using a small-diameter videoscope and narrow-band imaging. Dig Endosc. 2010;22(2):119–23.
33. Yelamali A, Mansard MJ, Dama R, et al. Intraoperative pancreatoscopy with narrow band imaging: a novel method for assessment of resection margins in case of intraductal papillary mucinous neoplasm. Surg Endosc. 2012;26(12):3682–5.
34. El Hajj I, Brauer B, Fukami N, et al. Role of peroral pancreatoscopy (POP) in the evaluation of suspected main pancreatic duct neoplasia: a 13-year U.S. single center experience. Gastrointest Endosc. 2014;79(5): AB130 [Abstract].

14 Recent Advances in Cytologic and Histologic Specimen Evaluation, FISH, and Molecular Markers

Ferga C. Gleeson and Michael J. Levy

Introduction

The introduction of endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) has improved the diagnostic accuracy and reduced the frequency of nondiagnostic testing in patients with solid pancreatic masses. As EUS-FNA has replaced the historical histopathologic biopsy and is less expensive, it fulfills the Christensen criterion of a disruptive innovation effect [1]. A recent meta-analysis evaluating 41 EUS-FNA studies (1996–2012; $n=4766$) revealed a pooled sensitivity and specificity of 87 % (range, 44–98 %) and 96 % (range, 35–100 %) for determining the etiology of solid pancreatic masses (Figs. 14.1 and 14.2) [2]. Several factors have been shown to negatively impact EUS-FNA sensitivity in this setting, including the presence of well-differentiated tumors, coexisting acute or chronic pancreatitis, and cytologic smears containing blood, necrosis, and/or low cellularity. When compared to a surgical gold standard, the false-negative rate of EUS-FNA is reported to be 19 %, which has been attributed to inadequate sampling (90 %) or interpretive error (10 %) [3]. The reported EUS-FNA false-positive rate for solid pancreatic masses ranges from 1.1 to 3.8 % depending on whether "positive" alone or "positive and suspicious" cytology interpretations are considered diagnostic of malignancy [4]. Although supporting data are limited and often contradictory, the diagnostic sensitivity may be impacted by variations in needle caliber, use of negative pressure, use of a stylet and a fanning technique, methods for expressing the aspirate, and use of predetermined thresholds regarding the ideal number of needle passes [5–10].

F.C. Gleeson, M.D. (✉) • M.J. Levy, M.D.
Division of Gastroenterology and Hepatology,
Mayo Clinic, 200 1st St. SW, Rochester,
MN 55905, USA
e-mail: gleeson.ferga@mayo.edu

Rapid Onsite Evaluation and *Telecytology*

Rapid onsite evaluation (ROSE) of EUS-FNA cytological samples is an important process for evaluating specimen adequacy and for determining the need for additional FNA passes or ancillary testing to enhance diagnostic accuracy [11, 12]. The smear method has been shown to be more sensitive and accurate than ThinPrep in detecting malignancy from cytology specimens [13]. ROSE significantly reduces the number of repeat procedures, from 5.8 %, when an onsite cytopathologist is unavailable, to 2.9 % when available [14].

A recent meta-analysis found that the practice of ROSE improved FNA sample adequacy rates among institutions having an initially low adequacy rate (<90 %); however, it did not improve

M.S. Wagh, P.V. Draganov (eds.), *Pancreatic Masses*, DOI 10.1007/978-3-319-19677-0_14

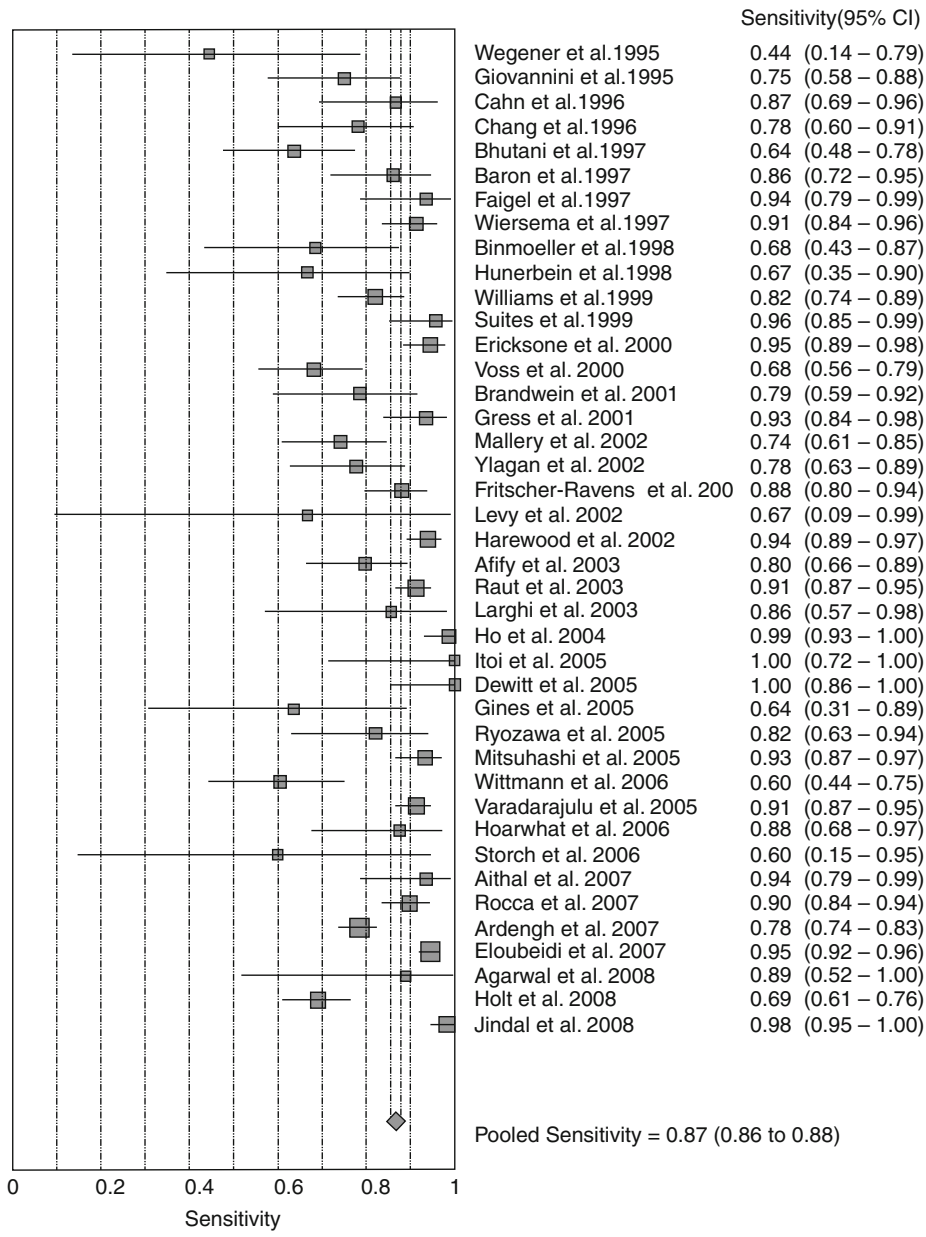

Fig. 14.1 The distribution of sensitivities of EUS-FNA in a forest plot (reproduced with permission, Wolters Kluwer Health [2])

the diagnostic yield [15]. The study also found that the adequacy rates were superior for onsite cytopathologists compared to cytotechnologists or residents. Studies also show that cytopathologist and cytotechnologist training and experience improve the diagnostic accuracy and decrease the number of FNA passes required to achieve a diagnosis [16]. Such training is key when evaluating specimens that are often paucicellular and typically include contaminating material collected from the GI epithelium, intervening tissues, or nondiagnostic regions of the target lesion [17].

The clinical demands and limited reimbursement prohibits the use of cytopathologists in

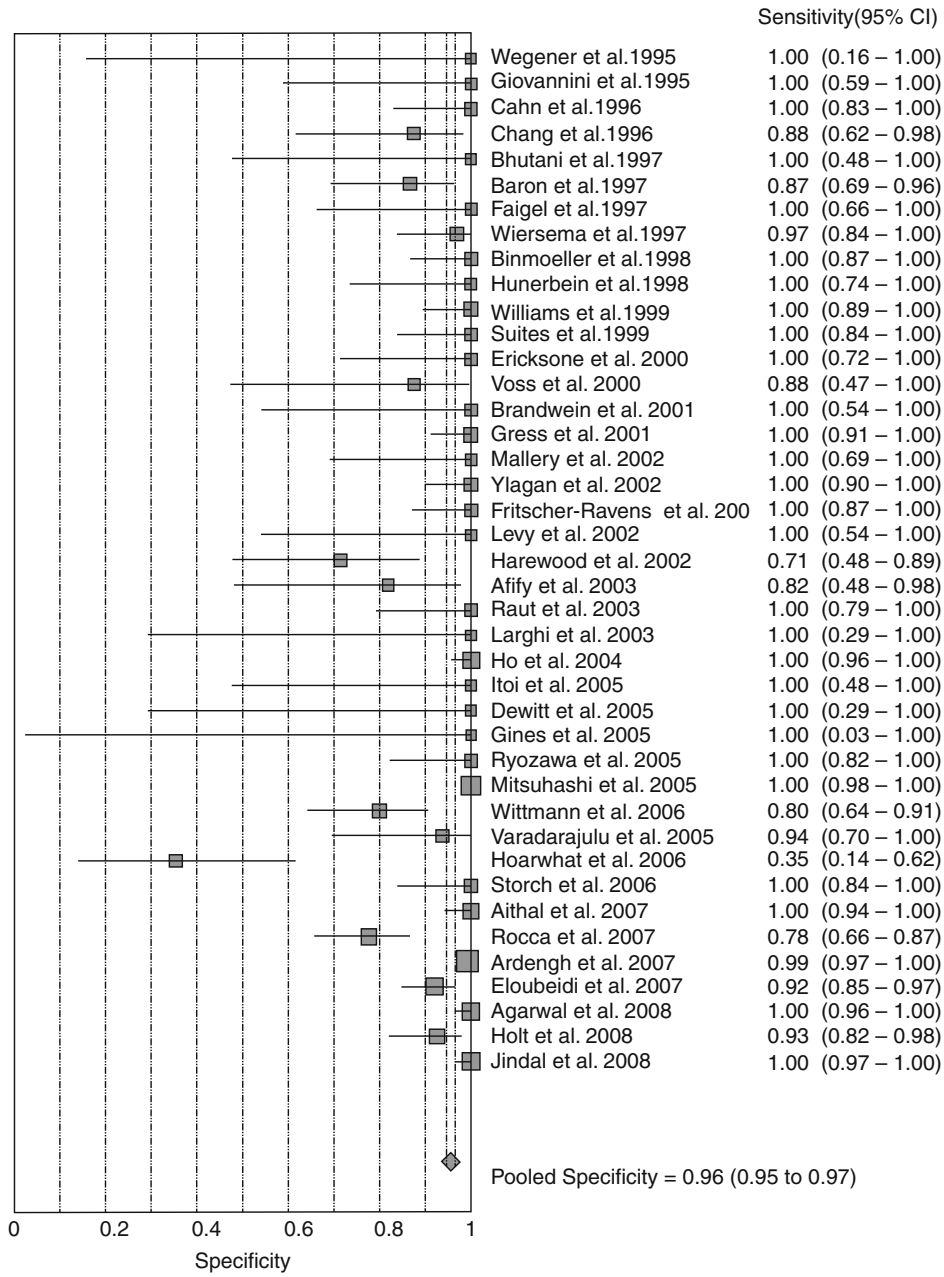

Fig. 14.2 The specificity of EUS-FNA of individual studies with respect to the pooled estimate (reproduced with permission, Wolters Kluwer Health [2])

most centers. Therefore, cytotechnologists and residents are more often relied upon to assess FNA specimens within the EUS suite, with real-time telecytology review available in few centers [12]. Incorporation of telecytology has increased cytopathologist efficiency[18, 19]. Using a microscope and a camera with software, real-time dynamic images of air-dried stained smears can be transmitted to a remotely located cytopathologist using a secure internet connection as a surrogate to conventional onsite evaluation.

Table 14.1 Summary of the Advantages and Disadvantages of ROSE

Advantages	Disadvantages
Abbreviation: ROSE, rapid onsite evaluation	
Reduces the need for additional sampling (core needle biopsies) with a lower risk of procedure complications	Need for an experienced onsite cytopathologist (experience and familiarity with results)
Cost-effective (fewer ancillary techniques)	Equivocal onsite diagnosis may prematurely end a procedure
Improves the adequacy rate	Need for extra time from the cytopathologist
Decreases the number of passes needed for an adequate sample	Financial undercompensation of pathologist's time
Assists further diagnostic triage (assess whether extra material is needed, decide how to preserve material for further ancillary studies)	Need for optimal staining quality
Stores fresh cells when needed, optimization of storing material for molecular analysis	Extended time for procedure, as well as extended anesthesia time (higher doses of narcotics)
Improves overall diagnostic yield	Relies solely on morphology (thus a need for an experienced cytopathologist)
Improves diagnostic yield of cystic lesions	Need for optimal clinical-pathologist communication
Improves sensitivity	

Source: da Cunha Santos G, Ko HM, Saieg MA, Geddie WR. "The petals and thorns" of ROSE (rapid on-site evaluation). Cancer Cytopathol. 2013;121(1):4–8 (reproduced with permission from Wiley [54])

Despite the utility of ROSE, the risk of inaccurate in-room interpretation remains, sometimes necessitating repeat EUS. As a result, there has been a migration in the expectations and role of the onsite cytopathology review. Historically in our center, and still true in many others, the goal of onsite review was limited to establishing sample adequacy. We view this as no longer an acceptable endpoint, as EUS specimens often contain a large quantity of the representative organ or tissue and may be deemed adequate but fail to contain the material necessary to establish a diagnosis. We instead work to achieve a diagnosis rather than simply indicating the cellularity or presence of a representative sample. A summary of the advantages and the disadvantages of ROSE are presented in Table 14.1.

Pancreatobiliary *Cytologic* Nomenclature *Update*

While most pancreas lesions are cytologically classified as benign or malignant, some may only be deemed "atypical" or "suspicious" for malignancy. In 2014, the Papanicolaou Society of Cytopathology (PSC) developed guidelines for pancreatobiliary cytology that addressed the proper indications for EUS-FNA sampling, techniques of EUS-FNA, terminology and nomenclature for pancreatobiliary cytology, ancillary testing, and postprocedure management [20].

The new guidelines propose use of a six-tiered system for cytologic interpretations that includes (1) nondiagnostic, (2) negative, (3) atypical, (4) neoplastic (benign or other), (5) suspicious, or (6) positive for malignancy. Unique to this scheme is the "neoplastic" category separated into "benign" (serous cystadenoma) or "other" (premalignant mucinous cysts, neuroendocrine tumors, and solid-pseudopapillary neoplasms). The positive for malignancy category is reserved for high-grade, aggressive malignancies including ductal adenocarcinoma, acinar cell carcinoma, poorly differentiated neuroendocrine carcinomas, pancreatoblastoma, lymphoma, and metastases. Using this six-tiered system, two centers reviewed their pancreas mass EUS-FNA experience when compared to a surgical pathology or long-term (at least 3 years) clinical follow-up [21]. Malignancy was ultimately diagnosed for samples initially interpreted as nondiagnostic, benign, atypical, suspicious for malignancy, neoplastic, and malignant in 21 %,

13 %, 74 %, 82 %, 14 %, and 97 % of patients, respectively.

Layfield and colleagues reviewed the EUS-FNA "atypical" or "suspicious" for malignancy cytology interpretations ($n=646$) of solid pancreatic lesions from four tertiary referral centers [22]. Patients were selected for analysis when histologic gold-standard biopsy or more than 18 months' clinical follow-up was available when a patient was ultimately diagnosed with malignancy. A diagnosis of "suspicious" was associated with an absolute risk of malignancy of 96.3 % (95 % CI, 92.60–98.5). The risk of malignancy associated with "suspicious" for malignancy was significantly greater than the relative risk associated with "atypical" ($P<0.001$).

In the appropriate clinical setting, specimens reported as negative or positive for malignancy are usually presumed to be true. Confusion often arises for other cytology interpretations. Some consider atypical interpretations as indicative of a negative or inadequate sample. Some also consider suspicious interpretations as indicative of a positive result. The authors of the aforementioned study proposed reclassification of samples interpreted as "suspicious for malignancy" as instead malignant in order to optimize diagnostic sensitivity and specificity. However, we caution the adoption of this approach, given the resulting 3.7 % false-positive rate that risks inappropriate therapy and worsened outcome. This issue highlights the importance of providing adequate specimens for the cytopathologist to review to decrease the risk of nondiagnostic interpretations. In our practice, unless the clinical history is consistent with malignancy in a patient with an EUS-FNA resulting in suspicious cytology, we encourage rebiopsy of any lesion with an inadequate, atypical, or suspicious interpretation.

Ancillary Testing

Onsite cytological evaluation using Diff-Quick stain, Papanicolaou stain, and subsequent histology with immunohistochemical staining for assessment of solid pancreatic mass EUS-FNA is reported to provide a diagnostic accuracy of 71 %, 80 %, and 80 %, respectively [23]. The diagnostic accuracy using this combined method of sample processing and interpretation is significantly greater than relying on Papanicolaou staining alone (95 % vs. 80 %; $p=0.007$).

The use of ancillary testing is still largely in an experimental phase with only preliminary or methodologically limited studies available. As such, the true utility and role for most ancillary tests have not been clarified. Nevertheless, we present some preliminary findings that are very much in need of validation.

- Immunohistochemical testing

As a loss of CD10 is a consistent feature of pancreatic adenocarcinoma, it is felt by some to serve as a useful marker in conjunction with CEA to help cytopathologists identify neoplastic cells contained with a background rich in GI contaminant cells [24]. In addition, the application of S100P and X-linked inhibitor of apoptosis protein (XIAP) immunohistochemical staining may also help distinguish well-differentiated adenocarcinoma from reactive ductal epithelium [25]. The BCL10 immunostain expression may help identify acinar cell differentiation and aid in the diagnosis of acinar cell and adenosquamous carcinomas [26]. Quantification of S100A6 expression in EUS-FNA specimens also enhances the diagnostic adenocarcinoma sensitivity from 68 to 88 % [27]. Furthermore, the loss of immunohistochemical staining for the protein product of the SMAD4 gene and positive staining for mesothelin also support a diagnosis of pancreatic adenocarcinoma [28]. Positive immunohistochemical staining of ubiquitin and thymosin-β4 has been identified in IPMN with high-grade dysplasia [29].

However, not all immunohistochemistry evaluations enhance sensitivity. Dim et al. studied five proteins overexpressed in pancreatic adenocarcinoma: prostate stem cell antigen, fascin, 14-3-3 sigma, mesothelin, and S100P utilizing immunohistochemistry on paraffin sections from cellblocks obtained by EUS-FNA. The cytomorphology was superior to any of the immunohistochemical markers used for the study [30].

Pancreatic neuroendocrine tumors (pNETs) and solid pseudopapillary neoplasia (SPNs) of the pancreas may pose a diagnostic challenge.

SPNs express some markers also seen in pNETs and acinar cell neoplasms including alpha-1-antitrypsin, neuron-specific enolase, and CD56. Beta-catenin abnormalities are also characteristic of SPNs and diffuse nuclear positivity for this marker usually suffices for the confirmation of the diagnosis. In addition, SPNs lack the recognized somatic pathogenic alteration frequently seen in pancreatic adenocarcinoma and other cystic pancreatic neoplasms (GNAS, RNF43) which can be used in molecular assays when evaluating cystic lesions that may include SPN in the differential diagnosis.

Assessment of proliferation by the Ki-67 labeling index is an important parameter of pancreatic neuroendocrine tumor prognosis and should be included systematically in their prognostic workup [31, 32]. Burford and colleagues demonstrated that the EUS-FNA immunohistochemical staining of E-cadherin ($P=0.0003$), beta-catenin ($P=0.00004$), and CD10 ($P=0.00006$) demonstrated the greatest distinction between pancreas neuroendocrine tumors and SPNs [33].

- Fluorescence in situ hybridization—FISH

Fluorescence in situ hybridization (FISH) is an ancillary technique that uses fluorescently labeled DNA probes to detect chromosomal abnormalities in cytology specimens. The FISH probes can be designed to target different chromosomal alterations including aneuploidy, deletions, amplifications, and translocations and therefore are able to detect chromosomal abnormalities within neoplastic cell in a background of nonneoplastic diploid cells. The detection of aneuploidy by FISH has revolutionized the diagnosis of cholangiocarcinoma, and preliminary data also suggest a potential role for evaluating pancreatic adenocarcinoma (Fig. 14.3). The new PSC guidelines for pancreatobiliary cytology indicate that FISH appears to be the most clinically relevant ancillary technique for cytology of bile duct strictures and is proposed for solid pancreas masses [28] (Table 14.2). The addition of such analysis to routine cytologic evaluation yields the greatest sensitivity without, or with minimal, loss of specificity [34, 35]. A prospective evaluation of routine EUS-FNA cytology (lymph nodes, pancreas, gastrointestinal lumen wall, periluminal masses, and liver) when compared with that of FISH to detect malignancy revealed that the combination of routine cytology with FISH established malignancy with 11 % enhanced sensitivity versus routine cytology alone ($P=0.0002$), but reduced the specificity from 100% to 96 % [36]. Tables 14.3 and 14.4 represent the performance characteristics and sensitivity based on tumor type for pancreatic FNA.

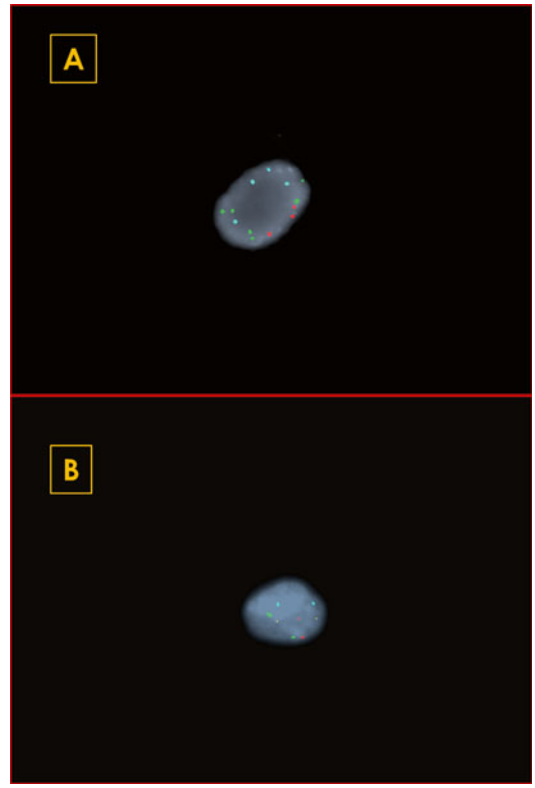

Fig. 14.3 These representative examples of cells demonstrate (**a**) polysomy and (**b**) disomic (normal) signal patterns [CEP 3 (*red*), CEP 7 (*green*), CEP 17 (*blue*), and 9p21 (*yellow*) indicate chromosome enumeration probe] (credit: Dr. Benjamin R. Kipp, Ph.D., Assistant Professor of Laboratory Medicine and Pathology, Mayo Clinic College of Medicine)

When FISH was used in the setting of inconclusive pancreas mass cytology, the sensitivity of cytology and FISH for malignancy was 62 % and 81 %, respectively [37]. The sensitivity and of composite FISH and cytology testing was enhanced to 89 %, while maintaining a specificity of 100 %. The most common FISH abnormality

Table 14.2 Proposed ancillary tests for solid pancreatic lesions

Marker	Purpose	Diagnostic finding	Utility
KRAS mutations	Identification of adenocarcinoma	Mutation present	Insufficient specificity for malignancy to warrant usage
SMAD4	Identification of adenocarcinoma	Mutation present [IHC shows loss of staining]	Supports the diagnosis of adenocarcinoma
FISH	Identification of adenocarcinoma	Presence of copy number abnormalities in CEP3, CEP7, CEP17 and abnormalities of band 9p21 favor malignancy	Most reliable test for confirming adenocarcinoma in conjunction with routine cytology
Mesothelin	Identification of malignancy	Overexpression of mesothelin by IHC	Supports the diagnosis of adenocarcinoma
Loss of heterozygosity	Identification of adenocarcinoma	Losses of chromosome arms 3p, 6Qp, and 10pq along with gains of 5q, 12q, 18q, and 20q supports a diagnosis adenocarcinoma	Clinical importance to be determined
microRNAs	Identification of adenocarcinoma	Presence of miRNA including miR-21 and mi-155 supports a diagnosis of adenocarcinoma	Clinical utility to be determined

Source: Layfield LJ, Ehya H, Filie AC, et al. Utilization of ancillary studies in the cytologic diagnosis of biliary and pancreatic lesions: the Papanicolaou Society of Cytopathology guidelines for pancreatobiliary cytology. Diagn Cytopathol. 2014;42(4):351–62 (reproduced with permission from Wiley, [28])

was a 9p21 deletion (58 %) followed by polysomy in 7 (46 %) patients. This enhanced ability to detect pancreatobiliary tract cancers offers the potential for earlier cancer detection when patients are amenable to surgical intervention.

- Non-FISH molecular markers to enhance diagnostic sensitivity

Telomerase activity is absent from normal human somatic cells but upregulated in neoplastic cells, including pancreatic adenocarcinoma. Mishra and colleagues sought to determine if telomerase activity obtained by EUS-FNA cytology could be detected in pancreatic adenocarcinoma, inflammatory masses in the setting of chronic pancreatitis, and malignant cystic neoplasia. The sensitivity and specificity of telomerase activity for detecting pancreatic adenocarcinoma in solid masses were 79 % (95 % CI, 64–89 %) and 100 % (95 % CI, 55–100 %), respectively. When used in combination with cytology, telomerase increased the diagnostic sensitivity from 85 to 98 % while maintaining specificity at 100 % [38]. DNA microsatellite loss analysis of neuroendocrine tumor EUS-FNA specimens revealed that malignant tumors contain significantly greater multiple microsatellite losses with greater fractional allelic loss than benign tumors and is associated with a significant survival difference at 5 years [39].

In a prospective study, Bournet et al. demonstrated the clinical feasibility and utility of low-density array analysis as a diagnostic marker using EUS-FNA samples obtained from locally advanced and/or metastatic pancreatic adenocarcinoma and chronic pancreatitis. Eight genes (S100P, PLAT, PLAU, MSLN, MMP-11, MMP-7, KRT7, and KRT17) were significantly overexpressed in pancreas cancer samples when compared to pseudotumoral chronic pancreatitis [40]. Furthermore, the combination of S100P with KRT7 provided superior diagnostic performance (AUC: 0.81; sensitivity, 81 %; specificity, 77 %).

Somatic *KRAS* mutations have also been studied as an adjunct marker to increase the diagnostic yield of FNA [41]. The *KRAS* oncogene is activated by somatic point substitution and is considered to be an initial event in pancreatic carcinogenesis and can be found in 90 % of patients with this disease [42]. *KRAS* mutational analysis (Sanger sequencing, allele-specific locked nucleic acid PCR, allelic discrimination and

Table 14.3 Performance characteristics for pancreatic FNA

	CC	DIA	FISH	DIA/FISH	CC/DIA	CC/FISH	CC/DIA/FISH
Sensitivity	74 (0.59–0.88)	53 (0.38–0.66)	79 (0.65–0.89)	79 (0.65–0.89)	79 (0.65–0.89)	91 (0.79–0.99)	91 (0.79–0.99)
		$P=0.0153$[a]				$P=0.0077$[b]	$P=0.0077$[b]
Specificity	100 (0.63–1)	100 (0.63–1)	88 (0.47–0.99)	88 (0.47–0.99)	100 (0.63–1)	88 (0.47–0.99)	88 (0.47–0.99)
Positive predictive value	100 (0.90–1)	100 (0.87–1)	98 (0.87–0.99)	98 (0.87–0.99)	100 (0.91–1)	98 (0.89–0.99)	98 (0.89–0.99)
Negative predictive value	36 (0.17–0.59)	24 (0.11–0.42)	39 (0.17–0.64)	39 (0.17–0.64)	42 (0.20–0.66)	58 (0.27–0.84)	58 (0.27–0.84)
Accuracy	77 (0.64–0.91)	59 (0.43–0.75)	80 (0.68–0.93)	80 (0.68–0.93)	82 (0.70–0.94)	90 (0.81–0.99)	90 (0.81–0.99)
		$P=0.0153$				$P=0.0133$	$P=0.0133$

Source: Levy MJ, Oberg TN, Campion MB, et al. Comparison of methods to detect neoplasia in patients undergoing endoscopic ultrasound-guided fine-needle aspiration. Gastroenterology. 2012;142(5):1112–1121.e2 (reproduced with permission from Elsevier [36])

Table 14.4 Sensitivity based on tumor type for pancreatic FNA

	CC	DIA	FISH	DIA/FISH	CC/DIA	CC/FISH	CC/DIA/FISH
Adenocarcinoma ($n=46$)	83 (0.68–0.92)	59 (0.43–0.73)	83 (0.68–0.92)	83 (0.68–0.92)	87 (0.73–0.95)	94 (0.82–0.98)	94 (0.82–0.98)
	$P=0.0008$[a]	$P=0.043$[a]			$P=0.0027$[a]		
Nonadenocarcinoma ($n=7$)	14 (0–0.57)	14 (0–0.57)	57 (0.18–0.90)	57 (0.18–0.90)	29 (0.03–70)	71 (0.29–0.96)	71 (0.29–0.96)

Source: Levy MJ, Oberg TN, Campion MB, et al. Comparison of methods to detect neoplasia in patients undergoing endoscopic ultrasound-guided fine-needle aspiration. Gastroenterology. 2012;142(5):1112–1121.e2 (reproduced with permission from Elsevier [36])

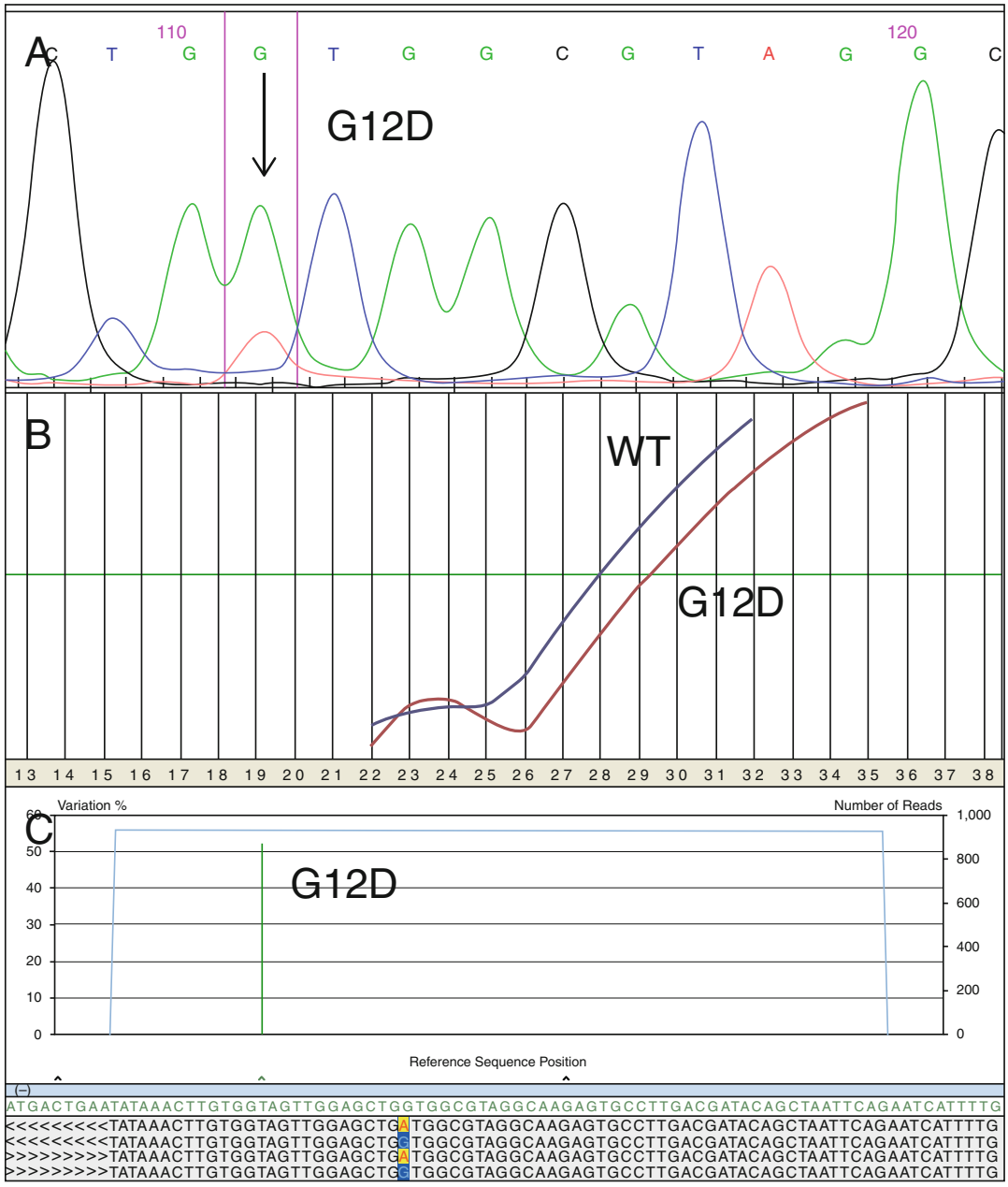

Fig. 14.4 KRAS sequencing in direct EUS-FNA material (reproduced with permission, Elsevier [43])

next-generation sequencing) can be performed from DNA extracted from cytologic smears following pathologic evaluation (Fig. 14.4) [43, 44]. In a recent prospective series evaluating 394 pancreatic masses, a combination of *KRAS* mutation analysis with cytology enhanced the diagnostic sensitivity and accuracy of EUS-FNA from 87 to 93 % ($P<0.001$) and from 89 to 94 % ($P<0.001$), respectively [45].

However, a recent meta-analysis (8 studies including 931 patients) determined that the pooled sensitivity and specificity of EUS-FNA alone was 80 % and 97 %, respectively. When cytology and *KRAS* mutation analysis results

were combined, the sensitivity was enhanced to 89 % and specificity reduced to 92 % [46]. From a practical perspective, when *KRAS* mutation results were applied to inconclusive cytology results, the false-negative rate was reduced by 56 %, with an accompanying false-positive rate of 11 %. The combination of routine cytology with FISH and *KRAS* mutational analyses enhances the EUS-FNA diagnostic sensitivity and accuracy to 87.9 %, 93.8 %, and 89.8 %, respectively, but reduced the specificity to 93.8 % [47]. While composite testing may be of value in increasing tumor detection, one must be cautious with this approach given the impact of test specificity that negatively impacts patient care.

In addition to *KRAS* mutations, a number of tumor suppressor genes were found to be affected by genetic alteration in pancreatic adenocarcinoma, such as p53, p16, and DPC4. Among inconclusive pancreas mass cytology cases, they enhance diagnostic sensitivity to 90–100 % [48]. Mutational analysis of CTNNB1 by next-generation sequencing for SPN is feasible using samples obtained by EUS-FNA [49].

In the research arena, whole-exome sequencing has been used to analyze benign and malignant pancreatic tumors. The objective was to potentially enhance the morphology-based classification of such tumors and to explore molecular discoveries for a potential role in preoperative diagnosis. In Reid and colleagues' elegant review of recent advances in this domain, they report that mutations in *KRAS*, *P16*, *TP53*, and *SMAD4* are commonly seen in ductal rather than nonductal cancers [50]. Adenocarcinomas with *SMAD4* loss are associated with widespread metastasis and poor prognosis. *GNAS* and *RNF43* mutations have been discovered in most intraductal pancreatic mucinous neoplasms [51]. Mutations in *DAXX* and *ATRX* have only been documented in pNET, making it a useful potential marker to distinguish these tumors from mimics. Loss of *DAXX* or *ATRX* expression by immunohistochemistry and telomeric fluorescence in situ hybridization is associated with chromosomal instability and shorter survival times for patients with pancreas neuroendocrine tumors [52].

A more recent development has been the introduction and validation of a microRNA-(miRNA) based test [53]. In this international multicenter study, a 5-miRNA expression classifier, consisting of MIR24, MIR130B, MIR135B, MIR148A, and MIR196, was established to identify adenocarcinoma in well-characterized, formalin-fixed, paraffin-embedded specimens. The subsequent application of this methodology to EUS-FNA specimens enhanced sensitivity from 79 to 91 % when combined with miRNA analysis. The miRNA classifier correctly identified 22 additional true ductal adenocarcinoma cases among 39 samples initially classified as

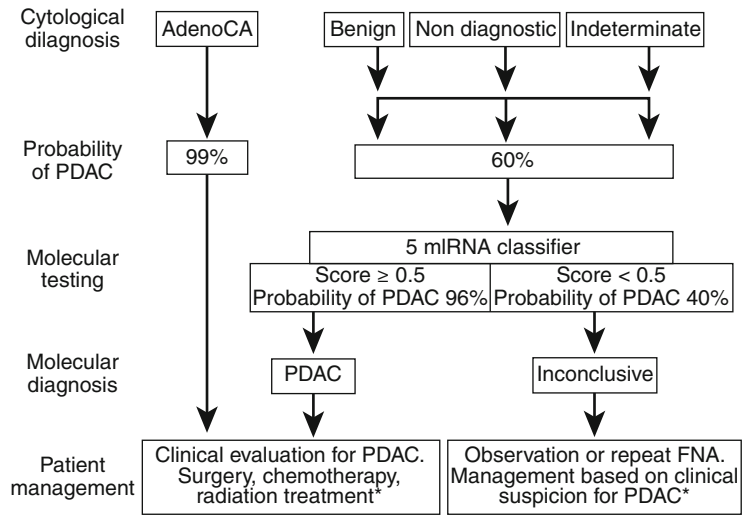

Fig. 14.5 Proposed integration of the 5-miRNA classifier into the current clinical management of patients with pancreatic solid masses ([53])

benign, indeterminate, or nondiagnostic by cytology (Fig. 14.5). Although promising, the associated cost, limited data, necessary cytopathology expertise, and paucity of data do not support the routine clinical use of molecular genetics as an ancillary diagnostic test.

Summary

EUS-FNA is an indispensable tool for the diagnostic workup of solid pancreas masses. High sensitivity, specificity, and diagnostic accuracy coupled with low rates of adverse events have made this procedure more suitable than computed tomography–guided biopsies. When cytomorphologic observations are coupled with molecular studies, our understanding of the morphomolecular signature associated with specific neoplasia will provide practicing clinicians with enhanced diagnostic accuracy. These discoveries offer the potential for individualized medicine approaches to patient care.

References

1. Eltoum IA, Alston EA, Roberson J. Trends in pancreatic pathology practice before and after implementation of endoscopic ultrasound-guided fine-needle aspiration: an example of disruptive innovation effect? Arch Pathol Lab Med. 2012;136(4):447–53.
2. Puli SR, Bechtold ML, Buxbaum JL, Eloubeidi MA. How good is endoscopic ultrasound-guided fine-needle aspiration in diagnosing the correct etiology for a solid pancreatic mass? A meta-analysis and systematic review. Pancreas. 2013;42(1):20–6.
3. Woolf KM, Liang H, Sletten ZJ, Russell DK, Bonfiglio TA, Zhou Z. False-negative rate of endoscopic ultrasound-guided fine-needle aspiration for pancreatic solid and cystic lesions with matched surgical resections as the gold standard: one institution's experience. Cancer Cytopathol. 2013;121(8):449–58.
4. Siddiqui AA, Kowalski TE, Shahid H, et al. False-positive EUS-guided FNA cytology for solid pancreatic lesions. Gastrointest Endosc. 2011;74(3):535–40.
5. Tarantino I, Di Mitri R, Fabbri C, et al. Is diagnostic accuracy of fine needle aspiration on solid pancreatic lesions aspiration-related? A multicentre randomised trial. Dig Liver Dis. 2014;46(6):523–6. doi:10.1016/j.dld.2014.02.023.
6. Puri R, Vilmann P, Săftoiu A, et al. Randomized controlled trial of endoscopic ultrasound-guided fine-needle sampling with or without suction for better cytological diagnosis. Scand J Gastroenterol. 2009;44:499–504.
7. Polkowski M, Larghi A, Weynand B, et al. Learning, techniques, and complications of endoscopic ultrasound (EUS)-guided sampling in gastroenterology: European Society of Gastrointestinal Endoscopy (ESGE) Technical Guideline. Endoscopy. 2012;44:190–206.
8. Bang JY, Magee SH, Ramesh J. Randomized trial comparing fanning with standard technique for endoscopic ultrasound-guided fine-needle aspiration of solid pancreatic mass lesions. Endoscopy. 2013;45:445–50.
9. Wee E, Lakhtakia S, Gupta R, et al. Endoscopic ultrasound guided fine-needle aspiration of lymph nodes and solid masses: factors influencing the cellularity and adequacy of the aspirate. J Clin Gastroenterol. 2012;46:487–93.
10. Rastogi A, Wani S, Gupta N, et al. A prospective, single-blind, randomized, controlled trial of EUS-guided FNA with and without a stylet. Gastrointest Endosc. 2011;74:58–64.
11. Hébert-Magee S, Bae S, Varadarajulu S, et al. The presence of a cytopathologist increases the diagnostic accuracy of endoscopic ultrasound-guided fine needle aspiration cytology for pancreatic adenocarcinoma: a meta-analysis. Cytopathology. 2013;24(3):159–71.
12. Olson MT, Ali SZ. Cytotechnologist on-site evaluation of pancreas fine needle aspiration adequacy: comparison with cytopathologists and correlation with the final interpretation. Acta Cytol. 2012;56(4):340–6.
13. LeBlanc JK, Emerson RE, Dewitt J, et al. A prospective study comparing rapid assessment of smears and ThinPrep for endoscopic ultrasound-guided fine-needle aspirates. Endoscopy. 2010;42(5):389–94.
14. Collins BT, Murad FM, Wang JF, Bernadt CT. Rapid on-site evaluation for endoscopic ultrasound-guided fine-needle biopsy of the pancreas decreases the incidence of repeat biopsy procedures. Cancer Cytopathol. 2013;121(9):518–24.
15. Schmidt RL, Witt BL, Matynia AP, Barraza G, Layfield LJ, Adler DG. Rapid on-site evaluation increases endoscopic ultrasound-guided fine-needle aspiration adequacy for pancreatic lesions. Dig Dis Sci. 2013;58:872–82.
16. Petrone MC, Arcidiacono PG, Carrara S, Mezzi G, Doglioni C, Testoni PA. Does cytotechnician training influence the accuracy of EUS-guided fine-needle aspiration of pancreatic masses? Dig Liver Dis. 2012;44:311–4.
17. Jenssen C, Dietrich CF. Endoscopic ultrasound-guided fine-needle aspiration biopsy and Trucut biopsy in gastroenterology—an overview. Best Pract Res Clin Gastroenterol. 2009;23:743–59.
18. Marotti JD, Johncox V, Ng D, Gonzalez JL, Padmanabhan V. Implementation of telecytology for immediate assessment of endoscopic ultrasound-guided fine-needle aspirations compared to conventional on-site evaluation: analysis of 240 consecutive cases. Acta Cytol. 2012;56(5):548–53.

19. Khurana KK, Rong R, Wang D, Roy A. Dynamic telecytopathology for on-site preliminary diagnosis of endoscopic ultrasound-guided fine needle aspiration of pancreatic masses. J Telemed Telecare. 2012; 18(5):253–9.
20. Pitman MB, Centeno BA, Ali SZ, et al. Standardized terminology and nomenclature for pancreatobiliary cytology: the Papanicolaou Society of Cytopathology guidelines. Diagn Cytopathol. 2014;42(4):338–50.
21. Layfield LJ, Dodd L, Factor R, Schmidt RL. Malignancy risk associated with diagnostic categories defined by the Papanicolaou Society of Cytopathology pancreaticobiliary guidelines. Cancer Cytopathol. 2013;122(6):420–7. doi:10.1002/cncy.21386.
22. Layfield LJ, Schmidt RL, Hirschowitz SL, Olson MT, Ali SZ, Dodd LL. Significance of the diagnostic categories "atypical" and "suspicious for malignancy" in the cytologic diagnosis of solid pancreatic masses. Diagn Cytopathol. 2014;42(4):292–6.
23. Lee YN, Moon JH, Kim HK, et al. A triple approach for diagnostic assessment of endoscopic ultrasound-guided fine needle aspiration in pancreatic solid masses and lymph nodes. Dig Dis Sci. 2014;59(9):2286–93.
24. Vigliar E, Troncone G, Bracale U, Iaccarino A, Napolitano V, Bellevicine C. CD10 is useful to identify gastrointestinal contamination in endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) cytology from pancreatic ductal adenocarcinoma. Cytopathology. 2015;26(2):83–7. doi:10.1111/cyt.12148.
25. Kosarac O, Takei H, Zhai QJ, Schwartz MR, Mody DR. S100P and XIAP expression in pancreatic ductal adenocarcinoma: potential novel biomarkers as a diagnostic adjunct to fine needle aspiration cytology. Acta Cytol. 2011;55(2):142–8.
26. Hosoda W, Sasaki E, Murakami Y, Yamao K, Shimizu Y, Yatabe Y. BCL10 as a useful marker for pancreatic acinar cell carcinoma, especially using endoscopic ultrasound cytology specimens. Pathol Int. 2013;63(3):176–82.
27. Zihao G, Jie Z, Yan L, et al. Analyzing S100A6 expression in endoscopic ultrasonography-guided fine-needle aspiration specimens: a promising diagnostic method of pancreatic cancer. J Clin Gastroenterol. 2013;47(1):69–75.
28. Layfield LJ, Ehya H, Filie AC, et al. Utilization of ancillary studies in the cytologic diagnosis of biliary and pancreatic lesions: the Papanicolaou Society of Cytopathology guidelines for pancreatobiliary cytology. Diagn Cytopathol. 2014;42(4):351–62.
29. Rebours V, Le Faouder J, Laouirem S, et al. In situ proteomic analysis by MALDI imaging identifies ubiquitin and thymosin-β4 as markers of malignant intraductal pancreatic mucinous neoplasms. Pancreatology. 2014;14(2):117–24.
30. Dim DC, Jiang F, Qiu Q, et al. The usefulness of S100P, mesothelin, fascin, prostate stem cell antigen, and 14-3-3 sigma in diagnosing pancreatic adenocarcinoma in cytological specimens obtained by endoscopic ultrasound guided fine-needle aspiration. Diagn Cytopathol. 2014;42(3):193–9.
31. Chatzipantelis P, Konstantinou P, Kaklamanos M, Apostolou G, Salla C. The role of cytomorphology and proliferative activity in predicting biologic behavior of pancreatic neuroendocrine tumors: a study by endoscopic ultrasound-guided fine-needle aspiration cytology. Cancer. 2009;117(3):211–6.
32. Weynand B, Borbath I, Galant C, Piessevaux H, Deprez PH. Optimizing specimen collection and laboratory procedures reduces the non-diagnostic rate for endoscopic ultrasound-guided fine-needle aspiration of solid lesions of the pancreas. Cytopathology. 2013;24(3):177–84.
33. Burford H, Baloch Z, Liu X, Jhala D, Siegal GP, Jhala N. E-cadherin/beta-catenin and CD10: a limited immunohistochemical panel to distinguish pancreatic endocrine neoplasm from solid pseudopapillary neoplasm of the pancreas on endoscopic ultrasound-guided fine-needle aspirates of the pancreas. Am J Clin Pathol. 2009;132(6):831–9.
34. Kubiliun N, Ribeiro A, Fan YS, et al. EUS-FNA with rescue fluorescence in situ hybridization for the diagnosis of pancreatic carcinoma in patients with inconclusive on-site cytopathology results. Gastrointest Endosc. 2011;74(3):541–7.
35. Henkes DN, Patel SN, Rosenkranz LA, Escobedo JL. The utility of UroVysion fluorescence in situ hybridization in pancreatic fine-needle aspiration samples directed and obtained by endoscopic ultrasonography. Arch Pathol Lab Med. 2013;137(1):64–71.
36. Levy MJ, Oberg TN, Campion MB, et al. Comparison of methods to detect neoplasia in patients undergoing endoscopic ultrasound-guided fine-needle aspiration. Gastroenterology. 2012;142(5):1112–1121.e2.
37. Ribeiro A, Peng J, Casas C, Shan-Fan Y. EUS FNA with FISH analysis in 104 patients with pancreatic mass. J Gastroenterol Hepatol. 2014;29(8):1654–8. doi:10.1111/jgh.12575.
38. Mishra G, Zhao Y, Sweeney J, et al. Determination of qualitative telomerase activity as an adjunct to the diagnosis of pancreatic adenocarcinoma by EUS-guided fine-needle aspiration. Gastrointest Endosc. 2006;63(4):648–54.
39. Fasanella KE, McGrath KM, Sanders M, Brody D, Domsic R, Khalid A. Pancreatic endocrine tumor EUS-guided FNA DNA microsatellite loss and mortality. Gastrointest Endosc. 2009;69(6):1074–80.
40. Bournet B, Pointreau A, Souque A, et al. Gene expression signature of advanced pancreatic ductal adenocarcinoma using low density array on endoscopic ultrasound-guided fine needle aspiration samples. Pancreatology. 2012;12(1):27–34.
41. Bournet B, Selves J, Grand D, et al. Endoscopic ultrasound-guided fine-needle aspiration biopsy coupled with a KRAS mutation assay using allelic discrimination improves the diagnosis of pancreatic cancer. J Clin Gastroenterol. 2015;49(1):50–6.
42. Almoguera C, Shibata D, Forrester K, Martin J, Arnheim N, Perucho M. Most human carcinomas of

the exocrine pancreas contain mutant c-K-ras genes. Cell. 1988;53:549–54.
43. de Biase D, Visani M, Baccarini P, et al. Next generation sequencing improves the accuracy of KRAS mutation analysis in endoscopic ultrasound fine needle aspiration pancreatic lesions. PLoS One. 2014; 9(2), e87651.
44. Wang X, Gao J, Ren Y, et al. Detection of KRAS gene mutations in endoscopic ultrasound-guided fine-needle aspiration biopsy for improving pancreatic cancer diagnosis. Am J Gastroenterol. 2011;106(12): 2104–11.
45. Ogura T, Yamao K, Sawaki A, et al. Clinical impact of K-ras mutation analysis in EUS-guided FNA specimens from pancreatic masses. Gastrointest Endosc. 2012;75(4):769–74.
46. Fuccio L, Hassan C, Laterza L, et al. The role of K-ras gene mutation analysis in EUS-guided FNA cytology specimens for the differential diagnosis of pancreatic solid masses: a meta-analysis of prospective studies. Gastrointest Endosc. 2013;78:596–608.
47. Reicher S, Boyar FZ, Albitar M, et al. Fluorescence in situ hybridization and K-ras analyses improve diagnostic yield of endoscopic ultrasound-guided fine-needle aspiration of solid pancreatic masses. Pancreas. 2011;40(7):1057–62.
48. Salek C, Benesova L, Zavoral M, et al. Evaluation of clinical relevance of examining K-ras, p16 and p53 mutations along with allelic losses at 9p and 18q in EUS-guided fine needle aspiration samples of patients with chronic pancreatitis and pancreatic cancer. World J Gastroenterol. 2007;13:3714–20.
49. Kubota Y, Kawakami H, Natsuizaka M, et al. CTNNB1 mutational analysis of solid-pseudopapillary neoplasms of the pancreas using endoscopic ultrasound-guided fine-needle aspiration and next-generation deep sequencing. J Gastroenterol. 2015; 50(2):203–10.
50. Reid MD, Saka B, Balci S, Goldblum AS, Adsay NV. Molecular genetics of pancreatic neoplasms and their morphologic correlates: an update on recent advances and potential diagnostic applications. Am J Clin Pathol. 2014;141(2):168–80.
51. Furukawa T, Kuboki Y, Tanji E, et al. Whole-exome sequencing uncovers frequent GNAS mutations in intraductal papillary mucinous neoplasms of the pancreas. Sci Rep. 2011;1:161.
52. Marinoni I, Kurrer AS, Vassella E, et al. Loss of DAXX and ATRX are associated with chromosome instability and reduced survival of patients with pancreatic neuroendocrine tumors. Gastroenterology. 2014;146(2):453–60.e5.
53. Brand RE, Adai AT, Centeno BA, et al. A microRNA-based test improves endoscopic ultrasound-guided cytologic diagnosis of pancreatic cancer. Clin Gastroenterol Hepatol. 2014;12(10):1717–23. doi:10.1016/j.cgh.2014.02.038.
54. da Cunha Santos SG, Ko HM, Saieg MA, Geddie WR. "The petals and thorns" of ROSE (rapid on-site evaluation). Cancer Cytopathol. 2013;121(1):4–8.

15 Evaluation and Surveillance Strategies for Patients at Increased Risk of Pancreatic Cancer

Jennifer Nayor, Shilpa Grover, and Sapna Syngal

Introduction

Pancreatic adenocarcinoma is the fourth leading cause of cancer-related death in the United States and the eighth leading cause worldwide [1]. Surgical resection is the only potentially curative treatment for exocrine pancreatic cancer; however, because of the late presentation at diagnosis, only 15–20 % of patients are candidates for surgery. Even in patients with potentially resectable disease, mortality is high, with an estimated 5-year survival of 25–30 % for node-negative and 10 % for node-positive tumors.

Population-based screening for pancreatic cancer is not feasible given the low incidence of pancreatic cancer and the lack of an available noninvasive diagnostic test with high sensitivity and specificity. However, specific subgroups with a significantly elevated lifetime risk of pancreatic cancer may benefit from screening and regular surveillance to detect and treat early pancreatic neoplastic lesions.

Epidemiology and Genetics

Although most cases of pancreatic adenocarcinomas are sporadic, it is estimated that 5–10 % may have an underlying hereditary basis [2]. Inherited gene mutations as seen in patients with inherited cancer syndromes (e.g., hereditary breast and ovarian cancer syndrome, Peutz–Jeghers syndrome, Lynch syndrome, familial atypical multiple mole melanoma) are associated with an increased risk of pancreatic cancer (Table 15.1). However, pancreatic cancers due to a known genetic defect only account for approximately 10 % of the familial clustering of pancreatic cancer cases. The majority of hereditary pancreatic cancer cases are due to nonsyndromic aggregation of pancreatic cancer cases or familial pancreatic cancer (FPC).

Familial Pancreatic Cancer

Although the term FPC has not been uniformly defined, it is most often used to describe kindred with at least two first-degree relatives (FDRs) with pancreatic cancer without a known genetic defect [3].

J. Nayor, M.D. • S. Syngal, M.D., M.P.H. (✉)
Division of Gastroenterology, Brigham and Women's Hospital, Boston, MA, USA

Population Sciences, Dana-Farber Cancer Institute, Boston, MA, USA

Harvard Medical School, Boston, MA, USA
e-mail: ssyngal@partners.org

S. Grover, M.D., M.P.H.
Division of Gastroenterology, Brigham and Women's Hospital, Boston, MA, USA

Harvard Medical School, Boston, MA, USA

M.S. Wagh, P.V. Draganov (eds.), *Pancreatic Masses*, DOI 10.1007/978-3-319-19677-0_15

Table 15.1 Risk of pancreatic cancer by inherited syndromes

Syndrome	Gene	Gene function	Relative risk of PC	Lifetime risk of PC (%)
Peutz–Jeghers syndrome [18]	*STK11*	Tumor suppressor, serine-threonine kinase	132	11–36
Familial atypical multiple mole melanoma (FAMMM) [21, 22]	*CDKN2A*	Tumor suppressor	13–47	10–17
Hereditary breast ovarian cancer syndrome [11, 26, 27, 29, 30]	*BRCA1*	Tumor suppressor	2.2–4.1	3.6
	BRCA2	Tumor suppressor	3.5–5.9	5
	PALB2	Tumor suppressor	Not quantified[a]	Not quantified[a]
Lynch syndrome [34, 35]	*MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*	Mismatch repair	8.6–10.7	3.7
Li–Fraumeni syndrome [41]	*tp53*	Tumor suppressor	7.3	Not quantified
Hereditary pancreatitis [43]	*PRSS1*	Cationic trypsinogen	53–80	40

Source: Adapted from [69, 70]
PC. pancreatic cancer
[a]Estimated to be similar to *BRCA2*

Individuals from FPC families are at an increased risk of pancreatic cancer. The risk of pancreatic cancer increases with the number of affected FDRs. In a prospective study of 838 FPC kindreds, individuals with one affected FDR had a 4.5-fold increased risk as compared with the general population [4]. Those with two affected FDRs had a 6.4-fold increased risk, and those with three or more affected FDRs with pancreatic cancer had a 32-fold increased risk of developing pancreatic cancer. Age at cancer diagnosis, family size, and the relationship between family members are also important determinants of the risk of pancreatic cancer in FPC families. The complexity in pancreatic cancer risk assessment has led to the development of a risk prediction model (PancPRO) that takes into account an individual's current age, personal and family history of cancer, age of cancer onset, and family size and provides the probability of carrying a susceptibility gene and the risk of developing pancreatic cancer by age [5].

Pancreatic cancer in families with FPC is thought be due to an unidentified, autosomal dominant gene with reduced penetrance [6]. Although initial linkage studies suggested that the palladin gene (*PALD*) may be a predisposition gene for FPC [7], these findings have not been validated [8]. Initial studies also suggested that germline *BRCA2* mutations may be found in 15–17 % of FPC kindreds with an incident pancreatic cancer [9, 10]. However, in larger cohort studies, deleterious *BRCA2* mutations were detected in only 6 % of moderate- and high-risk families [11, 12]. Mutations in the *PALB2* gene have also been associated with FPC. The PALB2 protein colocalizes with the BRCA2 protein to localize and stabilize key nuclear structures needed for DNA repair [13]. However, whole genome sequencing in small cohorts of British and German FPC families has identified *PALB2* mutations in only 3.1–3.7 % of families [14, 15]. The risk of pancreatic cancer in individuals with *PALB2* germline mutations has not been well characterized, but it is likely to be comparable to that of *BRCA2* given similarities in gene function [16]. More recently, heterozygous germline mutations of the ataxia telangiectasia mutated (*ATM*) gene have also been identified in FPC kindreds [17].

Pancreatic Cancer Associated with Inherited Cancer Syndromes

Peutz–Jeghers Syndrome

Peutz–Jeghers syndrome (PJS) is an autosomal dominant hamartomatous polyposis syndrome with high penetrance caused by a mutation in the *STK11* gene (also known as *LKB1*) encoding a serine threonine kinase mapped to chromosome 19p13.3. PJS is characterized by multiple hamartomatous polyps in the gastrointestinal tract,

mucocutaneous pigmentation, and an increased risk of gastrointestinal and nongastrointestinal cancer. Hamartomatous polyps occur most commonly in the small bowel and specifically the jejunum, but can develop throughout the gastrointestinal tract. Gastrointestinal polyps develop in the first decade of life and most patients become symptomatic between the ages of 10 and 30 years. Hamartomatous polyps may also occur outside the gastrointestinal tract, including the renal pelvis, urinary bladder, lungs, and nasopharynx. Mucocutaneous pigmented macules are present in more than 95 % of individuals with PJS. Pigmented macules most commonly occur on the lips, buccal mucosa, periorbital area, palms, and soles but may also been seen on the nose and in the perineum. Macules typically develop early in life and then fade after puberty, with the exception of lesions on the buccal mucosa.

A clinical diagnosis of PJS requires the presence of any one of the following: (1) two or more histologically confirmed Peutz–Jeghers (PJ) polyps; (2) any number of PJ polyps in an individual who has a family history of PJS in a close relative; (3) characteristic mucocutaneous pigmentation in an individual who has a family history of PJS in a close relative; (4) any number of PJ polyps in an individual who also has characteristic mucocutaneous pigmentation.

Individuals with PJS have an estimated lifetime risk of pancreatic cancer of 11–36 %, with an average age of 52 years at pancreatic cancer diagnosis. PJS is associated with an increased risk for gastrointestinal cancers, including colorectal (lifetime risk, 39 %), stomach (29 %), and small bowel (13 %) cancers. Individuals with PJS are also at an increased risk for cancers of the breast (24–54 %), ovary (21 %), cervix (10–23 %), uterus (9 %), testicle (9 %), and lung (7–17 %) [18, 19].

Familial Atypical Multiple Mole Melanoma

Familial atypical multiple mole melanoma (FAMMM) is an autosomal dominantly inherited syndrome. FAMMM is associated with mutations in the *CDKN2A* gene with incomplete penetrance and variable expressivity. Clinically, it is characterized by multiple melanocytic nevi and atypical melanocytic nevi and a history of melanoma in one or more first- or second-degree relatives. FAMMM is associated with an increased risk of malignant melanoma and pancreatic cancer [20]. It is estimated that individuals with a clinical diagnosis of FAMMM have a 13- to 22-fold increased risk of pancreatic cancer as compared with the general population; in individuals with the Leiden founder mutation in the *CDKN2A* gene, the risk is increased 47-fold [21]. Individuals with FAMMM are also at an increased risk for cancer of the respiratory tract, eye/brain, oropharynx, and nonmelanoma skin cancer [22].

Hereditary Breast and Ovarian Cancer Syndrome

Hereditary breast and ovarian cancer syndrome is characterized by early-onset breast and/or ovarian cancer due to autosomal dominant, highly penetrant, germline mutations in *BRCA1* and *BRCA2*. It is estimated that the carrier frequency of founder mutations in *BRCA1* and *BRCA2* in the Ashkenazi Jewish population is approximately 1 % compared to a carrier frequency of 0.05–0.24 % in the general population [23–25].

Individuals with germline mutations in *BRCA2* have a 3.5- to 5.9-fold increased risk of developing pancreatic cancer, with a mean age of 63 years at diagnosis [11, 26, 27]. Germline *BRCA2* mutations account for the highest proportion of known causes of inherited pancreatic cancer. *BRCA2* mutations have been found in 5–19 % of tested FPC kindreds with an incident pancreatic cancer [9–11]. Furthermore, in a retrospective cohort study of 145 Jewish patients who underwent resection for pancreatic adenocarcinoma, 5.5 % had a *BRCA* founder mutation [28].

In contrast to *BRCA2* carriers, individuals with germline mutations in *BRCA1* have a smaller increase in risk of pancreatic adenocarcinoma as compared to the general population and an estimated lifetime risk of 3.6 % [26, 29]. In a cohort study of 11,847 individuals from 699 families segregating a *BRCA1* mutation, the risk of pancreatic cancer was increased twofold as compared with the general population [30].

It is important to note that patients in the studies discussed above were ascertained for young onset of breast and/or ovarian cancers. Penetrance estimates may ultimately be different

for *BRCA-associated* pancreatic cancer in FPC families ascertained via pancreatic cancer probands [31].

Lynch Syndrome

Lynch syndrome or hereditary nonpolyposis colorectal cancer (HNPCC), the most common inherited familial colorectal cancer syndrome, has also been associated with an increased risk of pancreatic cancer. Lynch syndrome results from mutations in mismatch repair genes *MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM* and follows an autosomal dominant inheritance pattern.

Lynch syndrome is characterized by early-onset colorectal cancer with a lifetime risk of 60–80 %. Individuals with Lynch syndrome are at increased risk for cancers of the endometrium, ovary, stomach, small bowel, urinary tract, and brain [32, 33]. The risk of pancreatic cancer in individuals with Lynch syndrome is increased 8.6- to 10.7-fold as compared with the general population. Individuals with Lynch syndrome have a cumulative risk of pancreatic cancer of 3.7 % by age 70 [34, 35], with the average age at diagnosis of 52 years in men and 57 years in women [34].

Pancreatic adenocarcinomas in patients with Lynch syndrome demonstrate microsatellite instability as well as loss of expression of mismatch repair proteins [36, 37]. Medullary carcinoma of the pancreas, a rare variant of poorly differentiated adenocarcinoma, has been identified in patients with Lynch syndrome, suggesting a potentially different pathogenesis of pancreatic cancer in Lynch syndrome patients [38, 39].

Li–Fraumeni Syndrome

Li–Fraumeni syndrome (LFS) is an inherited autosomal dominant disorder due to a germline mutation in the *tp53* tumor suppressor gene. It is characterized by breast cancer, sarcomas, adrenocortical carcinoma, and brain tumors diagnosed at an early age. The lifetime risk of cancer in LFS approaches 100 % in females and 73 % in males [40]. Individuals with a *tp53* mutation may also have a 7.3-fold increased risk of pancreatic cancer [41].

Hereditary Pancreatitis

Hereditary pancreatitis is a rare condition characterized by chronic pancreatitis due to recurrent attacks of acute pancreatitis in childhood. Hereditary pancreatitis is associated with mutations in the *PRSS1* gene, which encodes cationic trypsinogen. Normally, cationic trypsinogen is secreted by the pancreas into the duodenum, where it is ultimately cleaved into trypsin. Trypsin functions to aid in proteolysis. The two most common mutations identified in *PRSS1* are R122H and N29I [42]. The R122H mutation in *PRSS1* results in cationic trypsinogen that is prematurely broken down into trypsin while still in the pancreas. This causes pancreatic tissue damage and inflammation, leading to pancreatitis. As a result of recurrent episodes of pancreatic inflammation, the risk of pancreatic cancer in these individuals is increased by 53-fold as compared with the general population. Individuals with hereditary pancreatitis have an estimated lifetime risk of 40 % and an average age of 57 years at pancreatic cancer diagnosis [43].

Management of Individuals at Risk for Pancreatic Cancer

The management of individuals at increased risk of pancreatic cancer consists largely of screening to identify precursor lesions. However, patients should also be counseled against smoking, which is an independent risk factor for pancreatic cancer. In a nested case control study that included 251 members of 28 families with two or more members with pancreatic cancer, smoking was an independent risk factor for pancreatic cancer (odds ratio [OR] 3.7; 95 % CI 1.8–7.6). FPC smokers developed pancreatic cancer a decade earlier as compared with nonsmokers (59 years vs. 69 years of age). The risk of pancreatic cancer was greatest in men and in individuals younger than 50 years (OR 5.2 and 7.6, respectively) [44]. In individuals with hereditary pancreatitis, in addition to smoking cessation, a low-fat diet should also be advised.

Targets for Screening for Pancreatic Cancer

Screening aims to identify high-risk individuals with precursors of pancreatic adenocarcinoma, which include intraductal papillary mucinous neoplasms (IPMNs) and pancreatic intraepithelial neoplasia (PanIN). IPMNs are grossly visible mucin-producing epithelial neoplasms. They can involve the main pancreatic duct, branch ducts, or both. Main duct IPMNs can be distinguished from branch-duct IPMNs by connection to and/or dilation of the main pancreatic duct on radiologic or endoscopic imaging. Features of IPMN on ERCP include mucin extruding from the pancreatic duct orifice, a "fish-mouth" appearance to the pancreatic duct orifice, and pancreatic duct dilation with filling defects [45]. IPMN characteristics suggestive of an underlying malignancy include a main pancreatic duct diameter >7 mm, a cystic lesion >3 cm, or the presence of a mural nodule [46]. Main duct IPMNs have a greater risk of malignancy as compared with branch-duct IPMNs [47].

PanINs are microscopic noninvasive neoplasms involving small ducts of the pancreas that are formed by metaplasia and proliferation of ductal epithelium. PanINs display varying degrees of dysplasia, which are characterized as mild (PanIN 1), moderate (PanIN 2), and severe (PanIN 3) [48]. Although the precise timeline for progression of PanIN to adenocarcinoma is unclear, studies suggest a 1 % probability of a single PanIN lesion progressing to invasive cancer [49].

Both IPMN and PanIN are found with greater frequency and at higher grade in patients with FPC as compared with controls [50]. Furthermore, high-grade precursor lesions in the pancreas of individuals with FPC are often multifocal [51].

Screening in high-risk families can detect precancerous changes in the pancreas (Table 15.2) [52]. In a multicenter prospective study of 215 high-risk individuals who underwent screening with computed tomography (CT), magnetic resonance imaging (MRI), and endoscopic ultrasonography (EUS), 92 (42 %) had at least one pancreatic mass, and 85 were reported to have either proven or suspected neoplasms (82 IPMN and 3 neuroendocrine tumors). Five individuals underwent surgical resection of the pancreas, of which three were found to have high-grade pancreatic dysplasia in <3-cm IPMNs and multiple intraepithelial neoplasias.

However, screening carries the risk of misdiagnosis and overtreatment of low-risk pancreatic lesions. In screening studies, some cysts noted on imaging were found to be benign serous cystadenomas at resection, while other resected pancreata had only low-grade PanIN associated with lobulocentric parenchymal atrophy. Pancreatic cancer has also been reported to develop in patients undergoing pancreatic screening in research protocols; however, these may be due to poor patient follow-up and low-quality imaging [53, 54]. In addition, data on long-term follow-up of pancreatic cancer screening cohorts are lacking and it is unclear if screening improves survival [53].

Imaging

Magnetic resonance cholangiopancreatogram (MRCP) and EUS are the two main imaging modalities for screening for pancreatic cancer. Secretin-enhanced MRCP further improves the sensitivity of MRCP for detecting smaller ductal lesions [55]. MRI/MRCP also has the advantage of avoiding the radiation exposure associated with CT scans but is limited by its cost and availability.

By combining endoscopy with high-frequency ultrasonography, EUS allows for high-resolution views of the pancreas. Similar to MRI, EUS does not require radiation. EUS can accurately detect IPMNs and has the advantage of being able to visualize mural nodules [56]. Chronic pancreatitis seen on EUS in individuals with FPC has been associated with lobulocentric atrophy and may be a marker of multifocal PanIN lesions [57]. EUS findings including heterogeneous parenchyma, hypoechoic nodules, hyperechoic main-duct walls, and discrete masses have a high positive predictive value for PanIN in high-risk individuals [58]. Targeted imaging agents, including those that detect plectin, a cell-surface protein expressed in PanIN 3 lesions, may improve

Table 15.2 Summary of diagnostic yield of screening programs in hereditary pancreatic cancer families

Study	High-risk groups	Imaging modalities [primary imaging (secondary imaging)]	*n*	Diagnostic yield[a]	Surgical resection	Successful yield[b]
Brentnall (1999) [58]	FPC	EUS + ERCP + CT	14	7 (50 %)	7 (50 %)	Not available[c]
Kimmey (2002) [66]	FPC	EUS (ERCP)	46	13 (28 %)	12 (26 %)	Not available[c]
Canto (2004) [72]	FPC, PJS	EUS (ERCP, EUS-FNA, CT)	38	12 (32 %)	7 (18 %)	2 (5.3 %)
Canto (2006) [60]	FPC, PJS	EUS (CT, EUS-FNA, ERCP)	78	17 (22 %)	7 (10 %)	3 (3.8 %)
Poley (2009) [73]	FPC, BRCA, PJS, p16, p53, HP	EUS (CT, MRI)	44	10 (23 %)	3 (6.8 %)	1 (2.3 %)
Langer (2009) [74]	FPC, BRCA	EUS + MRI/MRCP (EUS-FNA)	76	28 (36 %)	7 (9.2 %)	0 (0 %)
Verna (2010) [75]	FPC, BRCA, p16	EUS and/or MRCP	51	20 (39 %)	6 (12 %)	1 (2.0 %)
Ludwig (2011) [60]	FPC, BRCA	MRCP (EUS, EUS-FNA)	109	9 (8 %)	6 (6.4 %)	1 (0.9 %)
Vasen (2011) [54]	p16	MRI/MRCP	79	16 (20 %)	7 (10 %)	2 (2.5 %)
Al-Sukhni (2011) [53]	FPC, BRCA, PJS, p16, HP	MRI (CT, EUS, ERCP)	262	84 (32 %)	4 (1.5 %)	0 (0 %)
Schneider (2011) [76]	FPC, BRCA, PALB2	EUS + MRI/MRCP	72	26 (36 %)	9 (13 %)	2 (2.8 %)
Canto (2012) [52]	FPC, BRCA, PJS	CT + MRI/MRCP + EUS (ERCP)	216	92 (43 %)	5 (2.3 %)	3 (1.4 %)

Source: Adapted from [16, 71]

FPC, familial pancreatic cancer; *PJS,* Peutz–Jeghers syndrome; *HP,* hereditary pancreatitis; *EUS,* endoscopic ultrasound; *EUS-FNA,* endoscopic ultrasound with fine-needle aspiration; *ERCP,* endoscopic retrograde cholangiopancreatogram; *MRCP,* magnetic resonance cholangiopancreatogram

[a]Diagnostic yield is defined as pancreatic lesion found using screening modality

[b]Successful yield defined as surgical resection of PanIN-3, high-grade IPMN, or T1N0M0 disease

[c]All patients had dysplasia ranging from low grade to high grade

imaging for noncystic pancreatic lesions [59]. The limitations of EUS include high interobserver variability, high cost, and complications related to endoscopy.

While multidetector, contrast-enhanced helical CT with a pancreatic protocol and endoscopic retrograde cholangiopancreatography (ERCP) have also been used to screen for pancreatic cancer in high-risk individuals, few studies have compared these modalities directly. In one prospective study in 216 high-risk individuals, MRI/MRCP and EUS had a significantly higher sensitivity in detecting cystic or solid lesions as compared with CT (77 %, 79 %, and 14 %, respectively) [52]. MRI, EUS, and CT detected subcentimeter cysts in 33 %, 36 %, and 11 % of patients, respectively. The concordance between EUS and MRI/MRCP for detection of any pancreatic lesion was significantly higher as compared with EUS and CT scan (91 % vs. 73 %).

Given the limited sensitivity of CT scan and the risk of radiation, especially when repeated screening is required, CT is not used in current screening protocols. The use of ERCP is largely limited to follow-up of solid or cystic lesions on EUS or MRCP due to the risk of post-ERCP pancreatitis. In one study in which routine ERCP was performed to follow up all abnormal EUS findings, ERCP did not improve diagnostic yield and was associated with pancreatitis in 7 % of individuals [60].

Biomarkers

Limitations in current screening modalities in identifying microscopic dysplasia and characterizing small cysts have prompted the evaluation of biomarkers in pancreatic juice for early detection of pancreatic neoplasia. Somatic mutations in *GNAS*, which encodes the G protein, have been identified in 66 % of IPMNs [61]. Other than in a small percentage (<10 %) of PanINs, *GNAS* mutations have not been detected in pancreatic ductal adenocarcinomas or in mucinous or serous cystic neoplasms. In a study that included 291 subjects with a familial predisposition to pancreatic cancer who underwent pancreatic screening, and disease controls with normal pancreata, chronic pancreatitis, sporadic IPMN, or other neoplasms, mutant *GNAS* was detected in duodenal collections of pancreatic juice in 50 of 78 familial and sporadic IPMNs (64 %), 15 of 33 (46 %) with only diminutive cysts (<5 mm), but none of 57 disease controls. Additionally, mutant *GNAS* detected in baseline juice samples was associated with the emergence of a new cyst at follow-up [62]. *tp53* mutations occur late in the progression of PanIN lesions. In a study in which 180 individuals at high risk for pancreatic cancer underwent *tp53* mutational analysis from duodenal samples of pancreatic juice, *tp53* mutations were detected only in PanINs and IPMNs with intermediate-grade (15 %) and high-grade dysplasia (43 %) and not in any low-grade IPMNs or PanIN 1 lesions [63]. The sensitivity of *tp53* mutation analysis was 67 %. *tp53* mutations were not detected in duodenal samples of pancreatic juice in 14 of 43 patients (32 %) with pancreatic ductal adenocarcinoma. Additional studies are needed to evaluate the diagnostic accuracy of mutant *tp53* and *GNAS* in detecting pancreatic cancer precursor lesions in patients undergoing screening.

Guidelines for Pancreatic Cancer Screening

It is uncertain whether early identification and treatment of PanIN and IPMNs will improve outcomes in high-risk individuals, given that only a small fraction of these lesions progress to invasive cancer. Current guidelines, based on expert opinion, recommend screening for pancreatic cancer only in individuals with a greater than 5 % lifetime risk or a fivefold or greater relative risk of developing pancreatic cancer (Table 15.3) [16]. Screening should be performed at high-volume centers with EUS and MRI/MRCP and preferably within research protocols.

Screening for pancreatic cancer is recommended in patients with PJS or a mutation in *STK11* and patients with hereditary pancreatitis with longstanding chronic pancreatitis regardless of the family history of pancreatic cancer [64]. Screening should also be considered in mutation

Table 15.3 Groups at a high risk of pancreatic cancer recommended for screening [16]

High-risk group	Subgroups recommended for screening
Peutz–Jeghers syndrome	Regardless of family history
p16 (*CDKN2A*) carriers	One or more FDR with PC
BRCA1/2 mutation carriers	One or more FDR with PC, or
	Two or more blood relatives with PC (even without a FDR)
PALB2 mutation carriers	One or more FDR with PC
	Two or more blood relatives with PC (even without a FDR)
Lynch syndrome	One or more FDR with PC
	Two or more blood relatives with PC (even without a FDR)
Familial pancreatic cancer	Two or more affected blood relatives with PC, with at least one affected being a FDR
Hereditary pancreatitis	Regardless of family history (requires longstanding chronic pancreatitis)

Source: Adapted from [16]
PC pancreatic cancer, *FDR* first-degree relative

carriers of *BRCA1/2*, mismatch repair gene, *MSH2*, *MLH1*, *MSH6*, and *PMS2* and *EPCAM* (Lynch syndrome), *CDKN2A*, or *PALB-2* who have one or more FDRs with pancreatic cancer or two non-FDRs with pancreatic cancer. In FPC families, screening should be considered for individuals with two or more affected blood relatives with pancreatic cancer in the family, with at least one affected being a FDR.

There are limited data to guide the interval for screening for pancreatic cancer in high-risk individuals. Our practice is to initiate screening in FPC families at age 50 years or 10 years prior to the youngest relative diagnosed with pancreatic cancer, at age 40 in patients with hereditary pancreatitis, and at age 30 in individuals with PJS. We perform annual MRI/MRCP alternating with EUS. As this is a relatively recent area of investigation with several ongoing studies, new data will continue to inform us in the next several years regarding optimal algorithms for surveillance intervals, nuances of when to initiate surveillance, and whether ancillary molecular markers are beneficial as supplemental tests.

Management of Lesions Detected on Screening

At the current time, there are limited studies available to guide evidence-based management of pancreatic lesions detected on imaging in individuals at high risk for pancreatic cancer. Our recommendations are consistent with those of the International Cancer of the Pancreas Screening (CAPS) Consortium [16]. Patients with a newly detected indeterminate solid lesion should have follow-up imaging at 3 months if surgery is not imminent. For an indeterminate main pancreatic duct stricture without an associated mass, repeat imaging should be performed within 3 months.

For patients with IPMN, the Sendai Consensus Guidelines for the management of IPMNs recommend more aggressive surveillance in high-risk individuals, specifically those with two or more FDRs with pancreatic cancer [65]. Patients with a newly diagnosed branch-duct IPMN should undergo MRI/MRCP or CT and EUS. High-risk malignant stigmata associated with IPMNs include an enhanced solid component and a main pancreatic duct size of ≥10 mm. Worrisome features associated with IPMNs include cysts of ≥3 cm, thickened enhanced cyst walls, nonenhanced mural nodules, main pancreatic duct size of 5–9 mm, and abrupt change in main pancreatic duct caliber with distal pancreatic atrophy and lymphadenopathy. If malignant stigmata or worrisome features are present, then surgical resection should be considered. If there are no worrisome features, then MRI/MRCP or CT should be done at 3-month intervals and EUS should be done annually for the first 2 years to evaluate for the development of worrisome features. Rapidly growing cysts or cysts that develop worrisome features should strongly be considered for resection.

Surgery

Indications for surgical resection include solid lesions at least 1 cm in size and all main-duct or mixed IPMNs [16, 65]. Resection of branch-duct

IPMNs in high-risk individuals should be considered if they are symptomatic, ≥2 cm, or contain a mural nodule and/or abnormal cytology [16].

The management of PanIN lesions is more controversial. PanIN lesions are often multifocal, and unlike IPMNs, these lesions are difficult to detect by imaging. In screening studies, the majority of PanIN 3 lesions were found in patients who underwent resection for other lesions, including a dilated pancreatic duct, pancreatitis, or a pancreatic mass [52, 60, 66, 67]. While there is consensus that surgical resection should be considered in patients with PanIN 3 lesions, there is debate with regard to the timing and extent of surgery. While total pancreatectomy is the only definitive management for PanIN 3 lesions, it is associated with significant morbidity and brittle diabetes. In high-risk individuals with changes consistent with chronic pancreatitis on EUS or abnormal duct changes on ERCP/MRCP, and multifocal PanIN 3 lesions documented on pancreatic resection, some experts advocate total pancreatectomy, while most suggest that in the absence of pancreatic cancer, such patients undergo continued surveillance with imaging within 6 months of partial pancreatectomy [16].

Prophylactic surgery is not recommended for asymptomatic high-risk individuals without an identifiable lesion due to the risks associated with pancreatectomy. When surgery is indicated, it should be performed at a high-volume specialty center [68].

Conclusions

High-risk individuals with clustering of pancreatic cancer cases and individuals with inherited cancer syndromes associated with pancreatic cancer may benefit from screening for pancreatic cancer with the goal of detecting precursor lesions including PanIN lesions and IPMNs. Several studies have demonstrated that with EUS and MRI/MRCP, pancreatic precursor lesions are detectable and have a significant yield in appropriately selected, high-risk individuals. A combination of biomarkers and imaging may further improve the detection of pancreatic precursor lesions and allow for early resection. Data are needed to guide the optimal approach and frequency of screening as well as the management of suspected pancreatic lesions. As screening for pancreatic cancer becomes more prevalent in high-risk individuals, it remains important to determine whether it translates into a meaningful improvement in cancer outcomes.

References

1. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin. 2014;64(1):9–29.
2. Permuth-Wey J, Egan KM. Family history is a significant risk factor for pancreatic cancer: results from a systematic review and meta-analysis. Fam Cancer. 2009;8(2):109–17.
3. Rustgi AK. Familial pancreatic cancer: genetic advances. Genes Dev. 2014;28(1):1–7.
4. Klein AP, Brune KA, Petersen GM, et al. Prospective risk of pancreatic cancer in familial pancreatic cancer kindreds. Cancer Res. 2004;64(7):2634–8.
5. Wang W, Chen S, Brune KA, Hruban RH, Parmigiani G, Klein AP. PancPRO: risk assessment for individuals with a family history of pancreatic cancer. J Clin Oncol. 2007;25(11):1417–22.
6. Klein AP, Beaty TH, Bailey-Wilson JE, Brune KA, Hruban RH, Petersen GM. Evidence for a major gene influencing risk of pancreatic cancer. Genet Epidemiol. 2002;23(2):133–49.
7. Pogue-Geile KL, Chen R, Bronner MP, et al. Palladin mutation causes familial pancreatic cancer and suggests a new cancer mechanism. PLoS Med. 2006; 3(12), e516.
8. Klein AP, Borges M, Griffith M, et al. Absence of deleterious Palladin mutations in patients with familial pancreatic cancer. Cancer Epidemiol Biomarkers Prev. 2009;18(4):1328–30.
9. Hahn SA, Greenhalf B, Ellis I, et al. BRCA2 germline mutations in familial pancreatic carcinoma. J Natl Cancer Inst. 2003;95(3):214–21.
10. Murphy KM, Brune KA, Griffin C, et al. Evaluation of candidate genes MAP2K4, MADH4, ACVR1B, and BRCA2 in familial pancreatic cancer: deleterious BRCA2 mutations in 17%. Cancer Res. 2002;62(13): 3789–93.
11. Couch FJ, Johnson MR, Rabe KG, et al. The prevalence of BRCA2 mutations in familial pancreatic cancer. Cancer Epidemiol Biomarkers Prev. 2007; 16(2):342–6.
12. Slater EP, Langer P, Fendrich V, et al. Prevalence of BRCA2 and CDKN2a mutations in German familial pancreatic cancer families. Fam Cancer. 2010;9(3): 335–43.

13. Xia B, Sheng Q, Nakanishi K, et al. Control of BRCA2 cellular and clinical functions by a nuclear partner, PALB2. Mol Cell. 2006;22(6):719–29.
14. Slater EP, Langer P, Niemczyk E, et al. PALB2 mutations in European familial pancreatic cancer families. Clin Genet. 2010;78(5):490–4.
15. Jones S, Hruban RH, Kamiyama M, et al. Exomic sequencing identifies PALB2 as a pancreatic cancer susceptibility gene. Science. 2009;324(5924):217.
16. Canto MI, Harinck F, Hruban RH, et al. International Cancer of the Pancreas Screening (CAPS) consortium summit on the management of patients with increased risk for familial pancreatic cancer. Gut. 2013;62(3): 339–47.
17. Roberts NJ, Jiao Y, Yu J, et al. ATM mutations in patients with hereditary pancreatic cancer. Cancer Discov. 2012;2(1):41–6.
18. van Lier MG, Wagner A, Mathus-Vliegen EM, Kuipers EJ, Steyerberg EW, van Leerdam ME. High cancer risk in Peutz–Jeghers syndrome: a systematic review and surveillance recommendations. Am J Gastroenterol. 2010;105(6):1258–64; author reply 1265.
19. Resta N, Pierannunzio D, Lenato GM, et al. Cancer risk associated with STK11/LKB1 germline mutations in Peutz–Jeghers syndrome patients: results of an Italian multicenter study. Dig Liver Dis. 2013; 45(7):606–11.
20. Grover S, Kastrinos F, Steyerberg EW, et al. Prevalence and phenotypes of APC and MUTYH mutations in patients with multiple colorectal adenomas. JAMA. 2012;308(5):485–92.
21. Goldstein AM, Fraser MC, Struewing JP, et al. Increased risk of pancreatic cancer in melanoma-prone kindreds with p16INK4 mutations. N Engl J Med. 1995;333(15):970–4.
22. de Snoo FA, Bishop DT, Bergman W, et al. Increased risk of cancer other than melanoma in CDKN2A founder mutation (p16-Leiden)-positive melanoma families. Clin Cancer Res. 2008;14(21):7151–7.
23. Struewing JP, Abeliovich D, Peretz T, et al. The carrier frequency of the BRCA1 185delAG mutation is approximately 1 percent in Ashkenazi Jewish individuals. Nat Genet. 1995;11(2):198–200.
24. Whittemore AS, Gong G, John EM, et al. Prevalence of BRCA1 mutation carriers among U.S. non-Hispanic whites. Cancer Epidemiol Biomarkers Prev. 2004;13(12):2078–83.
25. Antoniou AC, Pharoah PD, McMullan G, et al. A comprehensive model for familial breast cancer incorporating BRCA1, BRCA2 and other genes. Br J Cancer. 2002;86(1):76–83.
26. Mocci E, Milne RL, Mendez-Villamil EY, et al. Risk of pancreatic cancer in breast cancer families from the breast cancer family registry. Cancer Epidemiol Biomarkers Prev. 2013;22(5):803–11.
27. van Asperen CJ, Brohet RM, Meijers-Heijboer EJ, et al. Cancer risks in BRCA2 families: estimates for sites other than breast and ovary. J Med Genet. 2005;42(9):711–9.
28. Ferrone CR, Levine DA, Tang LH, et al. BRCA germline mutations in Jewish patients with pancreatic adenocarcinoma. J Clin Oncol. 2009;27(3):433–8.
29. Brose MS, Rebbeck TR, Calzone KA, Stopfer JE, Nathanson KL, Weber BL. Cancer risk estimates for BRCA1 mutation carriers identified in a risk evaluation program. J Natl Cancer Inst. 2002;94(18): 1365–72.
30. Thompson D, Easton DF, Breast Cancer Linkage Consortium. Cancer incidence in BRCA1 mutation carriers. J Natl Cancer Inst. 2002;94(18):1358–65.
31. Skudra S, Staka A, Pukitis A, et al. Association of genetic variants with pancreatic cancer. Cancer Genet Cytogenet. 2007;179(1):76–8.
32. Aarnio M, Sankila R, Pukkala E, et al. Cancer risk in mutation carriers of DNA-mismatch-repair genes. Int J Cancer. 1999;81(2):214–8.
33. Watson P, Vasen HF, Mecklin JP, et al. The risk of extra-colonic, extra-endometrial cancer in the Lynch syndrome. Int J Cancer. 2008;123(2):444–9.
34. Kastrinos F, Mukherjee B, Tayob N, et al. Risk of pancreatic cancer in families with Lynch syndrome. JAMA. 2009;302(16):1790–5.
35. Win AK, Young JP, Lindor NM, et al. Colorectal and other cancer risks for carriers and noncarriers from families with a DNA mismatch repair gene mutation: a prospective cohort study. J Clin Oncol. 2012;30(9): 958–64.
36. Goggins M, Offerhaus GJ, Hilgers W, et al. Pancreatic adenocarcinomas with DNA replication errors (RER+) are associated with wild-type K-ras and characteristic histopathology. Poor differentiation, a syncytial growth pattern, and pushing borders suggest RER+. Am J Pathol. 1998;152(6):1501–7.
37. Laghi L, Beghelli S, Spinelli A, et al. Irrelevance of microsatellite instability in the epidemiology of sporadic pancreatic ductal adenocarcinoma. PLoS One. 2012;7(9), e46002.
38. Banville N, Geraghty R, Fox E, et al. Medullary carcinoma of the pancreas in a man with hereditary non-polyposis colorectal cancer due to a mutation of the MSH2 mismatch repair gene. Hum Pathol. 2006;37(11):1498–502.
39. Wilentz RE, Goggins M, Redston M, et al. Genetic, immunohistochemical, and clinical features of medullary carcinoma of the pancreas: a newly described and characterized entity. Am J Pathol. 2000;156(5): 1641–51.
40. Chompret A, Brugieres L, Ronsin M, et al. P53 germline mutations in childhood cancers and cancer risk for carrier individuals. Br J Cancer. 2000;82(12):1932–7.
41. Ruijs MW, Verhoef S, Rookus MA, et al. TP53 germline mutation testing in 180 families suspected of Li–Fraumeni syndrome: mutation detection rate and relative frequency of cancers in different familial phenotypes. J Med Genet. 2010;47(6):421–8.
42. Teich N, Rosendahl J, Toth M, Mossner J, Sahin-Toth M. Mutations of human cationic trypsinogen (PRSS1) and chronic pancreatitis. Hum Mutat. 2006;27(8): 721–30.

43. Lowenfels AB, Maisonneuve P, Di Magno EP, et al. Hereditary pancreatitis and the risk of pancreatic cancer. International Hereditary Pancreatitis Study Group. J Natl Cancer Inst. 1997;89(6):442–6.
44. Rulyak SJ, Lowenfels AB, Maisonneuve P, Brentnall TA. Risk factors for the development of pancreatic cancer in familial pancreatic cancer kindreds. Gastroenterology. 2003;124(5):1292–9.
45. Raijman I, Kortan P, Walden D, Kandel G, Marcon NE, Haber GB. Mucinous ductal ectasia: cholangiopancreatographic and endoscopic findings. Endoscopy. 1994;26(3):303–7.
46. Kim KW, Park SH, Pyo J, et al. Imaging features to distinguish malignant and benign branch-duct type intraductal papillary mucinous neoplasms of the pancreas: a meta-analysis. Ann Surg. 2014;259(1):72–81.
47. Serikawa M, Sasaki T, Fujimoto Y, Kuwahara K, Chayama K. Management of intraductal papillary-mucinous neoplasm of the pancreas: treatment strategy based on morphologic classification. J Clin Gastroenterol. 2006;40(9):856–62.
48. Hruban RH, Adsay NV, Albores-Saavedra J, et al. Pancreatic intraepithelial neoplasia: a new nomenclature and classification system for pancreatic duct lesions. Am J Surg Pathol. 2001;25(5):579–86.
49. Terhune PG, Phifer DM, Tosteson TD, Longnecker DS. K-ras mutation in focal proliferative lesions of human pancreas. Cancer Epidemiol Biomarkers Prev. 1998;7(6):515–21.
50. Shi C, Klein AP, Goggins M, et al. Increased prevalence of precursor lesions in familial pancreatic cancer patients. Clin Cancer Res. 2009;15(24):7737–43.
51. Brune K, Abe T, Canto M, et al. Multifocal neoplastic precursor lesions associated with lobular atrophy of the pancreas in patients having a strong family history of pancreatic cancer. Am J Surg Pathol. 2006;30(9):1067–76.
52. Canto MI, Hruban RH, Fishman EK, et al. Frequent detection of pancreatic lesions in asymptomatic high-risk individuals. Gastroenterology. 2012;142(4):796–804; quiz e14–5.
53. Al-Sukhni W, Borgida A, Rothenmund H, et al. Screening for pancreatic cancer in a high-risk cohort: an eight-year experience. J Gastrointest Surg. 2012;16(4):771–83.
54. Vasen HF, Wasser M, van Mil A, et al. Magnetic resonance imaging surveillance detects early-stage pancreatic cancer in carriers of a p16-Leiden mutation. Gastroenterology. 2011;140(3):850–6.
55. Fukukura Y, Fujiyoshi F, Sasaki M, Nakajo M. Pancreatic duct: morphologic evaluation with MR cholangiopancreatography after secreting stimulation. Radiology. 2002;222(3):674–80.
56. Aithal GP, Chen RY, Cunningham JT, et al. Accuracy of EUS for detection of intraductal papillary mucinous tumor of the pancreas. Gastrointest Endosc. 2002;56(5):701–7.
57. Brune K, Abe T, Canto M, et al. Multifocal neoplastic precursor lesions associated with lobular atrophy of the pancreas in patients having a strong family history of pancreatic cancer. Am J Surg Pathol. 2006;30(9):1067–76.
58. Brentnall TA, Bronner MP, Byrd DR, Haggitt RC, Kimmey MB. Early diagnosis and treatment of pancreatic dysplasia in patients with a family history of pancreatic cancer. Ann Intern Med. 1999;131(4):247–55.
59. Kelly KA, Bardeesy N, Anbazhagan R, et al. Targeted nanoparticles for imaging incipient pancreatic ductal adenocarcinoma. PLoS Med. 2008;5(4), e85.
60. Canto MI, Goggins M, Hruban RH, et al. Screening for early pancreatic neoplasia in high-risk individuals: a prospective controlled study. Clin Gastroenterol Hepatol. 2006;4(6):766–81; quiz 665.
61. Wu J, Matthaei H, Maitra A, et al. Recurrent GNAS mutations define an unexpected pathway for pancreatic cyst development. Sci Transl Med. 2011;3:92.
62. Kanda M, Knight S, Topazian M, et al. Mutant GNAS detected in duodenal collections of secretin-stimulated pancreatic juice indicates the presence or emergence of pancreatic cysts. Gut. 2013;62(7):1024–33.
63. Kanda M, Sadakari Y, Borges M, et al. Mutant TP53 in duodenal samples of pancreatic juice from patients with pancreatic cancer or high-grade dysplasia. Clin Gastroenterol Hepatol. 2013;11(6):719–30; e5.
64. Vitone LJ, Greenhalf W, Howes NR, Neoptolemos JP. Hereditary pancreatitis and secondary screening for early pancreatic cancer. Rocz Akad Med Bialymst. 2005;50:73–84.
65. Tanaka M, Fernandez-del Castillo C, Adsay V, et al. International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas. Pancreatology. 2012;12(3):183–97.
66. Kimmey MB, Bronner MP, Byrd DR, Brentnall TA. Screening and surveillance for hereditary pancreatic cancer. Gastrointest Endosc. 2002;56(4 Suppl):S82–6.
67. Ludwig E, Olson SH, Bayuga S, et al. Feasibility and yield of screening in relatives from familial pancreatic cancer families. Am J Gastroenterol. 2011;106(5):946–54.
68. Finks JF, Osborne NH, Birkmeyer JD. Trends in hospital volume and operative mortality for high-risk surgery. N Engl J Med. 2011;364(22):2128–37.
69. Grover S, Syngal S. Hereditary pancreatic cancer. Gastroenterology. 2010;139(4):1076–80; e1–2.
70. Steinberg WM, Barkin JS, Bradley EL, et al. Should patients with a strong family history of pancreatic cancer be screened on a periodic basis for cancer of the pancreas? Pancreas. 2009;38(5):e137–50.
71. Templeton AW, Brentnall TA. Screening and surgical outcomes of familial pancreatic cancer. Surg Clin North Am. 2013;93(3):629–45.
72. Canto MI, Goggins M, Yeo CJ, et al. Screening for pancreatic neoplasia in high-risk individuals: an EUS-based approach. Clin Gastroenterol Hepatol. 2004;2(7):606–21.
73. Poley JW, Kluijt I, Gouma DJ, et al. The yield of first-time endoscopic ultrasonography in screening individuals at a high risk of developing pancreatic cancer. Am J Gastroenterol. 2009;104(9):2175–81.

74. Langer P, Kann PH, Fendrich V, et al. Five years of prospective screening of high-risk individuals from families with familial pancreatic cancer. Gut. 2009;58(10):1410–8.
75. Verna EC, Hwang C, Stevens PD, et al. Pancreatic cancer screening in a prospective cohort of high-risk patients: a comprehensive strategy of imaging and genetics. Clin Cancer Res. 2010;16(20):5028–37.
76. Schneider R, Slater EP, Sina M, et al. German national case collection for familial pancreatic cancer (FaPaCa): Ten years' experience. Fam Cancer. 2011;10(2):323–30.

Differential Diagnosis and Diagnostic Evaluation Algorithm

16

Michael Bartel, Milena Di Leo, and Massimo Raimondo

Introduction

Diagnosis of a pancreatic mass has a broad differential comprising both solid and cystic lesions. The increasing utilization of cross-sectional imaging frequently leads to incidental pancreatic masses, including solid pancreatic tumors in up to 7 % and pancreatic cystic lesions in up to 16 % [1–3].

Taking into account the epidemiology of solid pancreatic lesions, the majority of incidental pancreatic solid masses are pancreatic ductal adenocarcinomas [1]. However, a thorough medical history and physical examination have to consider the differential diagnosis, including pancreatic neuroendocrine tumors (PNETs), metastasis, and other malignant and benign pancreatic conditions. Another challenge is avoiding unnecessary surgical procedures in the treatment of diseases that can mimic pancreatic cancer, such as autoimmune pancreatitis (AIP), chronic pancreatitis, and lymphoma.

M. Bartel, M.D. • M. Di Leo, M.D.
Division of Gastroenterology and Hepatology, Mayo Clinic, Jacksonville, FL, USA
e-mail: Bartel.Michael@mayo.edu; Dileomilena1984@gmail.com

M. Raimondo, M.D. (✉)
Department of Gastroenterology, Mayo Clinic, 4500 San Pablo Road, Jacksonville, FL 32224, USA
e-mail: Raimondo.Massimo@mayo.edu

The same is true for the differential diagnosis of cystic pancreatic lesions, which encompasses benign lesions, low-grade malignant lesions, and malignant lesions, including pancreatic cancer. This chapter focuses on the differential diagnosis of solid and cystic pancreatic masses, as well as their diagnostic approach. Following the description of different etiologies of pancreatic lesions as well as their epidemiology and diagnostic hallmarks, an evidence-based diagnostic algorithm will be illustrated focusing on cross-sectional, endoscopic imaging, and laboratory testing (Table 16.1 and Fig. 16.1).

Pancreatic Adenocarcinoma

Pancreatic adenocarcinoma is the fourth leading cause of cancer death despite its relatively low incidence [25]. The average age at the time of diagnosis is 71 years, with a slight male predominance [26]. It is speculated that males have more exposure to risk factors for developing pancreatic cancer, including cigarette smoking and alcohol use. Other associated factors are chronic pancreatitis, obesity, high intake of animal fat, inherited genetic predisposition, non-"O" blood group, and occupational exposure to nickel and chlorinated hydrocarbon [27]. In addition, several studies have reported a relationship between pancreatic adenocarcinoma and diabetes mellitus. In fact, more than two thirds of patients with pancreatic adenocarcinoma have

M.S. Wagh, P.V. Draganov (eds.), *Pancreatic Masses*, DOI 10.1007/978-3-319-19677-0_16

Table 16.1 Synopsis of differential diagnosis of most common pancreatic masses

Characteristic	Pancreatic adenocarcinoma [4]	Chronic pancreatitis [5, 6]	Autoimmune pancreatitis [7, 8]	BD-IPMN [9, 10]	MCN [9, 10]	Microcystic SCN [9, 10]	Pseudopapillary tumor [11–13]	PNET [14–18]	Pancreatic metastasis [14, 19–24]
Sex	Male (56 %)	Male (70 %)	Male (75 %)	Male (60 %)	Female (99.8 %)	Female (80 %)	Female (85 %)	Female (50 %)	Male (58 %)
Median age	70	40	Type 1: 60 Type 2: 50	65	50	60	25	60 (younger if functional tumor)	60
Location	Head (75 %)	Head	Anywhere	Uncinate	Body/Tail	Anywhere	Anywhere (predilection tail)	Anywhere	Head (45 %)
Multifocal	No	No	N/A	Yes	No	No	No	No	Localized mass (50 %–70 %), multifocal mass (15 %–44 %), diffuse enlargement of the gland (5–10 %)
Calcification	Possible, not specific	Frequent	Possible, not specific	Rare	Peripheral, rare	Central, 30 %	Yes (peripheral, 30 %)	Possible, not specific	Possible, not specific
Histologic	Adenocarcinoma with desmoplastic reaction	Destruction of acinar tissue and replacement with extensive fibrosis	Type 1: Periductal lymphoplasmacytic infiltrate, obliterative phlebitis, storiform fibrosis and abundant IgG4-positive cells Type 2: granulocytic epithelial lesion in pancreatic duct, minimal IgG4-positive cells	Subtype are gastric, intestinal, pancreatobiliary and oncocytic IPMN	Ovarian stroma	Glycogen-rich cuboidal epithelial cells	Pseudopapillae	Well Differentiated: solid, trabecular, gyriform patter of cells with “organoid” growth Poorly differentiate: sheet like, diffuse architecture, with high nuclear/cytoplasmatic ratio, necrosis	Depends on the primary tumor
Capsule	No	No	No	No	Yes	No	Yes	Possible, not specific	No
Communication with MPD	N/A	N/A	N/A	Yes	No	No	No	N/A	N/A

Malignant potential	N/A	No	No	Yes (higher if combined type)	Yes	No	None or low	Yes	N/A
Imaging (CT/MRI/EUS)	Mass (EUS) with or without indirect signs (mass effect)	Solid mass in a context of calcific chronic pancreatitis	Diffuse or segmental/focal enlargement with PD stricture or strictures without upstream dilation	Fine septated cystic lesion, grape-like appearance	Single spherical lesion (unilocular or multilocular), orange-like	Complex cystic lesion with central scar, honeycomb-like	Solid encapsulated tumor with a cystic component, possible area of hemorrhage	Thick enhancing peripheral rim, fluid with clear or hemorrhagic content	Not specific, 45–95 % of patients have metastasis in other sites
			Other organ involvement (Type 1: 60 %; Type 2: infrequent)					Sharp defined mass, lobulated borders	
Contrast enhancement	Hypoenhancing mass	Hypoenhancing area	Hypoenhancing area (delayed contrast enhancement)	Mural nodules, wall thickening (if present)	Fibrous capsule, septations and mural nodules (if present)	Fibrous septation	Peripheral mild enhancement	Hyperenhancing	Wide variability between metastases of different primary tumors, but also between metastases from the same primary tumor
Cytology	Adenocarcinoma cells	Inflammatory cell, negative for malignancies	Not diagnostic	Mucinous epithelium with/without dysplasia	Mucinous epithelium with/without dysplasia	Serous, frequently acellular, bloody fluid (not diagnostic)	Papillary structures with fibrovascular stalks	Monotonous, poorly cohesive small cells with plasmacytoid morphology	Depends on primary tumor
Miscellaneous				Cyst fluid CEA: High	Cyst fluid CEA: High	Cyst fluid CEA: Low	Immunochemistry: Vimentin, CD10, progesterone receptor, nuclear expression of beta-catenin, CD56 +	Immunochemistry : Chromogranin A, Synaptophysin	Immunochemical staining depend on primary tumor
				Cystic fluid Amylase: High	Cystic fluid Amylase: Low	Cystic fluid Amylase: Low		Prognostic evaluation: mitotic rate, Ki67	

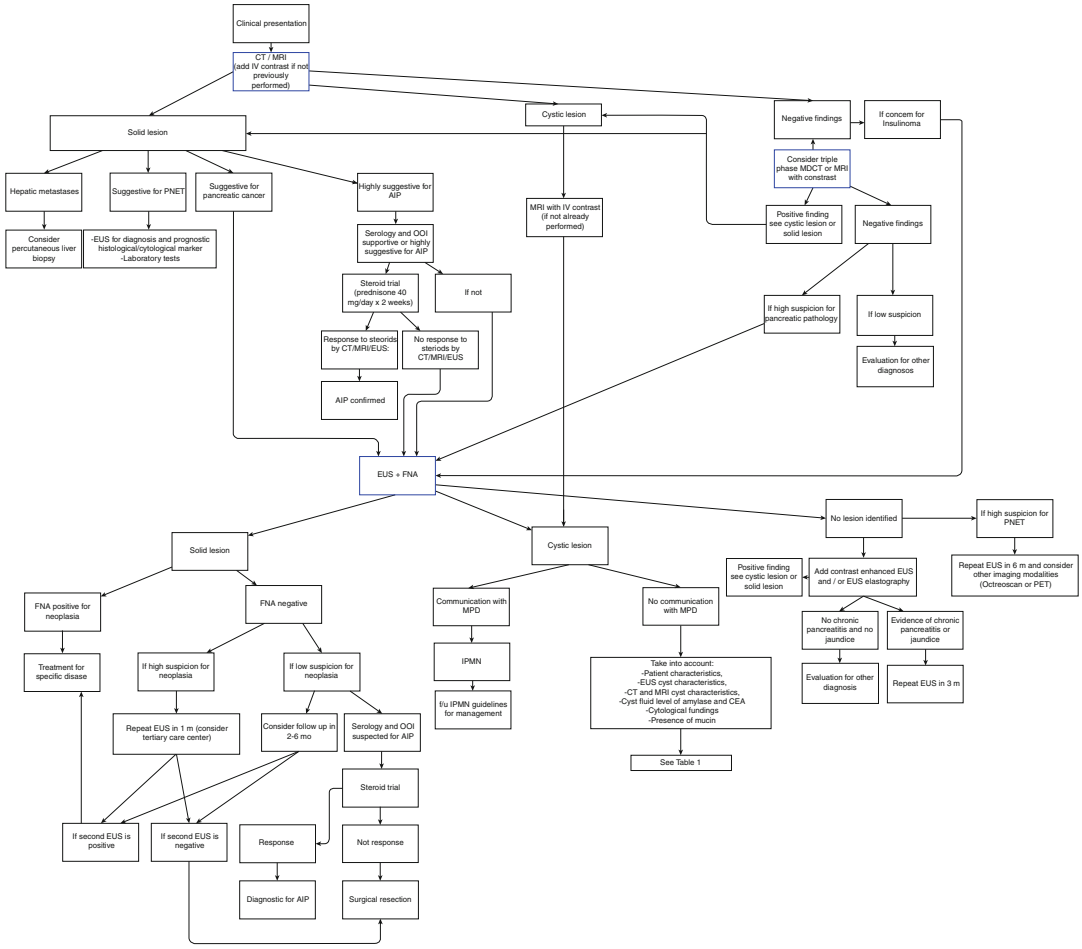

Fig. 16.1 Diagnostic algorithm for pancreatic masses

diabetes mellitus at the time of diagnosis, and more than 50 % of patients with pancreatic cancer have a new onset of diabetes mellitus preceding the cancer diagnosis by 2 years [28–31].

In most cases, pancreatic cancer is detected based on imaging, which includes both the incidental finding of a solid pancreatic mass and focused hepato-pancreato-biliary evaluation in symptomatic patients. No laboratory test with high sensitivity and specificity exists to reliably distinguish pancreatic cancer from benign pancreatic conditions [32]. The differential diagnosis is initially based on imaging findings, which emphasizes the importance of recognizing the strengths and weaknesses of the available imaging techniques.

Abdominal ultrasound has been proven to be of low yield for diagnosing pancreatic cancer, with accuracy ranging between 50–70 % [33]. Computed tomography (CT) is the preferred test to diagnose pancreatic cancer, as long as intravenous contrast is appropriately utilized (pancreas protocol). Multidetector CT (MDCT) with iodine contrast has a sensitivity of 76–92 % [34, 35]. Herein pancreatic cancer enhances poorly due to its hypovascularity, whereas 11 % of cases show isoattenuating lesions [36]. In such cases, indirect signs, including mass effect, abrupt pancreatic duct cutoff, and "double-duct sign," defined as dilation of both pancreatic and biliary ducts, can be helpful to raise the suspicion of pancreatic cancer [36, 37]. Pancreatic protocol CT scan with

imaging of both arterial and venous phases further increases the diagnostic yield of pancreatic cancer up to a sensitivity of 89–97 % [38–40].

Endoscopic ultrasound (EUS) has been a fundamental tool for the evaluation of solid pancreatic masses since the 1990s. The sensitivity of EUS to detect pancreatic cancer ranges between the mid-80s and 100 % [41–50]. An important advantage of EUS is its ability to acquire tissue samples for cytology utilizing fine-needle aspiration (FNA). Multiple authors have found that EUS-FNA provides the most definite nonoperative diagnosis of pancreatic cancer; the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were 95–98 %, 85–100 %, 98–100 %, and <85 %, respectively [51–54]. A recent meta-analysis included 4984 patients who underwent EUS-FNA for a solid pancreatic mass. Hewitt et al. found a pooled sensitivity, specificity, PPV, and NPV of 91 %, 94 %, 98 %, and 72 %, respectively, to diagnose pancreatic cancer based on EUS-acquired cytology [55]. By contrast, the absence of pancreatic solid mass on EUS in patients with clinical concern for pancreatic cancer has an NPV that approaches 100 % [56, 57]. Based on the available data, a negative or nondiagnostic FNA does not exclude pancreatic cancer. However, the absence of a pancreatic mass lesion on EUS excludes pancreatic cancer in the majority of cases. Yet, a repeat EUS within 2 months following a negative or nondiagnostic EUS needs to be considered, especially in the realm of high clinical suspicion for hepato-pancreato-biliary malignancy. This diagnostic approach is backed up by three studies. Bhutani et al. reported on 20 patients with missed pancreatic cancer by EUS. Factors contributing to false-negative EUS results were concomitant chronic pancreatitis ($n=12$), diffuse infiltrating cancer ($n=3$), ventral/dorsal split ($n=2$), and an episode of acute pancreatitis within less than 4 weeks prior to EUS ($n=1$) [58]. In another study, Eloubeidi et al. reported on 22 patients with clinical suspicion for pancreatic cancer who underwent a repeat EUS-FNA for initially suspicious (41.6 %), benign (41.6 %), or indeterminate (8.3 %) EUS-FNA. Eighty percent of patients with initially suspicious EUS-FNA were diagnosed with malignancy. Moreover, in 20 % of patients with initially benign EUS-FNA findings, the diagnosis was changed to a malignant condition [59]. Accordingly, Suzuki et al. reported on 84 patients with initially inconclusive EUS-FNA who underwent a repeat EUS-FNA at a high-volume tertiary center for evaluation of a solid pancreatic mass. The repeat EUS-FNA established a diagnosis in 82.1 %, of which all cases harbored a malignancy (mostly pancreatic adenocarcinoma, followed by PNET, metastasis, and lymphoma) [60].

Not every solid pancreatic mass harbors pancreatic adenocarcinoma. The challenge to distinguish between the differential diagnoses of solid pancreatic masses was evaluated by Tummala et al. Based on EUS, malignant neoplasms were detected in the majority (81.2 %) of patients with solid mass and dilated main pancreatic duct. Most were pancreatic ductal adenocarcinoma (71.6 %) followed by PNET, giant cell neoplasm, metastatic, nonsmall cell lung carcinoma, and spindle cell carcinoma. It was found that 18.7 % of the lesions were benign, including chronic pancreatitis and cystic neoplasms. By contrast, in patients with a nondilated pancreatic duct, most pancreatic masses (66.2 %) were benign and included chronic pancreatitis, cystic lesions, and lymph nodes. PNETs represented the majority of the 33.7 % malignant lesions, followed by pancreatic ductal adenocarcinoma and metastasis to the pancreas [61].

Additionally, EUS is important for evaluating nonspecific pancreatic changes seen on CT and MRI, such as pancreatic ductal dilation and diffuse pancreatic head enlargement. Sixty-five percent of patients with those findings were diagnosed with pancreatic cancer based on EUS imaging [62, 63].

When compared with CT, EUS was found to be superior for detecting pancreatic cancer, which was reflected by a higher sensitivity of 94–99 % vs. 57–86 % [64–66]. This was especially true for pancreatic cancer under 3 cm in size [46]. Likewise, a systematic review of 678 patients confirmed the higher sensitivity of EUS to detect pancreatic cancer than CT (93–100 % vs.

50–89 %) [67]. However, those studies are limited by their partially outdated CT techniques.

Despite the superior sensitivity of EUS to detect pancreatic cancer, as of now MDCT scan with IV contrast is the initial, preferred diagnostic imaging test to detect pancreatic cancer. This is mostly based on limited EUS availability. Also, MDCT is interchangeable with MRI [68].

Chronic Pancreatitis

Chronic pancreatitis is an inflammatory condition resulting in permanent structural changes in the pancreas leading to exocrine and endocrine pancreatic insufficiency. It can be complicated by inflammatory mass formation, especially in focal chronic pancreatitis leading to bile duct or pancreatic duct obstruction, which can resemble pancreatic cancer. Additionally, chronic pancreatitis is a risk factor for pancreatic cancer, which was confirmed by a recent meta-analysis in which 5 % of patients with chronic pancreatitis developed pancreatic cancer over 20 years [69].

Historically, cross-sectional imaging has poor sensitivity and specificity for differentiating chronic pancreatitis from pancreatic cancer. However, recent progress in CT and MRI techniques improved the diagnostic yield. Triple-phase CT scan was shown to differentiate between pancreatic cancer and chronic pancreatitis with a sensitivity, specificity, PPV, and NPV of 94.1 %, 83.6 %, 91.4 %, and 88.2 %, respectively [70]. In terms of MRI, Sandrasegaran et al. showed that a distinct mass was helpful in distinguishing between chronic pancreatitis and pancreatic cancer; however, the diagnostic yield remained low [71]. Fewer data are available for EUS. A small study revealed the sensitivity, specificity, and accuracy of EUS to distinguish between cancer and focal pancreatitis to be 73 %, 100 %, and 83 %, respectively [72]. The combination of EUS and FNA for solid pancreatic masses was shown to improve the sensitivity, specificity, PPV, and accuracy to 89.5 %, 98.4 %, 99.5 %, and 91.5 %, respectively. The additional value of EUS elastography to distinguish between pancreatic inflammatory masses and pancreatic cancer was reflected in a meta-analysis showing a pooled sensitivity and specificity of 92 % and 68 %, respectively [73].

Apart from imaging, pancreatic juice analysis of DNA methylation markers appears to be a promising approach to distinguish between chronic pancreatitis and pancreatic cancer with high sensitivity and specificity [74].

Groove pancreatitis is postulated to be a subtype of chronic segmental pancreatitis localized between the pancreatic head, duodenum, and bile duct. It is a particular challenge to distinguish groove pancreatitis from pancreatic cancer. Insufficient data are available for CT, MRI, and EUS imaging to distinguish between both disease identities. Pancreaticoduodenectomy remains the mainstay of treatment, achieving both resolution of obstructive symptoms caused by the inflammation and tissue diagnosis to exclude pancreatic cancer [75].

Acute Pancreatitis

Acute pancreatitis was shown to be the presenting diagnosis of patients with pancreatic cancer in 1.3 %. Therefore, pancreatic cancer needs to be excluded by imaging in all patients above the age of 40 years who are diagnosed with new-onset acute pancreatitis, despite the absence of gallstone disease, alcohol use, and hyperlipidemia [76]. Imaging is also indicated for patients with new-onset acute pancreatitis suspected to be secondary to alcohol or tobacco abuse, as both are also risk factors for pancreatic cancer [27, 76].

Local complications of acute pancreatitis, such as acute necrotic collection and walled-off necrosis, could mimic or mask pancreatic cancer; however, no literature exists on this topic.

Autoimmune Pancreatitis

Autoimmune pancreatitis (AIP) is a well-recognized differential diagnosis for pancreatic cancer. To date, two types of AIP are described: AIP type 1 and AIP type 2. This is described in detail in Chap. 5 in this book.

Sausage-shaped enlargement of the pancreas with a peripheral rim of hypoattenuation is the hallmark presentation of AIP based on contrast-enhanced CT (CECT) imaging. Similarly, MRI reveals diffuse enlargement of the pancreas with a hypointense capsule-like rim. In addition, cross-sectional imaging adds the advantage of assessing for extrapancreatic other organ involvement [77].

Both AIP types can present with focal features, including a pancreatic inflammatory mass and pancreatic duct stricture, resembling pancreatic cancer. This occurs more frequently in AIP type 2 (85 %) [78]. A frequent diagnostic challenge is a common bile duct (CBD) stenosis, which can be present in both AIP and pancreatic cancer. Yet the CBD wall thickening of the stenotic area is smoother in AIP than it is in pancreatic cancer.

EUS-FNA increases the diagnostic yield of AIP in comparison with CT and MRI. Hypoechoic enlargement of the pancreas with hyperechoic spots and the absence of a discrete mass are typical features of AIP seen on EUS exam [7, 79]. The addition of an EUS-guided 19-gauge biopsy can be diagnostic for AIP type 1 in up to 94 % of patients, but only 42 % with AIP type 2 [80].

Chari et al. compared both imaging and laboratory findings of patients with AIP and pancreatic cancer. According to their published algorithm, only 30 % of patients with mainly AIP type 1 required either a steroid trial or a pancreatic specimen, which also included two pancreatic resections, for the diagnosis of AIP [81]. However, the nonoperative diagnosis of AIP type 2 lacks both sensitivity and specificity. According to HISORt criteria, the diagnosis of AIP type 2 cannot be made unless histology is available, although robust data on diagnostic accuracy are lacking [77]. Therefore, close follow-up is recommended when nonoperative workup is consistent for AIP type 2 and excludes pancreatic cancer [82].

Cystic Pancreatic Tumors

Cystic tumors of the pancreas encompass mainly three different tumor identities, including serous cystic neoplasm, mucinous cystic neoplasm, and intraductal papillary mucinous neoplasm (IPMN). These types are described in detail elsewhere in this book.

Rare Pancreatic Tumors

Pseudopapillary tumor is a rare benign or low-grade malignant neoplasm predominantly in young women located mostly in the pancreatic tail [83–86]. MRI was shown to be superior to CT to identify characteristic features such as a well-demarcated cystic or solid mass with fibrous capsule as well as possible peripheral calcification and hemorrhagic areas [87]. Accordingly, EUS reveals a well-defined, hypovascular, hypoechoic mass, with solid, cystic, or mixed solid and cystic pancreatic component [88].

PNETs are a heterogeneous group representing less than 10 % of all pancreatic neoplasms. They occur in equal frequency in men and women, most often between the sixth and seventh decades. Between 5–10 % have a cystic appearance, whereas the remaining tumors are solid [89]. Further, PNETs can be divided into nonfunctional and functional PNETs. Functional PNETs include insulinoma, glucagonoma, gastrinoma, and VIPoma tumors and are associated with a variety of clinical syndromes caused by respective hormones secreted by the tumor [90, 91]. Nonfunctional PNETs are not associated with a particular clinical syndrome. However, these neoplasms also secret tumor-specific peptides like Chromogranin A (CgA). In addition to imaging and FNA of the tumor mass, CgA is currently utilized as a biomarker providing both additional evidence for diagnosis as well as a marker for surveillance of PNETs [92–95].

Pancreatic Metastasis

The pancreas is rarely a site of metastasis. In this context, renal cell carcinoma is the most common metastasizing cancer followed by lung (both small cell and non-small cell cancer), melanoma, breast, colon, and other cancers (hepatocellular carcinoma, ovarian cancer, carcinoid, liposarcoma).

In the majority of cases, patients already have evidence of the primary cancer as well as metastasis to other organs. The exception is renal cell carcinoma, which can present up to a decade following the treatment of the primary tumor [96].

Metastatic disease is most commonly detected as a localized solitary mass. However, multifocal metastases as well as diffuse enlargement of the pancreas due to metastasis were previously reported [14, 19, 20]. EUS-FNA was shown to be diagnostic for renal cell cancer, lung cancer, and melanoma. Additionally, renal cell cancer can be distinguished from pancreatic adenocarcinoma by its hypervascularity [21, 97].

Other Diseases

An intrapancreatic accessory spleen is a congenital abnormality with an estimated prevalence of 1:500. Hereby, the pancreatic tail is the second most common site of an accessory spleen [98]. Contrast-enhanced cross-sectional imaging reveals a hypervascular mass which enhances similarly as the spleen [98, 99].

Further rare solid pancreatic masses include acinar cell carcinoma, benign fibrous tumor, giant cell osteoclastoma, adenosquamous carcinoma, lymphoma, and teratoma with substantial overlap with rare cystic tumors. Those include metastatic disease, teratoma, pancreatoblastoma, lymphangioma, and lymphoepithelial cyst [9, 14]. A specific diagnosis of those uncommon tumors is rarely made by sole imaging. Accordingly, a tissue diagnosis is required and usually obtained by EUS-FNA or by pancreatectomy, which is also the definitive therapy in most cases.

Diagnostic Algorithm for a Pancreatic Mass

Each patient with a new pancreatic mass requires a thorough anamnesis, which should at best predate the index abdominal imaging. Thus, a delay of diagnosis of unusual causes of a pancreatic mass (e.g., PNET or metastasis) can be avoided. Most patients will have an incidental pancreatic mass found during evaluation for nonspecific symptoms, whereas only a minority of patients will have painless jaundice, which is a hallmark for pancreatic cancer. Any unexplained acute pancreatitis after the age of 40 years as well as a worsening course of chronic pancreatitis should include pancreatic cancer in the differential diagnosis [27, 76].

Following the anamnesis, the attention is drawn to the imaging study. Given the limitation of transabdominal ultrasound as well as noncontrast CT, each patient should undergo a cross-sectional imaging study utilizing intravenous contrast [33]. Alternatively, EUS can be offered for patients with contrast allergy or contrast intolerance (e.g., due to renal failure).

Any new solid pancreatic lesion raises the concern for pancreatic malignancy, with pancreatic adenocarcinoma being the most common one. Depending on the contrast enhancement pattern as well as the evaluation of a possible local and distant spreading, pancreatic carcinoma can be distinguished from PNET and metastasis as well as from benign conditions most of the time [34–36]. According to local surgical preference and availability of neoadjuvant therapy, EUS can be offered to obtain a tissue diagnosis. Hereby, the presence of a dilated pancreatic duct shifts the likelihood from a benign condition to a malignant condition [61].

The workup of a pancreatic mass in patients with underlying chronic pancreatitis is challenging. Neither cross-sectional imaging nor EUS-FNA reaches a sufficient sensitivity and specificity to distinguish benign from malignant masses, which implicates the frequent need for pancreatic surgery [100].

Patients with no risk factors for chronic pancreatitis or pancreatic cancer who are diagnosed with a new pancreatic mass or a diffuse pancreatic duct stricture without typical features of a pancreatic adenocarcinoma require additional workup. This requires the measurement of serum IgG4 level as well as a focused review of cross-sectional imaging for rim enhancement and the so-called other-organ involvement to evaluate for AIP. Hereby, most cases of AIP type 1 can be diagnosed noninvasively [78, 81, 101, 102].

EUS-FNA adds additional diagnostic information for both AIP type 1 and type 2 although that approach has low yield for AIP type 2 [80]. A steroid trial for suspected AIP requires a repeat imaging test to document resolution of pancreatic mass or pancreatic duct stricture. The absence of improvement raises the concern for a malignant process necessitating a surgical resection in patients with resectable disease.

A solid pancreatic mass visualized on both cross-sectional imaging followed by a nondiagnostic EUS-FNA remains of high concern for pancreatic cancer [103]. Therefore, indeterminate imaging studies of a solid pancreatic mass in conjunction with a negative, indeterminate, and/or benign FNA require close follow-up. As EUS-FNA is limited by an NPV of approximately 80 %, a repeat FNA is indicated within 1–2 months, preferably at a high-volume tertiary center [51–53, 58, 60]. Concomitantly, evaluation for AIP needs to be performed as delineated above.

The absence of a visualized mass on EUS despite a documented pancreatic solid lesion on initial cross-sectional imaging requires further attention. When available, contrast-enhanced EUS and EUS elastography add valuable information to identify a target lesion for FNA [51, 73, 104, 105]. This applies particularly for patients with underlying chronic pancreatitis which is associated with false-negative EUS results [58, 72, 100]. The presence of chronic pancreatitis or dilation of the pancreatic duct, in the absence of a distinct pancreatic mass on EUS, needs to be followed by a repeat EUS exam within 2 months [58, 61, 72, 100]. Contrary, a pristine pancreas on EUS virtually excludes pancreatic cancer [56, 57].

Negative cross-sectional imaging studies in the context of a high clinical concern for pancreatic malignancy require a high-quality contrast CT if not already performed initially. Depending on local preference, CT is interchangeable with MRI [68]. Insulinoma is an exemption, as EUS was shown to be superior compared with contrast-enhanced cross-sectional imaging for its detection [106]. Following a negative or nondiagnostic high-quality CT study, EUS adds further information. A normal pancreatic EUS exam excludes pancreatic cancer as described above with a high NPV, and an alternative diagnosis needs to be considered [56, 57]. In selected cases with substantial concern for pancreatic cancer, EUS can be repeated within 1–2 months to reevaluate for pancreatic mass lesion given the small chance of an initially false-negative test [58].

Correct identification of a cystic lesion on cross-sectional imaging is particularly challenging. The majority of cystic lesions encompass serous cystic neoplasm, mucinous cystic neoplasm, and IPMN, which can be best distinguished by their characteristic epidemiologic profile in combination with typical features on contrast-enhanced cross-sectional imaging and cystic fluid evaluation (cytology, CEA, and amylase level). Management of cystic neoplasms depends on their type, size, main pancreatic duct involvement in case of IPMN, presence of concerning EUS features (mural nodules), interval tumor growth, and the presence of symptoms which eventually leads to the decision to perform surgery [107–111].

Atypical features of solid and cystic pancreatic masses on cross-sectional imaging, which can include atypical contrast enhancement pattern of the mass, require evaluation with EUS-FNA. In the setting of a broad differential diagnosis, including malignant tumors like PNET, metastatic disease, lymphoma, teratoma, pancreatoblastoma, solid pseudopapillary tumor, as well as benign findings such as accessory spleen, EUS-FNA is of particular interest to provide a nonoperative diagnosis [9, 14, 21, 97–99].

References

1. Goodman M, Willmann JK, Jeffrey RB. Incidentally discovered solid pancreatic masses: imaging and clinical observations. Abdom Imaging. 2012;37:91–7.
2. de Jong K, Nio CY, Hermans JJ, Dijkgraaf MG, Gouma DJ, van Eijck CH, van Heel E, Klass G, Fockens P, Bruno MJ. High prevalence of pancreatic cysts detected by screening magnetic resonance imaging examinations. Clin Gastroenterol Hepatol. 2010;8:806–11.

3. Lee KS, Sekhar A, Rofsky NM, Pedrosa I. Prevalence of incidental pancreatic cysts in the adult population on MR imaging. Am J Gastroenterol. 2010;105: 2079–84.
4. Rosch T, Lorenz R, Braig C, Feuerbach S, Siewert JR, Schusdziarra V, Classen M. Endoscopic ultrasound in pancreatic tumor diagnosis. Gastrointest Endosc. 1991;37:347–52.
5. Perumal S, Palaniappan R, Pillai SA, Velayutham V, Sathyanesan J. Predictors of malignancy in chronic calcific pancreatitis with head mass. World J Gastrointest Surg. 2013;5:97–103.
6. Yadav D, Notahara K, Smyrk TC, Clain JE, Pearson RK, Farnell MB, Chari ST. Idiopathic tumefactive chronic pancreatitis: clinical profile, histology, and natural history after resection. Clin Gastroenterol Hepatol. 2003;1:129–35.
7. Farrell JJ, Garber J, Sahani D, Brugge WR. EUS findings in patients with autoimmune pancreatitis. Gastrointest Endosc. 2004;60:927–36.
8. Hoki N, Mizuno N, Sawaki A, Tajika M, Takayama R, Shimizu Y, Bhatia V, Yamao K. Diagnosis of autoimmune pancreatitis using endoscopic ultrasonography. J Gastroenterol. 2009;44:154–9.
9. Dewhurst CE, Mortele KJ. Cystic tumors of the pancreas: imaging and management. Radiol Clin North Am. 2012;50:467–86.
10. Yoon WJ, Brugge WR. Pancreatic cystic neoplasms: diagnosis and management. Gastroenterol Clin North Am. 2012;41:103–18.
11. Butte JM, Brennan MF, Gonen M, Tang LH, D'Angelica MI, Fong Y, Dematteo RP, Jarnagin WR, Allen PJ. Solid pseudopapillary tumors of the pancreas. Clinical features, surgical outcomes, and long-term survival in 45 consecutive patients from a single center. J Gastrointest Surg. 2011;15: 350–7.
12. Buetow PC, Buck JL, Pantongrag-Brown L, Beck KG, Ros PR, Adair CF. Solid and papillary epithelial neoplasm of the pancreas: imaging-pathologic correlation on 56 cases. Radiology. 1996;199:707–11.
13. Yao X, Ji Y, Zeng M, Rao S, Yang B. Solid pseudopapillary tumor of the pancreas: cross-sectional imaging and pathologic correlation. Pancreas. 2010;39:486–91.
14. Megibow AJ. Unusual solid pancreatic tumors. Radiol Clin North Am. 2012;50:499–513.
15. Byrne MF, Jowell PS. Gastrointestinal imaging: endoscopic ultrasound. Gastroenterology. 2002;122:1631–48.
16. Anderson MA, Carpenter S, Thompson NW, Nostrant TT, Elta GH, Scheiman JM. Endoscopic ultrasound is highly accurate and directs management in patients with neuroendocrine tumors of the pancreas. Am J Gastroenterol. 2000;95:2271–7.
17. Tenner SM, Banks PA, Wiersema MJ, Van Dam J. Evaluation of pancreatic disease by endoscopic ultrasonography. Am J Gastroenterol. 1997;92:18–26.
18. Chatzipantelis P, Salla C, Konstantinou P, Karoumpalis I, Sakellariou S, Doumani I. Endoscopic ultrasound-guided fine-needle aspiration cytology of pancreatic neuroendocrine tumors: a study of 48 cases. Cancer. 2008;114:255–62.
19. Scatarige JC, Horton KM, Sheth S, Fishman EK. Pancreatic parenchymal metastases: observations on helical CT. Am J Roentgenol. 2001;176:695–9.
20. Merkle EM, Boaz T, Kolokythas O, Haaga JR, Lewin JS, Brambs HJ. Metastases to the pancreas. Br J Radiol. 1998;71:1208–14.
21. Waters L, Si Q, Caraway N, Mody D, Staerkel G, Sneige N. Secondary tumors of the pancreas diagnosed by endoscopic ultrasound-guided fine-needle aspiration: A 10-year experience. Diagn Cytopathol. 2014;42(9):738–43.
22. Klein KA, Stephens DH, Welch TJ. CT characteristics of metastatic disease of the pancreas. Radiographics. 1998;18:369–78.
23. Ferrozzi F, Bova D, Campodonico F, Chiara FD, Passari A, Bassi P. Pancreatic metastases: CT assessment. Eur Radiol. 1997;7:241–5.
24. Palmowski M, Hacke N, Satzl S, Klauss M, Wente MN, Neukamm M, Kleeff J, Hallscheidt P. Metastasis to the pancreas: characterization by morphology and contrast enhancement features on CT and MRI. Pancreatology. 2008;8:199–203.
25. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin. 2014;64:9–29.
26. http://seer.cancer.gov/statfacts/html/pancreas.html. SEER 18 2007–2011, Age-Adjusted, pancreas
27. Muniraj T, Jamidar PA, Aslanian HR. Pancreatic cancer: a comprehensive review and update. Dis Mon. 2013;59:368–402.
28. Ben Q, Xu M, Ning X, Liu J, Hong S, Huang W, Zhang H, Li Z. Diabetes mellitus and risk of pancreatic cancer: a meta-analysis of cohort studies. Eur J Cancer. 2011;47:1928–37.
29. Pannala R, Leirness JB, Bamlet WR, Basu A, Petersen GM, Chari ST. Prevalence and clinical profile of pancreatic cancer-associated diabetes mellitus. Gastroenterology. 2008;134:981–7.
30. Permert J, Ihse I, Jorfeldt L, von Schenck H, Arnqvist HJ, Larsson J. Pancreatic cancer is associated with impaired glucose metabolism. Eur J Surg. 1993;159:101–7.
31. Batabyal P, Vander Hoorn S, Christophi C, Nikfarjam M. Association of diabetes mellitus and pancreatic adenocarcinoma: a meta-analysis of 88 studies. Ann Surg Oncol. 2014;21(7):2453–62.
32. Duffy MJ, Sturgeon C, Lamerz R, Haglund C, Holubec VL, Klapdor R, Nicolini A, Topolcan O, Heinemann V. Tumor markers in pancreatic cancer: a European group on tumor markers (EGTM) status report. Ann Oncol. 2010;21:441–7.
33. Rickes S, Unkrodt K, Neye H, Ocran KW, Wermke W. Differentiation of pancreatic tumours by conventional ultrasound, unenhanced and echo-enhanced power Doppler sonography. Scand J Gastroenterol. 2002;37:1313–20.
34. Amin Z, Theis B, Russell RC, House C, Novelli M, Lees WR. Diagnosing pancreatic cancer: the role of

percutaneous biopsy and CT. Clin Radiol. 2006;61: 996–1002.
35. Ahn SS, Kim MJ, Choi JY, Hong HS, Chung YE, Lim JS. Indicative findings of pancreatic cancer in prediagnostic CT. Eur Radiol. 2009;19:2448–55.
36. Prokesch RW, Chow LC, Beaulieu CF, Bammer R, Jeffrey Jr RB. Isoattenuating pancreatic adenocarcinoma at multi-detector row CT: secondary signs. Radiology. 2002;224:764–8.
37. Ahualli J. The double duct sign. Radiology. 2007; 244:314–5.
38. Valls C, Andia E, Sanchez A, Fabregat J, Pozuelo O, Quintero JC, Serrano T, Garcia-Borobia F, Jorba R. Dual-phase helical CT of pancreatic adenocarcinoma: assessment of resectability before surgery. Am J Roentgenol. 2002;178:821–6.
39. Bronstein YL, Loyer EM, Kaur H, Choi H, David C, DuBrow RA, Broemeling LD, Cleary KR, Charnsangavej C. Detection of small pancreatic tumors with multiphasic helical CT. Am J Roentgenol. 2004;182:619–23.
40. Karmazanovsky G, Fedorov V, Kubyshkin V, Kotchatkov A. Pancreatic head cancer: accuracy of CT in determination of resectability. Abdom Imaging. 2005;30:488–500.
41. Palazzo L, Roseau G, Gayet B, Vilgrain V, Belghiti J, Fekete F, Paolaggi JA. Endoscopic ultrasonography in the diagnosis and staging of pancreatic adenocarcinoma. Results of a prospective study with comparison to ultrasonography and CT scan. Endoscopy. 1993;25:143–50.
42. Muller MF, Meyenberger C, Bertschinger P, Schaer R, Marincek B. Pancreatic tumors: evaluation with endoscopic US, CT, and MR imaging. Radiology. 1994;190:745–51.
43. Melzer E, Avidan B, Heyman Z, Coret A, Bar-Meir S. Preoperative assessment of blood vessel involvement in patients with pancreatic cancer. Isr J Med Sci. 1996;32:1086–8.
44. Marty O, Aubertin JM, Bouillot JL, Hernigou A, Bloch F, Petite JP. Prospective comparison of ultrasound endoscopy and computed tomography in the assessment of locoregional invasiveness of malignant ampullar and pancreatic tumors verified surgically. Gastroenterol Clin Biol. 1995;19:197–203.
45. Dufour B, Zins M, Vilgrain V, Levy P, Bernades P, Menu Y. Comparison between spiral x-ray computed tomography and endosonography in the diagnosis and staging of adenocarcinoma of the pancreas. Clinical preliminary study. Gastroenterol Clin Biol. 1997;21:124–30.
46. Legmann P, Vignaux O, Dousset B, Baraza AJ, Palazzo L, Dumontier I, Coste J, Louvel A, Roseau G, Couturier D, Bonnin A. Pancreatic tumors: comparison of dual-phase helical CT and endoscopic sonography. Am J Roentgenol. 1998;170:1315–22.
47. Akahoshi K, Chijiiwa Y, Nakano I, Nawata H, Ogawa Y, Tanaka M, Nagai E, Tsuneyoshi M. Diagnosis and staging of pancreatic cancer by endoscopic ultrasound. Br J Radiol. 1998;71:492–6.
48. Gress FG, Hawes RH, Savides TJ, Ikenberry SO, Cummings O, Kopecky K, Sherman S, Wiersema M, Lehman GA. Role of EUS in the preoperative staging of pancreatic cancer: a large single-center experience. Gastrointest Endosc. 1999;50:786–91.
49. Ainsworth AP, Rafaelsen SR, Wamberg PA, Durup J, Pless TK, Mortensen MB. Is there a difference in diagnostic accuracy and clinical impact between endoscopic ultrasonography and magnetic resonance cholangiopancreatography? Endoscopy. 2003; 35:1029–32.
50. Harrison JL, Millikan KW, Prinz RA, Zaidi S. Endoscopic ultrasound for diagnosis and staging of pancreatic tumors. Am Surg. 1999;65:659–64; discussion 664–5.
51. Giovannini M, Thomas B, Erwan B, Christian P, Fabrice C, Benjamin E, Genevieve M, Paolo A, Pierre D, Robert Y, Walter S, Hanz S, Carl S, Christoph D, Pierre E, Jean-Luc VL, Jacques D, Peter V, Andrian S. Endoscopic ultrasound elastography for evaluation of lymph nodes and pancreatic masses: a multicenter study. World J Gastroenterol. 2009;15:1587–93.
52. Eloubeidi MA, Varadarajulu S, Desai S, Shirley R, Heslin MJ, Mehra M, Arnoletti JP, Eltoum I, Wilcox CM, Vickers SM. A prospective evaluation of an algorithm incorporating routine preoperative endoscopic ultrasound-guided fine needle aspiration in suspected pancreatic cancer. J Gastrointest Surg. 2007;11:813–9.
53. Eloubeidi MA, Jhala D, Chhieng DC, Chen VK, Eltoum I, Vickers S, Mel Wilcox C, Jhala N. Yield of endoscopic ultrasound-guided fine-needle aspiration biopsy in patients with suspected pancreatic carcinoma. Cancer. 2003;99:285–92.
54. Buscail L, Faure P, Bournet B, Selves J, Escourrou J. Interventional endoscopic ultrasound in pancreatic diseases. Pancreatology. 2006;6:7–16.
55. Hewitt MJ, McPhail MJ, Possamai L, Dhar A, Vlavianos P, Monahan KJ. EUS-guided FNA for diagnosis of solid pancreatic neoplasms: a meta-analysis. Gastrointest Endosc. 2012;75:319–31.
56. Klapman JB, Chang KJ, Lee JG, Nguyen P. Negative predictive value of endoscopic ultrasound in a large series of patients with a clinical suspicion of pancreatic cancer. Am J Gastroenterol. 2005;100:2658–61.
57. Catanzaro A, Richardson S, Veloso H, Isenberg GA, Wong RC, Sivak Jr MV, Chak A. Long-term follow-up of patients with clinically indeterminate suspicion of pancreatic cancer and normal EUS. Gastrointest Endosc. 2003;58:836–40.
58. Bhutani MS, Gress FG, Giovannini M, Erickson RA, Catalano MF, Chak A, Deprez PH, Faigel DO, Nguyen CC. The No Endosonographic Detection of Tumor (NEST) Study: a case series of pancreatic cancers missed on endoscopic ultrasonography. Endoscopy. 2004;36:385–9.
59. Eloubeidi MA, Varadarajulu S, Desai S, Wilcox CM. Value of repeat endoscopic ultrasound-guided fine needle aspiration for suspected pancreatic cancer. J Gastroenterol Hepatol. 2008;23:567–70.

60. Suzuki R, Lee JH, Krishna SG, Ramireddy S, Qiao W, Weston B, Ross WA, Bhutani MS. Repeat endoscopic ultrasound-guided fine needle aspiration for solid pancreatic lesions at a tertiary referral center will alter the initial inconclusive result. J Gastrointestin Liver Dis. 2013;22:183–7.
61. Tummala Md P, Rao Md S, Agarwal MB. Differential diagnosis of focal non-cystic pancreatic lesions with and without proximal dilation of pancreatic duct noted on CT scan. Clin Transl Gastroenterol. 2013;4, e42.
62. Singh S, Reddymasu S, Waheed S, Vail M, He J, Talapaneni J, Olyaee M. Endoscopic ultrasonography findings in patients with non-specific changes of the pancreas on computed tomography: a single-center experience. Dig Dis Sci. 2008;53:2799–804.
63. Agarwal B, Krishna NB, Labundy JL, Safdar R, Akduman EI. EUS and/or EUS-guided FNA in patients with CT and/or magnetic resonance imaging findings of enlarged pancreatic head or dilated pancreatic duct with or without a dilated common bile duct. Gastrointest Endosc. 2008;68:237–42; quiz 334, 335.
64. DeWitt J, Devereaux B, Chriswell M, McGreevy K, Howard T, Imperiale TF, Ciaccia D, Lane KA, Maglinte D, Kopecky K, LeBlanc J, McHenry L, Madura J, Aisen A, Cramer H, Cummings O, Sherman S. Comparison of endoscopic ultrasonography and multidetector computed tomography for detecting and staging pancreatic cancer. Ann Intern Med. 2004;141:753–63.
65. Agarwal B, Abu-Hamda E, Molke KL, Correa AM, Ho L. Endoscopic ultrasound-guided fine needle aspiration and multidetector spiral CT in the diagnosis of pancreatic cancer. Am J Gastroenterol. 2004;99:844–50.
66. Harewood GC, Wiersema MJ. Endosonography-guided fine needle aspiration biopsy in the evaluation of pancreatic masses. Am J Gastroenterol. 2002;97:1386–91.
67. Dewitt J, Devereaux BM, Lehman GA, Sherman S, Imperiale TF. Comparison of endoscopic ultrasound and computed tomography for the preoperative evaluation of pancreatic cancer: a systematic review. Clin Gastroenterol Hepatol. 2006;4:717–25. quiz 664.
68. Tummala P, Junaidi O, Agarwal B. Imaging of pancreatic cancer: an overview. J Gastrointest Oncol. 2011;2:168–74.
69. Raimondi S, Lowenfels AB, Morselli-Labate AM, Maisonneuve P, Pezzilli R. Pancreatic cancer in chronic pancreatitis; aetiology, incidence, and early detection. Best practice & research. Clin Gastroenterol. 2010;24:349–58.
70. Yamada Y, Mori H, Matsumoto S, Kiyosue H, Hori Y, Hongo N. Pancreatic adenocarcinoma versus chronic pancreatitis: differentiation with triple-phase helical CT. Abdom Imaging. 2010;35:163–71.
71. Sandrasegaran K, Nutakki K, Tahir B, Dhanabal A, Tann M, Cote GA. Use of diffusion-weighted MRI to differentiate chronic pancreatitis from pancreatic cancer. Am J Roentgenol. 2013;201:1002–8.
72. Norton ID, Zheng Y, Wiersema MS, Greenleaf J, Clain JE, Dimagno EP. Neural network analysis of EUS images to differentiate between pancreatic malignancy and pancreatitis. Gastrointest Endosc. 2001;54:625–9.
73. Li X, Xu W, Shi J, Lin Y, Zeng X. Endoscopic ultrasound elastography for differentiating between pancreatic adenocarcinoma and inflammatory masses: a meta-analysis. World J Gastroenterol. 2013;19:6284–91.
74. Raimondo MY, Yab TC, Mahoney DW, Taylor WR, Anderson KS, Ahlquist DA. Methylated DNA markers in pancreatic juice discriminate pancreatic cancer from chronic pancreatitis and normal controls. Gastroenterology. 2013;144:S-90.
75. Latham J, Sanjay P, Watt DG, Walsh SV, Tait IS. Groove pancreatitis: a case series and review of the literature. Scott Med J. 2013;58:e28–31.
76. Munigala S, Kanwal F, Xian H, Scherrer JF, Agarwal B. Increased risk of pancreatic adenocarcinoma after acute pancreatitis. Clin Gastroenterol Hepatol. 2014;12(7):1143–1150.e1.
77. Shimosegawa T, Chari ST, Frulloni L, Kamisawa T, Kawa S, Mino-Kenudson M, Kim MH, Kloppel G, Lerch MM, Lohr M, Notohara K, Okazaki K, Schneider A, Zhang L. International consensus diagnostic criteria for autoimmune pancreatitis: guidelines of the International Association of Pancreatology. Pancreas. 2011;40:352–8.
78. Sah RP, Chari ST. Autoimmune pancreatitis: an update on classification, diagnosis, natural history and management. Curr Gastroenterol Rep. 2012;14:95–105.
79. Mizuno N, Bhatia V, Hosoda W, Sawaki A, Hoki N, Hara K, Takagi T, Ko SB, Yatabe Y, Goto H, Yamao K. Histological diagnosis of autoimmune pancreatitis using EUS-guided Trucut biopsy: a comparison study with EUS-FNA. J Gastroenterol. 2009;44:742–50.
80. Zhang L, Notohara K, Levy MJ, Chari ST, Smyrk TC. IgG4-positive plasma cell infiltration in the diagnosis of autoimmune pancreatitis. Mod Pathol. 2007;20:23–8.
81. Chari ST, Takahashi N, Levy MJ, Smyrk TC, Clain JE, Pearson RK, Petersen BT, Topazian MA, Vege SS. A diagnostic strategy to distinguish autoimmune pancreatitis from pancreatic cancer. Clin Gastroenterol Hepatol. 2009;7:1097–103.
82. Kamisawa T, Chari ST, Lerch MM, Kim MH, Gress TM, Shimosegawa T. Recent advances in autoimmune pancreatitis: type 1 and type 2. Gut. 2013;62:1373–80.
83. Yoon WJ, Lee JK, Lee KH, Ryu JK, Kim YT, Yoon YB. Cystic neoplasms of the exocrine pancreas: an

update of a nationwide survey in Korea. Pancreas. 2008;37:254–8.
84. Tipton SG, Smyrk TC, Sarr MG, Thompson GB. Malignant potential of solid pseudopapillary neoplasm of the pancreas. Br J Surg. 2006;93: 733–7.
85. Estrella JS, Li L, Rashid A, Wang H, Katz MH, Fleming JB, Abbruzzese JL. Solid pseudopapillary neoplasm of the pancreas: clinicopathologic and survival analyses of 64 cases from a single institution. Am J Surg Pathol. 2014;38:147–57.
86. Kloppel G, Hruban RH, Klimstra DS, Maitra A, Morohoshi T, Notohara K, Shimizu M, Terris B Solid-pseudopapillary neoplasm of the pancreas. In: Bosman FT, Carneiro F, Hruban RH, Theise ND, editors. WHO Classification of Tumors of the Digestive System. 4th ed. WHO; 2010. p. 327–330.
87. Cantisani V, Mortele KJ, Levy A, Glickman JN, Ricci P, Passariello R, Ros PR, Silverman SG. MR imaging features of solid pseudopapillary tumor of the pancreas in adult and pediatric patients. Am J Roentgenol. 2003;181:395–401.
88. Jani N, Dewitt J, Eloubeidi M, Varadarajulu S, Appalaneni V, Hoffman B, Brugge W, Lee K, Khalid A, McGrath K. Endoscopic ultrasound-guided fine-needle aspiration for diagnosis of solid pseudopapillary tumors of the pancreas: a multicenter experience. Endoscopy. 2008;40:200–3.
89. Lewis RB, Lattin Jr GE, Paal E. Pancreatic endocrine tumors: radiologic-clinicopathologic correlation. Radiographics. 2010;30:1445–64.
90. Metz DC, Jensen RT. Gastrointestinal neuroendocrine tumors: pancreatic endocrine tumors. Gastroenterology. 2008;135:1469–92.
91. Kulke MH, Anthony LB, Bushnell DL, de Herder WW, Goldsmith SJ, Klimstra DS, Marx SJ, Pasieka JL, Pommier RF, Yao JC, Jensen RT. NANETS treatment guidelines: well-differentiated neuroendocrine tumors of the stomach and pancreas. Pancreas. 2010;39:735–52.
92. Seregni E, Ferrari L, Bajetta E, Martinetti A, Bombardieri E. Clinical significance of blood chromogranin A measurement in neuroendocrine tumours. Ann Oncol. 2001;12 Suppl 2:S69–72.
93. Dickson PV, Behrman SW. Management of pancreatic neuroendocrine tumors. Surg Clin North Am. 2013;93:675–91.
94. Campana D, Nori F, Piscitelli L, Morselli-Labate AM, Pezzilli R, Corinaldesi R, Tomassetti P. Chromogranin A: is it a useful marker of neuroendocrine tumors? J Clin Oncol. 2007;25:1967–73.
95. Stivanello M, Berruti A, Torta M, Termine A, Tampellini M, Gorzegno G, Angeli A, Dogliotti L. Circulating chromogranin A in the assessment of patients with neuroendocrine tumours. A single institution experience. Ann Oncol. 2001;12 Suppl 2:S73–7.
96. Sohn TA, Yeo CJ, Cameron JL, Nakeeb A, Lillemoe KD. Renal cell carcinoma metastatic to the pancreas: results of surgical management. J Gastrointest Surg. 2001;5:346–51.
97. Ascenti G, Visalli C, Genitori A, Certo A, Pitrone A, Mazziotti S. Multiple hypervascular pancreatic metastases from renal cell carcinoma: dynamic MR and spiral CT in three cases. Clin Imaging. 2004;28:349–52.
98. Mortele KJ, Mortele B, Silverman SG. CT features of the accessory spleen. Am J Roentgenol. 2004;183:1653–7.
99. Spencer LA, Spizarny DL, Williams TR. Imaging features of intrapancreatic accessory spleen. Br J Radiol. 2010;83:668–73.
100. Varadarajulu S, Tamhane A, Eloubeidi MA. Yield of EUS-guided FNA of pancreatic masses in the presence or the absence of chronic pancreatitis. Gastrointest Endosc. 2005;62:728–36; quiz 751, 753.
101. Chari ST, Kloeppel G, Zhang L, Notohara K, Lerch MM, Shimosegawa T. Histopathologic and clinical subtypes of autoimmune pancreatitis: the Honolulu consensus document. Pancreas. 2010;39: 549–54.
102. Kamisawa T, Chari ST, Giday SA, Kim MH, Chung JB, Lee KT, Werner J, Bergmann F, Lerch MM, Mayerle J, Pickartz T, Lohr M, Schneider A, Frulloni L, Webster GJ, Reddy DN, Liao WC, Wang HP, Okazaki K, Shimosegawa T, Kloeppel G, Go VL. Clinical profile of autoimmune pancreatitis and its histological subtypes: an international multicenter survey. Pancreas. 2011;40:809–14.
103. Maker AV, Lee LS, Raut CP, Clancy TE, Swanson RS. Cytology from pancreatic cysts has marginal utility in surgical decision-making. Ann Surg Oncol. 2008;15:3187–92.
104. Kitano M, Sakamoto H, Kudo M. Contrast-enhanced endoscopic ultrasound. Dig Endosc. 2014;26 Suppl 1:79–85.
105. Park JS, Kim HK, Bang BW, Kim SG, Jeong S, Lee DH. Effectiveness of contrast-enhanced harmonic endoscopic ultrasound for the evaluation of solid pancreatic masses. World J Gastroenterol. 2014;20:518–24.
106. Cirillo F, Falconi M, Bettini R. Clinical manifestations and therapeutic management of hyperfunctioning endocrine tumors. In: Procacci C, Megibow AJ, editors. Imaging of the pancreas: cystic and rare tumors. Berlin; New York: Springer; 2003. p. 141–52.
107. Zamboni GFN, Hruban RH, et al. Mucinous cystic neoplasms of the pancreas. In: Bosman FT, Carneiro F, Hruban RH, et al., editors. World Health Organization classification of tumours of the digestive system. 4th ed. Lyon (France): IARC; 2010. p. 300–3.
108. Tanaka M, Fernandez-del Castillo C, Adsay V, Chari S, Falconi M, Jang JY, Kimura W, Levy P, Pitman MB, Schmidt CM, Shimizu M, Wolfgang CL, Yamaguchi K, Yamao K. International consensus guidelines 2012

for the management of IPMN and MCN of the pancreas. Pancreatology. 2012;12:183–97.
109. Wu BU, Sampath K, Berberian CE, Kwok KK, Lim BS, Kao KT, Giap AQ, Kosco AE, Akmal YM, Difronzo AL, Yu W, Ngor EW. Prediction of malignancy in cystic neoplasms of the pancreas: a population-based cohort study. Am J Gastroenterol. 2014;109:121–9. quiz 130.
110. Khalid A, Brugge W. ACG practice guidelines for the diagnosis and management of neoplastic pancreatic cysts. Am J Gastroenterol. 2007;102:2339–49.
111. Grobmyer SR, Cance WG, Copeland EM, Vogel SB, Hochwald SN. Is there an indication for initial conservative management of pancreatic cystic lesions? J Surg Oncol. 2009;100:372–4.

Part III

Treatment: Solid Lesions and Cystic Lesions

Surgery for Solid Pancreatic Neoplasms

17

Moshim Kukar and Steven N. Hochwald

Curative Surgery

Adenocarcinoma of the pancreas remains the predominant tumor type, while the neuroendocrine tumors comprise approximately 10 % of pancreatic tumors. Acinar cell carcinoma accounts for approximately 2 % of solid pancreatic tumors. From a surgical perspective, the first objective in the management of suspected or confirmed pancreatic cancer is to determine the potential for resection. Unfortunately, the vast majority of patients who present with pancreatic adenocarcinoma have unresectable disease due to either metastasis or local vessel involvement. Acinar cell carcinoma and neuroendocrine tumors of the pancreas are more commonly amenable to surgical removal than adenocarcinoma of the pancreas. Routine exploratory laparotomy for the purpose of operatively determining resectability or for achieving palliation has been diminished by modern 3D radiographic imaging, along with effective and sustainable nonoperative methods of palliation. Based on the preoperative workup, the tumor is classified as resectable, borderline resectable, or unresectable. Although there is some ambiguity about these definitions, an expert panel published the consensus statement in 2009 as detailed below [1]:

Resectable tumors

1. No distant metastasis
2. No radiographic evidence of superior mesenteric vein (SMV) or portal vein (PV) distortion
3. Clear fat planes around the celiac axis, hepatic artery, and superior mesenteric artery (SMA)

Borderline resectable

1. No distant metastasis
2. Venous involvement of the SMV or PV with distortion or narrowing of the vein or occlusion of the vein with suitable vessel proximal and distal, allowing for safe resection and replacement
3. Gastroduodenal artery (GDA) encasement up to the hepatic artery with either short segment encasement or direct abutment of the hepatic artery without extension to the celiac axis
4. Tumor abutment of the SMA not to exceed greater than 180° of the circumference of the vessel wall

Unresectable

1. Distant metastasis
2. Greater than 180° SMA encasement, any celiac abutment
3. Unreconstructible SMV/PV occlusion
4. Aortic invasion
5. Metastasis to lymph nodes beyond the field of resection should be considered unresectable

M. Kukar, M.D. • S.N. Hochwald, M.D., F.A.C.S. (✉)
Department of Surgical Oncology, Roswell Park Cancer Institute, Elm and Carlton streets, Buffalo, NY 14263, USA
e-mail: steven.hochwald@roswellpark.org

M.S. Wagh, P.V. Draganov (eds.), *Pancreatic Masses*, DOI 10.1007/978-3-319-19677-0_17

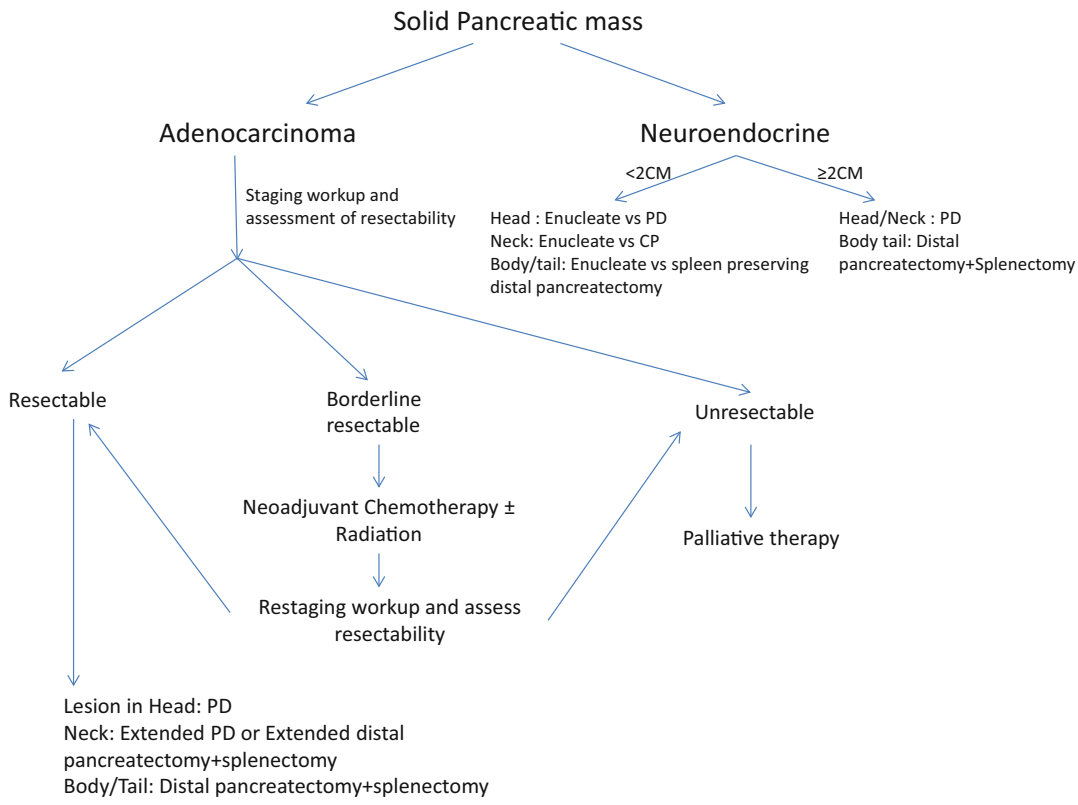

Fig. 17.1 Decision algorithm for managing solid pancreatic neoplasms. *PD,* pancreaticoduodenectomy; *CP* central pancreatectomy

Once resectability is determined, the next step is a thorough assessment of the patient's overall health status, including further investigations as needed, to determine surgical candidacy. In terms of the resection for solid masses, the most common utilized techniques for surgical resection and their indications are summarized below (Fig. 17.1):

1. Pancreaticoduodenectomy: lesions in the uncinate process and head of the pancreas. An extended pancreaticoduodenectomy to remove the head and the neck of the pancreas can be performed for lesions in the neck of the pancreas.
2. Distal pancreatectomy with or without splenectomy: lesions in the body and tail of the pancreas. An extended distal subtotal pancreatectomy to remove the pancreatic tail, body, and neck can be performed for lesions in the neck of pancreas.
3. Central pancreatectomy: lesions in the neck of the pancreas.
4. Total pancreatectomy: for multifocal lesions, positive margins on intraoperative frozen section or for large tumors of the pancreatic neck.
5. Enucleation: small neuroendocrine tumor on the surface of the pancreas.

Role of Staging Laparoscopy

Studies have consistently shown that up to one third of patients with pancreatic adenocarcinoma thought to be resectable by state-of-the-art imaging will be found to be unresectable based upon laparoscopic findings [2–5]; however, some suggest a selective approach to staging laparoscopy to maximize yield by limiting the procedure to those with the highest likelihood of occult metastatic disease [6]. Mayo et al. [5] utilized the

Oregon state cancer registry and reviewed 298 patients from 1996 to 2003 and concluded that in the current era of high-quality imaging, selective application of laparoscopy with a dual-phase computed tomography (CT) scan is a sound clinical approach to evaluate pancreatic cancer patients for potential resectability. Based on the expert consensus statement [1], the following are the indications for staging laparoscopy:

1. For apparent resectable pancreatic cancer, staging laparoscopy should be used selectively on the basis of clinical predictors that optimize yield. These predictors include
   (a) Pancreatic head tumors >3 cm.
   (b) Tumors of the pancreas body and tail.
   (c) Equivocal findings on CT scan.
   (d) High CA 19-9 levels (>100 U/mL).
2. For locally advanced unresectable pancreatic cancer without radiographic evidence of distant metastasis, staging laparoscopy may be used to rule out subclinical metastatic disease to optimize treatment selection.

Surgical Volume and Outcome

Numerous studies suggest that there is an inverse relation between hospital volume of surgical procedures and surgical mortality, and this has been well studied for pancreatectomy [7–9]. Lieberman et al. [10] utilized the statewide planning and research cooperative system database to study the outcome differences in patients between high- and low-volume hospitals and concluded that perioperative mortality rate was significantly higher in low-volume hospitals.

Similarly, Rosemurgy et al. [11, 12] utilized the state of Florida agency for health care administration database and concluded that for the period of 2003–2005, the frequencies with which pancreaticoduodenectomies were conducted inversely correlated with average lengths of stay, hospital charges, and in-hospital mortality.

Birkmeyer et al. have extensively published on this topic and have studied multiple procedures including pancreatic resection using national Medicare claims data and demonstrated that both hospital volume and surgeon volume are inversely proportional to perioperative mortality. In addition, they showed that the mortality decreased as volume increased for all 14 types of procedures, but the relative importance of volume varied markedly according to the type of procedure. Absolute differences in adjusted mortality rates between very-low-volume hospitals and very-high-volume hospitals were among the highest for pancreatic resection (12 %) [13–15].

Technical Details and Complications

A. Pancreaticoduodenectomy:
   The goals of resection are
   1. Achieve an R0 resection since a margin-positive resection is associated with poor long-term survival [16, 17].
   2. Adequate nodal dissection: Randomized trials [18–20] and meta-analysis [21, 22] comparing standard with extended lymphadenectomy for pancreaticoduodenectomy for pancreatic cancer showed that standard lymphadenectomy has an equivalent survival with less morbidity compared to extended lymphadenectomy.

   Surgical technique
   Preoperative: Patient is instructed to stay on a clear liquid diet a day prior. Patient receives routine DVT prophylaxis and preoperative antibiotics. Central venous monitoring and arterial line is placed in selected cases.

   Operative: A midline or upper abdominal transverse incision is utilized after a staging laparoscopy, if needed, as discussed above. The abdomen is thoroughly explored for any evidence of metastatic disease and any suspicious lesions biopsied and sent for frozen section. For ease of discussion, the procedure can be divided into a resection phase and a reconstruction phase.

Resection phase:

The procedure can be essentially divided into six key steps:

1. Entry into lesser sac and mobilization: The lesser sac is entered by dividing the gastrocolic ligament and the right colon is mobilized, completely exposing the duodenum.
2. Kocher's maneuver: An extensive Kocher maneuver is performed exposing the inferior vena cava and take-off of the left renal vein. Once the pancreatic head is mobilized, the tumor is palpated, and its relationship to the SMA and SMV are appreciated.
3. Creation of retropancreatic tunnel: With the use of some blunt and sharp dissection, a tunnel is created behind the neck of the pancreas overlying the SMV.
4. Cholecystectomy and dissection in hepatoduodenal ligament: A cholecystectomy is performed and the cystic duct traced to its insertion into the common bile duct (CBD). The CBD is isolated and transected. The GDA is identified, ligated, and divided. If pyloric preservation is not being performed, the stomach is divided, removing the pylorus. For pyloric preservation, the duodenum is divided and the pylorus is preserved.
5. Dissection at the ligament of Treitz and division of duodenal mesentery: The ligament of Treitz is exposed and lysed at the base of the transverse mesocolon. The first portion of the jejunum is transected, the duodenal mesentery is divided, and the duodenum is passed posterior to the superior mesenteric vessels, toward the right side of the operative field.
6. Division of the pancreas and dissection of the uncinate process: The pancreatic neck is divided and the uncinate process and pancreatic head are carefully dissected off the SMA/SMV. The specimen consisting of the gallbladder, portion of bile duct, duodenum, pancreatic head and uncinate process, and portion of stomach are sent to pathology as a single intact specimen.

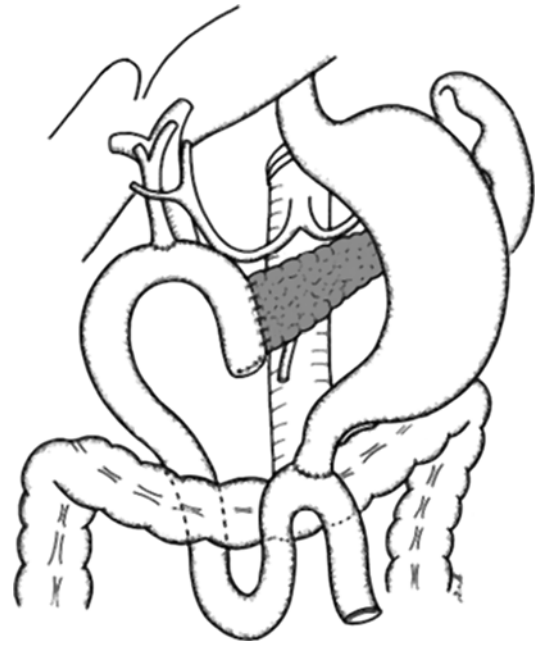

Fig. 17.2 Completed reconstruction following a pylorus preserving pancreaticoduodenectomy (Reprinted with permission from Blumgart's Surgery of Liver, biliary tract and pancreas, Vol. 1, Resectional Techniques, J. Werner and M.W. Buchler, Chapter 62A, P. 957, copyright Elsevier)

Reconstruction

A defect is made in the transverse mesocolon to the right of the middle colic vessels. The proximal jejunum is delivered through this defect. The pancreatic remnant is mobilized for a distance of 2–3 cm off the splenic vein to facilitate the creation of the pancreaticojejunostomy (PJ). A two-layered duct-to-mucosa anastomosis is constructed utilizing a modified Blumgart technique [23] (Fig. 17.2). Next, a single-layer end-to-side hepaticojejunostomy is constructed. Finally, the gastrojejunal/duodenojejunal anastomosis is performed in an antecolic fashion in *two* layers. Figure 17.3 depicts the completed reconstruction following a pylorus-preserving pancreaticoduodenectomy (PPPD).

Complications:

1. Postoperative pancreatic fistula (POPF): Experienced pancreatic surgeons are

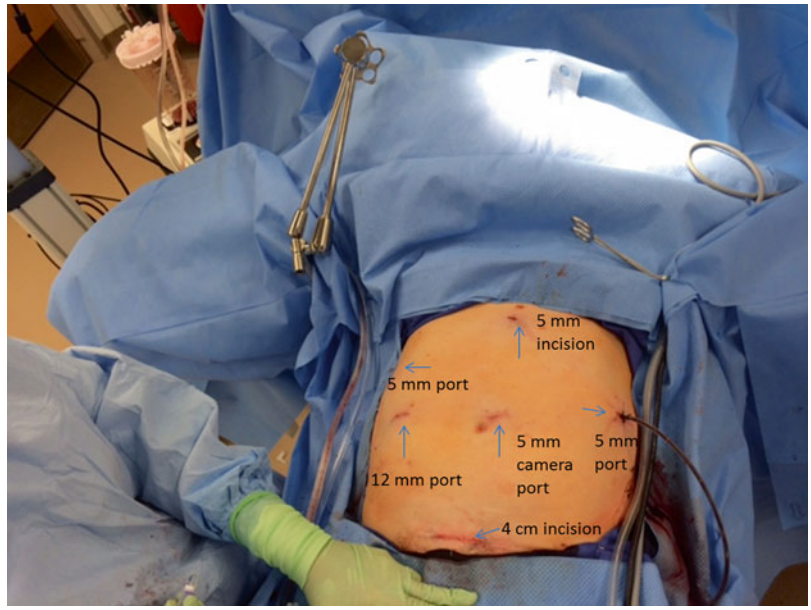

Fig. 17.3 Completed laparoscopic distal pancreatectomy and splencectomy, specimen extracted through a Pfannensteil incision

Table 17.1 Grades of post operative pancreatic fistula as per the ISGPS classification

Grade	A	B	C
Clinical conditions	Well	Often well	Ill-appearing/bad
Specific treatment[a]	No	Yes/no	Yes
US/CT (if obtained)	Negative	Negative/positive	Positive
Persistent drainage (after 3 weeks)[b]	No	Usually yes	Yes
Reoperation	No	No	Yes
Death related to POPF	No	No	Possibly yes
Signs of infections	No	Yes	Yes
Sepsis	No	No	Yes
Readmission	No	Yes/no	Yes/no

Source: Reproduced with permission from Elsevier [23]
US, ultrasonography; *CT,* computed tomographic scan; *POPR,* postoperative pancreatic fistula
[a]Partial (peripheral) or total parenteral nutrition, antibiotics, enteral nutrition, somatostatin analog and/or minimally invasive drainage
[b]With or without a drain in situ

utilizing surgically placed drains with less frequency and for shorter postoperative durations. There has been a trend for early drain removal as they may promote pancreatic fistulas [24]. A pancreatic fistula is diagnosed when the amylase content of any measurable volume of fluid on or after postoperative day 3 is greater than three times the upper limit of the normal serum amylase content, based on standards from the International Study Group on Pancreatic Fistulas (ISGPF) [24, 25]. Three different grades of POPFs (grades A, B, C) are defined according to the clinical impact on the patient's hospital course summarized in Table 17.1. Clinically significant POPFs occur in approximately 5–10 % of patients, although in some series the incidence is as high as 22 % [26, 27]. Particular risk factors for breakdown of the pancreatic anastomosis are a soft parenchymal texture of the pancreatic remnant and a small duct size.

The key to the successful management of an established leak is early recognition. Many grade A leaks can be managed by drainage catheters alone. For grade B and C leaks, management algorithms will be dictated by the patient's condition. The general consensus is for conservative management in the absence of peritonitis, sepsis, hemorrhage, or organ failure [28–30]. This would consist of effective control of the leak through some form of external drainage, intravenous antibiotics, adequate nutritional support, and close monitoring [31]. Abdominal CT scans are mandatory to exclude intraabdominal fluid collections or abscess.

The value of octreotide in the treatment of an established pancreatic fistula is not clear, with studies showing conflicting results [24, 32–34]. The majority of cases (70–90 %) with a low-output fistula can be successfully managed in this manner. Rarely, operative intervention in the form of washout and drainage, pancreatic debridement, and completion pancreatectomy may be required.

Prophylactic somatostatin analogs—In theory, somatostatin or its analogs, which reduce pancreatic, gastric, and enteric secretions, should be helpful for reducing POPFs, but studies evaluating this issue are conflicting [35–41]. No significant differences in mortality have been identified in several systematic reviews, whether or not somatostatin is utilized [35, 37, 42]. However, recently Allen et al. [43] published the results of their single-center, randomized, double-blind trial of perioperative subcutaneous pasireotide in patients undergoing either pancreaticoduodenectomy or distal pancreatectomy. Three hundred patients were randomized to receive 900 μg of subcutaneous pasireotide (152 patients) or placebo (148 patients) twice daily beginning preoperatively on the morning of the operation and continuing for 7 days (14 doses). They demonstrated that the rate of grade 3 or higher POPF, leak, or abscess was significantly lower among patients who received pasireotide than among patients who received placebo (9 % vs. 21 %; relative risk, 0.44; 95 % confidence interval [CI], 0.24–0.78; $P = 0.006$).

2. Intraabdominal abscess: The incidence of intraabdominal abscess following pancreatic resection ranges from 1 to 12 % [30] and is frequently secondary to an anastomotic leak at the pancreaticoenterostomy, less commonly due to a problem at the hepaticojejunostomy, gastrojejunostomy, or duodenojejunostomy. These often manifest as right subhepatic or left subdiaphragmatic collections [29, 44]. Whenever an intraabdominal collection is suspected, a high-quality contrast-enhanced CT should be performed. The preferred method of drainage is by a percutaneous radiologically guided technique. For as long as the underlying cause (fistula, leakage) is controlled, such measures are usually adequate. In the event that less invasive measures fail, surgical exploration and drainage may be necessary. However, this should be a rare event.
3. Hemorrhage: Postoperative bleeding occurs in 3–13 % of patients following pancreatic surgery as reported by some recent series [28, 41, 45]. The International Study Group of Pancreatic Surgery (ISGPS) developed a consensus definition on postpancreatectomy hemorrhage (PPH) and utilized three parameters to define it: onset, location, and severity. The onset is either early (≤24 h after the end of the index operation) or late (>24 h). The location is either intraluminal or extraluminal. The severity of bleeding may be either mild or severe. Three different grades of PPHs (grades A, B, and C) are defined according to the time of onset, site of bleeding, severity, and clinical impact, which are detailed in Tables 17.2 and 17.3 [46].

Table 17.2 ISGPS proposed definition of post pancreatectomy hemorrhage

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, nasograstic 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 relaparotomy)

Source: Reproduced with permission from Elsevier [45]

Table 17.3 ISGPS proposed classification of post pancreatectomy hemorrhage

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/ immediate, very rarely life-threatening	Observation, blood count, ultrasonography, computed tomography, angiography, endoscopy[b]	Transfusion of flood/ blood, intermediate care unit (or ICU), therapeutic endoscopy,[b] embolization relaparotomy for early PPH
C	Late, intra- or extraluminal, severe	Late, intra- or extraluminal, severe	Severely impaired, life-threatening	Angiography, computed tomography, endoscopy[b]	Localization of bleeding, angiography and embolization, (endoscopy[b]) *or* relaparotomy, ICU

Source: Reproduced with permission from Elsevier [45]
ICU, intensive care unit; *PPH,* postpancreatectomy hemorrhage
[a]Late, intra- or extraluminal, mild bleeding may not be immediately life-threatening to the patient but may be a warning sign for alter 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)

Table 17.4 ISGPS consensus definition of delayed gastric emptying after pancreatic surgery

DGE grade	NGT required	Unable to tolerate solid oral intake by POD	Vomiting/ gastric distension	Use of prokinetics
A	4–7 days or reinsertion > POD 3	7	±	±
B	8–14 days or reinsertion > POD 7	14	+	+
C	>14 days or reinsertion > POD 14	21	+	+

Source: Reproduced with permission from Elsevier [48]
To exclude mechanical causes of abnormal gastric emptying, the patency of either the gastrojejunostomy or the duodenojejunostomy should be confirmed by endoscopy or upper gastrointestinal gastrographin series
DGE, delayed gastric empyting; *POD,* postoperative day; *NGT,* nasogastric tube

4. Delayed gastric emptying (DGE): With the decline in the incidence of pancreatic leaks, DGE has emerged as the leading procedure-related morbidity [47, 28]. The reported incidence ranged from 8 to 45 % [48]. This wide range may be due to different definitions used, as there is still no accepted general criterion. Table 17.4 details the consensus definition proposed by the ISGPF group and divides it into three different grades (A, B, and C) based on the impact on the clinical course and on postoperative management [49]. It has been previously attributed in large part to pylorus preservation. There are eight studies (evidence level I and II) comparing DGE in pancreaticoduodenectomy (PD) and PPPD. While three studies showed no difference in DGE, three favored PPPD, and two showed lower DGE rates after PD compared to PPPD [30, 50–56]. While DGE resolves spontaneously most of the time, it is still a major source of discomfort to patients because of the prolonged gastric decompression, not to mention prolonged hospital stay and higher healthcare costs. Yeo et al. [57] have shown that DGE could be reduced by up to 37 % following PD with intravenous erythromycin, a motilin agonist. But if such measures fail, the immediate task is to exclude concomitant intraabdominal complications since DGE may herald an otherwise undetected pancreaticoenteric or bilioenteric anastomotic leak. Treatment consists of nasogastric decompression, attention to nutritional support, reassurance, and watchful waiting. In an effort to reduce DGE, some authors have advocated performing an additional Braun enteroenterostomy downstream of the gastrojejunostomy to reduce biliary reflux and allow for gastric emptying down either the afferent or efferent limbs of the gastrojejunostomy [58].
5. Bile leak—Bile leaks from the choledochojejunal anastomosis occur in 1–2 % of cases and are heralded by the appearance of bile in the drainage fluid. If this occurs, the drain should be left in place until the leak stops. If it is still present when the patient is ready for discharge, the patient can go home with the drain in place. Occasionally endoscopic interventions are required to stent the leak. Rarely operative exploration, washout, and additional drains are needed to control sepsis.

B. Distal pancreatectomy with splenectomy

Surgical technique

The abdomen is thoroughly inspected for any evidence of metastatic disease. The gastrocolic ligament is divided and dissection extended along the greater curvature of stomach to carefully ligate all of the short gastric vessels. The point of pancreatic transection is selected to the right of the lesion in an area of normal pancreas and the overlying peritoneum is divided along the superior and inferior borders of the pancreas. The splenic artery is identified along the superior border of pancreas, isolated, and ligated. Based on surgeon preference, the subsequent dissection can be performed in either an antegrade or retrograde fashion. We prefer the antegrade

approach and a tunnel is created at the site of transection of the pancreas deep to the splenic vein. Based on the thickness of the gland, a staple line enforced with peristrips is utilized to transect the gland and the vein en masse. The distal stump is then elevated off the retroperitoneum and the dissection proceeds to the left and all splenic attachments are divided.

We perform a routine lymphadenectomy, which involves excision of the nodal tissues along the common hepatic artery, left gastric artery, celiac axis, along the SMV, as well as the peripancreatic and retroperitoneal lymph nodes [59]. A similar approach called the radical antegrade modular pancreatosplenectomy allows a more comprehensive lymphadenectomy of the NI nodes and reduces the risk of positive posterior resection margins [60].

Splenic preservation: It is recommended for low-grade, small, malignant tumors that do not involve the splenic artery or vein [61]. Splenic preservation has the advantages of fewer postoperative complications such as abscesses in the resection bed, shorter length of hospitalization, and avoidance of the long-term risk of postsplenectomy sepsis related to encapsulated bacteria. Two techniques can be used to save the spleen: either by dissecting out the splenic artery and vein with division of the arterial and venous branches between the pancreas and the splenic artery and vein; or by resecting the splenic artery and vein along with the pancreas but with careful preservation of the vascular collaterals in the splenic hilum, which allows the spleen to survive on the short gastric vessels (Warshaw technique) [62]. The paramount prerequisite in this approach is preservation of the gastrosplenic vessels to ensure splenic perfusion and allow venous drainage.

Complications:
Pancreatic leak or fistula is the most common complication and the incidence has been reported to be as high as 26 % in some series [63]. The conventional method for preventing leakage of pancreatic juice from the cut surface is ligation of the main pancreatic duct and additional suturing of the stump to approximate the anterior and posterior capsule [64]. With the advent of surgical stapling devices, new tools have been added to the armamentarium of techniques for sealing the pancreatic stump, which includes the harmonic scalpel, fibrin glue, and prolamine injection. Stapling has been touted as simple, quick, and secure but has been associated with significant leak rates. However, different groups have reported no difference in pancreatic leak rates when the pancreatic stump was stapled or sutured [63, 65]. Hamilton et al. conducted a single blinded, randomized, controlled trial and demonstrated that mesh staple line reinforcement of the pancreatic transection margin decreases the incidence of pancreatic occlusion failure following left pancreatectomy. The incidence of grade B and C fistulas was 1.9 % in the mesh reinforcement group vs. 20 % in the no-mesh group [66].

C. Central pancreatectomy
A central pancreatectomy is rarely performed as the indications are few; however, for the right indication it does offer the advantage of preserving maximal pancreatic endocrine and exocrine function [67]. It is usually performed for a benign or a low-grade malignant lesion located in the neck of the pancreas measuring less than 5 cm. Complications from this technique are higher than for distal pancreatectomy but less than for pancreaticoduodenectomy.

Technique:
The lesser sac is entered and gastropancreatic folds are divided. The anterior surface of the pancreas is exposed and intraoperative ultrasonography utilized as needed. A tunnel is created behind the pancreas overlying the SMV. After stay sutures have been placed on the superior and inferior margins, the pancreas is divided in the area of the pancreatic neck proximal to the tumor, with a knife or stapler ensuring an adequate margin. The pancreatic stump is carefully dissected

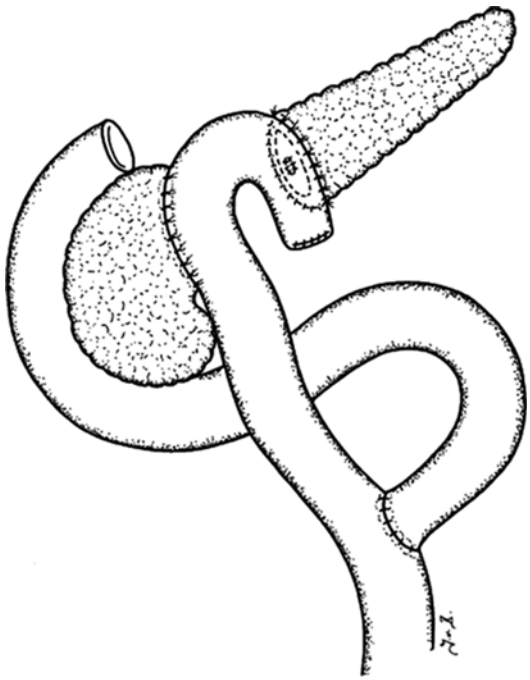

Fig. 17.4 Reconstruction following Central Pancreatectomy (Reprinted with permission from Blumgart's Surgery of Liver, biliary tract and pancreas, Vol. 1, Resectional Techniques, J. Werner and M.W. Buchler, Chapter 62A, P. 960, copyright Elsevier)

from right to left away from the splenic vein past the lesion and is divided again sharply. Margins are sent for frozen section analysis.

The usual technique of reconstruction consists of closure of the proximal pancreatic stump and a Roux-en-Y pancreaticojejunostomy for the distal stump. The pancreaticojejunal anastomosis is constructed in the same two-layered fashion as described above (Fig. 17.4).

D. Total pancreatectomy

This procedure is associated with high morbidity and mortality rates, thus making the indications far and few. Although controversial, it is sometime indicated in the event of a multifocal pancreatic cancer or the inability to achieve a margin-negative resection otherwise. Karpoff et al. [68] have demonstrated that total pancreatectomy for adenocarcinoma was associated with a significantly worse overall survival as compared to patients who underwent pancreaticoduodenectomy or distal pancreatectomy for adenocarcinoma. In addition, a positive intraoperative pancreatic transection margin was associated with a poor outcome, making an argument for not performing a completion pancreatectomy for a positive intraoperative transection margin. However, others have demonstrated that R0 resection is the single most important factor in determining patient outcome, making an argument to do a completion pancreatectomy for a positive margin on an intraoperative frozen section [69].

As expected, the procedure is associated with severe metabolic and nutritional consequences and requires close follow-up and multidisciplinary care in the postoperative setting.

E. Enucleation

Enucleation is usually reserved for sporadic insulinomas or small lesions less than 2 cm that are located toward the surface of the pancreas away from the main pancreatic duct. This can be safely accomplished laparoscopically as well and the port placement depends on the location of the lesion. Intraoperative ultrasound plays a useful adjunct. Enucleations have a high risk of postoperative fistula, mainly type A fistulas, so a drain is usually placed adjacent to the side of the enucleation.

Minimally Invasive Surgery/Role of Robotic Technology

Laparoscopic Pancreaticoduodenectomy

This is a technically challenging procedure and various reports have established that this can be accomplished relatively safely despite a steep learning curve. Although there are no randomized trials comparing the open vs. laparoscopic approach, a few small series show promise. Table 17.5 summarizes the available literature on laparoscopic pancreaticoduodenectomies [70]. Kendrick et al. [71] published the largest series on laparoscopic pancreaticoduodenectomy performed from July 2007 through July 2009 at a single center ($n=62$). There was one postopera-

Table 17.5 Literature review of laparoscopic pancreaticoduodenectomy

Authors [ref] (year)	No. of patients	Benign/ malignant	Hand-assisted/ totally laparoscopic	Operative time (min)[a]	Hospital stay (days)[a]	Blood loss (mL)[a]	Pancreatic fistula no. (%)	Postoperative morbidity no. (%)	Conversion to open no. (%)	Follow-up (month)[a]	No. of lymph nodes[a]	Positive margins	Reoperation no. (%)
Cuschieri et al. [93] (1994)	2	0/2	2/0										
Gagner et al. [39] (1997)	10	2/8		510	22.7			2 (20)	4 (40)				
Staudacher et al. [94] (2005)	4	2/2	4/0	416	12	325	0	0	0	4.5	26		
Kimoura et al. [16] (2005)	1	0/1	0/1						0				
Mabrut et al. [3] (2005)	3	0/3	1/2	300	7	300	0						
Zheng et al. [95] (2006)	1	0/1		390	30	50				6			
Dulucq et al. [21] (2006)	25	3/19	9/13	287	16.2	107		6 (27)	3 (12)	19	18	0	4 (18.2)
Lu b et al. [96] (2006)	5	0/5	0/5	528		770	1 (20)	3 (60)	1 (20)				1 (20)
Menon et al. [17] (2007)	1	0/1	0/1					0	0	12	17	0	0
Palanivelu et al. [18] (2007)	42	2/40	0/42	370	10.2	65	3 (7.1)		0	60		0	
Purligese et al. [7] (2008)	19	1/12	7/6	482	18.5	180	3 (23.1)	7 (54)	6 (32)	32	11.6	0	1 (7.7)
Sa Cuhna et al. [1] (2008)	2	0/2	0/2	510	18.7	300	1 (50)	1 (50)	0				
Cai et al. [1] (2008)	1	0/1	0/1	510	14	800	0	0	0	23			
Gumbs et al. [87] (2008)	3	3/0	0/3				1 (33)	1 (33)	1 (33)	20		0	
Ammori and Ayiomamitis (current series)	7	0/7	1/6	628.6	11.1	350	1 (14.3)	2 (28.6)	0	5	19.2	0	0
Total	126	13/104	25/81	448.3	16	324.7	10 of 86 (11.6)	22 of 77 (28.6)	15 of 120 (12.5)	20.2	18.4	0	6 of 48 (12.5)

Source: Reproduced with permission from Springer [68]

[a]Data are given as mean

tive mortality and perioperative morbidity occurred in 26 patients. The median length of hospital stay was 7 days. They concluded that laparoscopic pancreaticoduodenectomy is feasible, safe, and effective. Outcomes appear comparable with those via the open approach. It must be emphasized that the large available literature regarding postoperative complications following open pancreaticoduodenectomy should guide surgeons as to the expected high-quality outcomes following the laparoscopic approach. In addition, it is imperative that no shortcuts are taken in employing the laparoscopic approach, as grade C pancreatic fistulas can be a significant source of morbidity and mortality following pancreatic resection.

Laparoscopic Distal Pancreatectomy with Splenectomy

The report of the first laparoscopic distal pancreatectomy (LDP) was in 1996 [72, 73]. Subsequent studies have demonstrated that LDP is as safe as open distal pancreatectomy (ODP) [74]. Two meta-analyses further support that LDP is associated with a significantly lower blood loss and reduced length of stay compared to ODP [75, 76]. In addition, the meta-analysis completed by Venkat et al. [75] combined four retrospective studies to show that there is no difference in margin positivity between LDP and ODP, but there are more lymph nodes harvested in ODP than LDP. A retrospective study completed by Magge et al. [77] compared 62 consecutive patients undergoing ODP or minimally invasive distal pancreatectomy (MIDP) and found the median lymph node clearance is similar (OPD, $n=12$ and MIDP, $n=11$) and demonstrated that the rate of pancreatic fistula (ODP 29 % and MIDP 21 %) and the overall survival after ODP or MIDP were equivalent after adjusting for comorbidity and year of surgery. Tran et al. [78] recently published their results from a population-based analysis utilizing the Nationwide Inpatient Sample Database comparing minimally invasive vs. ODP and showed that the application of this approach has tripled in practice from 1998 to 2009. On multivariate analysis, the minimally invasive approach was associated with lower rates of overall postoperative complications, including lower incidences of infections and bleeding complications, as well as a shorter length of stay by 1.22 days. There were no differences in rates of in-hospital mortality, concomitant splenectomy, or total charges.

Role of Robotics

There are several advantages of robotic surgery over laparoscopic surgery that make it more feasible to complete complex procedures. Advantages include 3D visualization, stabilization of surgical arms allowing more precise suturing, increased angulation, and the ability to mimic anastomosis done through an open approach. Disadvantages include higher cost, more operating time, and a steep learning curve. A systematic review on robotic pancreaticoduodenectomy completed by Cirocchi et al. [79] found that the rate of conversion was 14 %, overall morbidity rate 58 %, and reoperation rate was 7.3 %. Data on cost analysis are lacking and further studies are needed to evaluate also the cost-effectiveness of the robotic approach. Giulianotti et al. [80] have published their experience utilizing the robot in pancreatic surgery. One hundred and thirty-four patients underwent robotic-assisted pancreatic surgery from October 2000 to January 2009. They reported a morbidity rate of 26 %, a mortality rate of 2.2 %, and a conversion rate of 10 %. Zureikat et al. [81] reported the largest series of pancreatic resections utilizing the robot. A total of 250 consecutive robotic pancreatic resections were analyzed: pancreaticoduodenectomy ($n=132$), distal pancreatectomy ($n=83$), central pancreatectomy ($n=13$), pancreatic enucleation ($n=10$), total pancreatectomy ($n=5$), Appleby resection ($n=4$), and Frey procedure ($n=3$). Thirty- and 90-day mortality were 0.8 % and 2.0 %, respectively. The grade C pancreatic fistula rate was 4 %. The mean operative time for the two most common procedures was 529 ± 103 min for pancreaticoduodenectomy and 257 ± 93 min for distal pancreatectomy. Conversion to an open procedure was required in 16 patients (6 %).

Although these studies demonstrate the feasibility and safety of robotics in pancreatic surgery, further prospective trials are needed to better evaluate their superiority and cost-effectiveness

Palliative Surgery

By the time most patients with pancreatic cancer come to a physician, many have locally advanced and/or metastatic disease (85–90 %). Because of the relative frequency of disease progression to gastric outlet or biliary obstruction and intractable abdominal pain, palliation of pain and obstructive symptoms become the most important considerations for improved quality of life. The majority of patients with unresectable pancreatic head lesions will experience biliary obstruction and jaundice and will therefore require palliative intervention. Furthermore, the incidence of gastric outlet obstruction because of tumor invasion of the duodenum likely ranges between 5 and 10 %, and it necessitates palliation if the patient is to maintain a reasonable nutritional status during chemotherapy. Finally, most patients will experience pain. When it is described to be located mostly in the patient's back, it is associated with tumor unresectability. Palliation of pain symptoms is critical for optimal quality of life for these patients.

The decision to palliate can be made preoperatively, intraoperatively, or postoperatively. Figure 17.5 depicts a decision algorithm; for the purpose of this chapter, the surgical options are discussed here. Considerations include biliary and gastric bypass and the need for intraoperative celiac nerve block. The extent of disease identified at exploration partially drives the need for these procedures, and most patients who have been offered resection will tolerate any indicated palliative procedures.

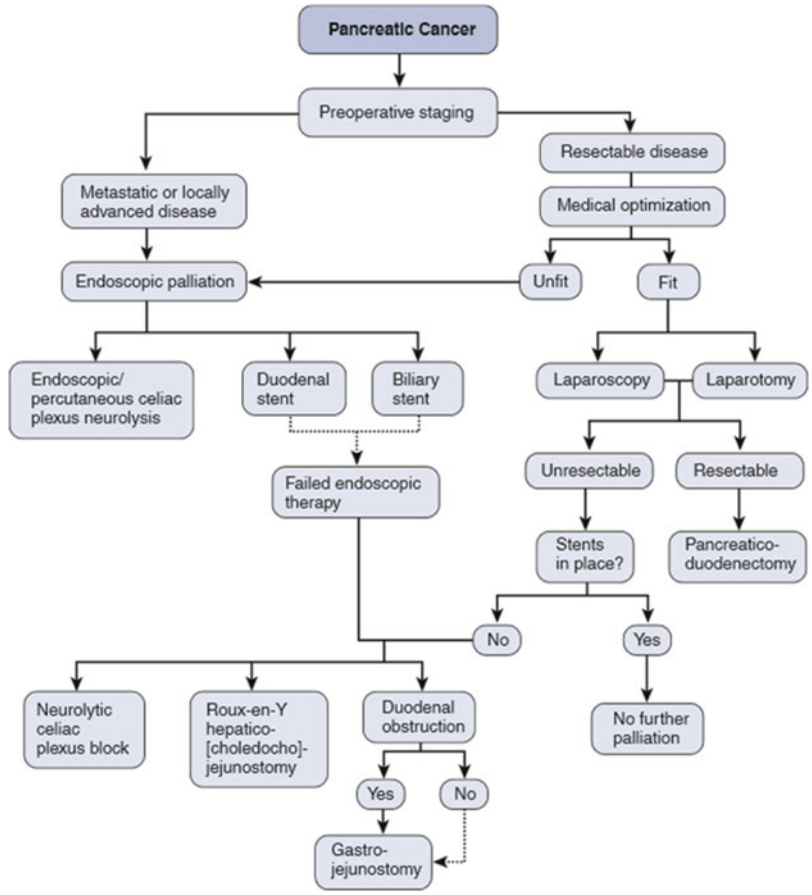

Fig. 17.5 Decision making algorithm for palliation of patients with unresectable pancreatic cancer. (Reprinted with permission from Current Surgical therapy, 10th edition, Palliative therapy for pancreatic cancer, J. C. King and O.J.Hines, P. 440, copyright Elsevier)

Biliary Bypass

Biliary bypass can be performed in patients who present with obstructive jaundice that have not been stented previously. The most frequent biliary bypass is a Roux-en-Y hepaticojejunostomy. This approach is probably associated with the lowest incidence of reobstruction and cholangitis. A patulous anastomosis is made between the hepatic duct and bowel in an end-to-side fashion with a running absorbable monofilament suture. If the gallbladder is in place, a cholecystectomy is performed as well. This can be safely accomplished laparoscopically as well.

Enteric Bypass

The decision to perform a gastrojejunostomy is based on the patient's symptoms at the time of surgery and the intraoperative findings. Patients complaining of nausea and vomiting or even early satiety will benefit from enteric bypass. At the time of exploration, assessment may reveal locally invasive tumor that predictably will lead to duodenal obstruction. Two randomized trials have demonstrated that prophylactic gastrojejunostomy significantly decreases the incidence of gastric outlet obstruction without increasing complication rates in patients found to have unresectable periampullary cancer on exploratory laparotomy [82, 83]. With the advent of laparoscopic staging, Espat et al. [84] analyzed 155 patients with unresectable pancreatic adenocarcinoma at their institution and found that laparoscopically staged patients do not frequently require subsequent surgical biliary or gastric bypass. Therefore, the patient should not be taken to the operating room for creation of a gastrojejunostomy in the absence of significant symptoms of gastric outlet obstruction. However, if the patient is undergoing attempted tumor resection and deemed to be unresectable after a laparotomy is performed, it is reasonable to proceed with prophylactic gastrojejunostomy.

The gastrojejunostomy should be constructed utilizing a loop of jejunum sutured to the posterior aspect of the stomach near the distal body of the stomach. A side-to-side anastomosis is constructed in two layers with running absorbable suture or a GIA stapler. The anastomoses may be positioned in an antecolic or retrocolic position as either method is acceptable, and neither seems to offer a significant advantage over the other.

References

1. Callery MP, Chang KJ, Fishman EK, Talamonti MS, William Traverso L, Linehan DC. Pretreatment assessment of resectable and borderline resectable pancreatic cancer: expert consensus statement. Ann Surg Oncol. 2009;16(7):1727–33.
2. John TG, Greig JD, Carter DC, Garden OJ. Carcinoma of the pancreatic head and periampullary region: tumor staging with laparoscopy and laparoscopic ultrasonography. Ann Surg. 1995;221(2):156–64.
3. Liu RC, Traverso LW. Diagnostic laparoscopy improves staging of pancreatic cancer deemed locally unresectable by computed tomography. Surg Endosc. 2005;19(5):638–42.
4. Thomson BNJ, Parks RW, Redhead DN, et al. Refining the role of laparoscopy and laparoscopic ultrasound in the staging of presumed pancreatic head and ampullary tumours. Br J Cancer. 2006;94(2):213–7.
5. Mayo SC, Austin DF, Sheppard BC, Mori M, Shipley DK, Billingsley KG. Evolving preoperative evaluation of patients with pancreatic cancer: does laparoscopy have a role in the current era? J Am Coll Surg. 2009;208(1):87–95.
6. Pisters PWT, Lee JE, Vauthey JN, Charnsangavej C, Evans DB. Laparoscopy in the staging of pancreatic cancer. Br J Surg. 2001;88(3):325–37.
7. Sosa JA, Bowman HM, Gordon TA, et al. Importance of hospital volume in the overall management of pancreatic cancer. Ann Surg. 1998;228(3):429–38.
8. Begg CB, Cramer LD, Hoskins WJ, Brennan MF. Impact of hospital volume on operative mortality for major cancer surgery. JAMA. 1998;280(20):1747–51.
9. Bliss LA, Yang CJ, Chau Z, et al. Patient selection and the volume effect in pancreatic surgery: unequal benefits? HPB. 2014;16:899–906.
10. Lieberman MD, Kilburn H, Lindsey M, Brennan MF. Relation of perioperative deaths to hospital volume among patients undergoing pancreatic resection for malignancy. Ann Surg. 1995;222(5):638–45.
11. Rosemurgy A, Cowgill S, Coe B, et al. Frequency with which surgeons undertake pancreaticoduodenectomy continues to determine length of stay, hospital charges, and in-hospital mortality. J Gastrointest Surg. 2008;12(3):442–9.
12. Rosemurgy AS, Bloomston M, Serafini FM, Coon B, Murr MM, Carey LC. Frequency with which surgeons undertake pancreaticoduodenectomy determines length of stay, hospital charges, and in-hospital mortality. J Gastrointest Surg. 2001;5(1):21–6.
13. Birkmeyer JD, Finlayson SRG, Tosteson ANA, Sharp SM, Warshaw AL, Fisher ES. Effect of hospital vol-

ume on in-hospital mortality with pancreaticoduodenectomy. Surgery. 1999;125(3):250–6.
14. Birkmeyer JD, Siewers AE, Finlayson EVA, et al. Hospital volume and surgical mortality in the United States. N Engl J Med. 2002;346(15):1128–37.
15. Birkmeyer JD, Stukel TA, Siewers AE, Goodney PP, Wennberg DE, Lucas FL. Surgeon volume and operative mortality in the United States. N Engl J Med. 2003;349(22):2117–27.
16. Bilimoria KY, Talamonti MS, Sener SF, et al. Effect of hospital volume on margin status after pancreaticoduodenectomy for cancer. J Am Coll Surg. 2008; 207(4):510–9.
17. Winter JM, Cameron JL, Campbell KA, et al. 1423 pancreaticoduodenectomies for pancreatic cancer: a single-institution experience. J Gastrointest Surg. 2006;10(9):1199–211.
18. Farnell MB, Pearson RK, Sarr MG, et al. A prospective randomized trial comparing standard pancreatoduodenectomy with pancreatoduodenectomy with extended lymphadenectomy in resectable pancreatic head adenocarcinoma. Surgery. 2005;138(4):618–30.
19. Yeo CJ, Cameron JL, Sohn TA, et al. Pancreaticoduodenectomy with or without extended retroperitoneal lymphadenectomy for periampullary adenocarcinoma: comparison of morbidity and mortality and short-term outcome. Ann Surg. 1999;229(5): 613–24.
20. Yeo CJ, Cameron JL, Lillemoe KD, et al. Pancreaticoduodenectomy with or without distal gastrectomy and extended retroperitoneal lymphadenectomy for periampullary adenocarcinoma, part 2: randomized controlled trial evaluating survival, morbidity, and mortality. Ann Surg. 2002;236(3):355–68.
21. Michalski CW, Kleeff J, Wente MN, Diener MK, Büchler MW, Friess H. Systematic review and meta-analysis of standard and extended lymphadenectomy in pancreaticoduodenectomy for pancreatic cancer. Br J Surg. 2007;94(3):265–73.
22. Iqbal N, Lovegrove RE, Tilney HS, et al. A comparison of pancreaticoduodenectomy with extended pancreaticoduodenectomy: a meta-analysis of 1909 patients. Eur J Surg Oncol. 2009;35(1):79–86.
23. Grobmyer SR, Kooby D, Blumgart LH, Hochwald SN. Novel pancreaticojejunostomy with a low rate of anastomotic failure-related complications. J Am Coll Surg. 2010;210(1):54–9.
24. Bassi C, Dervenis C, Butturini G, et al. Postoperative pancreatic fistula: an international study group (ISGPF) definition. Surgery. 2005;138(1):8–13.
25. Butturini G, Daskalaki D, Molinari E, Scopelliti F, Casarotto A, Bassi C. Pancreatic fistula: definition and current problems. J Hepatobiliary Pancreat Surg. 2008;15(3):247–51.
26. Bassi C, Falconi M, Salvia R, Caldiron E, Butturini G, Pederzoli P. Role of octreotide in the treatment of external pancreatic pure fistulas: a single-institution prospective experience. Langenbecks Arch Surg. 2000;385(1):10–3.
27. Lai ECH, Lau SHY, Lau WY. Measures to prevent pancreatic fistula after pancreatoduodenectomy: a comprehensive review. Arch Surg. 2009;144(11): 1074–80.
28. Buchler MW, Wagner M, Schmied BM, Uhl W, Friess H, Z'graggen K. Changes in morbidity after pancreatic resection: toward the end of completion pancreatectomy. Arch Surg. 2003;138(12):1310–4; discussion 1315.
29. Berberat PO, Friess H, Kleeff J, Uhl W, Büchler MW. Prevention and treatment of complications in pancreatic cancer surgery. Dig Surg. 1999;16(4):327–36.
30. Halloran CM, Ghaneh P, Bosonnet L, Hartley MN, Sutton R, Neoptolemos JP. Complications of pancreatic cancer resection. Dig Surg. 2002;19(2):138–46.
31. Cullen JJ, Sarr MG, Ilstrup DM. Pancreatic anastomotic leak after pancreaticoduodenectomy: incidence, significance, and management. Am J Surg. 1994; 168(4):295–8.
32. Torres AJ, Landa JI, Moreno-Azcoita M, et al. Somatostatin in the management of gastrointestinal fistulas: a multicenter trial. Arch Surg. 1992;127(1): 97–100.
33. Nubiola P, Badia JM, Martinez-Rodenas F, et al. Treatment of 27 postoperative enterocutaneous fistulas with the long half-life somatostatin analogue SMS 201-995. Ann Surg. 1989;210(1):56–8.
34. Alvarez C, McFadden DW, Reber HA. Complicated enterocutaneous fistulas: failure of octreotide to improve healing. World J Surg. 2000;24(5):533–7; discussion 538.
35. Connor S, Alexakis N, Garden OJ, Leandros E, Bramis J, Wigmore SJ. Meta-analysis of the value of somatostatin and its analogues in reducing complications associated with pancreatic surgery. Br J Surg. 2005;92(9):1059–67.
36. Zeng Q, Zhang Q, Han S, et al. Efficacy of somatostatin and its analogues in prevention of postoperative complications after pancreaticoduodenectomy: a meta-analysis of randomized controlled trials. Pancreas. 2008;36(1):18–25.
37. Hesse UJ, DeDecker C, Houtmeyers P, et al. Prospectively randomized trial using perioperative low-dose octreotide to prevent organ-related and general complications after pancreatic surgery and pancreaticojejunostomy. World J Surg. 2005;29(10):1325–8.
38. Alghamdi AA, Jawas AM, Hart RS. Use of octreotide for the prevention of pancreatic fistula after elective pancreatic surgery: a systematic review and meta-analysis. Can J Surg. 2007;50(6):459–66.
39. Shan YS, Sy ED, Tsai ML, Tang LY, Li PS, Lin PW. Effects of somatostatin prophylaxis after pylorus-preserving pancreaticoduodenectomy: increased delayed gastric emptying and reduced plasma motilin. World J Surg. 2005;29(10):1319–24.
40. Ramos-De la Medina A, Sarr MG. Somatostatin analogues in the prevention of pancreas-related complications after pancreatic resection. J Hepatobiliary Pancreat Surg. 2006;13(3):190–3.

41. Suc B, Msika S, Piccinini M, et al. Octreotide in the prevention of intra-abdominal complications following elective pancreatic resection: a prospective, multicenter randomized controlled trial. Arch Surg. 2004;139(3):288–94; discussion 295.
42. Sarr MG, Pancreatic Surgery Group. The potent somatostatin analogue vapreotide does not decrease pancreas-specific complications after elective pancreatectomy: a prospective, multicenter, double-blinded, randomized, placebo-controlled trial. J Am Coll Surg. 2003;196(4):556–64; discussion 564–5; author reply 565.
43. Allen PJ, Gonen M, Brennan MF, et al. Pasireotide for postoperative pancreatic fistula. N Engl J Med. 2014;370(21):2014–22.
44. Yeo CJ, Cameron JL, Lillemoe KD, et al. Pancreaticoduodenectomy for cancer of the head of the pancreas. 201 patients. Ann Surg. 1995;221(6): 721–31; discussion 731–3.
45. Adam U, Makowiec F, Riediger H, Schareck WD, Benz S, Hopt UT. Risk factors for complications after pancreatic head resection. Am J Surg. 2004;187(2): 201–8.
46. Wente MN, Veit JA, Bassi C, et al. Postpancreatectomy hemorrhage (PPH)—an International Study Group of Pancreatic Surgery (ISGPS) definition. Surgery. 2007;142(1):20–5.
47. Yeo CJ, Cameron JL, Sohn TA, et al. Six hundred fifty consecutive pancreaticoduodenectomies in the 1990s: pathology, complications, and outcomes. Ann Surg. 1997;226(3):248–57; discussion 257–60.
48. Schafer M, Mullhaupt B, Clavien PA. Evidence-based pancreatic head resection for pancreatic cancer and chronic pancreatitis. Ann Surg. 2002;236(2): 137–48.
49. Wente MN, Bassi C, Dervenis C, et al. Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). Surgery. 2007;142(5): 761–8.
50. Horstmann O, Markus PM, Ghadimi MB, Becker H. Pylorus preservation has no impact on delayed gastric emptying after pancreatic head resection. Pancreas. 2004;28(1):69–74.
51. van Berge Henegouwen MI, van Gulik TM, DeWit LT, et al. Delayed gastric emptying after standard pancreaticoduodenectomy versus pylorus-preserving pancreaticoduodenectomy: an analysis of 200 consecutive patients. J Am Coll Surg. 1997;185(4): 373–9.
52. Jimenez RE, Fernandez-del Castillo C, Rattner DW, Chang Y, Warshaw AL. Outcome of pancreaticoduodenectomy with pylorus preservation or with antrectomy in the treatment of chronic pancreatitis. Ann Surg. 2000;231(3):293–300.
53. Roder JD, Stein HJ, Huttl W, Siewert JR. Pylorus-preserving versus standard pancreatico-duodenectomy: an analysis of 110 pancreatic and periampullary carcinomas. Br J Surg. 1992;79(2):152–5.
54. Di Carlo V, Zerbi A, Balzano G, Corso V. Pylorus-preserving pancreaticoduodenectomy versus conventional Whipple operation. World J Surg. 1999;23(9): 920–5.
55. Mosca F, Giulianotti PC, Balestracci T, et al. Long-term survival in pancreatic cancer: pylorus-preserving versus Whipple pancreatoduodenectomy. Surgery. 1997;122(3):553–66.
56. Lin PW, Lin YJ. Prospective randomized comparison between pylorus-preserving and standard pancreaticoduodenectomy. Br J Surg. 1999;86(5):603–7.
57. Yeo CJ, Barry MK, Sauter PK, et al. Erythromycin accelerates gastric emptying after pancreaticoduodenectomy. A prospective, randomized, placebo-controlled trial. Ann Surg. 1993;218(3):229–37; discussion 237–8.
58. Hochwald SN, Grobmyer SR, Hemming AW, et al. Braun enteroenterostomy is associated with reduced delayed gastric emptying and early resumption of oral feeding following pancreaticoduodenectomy. J Surg Oncol. 2010;101(5):351–5.
59. Kleeff J, Diener MK, Z'graggen K, et al. Distal pancreatectomy: risk factors for surgical failure in 302 consecutive cases. Ann Surg. 2007;245(4):573–82.
60. Strasberg SM, Drebin JA, Linehan D. Radical antegrade modular pancreatosplenectomy. Surgery. 2003;133(5):521–7.
61. Shoup M, Brennan MF, McWhite K, Leung DHY, Klimstra D, Conlon KC. The value of splenic preservation with distal pancreatectomy. Arch Surg. 2002;137(2):164–8.
62. Warshaw AL. Conservation of the spleen with distal pancreatectomy. Arch Surg. 1988;123(5):550–3.
63. Fahy BN, Frey CF, Ho HS, Beckett L, Bold RJ. Morbidity, mortality, and technical factors of distal pancreatectomy. Am J Surg. 2002;183(3):237–41.
64. Fernandez-del Castillo C, Rattner DW, Warshaw AL. Standards for pancreatic resection in the 1990s. Arch Surg. 1995;130(3):295–9; discussion 299–300.
65. Sheehan MK, Beck K, Creech S, Pickleman J, Aranha GV. Distal pancreatectomy: does the method of closure influence fistula formation? Am Surg. 2002;68(3):264–7; discussion 267–8.
66. Hamilton NA, Porembka MR, Johnston FM, et al. Mesh reinforcement of pancreatic transection decreases incidence of pancreatic occlusion failure for left pancreatectomy: a single-blinded, randomized controlled trial. Ann Surg. 2012;255(6):1037–42.
67. Efron DT, Lillemoe KD, Cameron JL, Yeo CJ. Central pancreatectomy with pancreaticogastrostomy for benign pancreatic pathology. J Gastrointest Surg. 2004;8(5):532–8.
68. Karpoff HM, Klimstra DS, Brennan MF, Conlon KC. Results of total pancreatectomy for adenocarcinoma of the pancreas. Arch Surg. 2001;136(1):44–7; discussion 48.
69. Wagner M, Redaelli C, Lietz M, Seiler CA, Friess H, Buchler MW. Curative resection is the single most important factor determining outcome in patients with pancreatic adenocarcinoma. Br J Surg. 2004;91(5): 586–94.
70. Ammori BJ, Ayiomamitis GD. Laparoscopic pancreaticoduodenectomy and distal pancreatectomy: a UK

experience and a systematic review of the literature. Surg Endosc. 2011;25(7):2084–99.
71. Kendrick ML, Cusati D. Total laparoscopic pancreaticoduodenectomy: feasibility and outcome in an early experience. Arch Surg. 2010;145(1):19–23.
72. Cuschieri A, Jakimowicz JJ, van Spreeuwel J. Laparoscopic distal 70% pancreatectomy and splenectomy for chronic pancreatitis. Ann Surg. 1996; 223(3):280–5.
73. Gagner M, Pomp A. Laparoscopic pylorus-preserving pancreatoduodenectomy. Surg Endosc. 1994; 8(5):408–10.
74. Nakamura M, Nakashima H. Laparoscopic distal pancreatectomy and pancreatoduodenectomy: is it worthwhile? A meta-analysis of laparoscopic pancreatectomy. J Hepatobiliary Pancreat Sci. 2013;20(4):421–8.
75. Venkat R, Edil BH, Schulick RD, Lidor AO, Makary MA, Wolfgang CL. Laparoscopic distal pancreatectomy is associated with significantly less overall morbidity compared to the open technique: a systematic review and meta-analysis. Ann Surg. 2012;255(6):1048–59.
76. Jin T, Altaf K, Xiong JJ, et al. A systematic review and meta-analysis of studies comparing laparoscopic and open distal pancreatectomy. HPB (Oxford). 2012; 14(11):711–24.
77. Magge D, Gooding W, Choudry H, et al. Comparative effectiveness of minimally invasive and open distal pancreatectomy for ductal adenocarcinoma. JAMA Surg. 2013;148(6):525–31.
78. Tran Cao HS, Lopez N, Chang DC, et al. Improved perioperative outcomes with minimally invasive distal pancreatectomy: results from a population-based analysis. JAMA Surg. 2014;149(3):237–43.
79. Cirocchi R, Partelli S, Coratti A, Desiderio J, Parisi A, Falconi M. Current status of robotic distal pancreatectomy: a systematic review. Surg Oncol. 2013;22(3): 201–7.
80. Giulianotti PC, Sbrana F, Bianco FM, et al. Robot-assisted laparoscopic pancreatic surgery: single-surgeon experience. Surg Endosc. 2010;24(7):1646–57.
81. Zureikat AH, Moser AJ, Boone BA, Bartlett DL, Zenati M, Zeh III HJ. 250 robotic pancreatic resections: safety and feasibility. Ann Surg. 2013;258(4): 554–9; discussion 559–62.
82. Van Heek NT, De Castro SM, van Eijck CH, et al. The need for a prophylactic gastrojejunostomy for unresectable periampullary cancer: a prospective randomized multicenter trial with special focus on assessment of quality of life. Ann Surg. 2003;238(6):894–902; discussion 902–5.
83. Lillemoe KD, Cameron JL, Hardacre JM, et al. Is prophylactic gastrojejunostomy indicated for unresectable periampullary cancer? A prospective randomized trial. Ann Surg. 1999;230(3):322–8; discussion 328–30.
84. Espat NJ, Brennan MF, Conlon KC. Patients with laparoscopically staged unresectable pancreatic adenocarcinoma do not require subsequent surgical biliary or gastric bypass. J Am Coll Surg. 1999;188(6): 649–55; discussion 655–7.

Radiation Therapy for Pancreatic Cancer

18

R. Charles Nichols Jr.

Radiation Therapy

Radiation therapy has a useful role in cancer management primarily because normal cells are better able to repair radiation damage than are malignant cells. The challenge faced by the radiation oncologist is to deliver radiation doses that adequately eradicate deposits of malignant cells while shielding normal tissues from doses above the threshold that can cause damage to critical organs. In the setting of pancreatic malignancy, the efficacy of radiotherapy is limited because malignant tumors of the pancreas frequently abut highly radiosensitive normal tissues such as the duodenum, small intestine, and stomach. Additionally, when X-rays are used to treat these tumors, the beams must often pass through critical radiosensitive structures such as the spinal cord, liver, and kidneys. Encouragingly, over the past decade, newer radiotherapy technologies such as intensity-modulated radiation therapy and particle therapy (protons and carbon ions) have facilitated the delivery of effective radiotherapy doses to tumor targets while minimizing or eliminating the effective dose to critical normal structures.

R.C. NicholsJr., M.D. (✉)
Department of Radiation Oncology,
University of Florida Proton Therapy Institute,
2015 North Jefferson Street, Jacksonville,
FL 32206, USA
e-mail: rnichols@floridaproton.org

Radiation Therapy Techniques

Techniques for radiotherapy delivery in the treatment of pancreatic malignancies may involve external-beam radiation therapy delivered by either a medical linear accelerator (Fig. 18.1), a specialized system for stereotactic ablative radiotherapy (SABR), such as a CyberKnife (Fig. 18.2), or a cyclotron-based system in the setting of particle therapy (Fig. 18.3a–d). Brachytherapy, or the implantation of radioactive sources within tumors, is of historic interest as a technique in the treatment of pancreatic cancer but is not commonly used in current practice.

External-Beam Radiotherapy

Two-dimensional and three-dimensional conformal radiotherapy: Much of the historical data in the medical literature surrounding the use of radiotherapy in the treatment of pancreatic malignancies is based on the outcomes of patients treated with either two-dimensional (2D) radiotherapy or three-dimensional conformal radiotherapy (3DCRT). Usually delivered without the guidance of computerized tomography, 2D radiotherapy utilizes large radiotherapy fields with field borders determined primarily by bony anatomy (Fig. 18.4a–c). These large radiotherapy fields have been frequently associated with substantial gastrointestinal toxicity. Furthermore, the difficulty in accurately targeting the areas at

M.S. Wagh, P.V. Draganov (eds.), *Pancreatic Masses*, DOI 10.1007/978-3-319-19677-0_18

Fig. 18.1 A Varian Clinac iX Linear Accelerator (Varian Medical Systems, Palo Alto, CA). Imaging devices are incorporated within the delivery system to facilitate target localization for treatment (reproduced with permission from Varian Medical Systems)

Fig. 18.2 The Cyberknife Robotic Radiosurgery system (Accuray Inc., Sunnyvale, CA) (reproduced with permission, from Accuray Inc.)

highest risk of tumor involvement precluded safe delivery of radiotherapy doses likely to eradicate the tumor. While studies utilizing 2D conformal radiation therapy are of some historical interest, it would be wrong to infer that the toxicity profile associated with this treatment is indicative of the toxicity profile associated with the delivery of radiotherapy using newer, more conformal techniques.

In the late 1990s, 3DCRT came into common use in North America (Fig. 18.5), offering greater precision in radiation dose delivery since clinicians could use computerized tomography (CT) to locate tumor targets and delineate critical normal structures, such as the spinal cord, liver and kidneys, and duodenum. While more precise than 2D radiotherapy, field arrangements utilized with 3DCRT often resembled those used in the 2D era. For the most part, toxicity and efficacy profiles associated with 3DCRT have been similar to those seen in the 2D era.

Intensity-modulated radiotherapy: Intensity-modulated radiotherapy (IMRT) came into common use in North America around 2005. IMRT utilizes CT and other imaging techniques to delineate the target and normal tissue volumes while incorporating sophisticated mathematical algorithms to optimize radiation dose distributions in patients. Whereas conventional radiotherapy delivery utilizes rectangular apertures or static customized blocking, IMRT utilizes a device called a multileaf collimator (Figs. 18.6 and 18.7), integral to the linear accelerator, that allows the division of a static radiotherapy field into multiple subfields. With IMRT, a virtually limitless number of radiation fields can be delivered in an effort to optimize the conformality of the radiotherapy dose distribution (Fig. 18.8a, b).

Stereotactic ablative radiotherapy: Stereotactic ablative radiotherapy (SABR) utilizes delivery systems capable of highly precise conformal radiotherapy dose distributions to small targets (Fig. 18.9). The technology was initially developed for the treatment of intracranial lesions, such as acoustic neuromas and arteriovenous malformations, but more recently has evolved for use in extracranial tumor targets in the lung, liver, prostate, and pancreas.

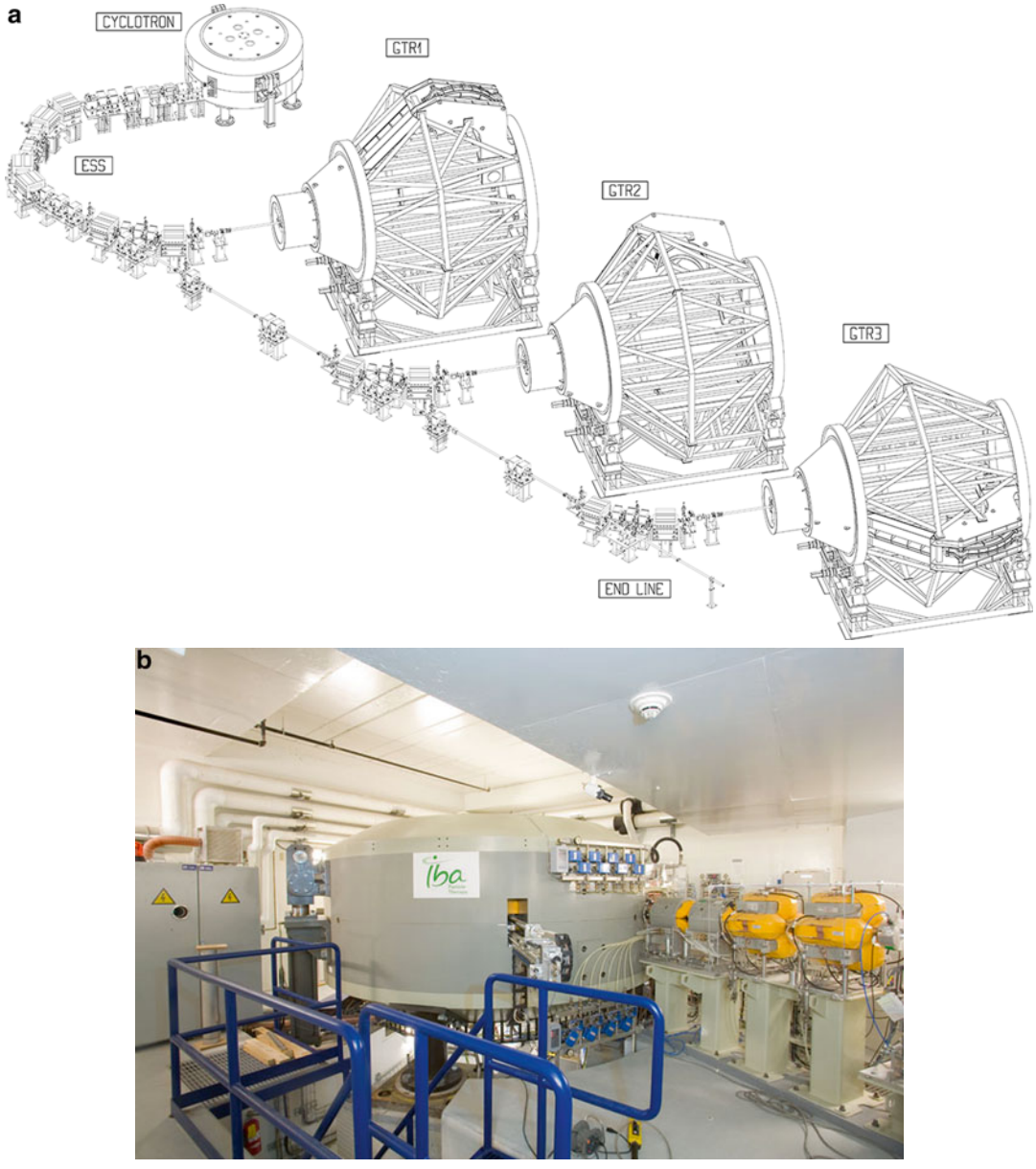

Fig. 18.3 (**a**) Particle therapy utilizing either protons or carbon ions is delivered using a cyclotron-based system. In the system shown, (**b**) protons are accelerated in a cyclotron and (**c**) delivered via an array of electromagnets (**d**) into one of three gantries where patients receive treatment (reproduced with permission from IBA Proton Therapy)

Fig. 18.3 (continued)

While other modalities of external radiation therapy deliver fractionated treatment over a period of several weeks, most SABR protocols deliver treatment at a high dose per fraction over a one- to five-fraction course. This higher dose per fraction is associated with a greater impact on the targeted tumor cells when compared to lower doses per fraction. On the other hand, normal tissues exposed to high doses per fraction also exhibit greater damage; therefore, meticulous targeting techniques are required with SABR. While SABR may play a meaningful role in ablating individual foci of tumor, this form of high-dose-per-fraction (or hypofractionated) radiotherapy generally cannot be utilized in the therapy of a malignancy if the treatment is intended not just to address the primary tumor but also to irradiate regional lymphatics felt to be at a high risk of harboring microscopic tumor cells.

Particle Therapy

Particle therapy, using protons or carbon ions, has also been utilized in the treatment of pancreatic malignancy. In contrast to X-ray–based therapies, particle therapy utilizes charged particles which penetrate to a finite depth in tissue whereupon their associated radiation dose is deposited in a region known as the "Bragg peak." By delivering a range of energies into tissue, a "spread-out Bragg peak" (SOBP) is formed (Figs. 18.10a, b and 18.11a, b). This allows for a radiation dose distribution to cover the targeted area with a relatively low entry dose and no exit dose. Particle therapy is believed to have tremendous potential in the treatment of pancreatic malignancy because the tumor target is adjacent to highly radiosensitive normal tissues. Dosimetric studies have demonstrated a significant potential for improvements in the therapeutic index when protons are used [1–5]. This hypothesis has been validated in various clinical outcome studies [6–8]. Figure 18.12a–c demonstrate a typical dose distribution when protons are used to treat a patient in the postoperative setting. In North America, proton therapy represents the dominant form of particle therapy offered. As of June 2014, 14 facilities were operational in the United States. Currently available in Japan, carbon ion therapy represents an alternative form of cyclotron-generated particle therapy.

Brachytherapy

Brachytherapy involves the implantation of radioactive sources, such as iodine-125 seeds,

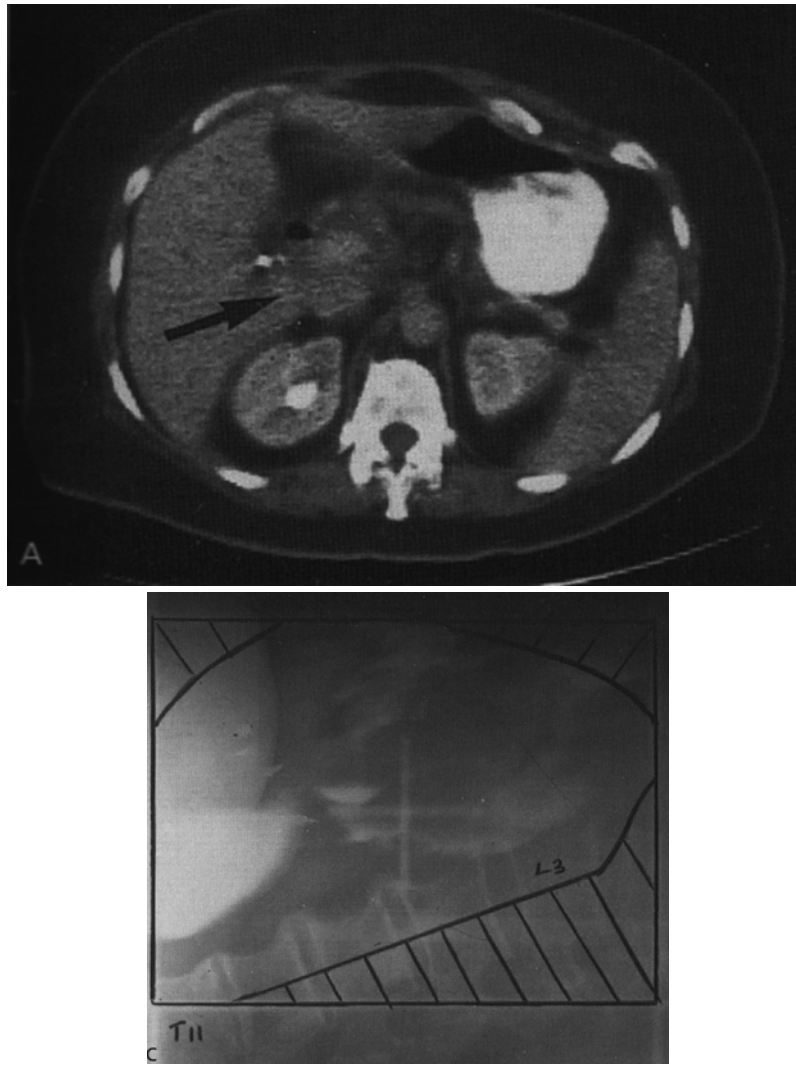

Fig. 18.4 External beam four-field technique for a pancreatic head lesion. (**a**) The lesion on CT scan. Note the dilated pancreatic duct and relation of the pancreas to the duodenal loop and stomach. (**b**) The anteroposterior/posteroanterior (AP/PA) field, which includes the tumor with the approximately 3-cm margin of the pancreas (body), the duodenal loop (plus approximately 50 % of the right kidney), and the nodal area at risk. Most of the left kidney is shielded. (**c**) The lateral field with an anterior margin 1.5–2.0 cm beyond gross disease and a posterior margin at least 1.5 cm behind the front edge of vertebral body (reproduced with permission from Halperin EC, Perez CA, Brady LW (eds)., Principles and Practice of Radiation Oncology, Fifth ed. Philadelphia: Lippincott Williams & Wilkins, 2008)

directly into tumors. While it is not commonly used in North America, Memorial Sloan-Kettering Cancer Center (New York, NY) has published extensively on this approach for patients with unresectable disease and its use is of historical interest [9, 10].

Intraoperative Radiotherapy

Intraoperative radiotherapy (IORT) requires a dedicated linear accelerator located in a shielded operating room. Generally, electron energies with limited penetration into normal tissues are

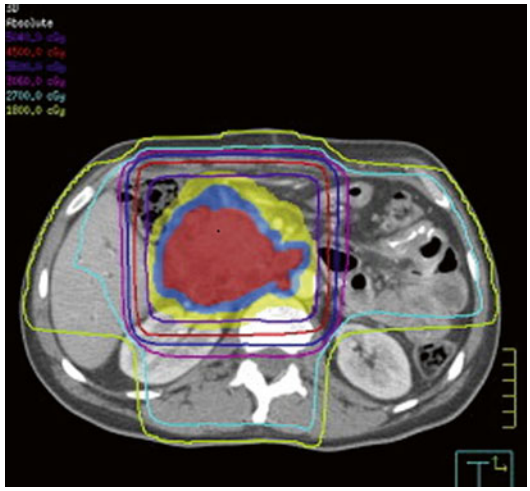

Fig. 18.5 A three-dimensional conformal radiotherapy dose distribution using a conventional four-field approach

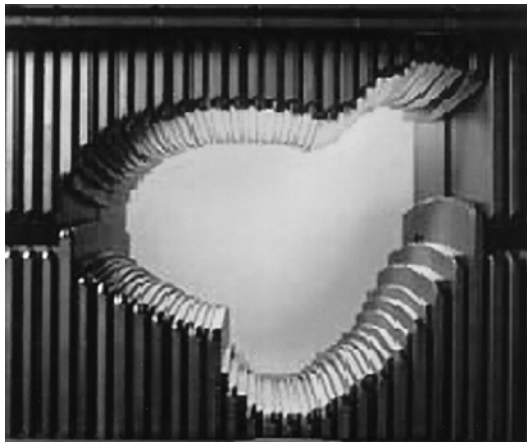

Fig. 18.6 A multileaf collimator allows for continuous field shaping during radiotherapy treatment

utilized during surgical procedures. The advantage of IORT is that the beam can be aimed at the gross tumor deposit using direct visual guidance. Normal bowel can be manually moved away from the targeted area. The disadvantage of intraoperative radiation therapy is that treatment cannot be fractionated. In other words, the entire dose is delivered in a single large fraction. This approach has biologic disadvantages in terms of normal tissue toxicity as well as tumor control.

Radiation Therapy for Malignant Pancreatic Neoplasms

Radiation therapy is utilized in conjunction with surgery for patients with resectable or marginally resectable disease. It also can be utilized as definitive therapy, usually in conjunction with chemotherapy, for patients with locally advanced unresectable disease. Radiotherapy can also be utilized for the palliation of patients with disseminated malignancy.

Postoperative Radiotherapy

Radiotherapy is commonly offered postoperatively for patients who have undergone definitive surgery for nonmetastatic pancreatic cancer. The postoperative radiotherapy target usually includes the preoperative tumor bed, the critical anastomoses (the pancreaticojejunostomy and hepaticojejunostomy), and the relevant abdominal nodal regions (peripancreatic, celiac, superior mesenteric porta hepatic, and para-aortic). Currently, the Radiation Therapy Oncology Group (RTOG) Atlas represents the standard guideline for postoperative target delineation [11].

Strong indications for postoperative radiotherapy include positive surgical margins or positive lymph nodes identified at surgery. The contemporary literature suggests that these events are quite common. The study from Memorial Sloan-Kettering Cancer Center reviewing the outcomes of 625 patients who underwent pancreatic cancer surgery from 2000 to 2009 indicated that 70 % of patients had positive lymph nodes in their final specimen and that 16 % had positive surgical margins [12]. A corresponding publication from Johns Hopkins University (Baltimore, MD) analyzing 905 patients undergoing pancreaticoduodenectomy from 1995 to 2005 demonstrated a 79 % node-positivity rate and a 41 % margin-positivity rate [13].

Postoperative radiotherapy may also be used in the setting of negative surgical margins since patients who undergo potentially curative surgery with negative margins still exhibit a local failure

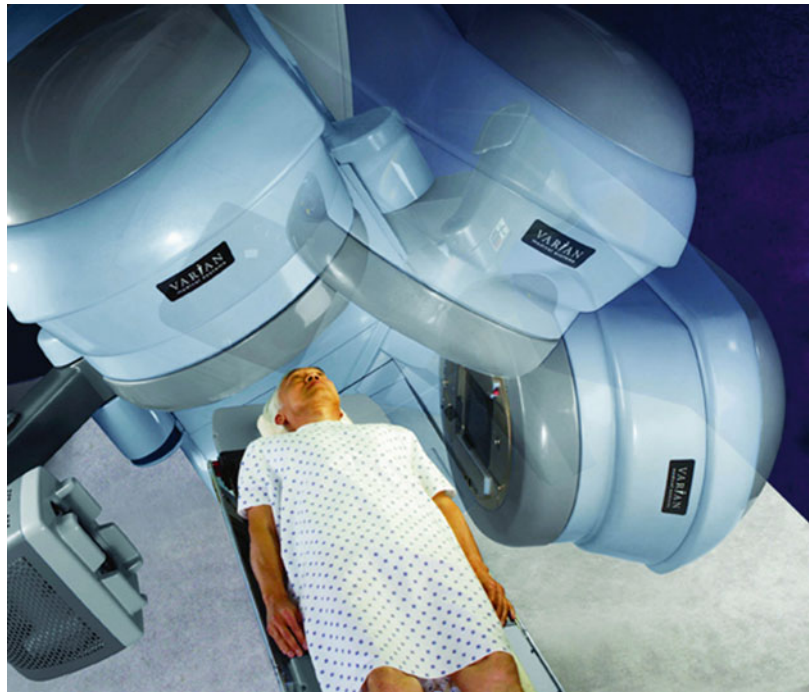

Fig. 18.7 The multileaf collimator (Fig. 18.6) is incorporated in the treatment head of the linear accelerator and changes shape while the gantry rotates around the patient

rate in the range of 50–80 % when radiotherapy is not used [14, 15]. Postoperative radiotherapy is thought to reduce this local recurrence rate to some degree.

Owing to the issues of convalescence after pancreaticoduodenectomy or other surgical interventions for pancreatic cancer, postoperative radiotherapy often cannot be initiated before 8–12 weeks after surgery. Additionally, given the intraoperative transposition of the radiosensitive small intestine, it is generally not possible to deliver conventionally fractionated postoperative radiotherapy doses over 50 Gy with chemotherapy. The series from the Massachusetts General Hospital (Boston, MA) demonstrated a 36 % local-regional failure rate at 3 years after treatment for patients receiving postoperative chemoradiotherapy [16]. Results from RTOG 97-04, a postoperative chemoradiotherapy trial, showed a 23–28 % local failure rate [17].

Three studies have explored the role of postoperative radiotherapy in the setting of resected disease [17–20]. An analysis by the Gastrointestinal Tumor Study Group [18] demonstrated a statistically significant improvement in survival for patients receiving 5-fluorouracil (5-FU)-based chemotherapy with radiotherapy after definitive surgery for nonmetastatic pancreatic cancer. The 5-year survival rate for patients receiving surgery alone was 5 % vs. 19 % for patients receiving chemoradiation. Based on this study, postoperative chemoradiation became accepted as a standard therapy in North America. The RTOG 97–04 trial [17] compared two different chemotherapy regimens combined with 5-FU-based chemoradiation. Patients were randomized between a control arm of 5-FU chemotherapy for two cycles followed by radiotherapy (with concomitant 5-FU) followed by two additional cycles of 5-FU vs. the study arm utilizing gemcitabine chemotherapy for two cycles followed by radiotherapy with 5-FU followed by two more cycles of gemcitabine-based chemotherapy. A statistically significant survival advantage was identified for patients with pancreatic head cancers receiving the gemcitabine regimen. A criticism of both studies was that neither study randomized patients between a radiotherapy vs. a nonradiotherapy arm. As such, it has been argued that the survival improvements seen with the

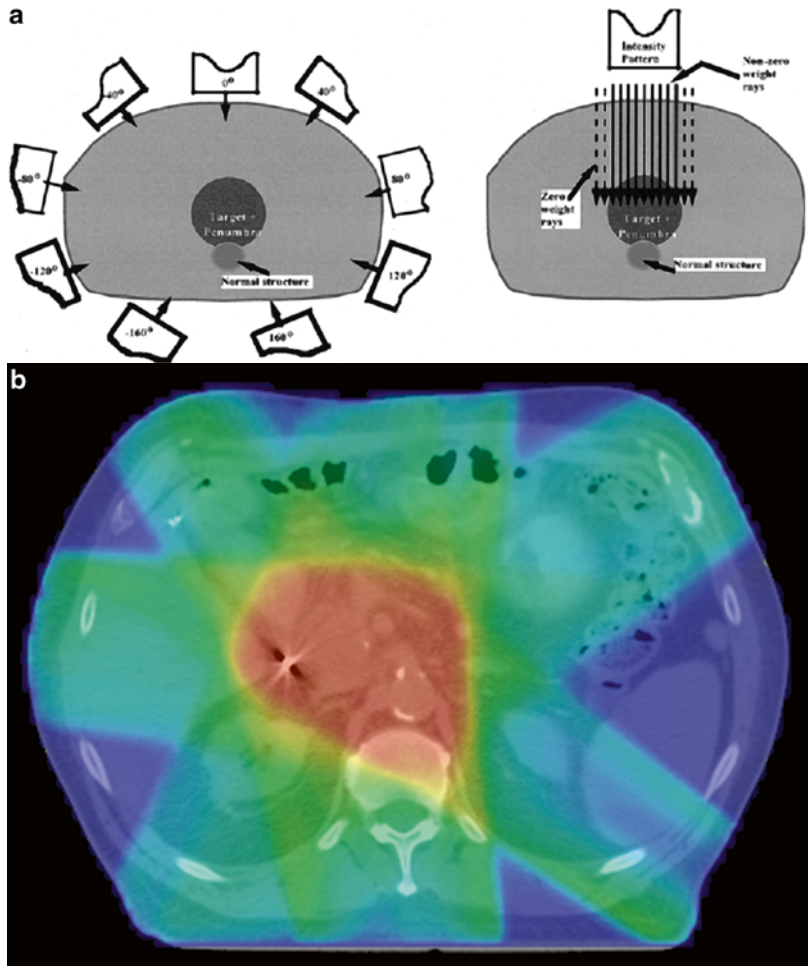

Fig. 18.8 (**a**) With intensity-modulated radiotherapy (IMRT) the radiotherapy beam can be delivered from virtually any angle and each field can be subdivided by the multileaf collimator to vary the dose intensity across the field. (**b**) This technology allows for the delivery of highly conformal dose distributions

postoperative regimens were owing to the chemotherapy rather than the radiotherapy. A counterargument was made when a secondary analysis of the RTOG 97–04 data indicated that patients who received high-quality radiotherapy per protocol guidelines had an improved survival outcome compared to patients treated with compromised radiotherapy fields [21], suggesting that effectively targeted radiotherapy is able to positively alter the natural history of resected pancreatic cancer.

Utilizing a complicated randomization scheme to determine the value of postoperative radiotherapy, treating physicians participating in the ESPAC-1 trial [19, 20] assigned patients to one of the following three randomized subtrials:

1. The first arm randomized patients between chemoradiation vs. no chemoradiation. Chemoradiation consisted of 20 Gy over 2 weeks with 5-FU chemotherapy that was repeated after a 2-week break.
2. The second arm randomized patients between chemotherapy vs. no chemotherapy. The chemotherapy regimen consisted of a bolus of 5-FU and leucovorin given for 5 days every 4 weeks for a total of 6 months.

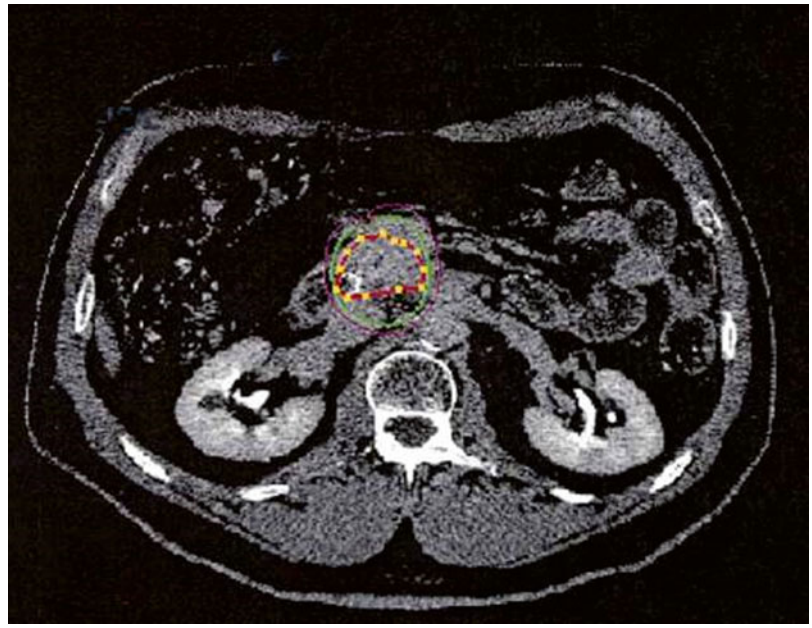

Fig. 18.9 Stereotactic ablative radiotherapy (SABR) allows for the delivery of very tight conformal radiotherapy dose distributions around the target, such as a pancreatic head tumor. A representative dose distribution is shown above

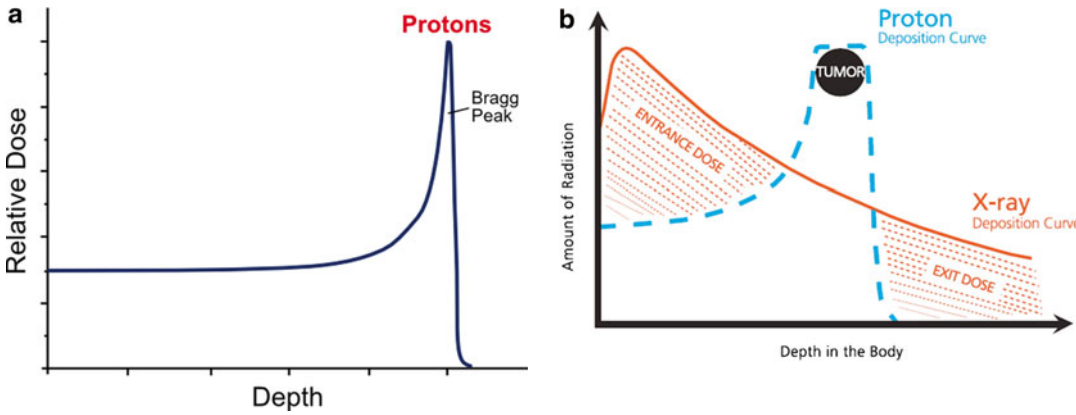

Fig. 18.10 (**a**) Charged particles like protons travel a finite distance into tissue, determined by their energy, and then release that energy in a tightly defined region called the "Bragg peak." (**b**) By delivering a range of energies toward the tumor target, a summation of these Bragg peaks allows for the creation of a "spread-out Bragg peak" (SOBP), which conforms to the depth and position of the tumor target (reproduced with permission from University of Florida Proton Therapy Institute)

3. The third arm randomized patients to one of chemoradiotherapy, chemotherapy alone, chemoradiotherapy with maintenance chemotherapy, or observation.

Data from these three groups were pooled. The trialists concluded that there was no survival benefit for the patients receiving chemoradiation compared to the patients who did not receive chemoradiation. The median survival for the irradiated patients was 15.5 months. The median survival for the patients who did not receive radiotherapy was 16.1 months. The difference was not statistically significant.

Criticisms of the ESPAC-1 trial have included the following [22]:

- Potential bias on the part of the treating physicians who were allowed to choose to which randomization their patient was assigned

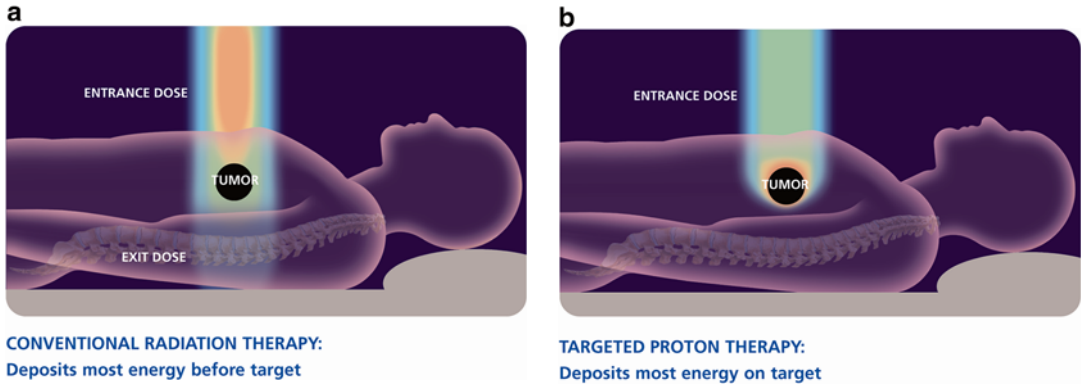

Fig. 18.11 With conventional radiotherapy (**a**) using X-rays (photons), the highest dose is near the point of beam entry into the patient. The tumor dose is significantly less than the entry dose. Also, an exit dose is delivered beyond the tumor target. With protons (**b**) and other particle therapies, such as carbon ions, the entry dose is low. The highest dose is at the depth of the tumor target and there is no exit dose beyond the target (reproduced with permission from the University of Florida Proton Therapy Institute)

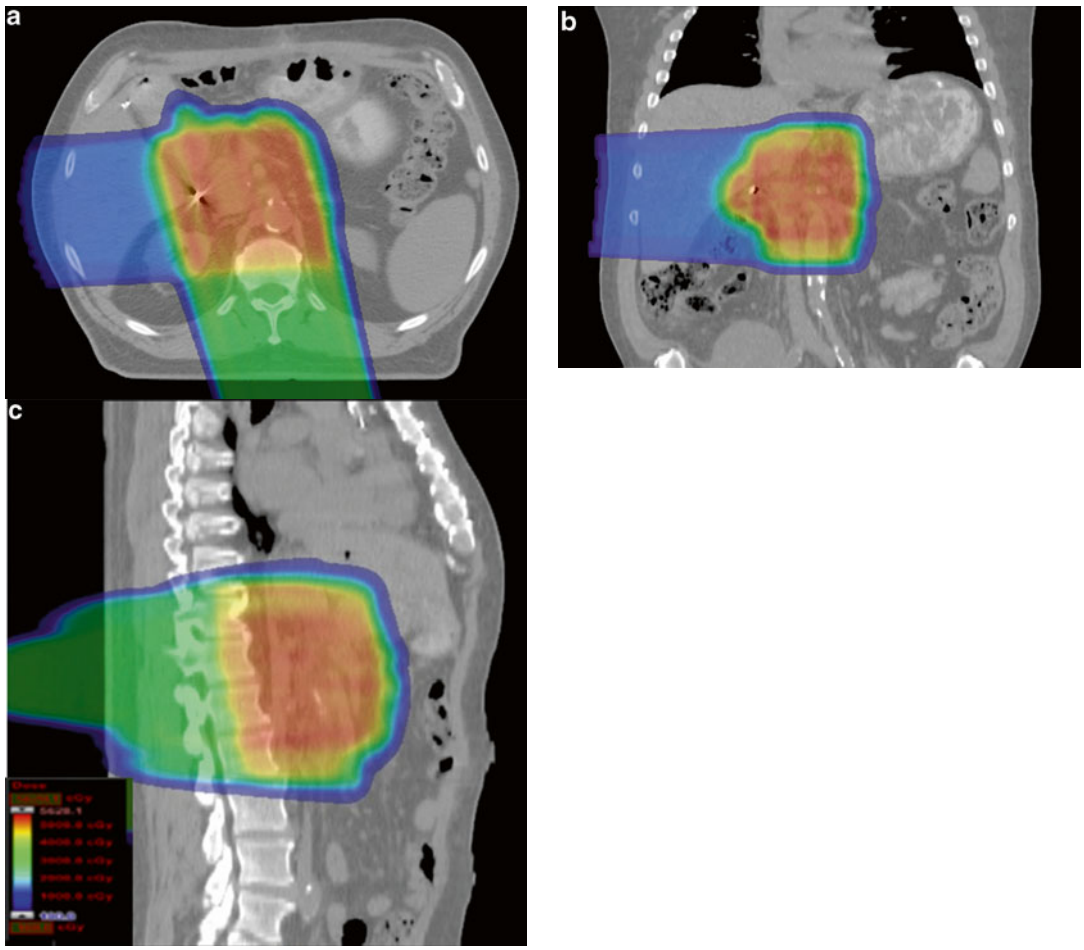

Fig. 18.12 By exploiting the spread-out Bragg peak, proton therapy allows for coverage of the tumor target while completely excluding large volumes of normal bowel and stomach. (**a**) Sagittal view; (**b**) coronal view; (**c**) sagittal view

- That approximately one third of the patients enrolled on the chemotherapy vs. no-chemotherapy arms actually received radiotherapy or background chemotherapy
- That the radiotherapy arms utilized a split-dose delivery, which is well recognized to be inferior from a radiobiological standpoint when compared with continuous-course treatment

As a result of the publication of the ESPAC-1 trial, chemotherapy alone represents the standard adjuvant therapy in Europe for patients who have undergone surgery for pancreatic cancer.

In light of the controversy regarding the value of postoperative radiotherapy, a multi-institutional trial involving NRG Oncology, Southwest Oncology Group, and European Organisation for Research and Treatment of Cancer (EORTC) is accruing patients who have had R0 or R1 resections for pancreatic head cancers [23]. The study offers a randomization between systemic therapy alone vs. systemic therapy plus chemoradiation (50.4 Gy with concomitant capecitabine or 5-FU).

Preoperative Radiotherapy

Planned preoperative radiotherapy is becoming recognized as a rational approach for patients with both resectable and marginally resectable disease. Advantages of preoperative radiotherapy include the following:

1. Sterilization of microscopic disease within the radiotherapy field to reduce the risk of hematogenous dissemination of malignancy at the time of surgery
2. Shrinkage of tumor to reduce the risk of positive surgical margins
3. Increased biologic efficacy of radiotherapy (compared to postoperative radiotherapy) since the irradiated tumor is well vascularized and well oxygenated
4. Elimination of a lengthy potential delay between surgery and radiotherapy

A frequently cited argument in favor of neoadjuvant therapies, particularly those that include chemotherapy, has been that neoadjuvant therapy, by delaying surgery, allows for identification of patients who develop hematogenous metastases during the neoadjuvant therapy. Recognition of such dissemination would spare those patients from a major surgical intervention that would be without curative potential.

Planned preoperative therapy for patients with pancreatic malignancy would be consistent with the evolving standard of care for other gastrointestinal malignancies, such as rectal and esophageal cancer, where preoperative radiotherapy represents a recognized and preferred treatment approach.

Although no prospective randomized trial has compared preoperative radiotherapy or preoperative chemoradiation with a surgery-first approach, some single-institution studies have demonstrated the feasibility of this approach with encouraging efficacy [24–27].

Definitive Radiotherapy

The most common use of radiotherapy for patients with pancreatic malignancy involves the treatment of patients with unresectable disease. The median survival for these patients is poor—in the range of 8.3–11.1 months [28–32], although some single-institution series have reported superior outcomes. Occasionally, patients treated with definitive radiotherapy for unresectable disease achieve a response allowing for curative surgery to be performed.

Palliative Radiotherapy for Disseminated Malignancy

The role of radiotherapy in the palliative treatment of metastatic pancreatic cancer is similar to the role of radiotherapy in the treatment of other disseminated malignancies. The radio-responsiveness of metastatic pancreatic cancer appears similar to the radio-responsiveness of other adenocarcinomas. Common sites of metastasis treatable with palliative radiation therapy

include symptomatic bone lesions. Additionally, therapies such as SABR may be used in the setting of oligometastases or limited metastases involving the liver or lung.

Summary

While most patients with pancreatic adenocarcinoma die as a result of hematogenous dissemination of their malignancy, some die exclusively with local and regional progression. Unfortunately, surgery as the sole definitive treatment frequently fails to secure local or regional disease control even in the setting of "resectable" disease. Radiotherapy can improve local control rates when used in conjunction with surgery and, occasionally, secure local disease control nonoperatively when delivered in conjunction with chemotherapy.

The value of conventionally delivered postoperative radiotherapy may be limited by the long delay between surgery and the initiation of radiotherapy resulting from postoperative convalescence. Additionally, postoperative radiotherapy doses tend to be limited because of transposed small bowel. While preoperative neoadjuvant radiotherapy may make sense from an oncologic perspective, many surgeons are reluctant to perform major pancreatic operations in previously irradiated fields. It is possible that the emergence of newer radiotherapy technologies, such as particle therapy using protons or carbon ions, will be associated with reduced critical normal-tissue exposure and allow for more widescale adoption of preoperative radiotherapy in the setting of this malignancy.

References

1. Hsiung-Stripp DC, McDonough J, Masters HM, et al. Comparative treatment planning between proton and X-ray therapy in pancreatic cancer. Med Dosim. 2001;26:255–9.
2. Bouchard M, Amos RA, Briere TM, et al. Dose escalation with proton or photon radiation treatment for pancreatic cancer. Radiother Oncol. 2009;92:238–43.
3. Kozak KR, Kachnic LA, Adams J, et al. Dosimetric feasibility of hypofractionated proton radiotherapy for neoadjuvant pancreatic cancer treatment. Int J Radiat Oncol Biol Phys. 2007;68:1557–66.
4. Nichols Jr RC, Huh SN, Prado KL, et al. Protons offer reduced normal-tissue exposure for patients receiving postoperative radiotherapy for resected pancreatic head cancer. Int J Radiat Oncol Biol Phys. 2012;83:158–63.
5. Zurlo A, Lomax A, Hoess A, et al. The role of proton therapy in the treatment of large irradiation volumes: a comparative planning study of pancreatic and biliary tumors. Int J Radiat Oncol Biol Phys. 2000;48:277–88.
6. Nichols Jr RC, George TJ, Zaiden Jr RA, et al. Proton therapy with concomitant capecitabine for pancreatic and ampullary cancers is associated with a low incidence of gastrointestinal toxicity. Acta Oncol. 2013;52:498–505.
7. Sachsman S, Nichols RC, Morris CG, Zaiden R, Johnson EA, Awad Z, Bose D, Ho MW, Huh SN, Li Z, Kelly P, Hoppe BS. Proton therapy and concomitant capecitabine for non-metastatic unresectable pancreatic adenocarcinoma. Int J Particle Ther. 2014;1(3):692–701.
8. Hong TS, Ryan DP, Blaszkowsky LS, et al. Phase I study of preoperative short-course chemoradiation with proton beam therapy and capecitabine for resectable pancreatic ductal adenocarcinoma of the head. Int J Radiat Oncol Biol Phys. 2011;79:151–7.
9. Raben A, Mychalczak B, Brennan MF, et al. Feasibility study of the treatment of primary unresectable carcinoma of the pancreas with 103Pd brachytherapy. Int J Radiat Oncol Biol Phys. 1996;35:351–6.
10. Peretz T, Nori D, Hilaris B, et al. Treatment of primary unresectable carcinoma of the pancreas with I-125 implantation. Int J Radiat Oncol Biol Phys. 1989;17:931–5.
11. Goodman KA, Regine WF, Dawson LA, et al. Radiation Therapy Oncology Group consensus panel guidelines for the delineation of the clinical target volume in the postoperative treatment of pancreatic head cancer. Int J Radiat Oncol Biol Phys. 2012;83:901–8.
12. Winter JM, Brennan MF, Tang LH, et al. Survival after resection of pancreatic adenocarcinoma: results from a single institution over three decades. Ann Surg Oncol. 2012;19:169–75.
13. Pawlik TM, Gleisner AL, Cameron JL, et al. Prognostic relevance of lymph node ratio following pancreaticoduodenectomy for pancreatic cancer. Surgery. 2007;141:610–8.
14. Tepper J, Nardi G, Sutt H. Carcinoma of the pancreas: review of MGH experience from 1963 to 1973. Analysis of surgical failure and implications for radiation therapy. Cancer. 1976;37:1519–24.
15. Gudjonsson B. Cancer of the pancreas. 50 years of surgery. Cancer. 1987;60:2284–303.
16. Hattangadi JA, Hong TS, Yeap BY, et al. Results and patterns of failure in patients treated with adjuvant combined chemoradiation therapy for resected pancreatic adenocarcinoma. Cancer. 2009;115:3640–50.

17. Regine WF, Winter KA, Abrams RA, et al. Fluorouracil vs gemcitabine chemotherapy before and after fluorouracil-based chemoradiation following resection of pancreatic adenocarcinoma: a randomized controlled trial. JAMA. 2008;299:1019–26.
18. Further evidence of effective adjuvant combined radiation and chemotherapy following curative resection of pancreatic cancer. Gastrointestinal Tumor Study Group. Cancer 1987;59:2006–10.
19. Neoptolemos JP, Dunn JA, Stocken DD, et al. Adjuvant chemoradiotherapy and chemotherapy in resectable pancreatic cancer: a randomised controlled trial. Lancet. 2001;358:1576–85.
20. Neoptolemos JP, Stocken DD, Friess H, et al. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. N Engl J Med. 2004;350:1200–10.
21. Abrams RA, Winter KA, Regine WF, et al. Failure to adhere to protocol specified radiation therapy guidelines was associated with decreased survival in RTOG 9704—a phase III trial of adjuvant chemotherapy and chemoradiotherapy for patients with resected adenocarcinoma of the pancreas. Int J Radiat Oncol Biol Phys. 2012;82:809–16.
22. Abrams RA, Lillemoe KD, Piantadosi S. Continuing controversy over adjuvant therapy of pancreatic cancer. Lancet. 2001;358:1565–6.
23. Abrams RA. RTOG 0848 Protocol Information. Radiation Therapy Oncology Group. 2014. http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0848.
24. Kim EJ, Ben-Josef E, Herman JM, et al. A multi-institutional phase 2 study of neoadjuvant gemcitabine and oxaliplatin with radiation therapy in patients with pancreatic cancer. Cancer. 2013;119:2692–700.
25. Shinoto M, Yamada S, Yasuda S, et al. Phase 1 trial of preoperative, short-course carbon-ion radiotherapy for patients with resectable pancreatic cancer. Cancer. 2013;119:45–51.
26. Pipas JM, Zaki BI, McGowan MM, et al. Neoadjuvant cetuximab, twice-weekly gemcitabine, and intensity-modulated radiotherapy (IMRT) in patients with pancreatic adenocarcinoma. Ann Oncol. 2012;23:2820–7.
27. Le Scodan R, Mornex F, Girard N, et al. Preoperative chemoradiation in potentially resectable pancreatic adenocarcinoma: feasibility, treatment effect evaluation and prognostic factors, analysis of the SFRO-FFCD 9704 trial and literature review. Ann Oncol. 2009;20:1387–96.
28. Hazel JJ, Thirlwell MP, Huggins M, et al. Multi-drug chemotherapy with and without radiation for carcinoma of the stomach and pancreas: a prospective randomized trial. J Can Assoc Radiol. 1981;32:164–5.
29. Klaassen DJ, MacIntyre JM, Catton GE, et al. Treatment of locally unresectable cancer of the stomach and pancreas: a randomized comparison of 5-fluorouracil alone with radiation plus concurrent and maintenance 5-fluorouracil—an Eastern Cooperative Oncology Group study. J Clin Oncol. 1985;3:373–8.
30. Treatment of locally unresectable carcinoma of the pancreas: comparison of combined-modality therapy (chemotherapy plus radiotherapy) to chemotherapy alone. Gastrointestinal Tumor Study Group. J Natl Cancer Inst 1988;80:751–5.
31. Poplin E, Feng Y, Berlin J, et al. Phase III, randomized study of gemcitabine and oxaliplatin versus gemcitabine (fixed-dose rate infusion) compared with gemcitabine (30-minute infusion) in patients with pancreatic carcinoma E6201: a trial of the Eastern Cooperative Oncology Group. J Clin Oncol. 2009;27:3778–85.
32. Loehrer Sr PJ, Feng Y, Cardenes H, et al. Gemcitabine alone versus gemcitabine plus radiotherapy in patients with locally advanced pancreatic cancer: an Eastern Cooperative Oncology Group trial. J Clin Oncol. 2011;29:4105–12.

Chemotherapy

19

Sarunas Sliesoraitis and Thomas J. George Jr.

Introduction

Pancreatic adenocarcinoma represents the fourth leading cause of cancer death in the United States, with most patients diagnosed with advanced disease or recurrence shortly after a surgical attempt at cure. Overall only 5% of diagnosed patients are alive at 5 years [1]. Surgery remains the only therapy with which cure is possible; thus, systemic therapy typically provides palliative disease and symptom control. The only exception is in the perioperative setting, where eradication of occult disease with systemic chemotherapy as an adjunct to surgery improves survival. Despite a paucity of clinical progress for several decades, the last few years have demonstrated an explosion of effort to bring new and effective systemic therapies to the clinic. Recent results from clinical trials assessing combination chemotherapy in pancreatic adenocarcinoma including FOLFIRINOX, gemcitabine with nab-paclitaxel, and gemcitabine with erlotinib have each met primary end points for overall survival improvement. Several additional studies are ongoing in an attempt to move these effective therapies into earlier stages of the disease in an effort to improve curability. Similar to pancreatic adenocarcinoma, pancreatic neuroendocrine tumors have seen a significant boost in effective systemic therapies. These treatments, including octreotide, chemotherapy, and targeted therapies, provide patients meaningful symptom and disease control. This chapter will review these contemporary study results, in the context of historical data, which support these improvements in clinical care for both pancreatic adenocarcinoma and neuroendocrine tumors.

Resectable Pancreatic Adenocarcinoma

Adjuvant Therapy

Following curative resection of pancreatic cancer, most patients recur with diffuse metastases in the liver and/or lungs. Attention has therefore been given to the use of postoperative systemic chemotherapy to sterilize occult micrometastases and thus improve survival. Prominent cancer treatment guidelines recommend adjuvant chemotherapy with or without radiation to decrease cancer recurrence rates and increase survival [2, 3]. The benefits of chemotherapy are more established than for radiotherapy in this setting. In this section we will review the evidence for these recommendations.

S. Sliesoraitis, D.O., Pharm.D.
T.J. George Jr., M.D., F.A.C.P. (✉)
Division of Oncology, Department of Medicine,
University of Florida, 1600 SW Archer Rd.,
PO Box 100278, Gainesville, FL 32610, USA
e-mail: thom.george@medicine.ufl.edu

M.S. Wagh, P.V. Draganov (eds.), *Pancreatic Masses*, DOI 10.1007/978-3-319-19677-0_19

Table 19.1 Adjuvant therapy trials for pancreatic adenocarcinoma

Study (reference)	Treatment	Control	Patients (n = total)	Median OS (mo)	5-year OS (%)	p-Value
GITSG [5]	CRT → 5-FU	Obs	43	20 vs. 11	18 vs. 8	0.3
EORTC 40891 [4]	CRT	Obs	218	24.5 vs. 19	51 vs. 41 (2 years)	0.208
ESPAC-1 [7, 8]	CRT → 5-FU; CRT; 5-FU	Obs	289	20.1 vs. 15.5 (chemo vs. not)	21 vs. 8 (chemo vs. not)	0.009
RTOG 9704 [10]	5-FU → CRT → 5-FU	Gem → CRT → Gem	451	17.1 vs. 20.5	18 vs. 22	0.12
JSAP-02 [13]	Gem (3 months)	Obs	118	22.3 vs. 18.4	48 vs. 40 (2 years)	0.19
CONCO-001 [14]	Gem (6 months)	Obs	354	22.8 vs. 20.2	20.7 vs. 10.4	0.01
ESPAC-3 [17]	Gem (6 months)	5-FU (6 months)	1088	23.6 vs. 23	NR	0.39

CRT chemoradiation, *5FU* 5-fluorouracil systemic chemotherapy, *Gem* gemcitabine systemic chemotherapy, *NR* not reported, *Obs* observation, *OS* overall survival

Several phase III trials have investigated the role of adjuvant chemoradiation treatments (CRT) in resected pancreatic cancer (Table 19.1). The Gastrointestinal Tumor Study Group (GITSG) trial randomized 43 patients to surgery alone or surgery followed by adjuvant CRT using bolus 5-fluorouracil (5-FU) during split-course radiotherapy (40 Gy total) and additional 5-FU adjuvant chemotherapy for 2 years thereafter [4, 5]. The adjuvant treatment group experienced longer median survival (20 vs. 11 months; p=0.3) compared to surgery alone. This relatively small trial established adjuvant 5-FU with radiation as a standard treatment for patients with resected pancreatic cancers.

However, other investigators questioned the magnitude of the benefit. The European Organisation for Research and Treatment of Cancer (EORTC) conducted a similar trial aimed to confirm the previous GITSG results [6]. In this EORTC study, after resection of the pancreatic head or periampullary region, patients with T1-2, N0-1 disease were randomized to either surgery alone vs. surgery plus adjuvant 5-FU with radiation. The 5-FU in this study was administered by continuous infusion at 25 mg/kg per 24 h (maximal daily dose of 1500 mg) starting the same time each day prior to radiotherapy. The radiation was given at 2 Gy per day Monday through Friday × 2 weeks and repeated again in 2 weeks (40 Gy total). Importantly, no additional systemic adjuvant chemotherapy was given after the CRT. Between 1987 and 1995, 110 patients were randomized to the treatment group and 108 patients to the observational group. The median survival was 24.5 months in the treatment group vs. 19.0 months for the observation groups (p=0.208) with 2-year survival estimates of 51% vs. 41%, respectively. The authors concluded that any benefit from adjuvant therapy appears to be small and CRT should not be the standard of care after the resection of the pancreatic head and periampullary region pancreatic cancers. The study was also criticized similar to the GITSG trial for a small sample size as well as the 5-FU dosing schedule and lack of systemic chemotherapy after CRT. After 11.7 years of follow-up in an updated analysis, the CRT group showed no difference in progression-free (30% vs. 32%) or overall survival (HR, 0.91; 95% CI, 0.68–1.23; p=0.540) [4]. Median survival (1.8 months) and 5-year survival rates (~25%) were nearly identical between the two arms. Similarly to prior studies, the authors concluded that although the CRT was well tolerated, it provided no improvement in survival.

Subsequently, the European Study Group for Pancreatic Cancer (ESPAC-1) recruited 289 patients to determine the effect of adjuvant therapy components after resection [7, 8]. In this two-by-two factorial design, patients following definitive resection were randomized to observation (n=69), CRT (n=73), chemotherapy alone (n=75), or CRT followed by chemotherapy (n=72). The CRT consisted of a 20-Gy dose given to the surgical tumor bed in 10 daily fractions over a 2-week period concurrent with IV

bolus 5-FU (500 mg/m^2 on the first 3 days of radiotherapy) repeated again after a planned break of 2 weeks. The chemotherapy arm included 6 months of IV bolus 5-FU (425 mg/m^2 on days 1–5 every 28 days). Finally, the CRT with chemotherapy arm included both of the above treatment protocols. Median survival was improved in patients receiving systemic chemotherapy, 20.1 months compared to 15.5 months for those not receiving chemotherapy (HR, 0.71; 95% CI, 0.55–0.92; $p=0.009$). Estimated survival at 5 years also significantly favored those receiving chemotherapy (21% vs. 8%; $p=0.009$). The use of CRT demonstrated a decreased median survival of 15.9 months compared to 17.9 months for those patients not receiving CRT (HR, 1.28; 95% CI, 0.99–1.66; $p=0.05$) with similarly worse 5-year survival estimates (10% vs. 20%, respectively; $p=0.05$). The authors concluded that adjuvant chemotherapy, but not CRT, improves survival in patients with resected pancreatic cancer. The study was criticized due to lack of quality control in the radiation group and lack of strict treatment assignments [9].

Shortly after the approval of gemcitabine for advanced disease [10] and due to conflicting results of the above studies, the U.S.-based Radiation Therapy Oncology Group (RTOG) randomized 451 patients with T1-4, N0-1, M0 disease following tumor resection to CRT with either 5-FU or gemcitabine [11]. The randomization to both arms included chemotherapy followed by CRT followed by more chemotherapy with the type of systemic chemotherapy before and after CRT representing the variable in the study. Chemotherapy consisted of either continuous-infusion 5-FU (250 mg/m^2 per day for 3 weeks) or gemcitabine (1000 mg/m^2 IV once weekly for 3 weeks). This was followed by CRT concurrently with continuous-infusion 5-FU (250 mg/m^2 daily with radiation delivered in 28 fractions 5 days/week to a total dose of 50.4 Gy). Three to 5 weeks after completion of the CRT, patients resumed either 5-FU or gemcitabine (based on their initial randomization) to complete 3 additional months of chemotherapy. Adverse events were common in both groups with grade 3 or higher hematologic toxicity with gemcitabine occurring in 58% compared to 9% with 5-FU. Diarrhea, stomatitis, and nausea/vomiting were more common with 5-FU. With a median follow-up of 1.5 years for all patients, the investigators did not observe any difference in survival. The median survival was 20.5 vs. 16.9 months with a 3-year survival of 31% vs. 22% in gemcitabine vs. fluorouracil arms, respectively (HR, 0.82; 95% CI, 0.65–1.03; $p=0.09$). Updated analysis at 5 years continued to show no statistically significant difference in survival between the groups [12]. Given the toxicity profile differences and similar survival outcomes, the authors concluded that in the context of adjuvant CRT, the use of systemic gemcitabine may be preferred.

Given that the ESPAC-1 trial did not show a benefit of CRT (in fact, it demonstrated a detriment), three subsequent studies employed adjuvant chemotherapy alone after surgical resection. First, the Japanese Study Group of Adjuvant Therapy for Pancreatic (JSAP-02) trial randomized 118 patients with resected disease to either observation or gemcitabine [13]. With 3 months of adjuvant gemcitabine (1000 mg/m^2 IV on days 1, 8, and 15 every 4 weeks), hematological toxicities were common, including 70% grade 3 or 4 neutropenia. Median overall survival was 22.3 vs. 18.4 months in favor of adjuvant gemcitabine (HR, 0.77; 95% CI, 0.51–1.14; $p=0.19$). A non-significant trend toward improvement in 2-year overall survival (48% vs. 40%) also favored gemcitabine.

The second adjuvant chemotherapy trial was conducted by the German Study Group for Pancreatic Cancer (CONKO-1). The investigators randomized 368 patients with T1-4, N0-1, M0 completely macroscopically resected pancreatic cancers to either observation or gemcitabine chemotherapy [14]. Gemcitabine was identical to the JSAP-02 study [13] but provided for a total of 6 months [15]. Most of the patients on the study had node-positive disease (70%). Toxicity was similar to what had previously been reported with this agent in pancreatic cancer. The 5-year overall survival rate was improved in the treatment group (20.7%) compared to observation (10.4%) (HR, 0.76; 95% CI, 0.61–0.95; $p=0.01$) [14].

Finally, the European Study Group for Pancreatic Cancer (ESPAC-3) randomized 1088 patients after complete macroscopic resection to either 5-FU or gemcitabine adjuvant chemotherapy [16]. Treatment with adjuvant chemotherapy was also for 6 months with the randomization between 5-FU (IV bolus folinic acid 20 mg/m^2 followed by 5-FU 425 mg/m^2 given for 5 consecutive days every 28 days) or gemcitabine (1000 mg/m^2 IV once a week for 3 out of every 4 weeks). Slightly more patients in the gemcitabine group received all six cycles of the planned chemotherapy (55% vs. 60%) as well as receiving a higher median dose intensity (79% vs. 89%). The hematological toxicities were similar between the two groups with grade 3–4 neutropenia of 22% in both groups, but there was more grade 3–4 diarrhea (13% vs. 2%) and stomatitis (10% vs. 0%) associated with 5-FU treatment. Estimated median survival rates were no different between the groups (23.2 vs. 23 months; $p = 0.39$).

Given challenges with postoperative recovery, a post hoc analysis of the ESPAC-3 data assessed the duration and timing of chemotherapy initiation [17]. In this analysis patients who were able to complete all 6 cycles of adjuvant chemotherapy were compared to those receiving <6 or an unspecified number of cycles. Those completing 6 months of chemotherapy had increased survival compared to less chemotherapy (28.0 vs. 14.6 months; $p < 0.001$). The time to starting chemotherapy after surgery even up to 12 weeks did not appear to influence survival. Although these findings may be related to study bias and confounding, they support the clinical practice that adjuvant chemotherapy may be initiated within 12 weeks of surgery, provided the added delay allows adequate recovery for patients to complete the full adjuvant treatment plan.

Summary. Adjuvant Therapy in Resected Pancreatic Adenocarcinoma

- Chemotherapy for 6 months after recovery from resection (up to 12 weeks) represents a standard of care.
- The choice of chemotherapy is either gemcitabine or 5-FU, noting different toxicity profiles and schedules.
- CRT may be considered in select patients in the adjuvant setting, but it is unclear if it improves outcomes.

Neoadjuvant Therapy

The vast majority of patients with resectable pancreatic cancer relapse at distant sites, emphasizing the need for more effective systemic therapies. Up to 25% of otherwise eligible patients never receive adjuvant chemotherapy due to surgical complications and delayed recovery [18]. Theoretically, chemotherapy given prior to surgery may improve tumor tissue penetration due to intact vasculature, decrease chemotherapy-associated toxicity, improve time to initiation of systemic treatment, and identify patients with a biologic predisposition to disease who would benefit from a major surgical intervention [18, 19]. However, despite these potential advantages, data to support this approach are limited to phase II studies. These studies are difficult to compare given that the definition of resectable and borderline resectable pancreatic cancer has only recently been consistently applied to pancreatic cancer clinical trials (Table 19.2) [2, 20].

One of the largest phase II trials published to date enrolled 86 patients with resectable pancreatic cancer. Neoadjuvant treatment consisted of CRT using gemcitabine (400 mg/m^2 IV weekly for a total of 7 doses) concurrent with radiotherapy (3 Gy per day delivered 5 days per week for a total of 2 weeks; 30 Gy total) [21]. All patients completed CRT and underwent restaging 4–6 weeks thereafter. However, only 74 went on to have surgery due to disease progression and previously unapparent medical comorbidities. Another 9 patients were found to have surgically unresectable disease at the time of attempted resection with occult hepatic or peritoneal metastatic implants not identified on preop imaging. Ultimately 64 patients (74%) had successful tumor resection. The entire cohort had a median overall survival of 22.7 months. However, the median survival was significantly improved in the surgically resected group compared to those who did not complete a surgical resection (34 vs. 7 months; $p < 0.001$).

Table 19.2 Definition of Resectable, Borderline Resectable, and Unresectable Pancreatic Adenocarcinoma by Cross-Sectional Imaging

Resectable	• Clear fat planes around celiac axis, hepatic artery, and SMA
	• No radiographic evidence of SMV or PV distortion
Borderline resectable	• Venous involvement of the SMV or PV with distortion of narrowing of the vein or occlusion of the vein with suitable vessel proximal and distal, allowing for safe resection and replacement
	• Encasement of a short segment of the hepatic artery, without evidence of tumor extension to the celiac axis and/or tumor abutment of the SMA involving ≤180° of the artery's circumference
Unresectable/ locally advanced	• Major venous thrombosis of the PV or SMV extending for several centimeters
	• Circumferential encasement of the SMA, celiac axis, or proximal hepatic artery

Source: From NCCN 2014 [2, 20]
SMA superior mesenteric artery, *SMV* superior mesenteric vein, *PV* portal vein

The 5-year overall survival was also improved in those having completed resection (36% vs. 0%). The investigators concluded that the provision of gemcitabine-based CRT successfully selected patients most likely to benefit from surgery. It was notable in this study that of the patients not benefiting from surgery, most had distant disease progression or were found to have peritoneal implants and/or hepatic metastases, but not local tumor progression. This further emphasizes the important biologic characteristic of early systematic disease spread.

It is important to distinguish between patients with pancreatic adenocarcinoma who are surgically resectable, borderline resectable, or locally advanced/unresectable. In each of these situations, patients do not have overt signs of metastases, but patients with locally advanced/unresectable disease are treated with palliative intentions. Neoadjuvant therapy has been tested as a "conversion" treatment, defined as "converting" a patient from inoperable to operable. Investigators from Massachusetts General Hospital reported their data of neoadjuvant chemotherapy in locally advanced disease [22]. Twenty-two patients were treated with 2 months of FOLFIRINOX (see section on "Metastatic Disease" for details) and then restaged. If stable disease or better was noted, patients were treated with infusional 5-FU or capecitabine with intensity-modulated radiation (50.4 Gy in 28 fractions). The most common toxicities were hematologic, infectious, and diarrhea. Five out of the 22 patients were able to undergo an attempted resection; however, three subsequently recurred. The authors questioned the utility of this approach. In general, patients with locally advanced pancreatic adenocarcinoma are highly unlikely to "convert" to resectable with currently available modalities of therapy and should be treated with palliative goals.

Summary. Neoadjuvant Therapy in Resectable Pancreatic Adenocarcinoma

- May be used to select patients most likely to benefit from surgery.
- No randomized controlled trials have determined the absolute benefit of a neoadjuvant therapy compared to a conventional approach.
- Should be considered investigational and performed in the context of a clinical trial, but of high clinical importance, particularly for borderline resectable cases.

Advanced and Metastatic Pancreatic Adenocarcinoma

Patients with unresectable or metastatic pancreatic adenocarcinoma are candidates for palliative interventions. Goals of palliative chemotherapy for this patient population are to delay or prevent symptoms associated with disease progression, maintain quality of life, and extend life. Some of these goals can be accomplished with or without chemotherapy. One of the most important variables to consider in determining candidacy for palliative chemotherapy is the patient's clinical performance status (PS), a global composite

Table 19.3 Select positive randomized controlled clinical trials in advanced and metastatic pancreatic adenocarcinoma

Study (reference)	Treatment	Control	Patients (n=total)	Median OS (mo)	1-Year OS (%)	p-Value (median OS)
Burris III HA [10]	Gem	5-FU	126	5.6 vs. 4.4	18 vs. 2	0.0025
NCI Canada [24]	Gem+erlotinib	Gem	569	6.2 vs. 5.9	23 vs. 17	0.038
Von Hoff DD [25]	Gem+nab-paclitaxel	Gem	861	8.5 vs. 6.7	35 vs. 22	<0.001
Groupe Tumeurs Digestives of Unicancer and the PRODIGE Intergroup [26]	FOLFIRINOX	Gem	342	11.1 vs. 6.8	48 vs. 20	<0.001

5FU 5-fluorouracil, *FOLFIRINOX* 5FU, folinic acid, irinotecan, oxaliplatin, *Gem* gemcitabine, *nab* nanoparticle albumin bound, *OS* overall survival

representation of a patient's ability to manage the short-term side effects of therapy and thus obtain longer-term benefit from the treatments. Despite multiple attempts to improve survival with innovative treatment combinations, only a few have demonstrated a survival benefit (Tables 19.3 and 19.4). In this section we review the pertinent trials which now form the mainstay of therapy and form a solid foundation upon which to further improve clinical outcomes.

In 1997, a landmark trial was published comparing gemcitabine with 5-FU in 126 patients with advanced pancreatic cancer [10]. The investigators chose 5-FU as a comparison group because it had previously shown some minor benefit in the treatment of pancreatic cancer and many considered it to be the standard treatment. A relatively nontraditional primary study endpoint was selected, the clinical benefit response, which was defined as a composite measure of patient weight, Karnofsky PS, and pain as assessed by analgesic consumption and pain intensity. This endpoint was felt to better represent the palliative goals desired in patients with this advanced disease. Survival was a secondary endpoint. Treatment consisted of either 5-FU (600 mg/m^2 weekly during a 28-day cycle) or gemcitabine (1000 mg/m^2 weekly for 7 weeks, followed by 1 week off, then weekly for 3 weeks out of every 4-week cycle). The gemcitabine group experienced more grade 3–4 neutropenia (25.9% vs. 4.9%) and anemia (9.7% vs. 0%). Despite these side effects, more patients in the gemcitabine group experienced clinical benefit (23.8% vs. 4.8%; p=0.022), which was the primary rationale for gemcitabine to receive subsequent FDA approval. Of note, gemcitabine also demonstrated an improvement in median overall survival (5.6 vs. 4.4 months; p=0.0025) and survival at 1 year (18% vs. 2%). Unfortunately, multiple subsequent studies failed to demonstrate any significant improvements to this new standard, despite promising scientific rationale and activity in early phase studies (Table 19.4).

A meta-analysis evaluating 51 trials with over 9970 patients found that chemotherapy improved overall survival as compared to best supportive care (HR, 0.64; 95% CI, 0.42–0.98) [23]. The analysis could not establish any superiority in survival for gemcitabine compared to 5-FU (HR, 0.75; 95% CI, 0.42–1.31); however, authors were limited in their conclusions due to wide confidence intervals. Gemcitabine-based combination therapies did appear to provide a survival improvement compared to single-agent therapy (HR, 0.91; 95% CI, 0.85–0.97), particularly for patients with an excellent performance status.

The second study that changed clinical practice was conducted by the National Cancer Institute of Canada Clinical Trials Group. This trial randomized 569 patients with locally advanced or metastatic pancreatic cancer, Eastern Cooperative Group (ECOG) PS 0-2 to gemcitabine with either erlotinib (150 mg/day) or placebo until disease progression or toxicity [24]. The addition of erlotinib, a small molecule tyrosine kinase inhibitor targeting the epidermal growth factor receptor (EGFR), increased grade 3–4 toxicities, including diarrhea (6% vs. 2%),

Table 19.4 Selected negative clinical trials in advanced and metastatic pancreatic adenocarcinoma

Study (reference)	Treatment	Control	Patients (n = total)	Median OS (mo)	1-Year OS (%)	p-Value (median OS)
Boeck 2008 [58]	Cape+Ox, Cape+Gem, Gem+Ox	N/A	190	8.1 (Cape+Ox); 9.0 (Cape+Gem); 6.9 (Gem+Ox)	29 (Cap+Ox); 33 (Cape+Gem); 22 (Gem+Ox)	0.56
Colucci 2002 [59]	Gem+Cis	Gem	107	30 vs. 20 weeks	11 vs. 11.3	0.43
Colucci 2010 [60]	Gem+Cis	Gem	400	7.2 vs. 8.3	30.7 vs. 34	0.38
Van Cutsem 2009 [61]	Gem+Erl+Bev	Gem+Erl	607	7.1 vs. 6	NR	0.2087
Cunningham 2009 [62]	Gem+Cape	Gem	533	7.1 vs. 6.2	24.3 vs. 22	0.077
Gonçalves 2012 [63]	Gem+Sor	Gem	104	9.2 vs. 8	NR	0.231
Harder 2012 [64]	Tras+Cape	None	17	6.9	29.4	—
Heinemann 2006 [65]	Gem+Cis	Gem	195	7.5 vs. 6	25.3 vs. 24.7	0.15
Herrmann 2007 [66]	Gem+Cape	Gem	319	8.4 vs. 7.2	32 vs. 30	0.234
Kindler 2010 [67]	Gem+Axi	Gem	632	8.5 vs. 8.3	NR	0.5436
Kindler 2011 [68]	Gem+Bev	Gem	535	5.8 vs. 5.9	NR	0.95
Louvet 2005 [69]	Gem+Ox	Gem	313	9 vs. 7.4	34.7 vs. 27.8	0.13
Moore 2003 [70]	BAY 12-9566	Gem	277	3.7 vs. 6.5	10 vs. 25	<0.001
Oettle 2005 [71]	Gem+Pem	Gem	565	6.2 vs. 6.3	21.4 vs. 20.1	0.8477
Philip 2010 [72]	Gem+Cetux	Gem	745	6.3 vs. 5.9	NR	0.23
Poplin 2009 [73]	GemFDR and Gem+Ox	Gem	832	6.2 (GemFDR), 5.7 (Gem+Ox), 4.9 (Gem)	21 (GemFDR); 21 (Gem+Ox); 16 (Gem)	0.15
Reni 2005 [74]	Gem+Cis+Epi+5-FU	Gem	97	NR	38.5 vs. 21.3	NR
Rougier 2013 [75]	Gem+Aflib	Gem	427	6.5 vs. 7.8	21 vs. 25	0.2034
Stathopoulos 2006 [76]	Gem+Iri	Gem	145	6.4 vs. 6.5	24.3 vs. 21.8	0.970

Aflib aflibercept, *Axi* axitinib, *Cape* capecitabine, *Cetux* cetuximab, *Cis* cisplatin, *Epi* epirubicin, *Erl* erlotinib, *Gem* gemcitabine, *GemFDR* gemcitabine fixed dose rate infusion, *Iri* irinotecan, *Ox* oxaliplatin, *Pem* pemetrexed, *Sor* Sorafenib, *Tras* trastuzumab, *5FU* fluorouracil, *NR* not reported, *OS* overall survival

rash (6% vs. 1%), and interstitial lung disease–like syndrome (2.1% vs. 0.4%). More treatment-related deaths occurred in the erlotinib group (6 vs. 0 deaths), mostly related to interstitial lung disease–like syndrome, sepsis, and CVA. The combination of gemcitabine and erlotinib demonstrated an improved median overall survival (6.24 vs. 5.91 months; HR, 0.82; 95% CI, 0.69–0.99; $p=0.038$) and 1-year survival (23% vs. 17%; $p=0.023$). The development of an erlotinib-associated skin rash was associated with a significant improvement in survival compared to not developing a rash ($p=0.037$; HR, 0.74; 95% CI, 0.56–0.98). The severity of the rash also predicted survival, with median survival rates for patients with grade 0, 1+, and 2+ rash being 5.3, 5.8, and 10.5 months, respectively. These findings suggest that the drug-induced rash can serve as a clinical biomarker to predict benefit from therapy [24].

Albumin-bound nanoparticle paclitaxel (nab-paclitaxel) was developed to reduce toxicity associated with the traditional chemotherapy, paclitaxel, which was notable for infusion-associated reactions and peripheral neuropathy. This agent had preclinical activity demonstrated in pancreatic adenocarcinoma and was subsequently tested in combination with gemcitabine. In this registration study, Von Hoff and colleagues demonstrated the superiority of gemcitabine with nab-paclitaxel over gemcitabine alone [25]. Patients received standard doses of gemcitabine (1000 mg/m^2 IV weekly for 3 weeks every 4-week cycle) with or without nab-paclitaxel (125 mg/m^2 IV on day 1 of each cycle). As expected, patients receiving nab-paclitaxel with gemcitabine experienced more grade 3 neutropenia (38% vs. 27%), leukopenia (31% vs. 16%), fatigue (17% vs. 7%), peripheral neuropathy (17% vs. 1%), and diarrhea (6% vs. 1%), but also demonstrated improved survival (median survival 8.5 vs. 6.7 months; $p<0.001$).

An alternate approach was taken by French investigators. The Groupe Tumeurs Digestives of Unicancer and the PRODIGE Intergroup randomized 342 patients with ECOG PS 0-1 to either FOLFIRINOX or gemcitabine [26]. The FOLFIRINOX regimen includes several antineoplastic agents with demonstrated activity in other digestive malignancies and is based on a 5-FU backbone instead of gemcitabine. Treatment involved FOLFIRINOX (oxaliplatin 85 mg/m^2 IV followed by leucovorin 400 mg/m^2 IV over 2 h, irinotecan 180 mg/m^2 with 5-FU 400 mg/m^2 bolus followed by a 46-h 5-FU infusion 2400 mg/m^2) repeated every 2 weeks or gemcitabine at standard treatment doses. Patients receiving FOLFIRINOX experienced a greater number of grade 3 or 4 toxicities, including neutropenia (46% vs. 21%), febrile neutropenia (5.4% vs. 2.1%), thrombocytopenia (9.1% vs. 3.6%), diarrhea (12.7% vs. 1.8%), and neuropathy (9% vs. 0%). The patients receiving gemcitabine experienced more liver function test abnormalities (20.8% vs. 7.3%). Despite the increased toxicities, patients receiving FOLFIRINOX had a prolonged median survival (11.1 vs. 6.8 months) and 1-year survival (48.4% vs. 20.6%) and, interestingly, demonstrated improved patient-reported quality of life [27]. In an attempt to improve the side effect profile, several investigators are currently testing dose modifications of FOLFIRINOX (m-FOLFIRINOX), including elimination of the bolus 5-FU or across-the-board dose reductions of all agents. Whether these m-FOLFIRINOX regimens improve toxicity yet maintain efficacy is yet to be determined.

In Asia, S-1 is an active fluoropyrimidine therapy used in digestive malignancies. A study conducted in Taiwan and Japan evaluated if S-1 was not inferior to gemcitabine alone [28]. The Gemcitabine and S-1 Trial (GEST) randomized 834 patients to treatment with gemcitabine (1000 mg/m^2 IV weekly for 3 weeks every 4-week cycle), S-1 (dosed based upon body surface area between 80 and 120 mg daily for 28 days of a 42-day cycle), or the combination. Patients experienced more hematological and liver function test abnormalities of grade 3 and higher in the gemcitabine groups, and slightly more diarrhea, nausea, or vomiting in the groups receiving S-1. The S-1 alone was shown to be not inferior to gemcitabine in median survival (9.7 vs. 8.8 months), while the combination was not superior to gemcitabine alone (10.1 vs. 8.8 months). The authors concluded that S1 is not inferior and well tolerated compared to gemcitabine. This agent serves as a single-agent treatment option for patients with advanced pancreatic cancer in Asia.

With the therapeutic options and improvements seen with first-line therapy, the need presented to determine if there was any benefit to sequencing therapy in the second-line setting. The German CONKO-2 study compared best supportive care alone to that with the addition of OFF (oxaliplatin 85 mg/m^2 IV on days 8 and 22, folinic acid 200 mg/m^2 IV and 5-FU 2000 mg/m^2 IV over 24 h on days 1, 8, 15 and 22, followed by 3 weeks' rest and repeated every 6 weeks) in 46 patients with metastatic pancreatic cancer who had previous disease progression with gemcitabine [29]. Although tested in a highly selected group of patients, very few experienced grade 3 or 4 toxicities with active therapy. The median survival was improved with OFF administration (4.8 vs. 2.3 months; HR, 0.45; 95 % CI, 0.24–0.83; $p=0.008$). The study was stopped prematurely due to slow accrual; however, the authors concluded that second-line chemotherapy with best supportive care improves survival compared to best supportive care alone.

Although palliative chemotherapy options have improved in the metastatic setting, with resultant increases in survival, the prognosis for patients with this disease remains poor and advances in the identification of new biomarkers of response, relapse, and targeted therapeutics is urgently needed. In this regard, patient participation in clinical trials represents an important therapeutic option and is strongly endorsed as such in most clinical guidelines and pathways. Supportive care, including pain control, protein/energy balance, biliary patency, and maintenance of performance status, remains critical issues in the palliative setting and serve an important foundation before consideration of chemotherapy or any targeted therapy. Moving the most active and effective palliative agents into the pre- and postoperative settings is the focus of several currently ongoing clinical trials with results eagerly awaited.

Summary. Chemotherapy in Advanced Pancreatic Adenocarcinoma

- Chemotherapy is palliative and serves as a supplement to best supportive care.
- Goals of therapy are to prolong survival and improve the quality of life.
- FOLFIRINOX, nab-paclitaxel with gemcitabine, gemcitabine with erlotinib, gemcitabine alone, and S1 (not available in the United States) are all reasonable treatment options with improved overall survival in a first-line setting. The optimal choice is based upon expected side effects, patient performance status, and shared decision making.
- Participation in clinical trials with new therapies represents an important therapeutic option.

Pancreatic Neuroendocrine Cancers

Pancreatic neuroendocrine tumors (NETs account for 1% of cancer incidence, but include up to 10% of all pancreatic cancers [30]. These tumors represent a diverse group of cancers historically recognized by their potential to generate classic hormone syndromes. Thus, gastropancreatic neuroendocrine tumors are noted as functional or nonfunctional based on hormone or other bioactive agent secretion (Table 19.5). These tumors are then further) classified based on the tumor grade, Ki-67 index, and TNM criteria, which are each good predictors for survival [31]. The tumor grade is based on the number of mitoses per 10 high-power field (HPF) (Table 19.6). Grade I tumors are defined by <2 mitoses per 10 HPF and/or Ki-67 < 2%. Grade II tumors have 2–20 mitoses per 10 HPF and/or Ki-67 index 3–20%. Grade III includes tumors with >21 mitoses per HPF and/or Ki-67 index > 20 % [32]. These markers of nuclear activity help guide risk stratification and selection of treatment, particularly in advanced disease.

Perioperative Medical Management

Although surgery is the only curative modality for this disease, 30–85% of pancreatic NETs have hepatic metastases at presentation [33]. These metastases can be best visualized with contrast-enhanced magnetic resonance imaging (MRI) or triple-phase computed tomography (CT) imaging of the liver. Pancreatic NET metastases have a characteristic arterial phase of enhancement and are commonly underappreciated at diagnosis

Table 19.5 Pancreatic neuroendocrine tumor hormone(s) produced, symptoms and management options [31, 32, 77]

NET type	Hormone	Symptoms/Signs	Management options
ACTH-producing tumor	ACTH	Cushings	Somatostatin analogs
Insulinoma	Insulin	Hypoglycemia, confusion, weakness, headache	Diazoxide
Gastrinoma	Gastrin	Zollinger–Ellison syndrome, gastric ulcers, diarrhea, fat malabsorption	PPI or H2 blockers
Glucagonoma	Glucagon	Diabetes, necrolytic migratory erythema, weight loss (fluid), poor healing	Somatostatin analogs
VIPomas	VIP	Flushing, nausea, vomiting, diarrhea	Somatostatin analogs, loperamide, cholestyramine, 5-HT_3 antagonists

ACTH, adrenocorticotropic hormone; *VIP,* vasoactive intestinal peptide; *PPI,* proton pump inhibitor

Table 19.6 Pancreatic neuroendocrine tumor grading (European Neuroendocrine Tumor Society [32])

Grade I	<2 mitosis per 10 HPF and/or Ki-67 <2 %
Grade II	2–20 mitosis per 10 HPF and/or Ki-67 index 3–20%
Grade III	>21 mitosis per HPF and/or Ki-67 index >20 %

without the appropriate use and phase of IV contrast (Fig. 19.1). FDG-PET scanning has a very limited role in the vast majority of this disease owing to the low metabolic rate of most NETs. For low- and intermediate-grade tumors, resection of oligo or isolated hepatic metastases can still provide a cure with up to 85% 5-year survival being reported in highly selected patient cohorts. Unfortunately, only 7–15% of patients are completely resectable at diagnosis.

To avoid a carcinoid crisis with manipulation/removal of any tumor at surgery, octreotide is infused 50 μg/h for 12 h prior to surgery and continued for 24–48 h after, even in patients receiving long-acting octreotide [31]. In initially asymptomatic patients with NETs (functional or nonfunctional), an unanticipated carcinoid crisis can be treated with a bolus octreotide 100–500 μg followed by continuous infusion at 50 μg/h for 24–48 h after. Depending on the hormones produced by the tumor, a number of additional supportive care measures could be instituted (Table 19.5). Given the risk of biliary sludging and gallstone formation with long-term octreotide use (see below), strong consideration should be given to prophylactic cholecystectomy at the time of surgery or exploration if ongoing octreotide use is being considered. There is no role for adjuvant or postoperative systemic therapy (see below) of completely resected NET, even in the setting of hepatic metastases that have been definitively treated.

Summary. Perioperative Medical Management of NETs

- Resection, even of isolated hepatic metastases, represents a curative option for some patients with NETs, particularly low or intermediate grade.
- Octreotide should be administered in the perioperative setting to reduce the risk of carcinoid crisis.
- There is no role for systemic therapy in an adjuvant fashion after complete resection of known tumor.

Liver-Directed Therapy of NET Metastases

Unfortunately, most patients with NET hepatic metastases will not be candidates for complete hepatic resections given the distribution of multifocal disease, even if it is all contained within the liver. However, there are multiple therapeutic modalities which are effective at decreasing liver metastases, controlling the disease, and improving symptoms, leading to enhanced quality of life

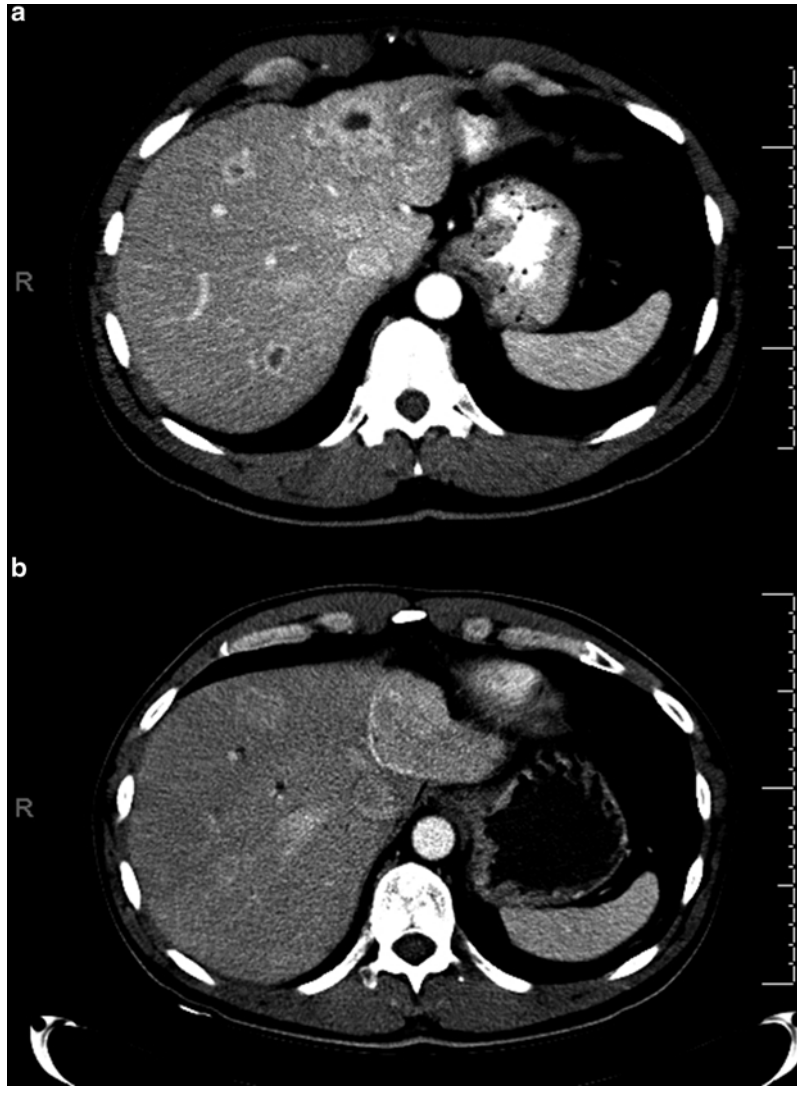

Fig. 19.1 (**a**) Pancreatic neuroendocrine tumor with multifocal liver metastases (arrows) demonstrating arterial contrast enhancement. (**b**) Pancreatic neuroendocrine tumor with multifocal liver metastases (*arrows*) including significant involvement of the left hepatic lobe (*circle*). All lesions demonstrate arterial contrast enhancement

Table 19.7 Nonoperative locoregional modalities used in neuroendocrine tumor liver metastases

Treatment (reference)	Reported responses	Toxicities
131I-mIBG [78]	PR 29%, SD 53%, PD 18%	Myelosuppression 4–6 weeks posttherapy, cumulative
90Y-Dotatoc and 90Y-Dotatate [79]	PR+CR 9–33%	Myelosuppression, nephrotoxicity
177Lu-Dotatate [80]	PR 23%, SD 77%	Myelosuppression, some nephrotoxicity
Transarterial embolization (hepatic artery embolization or chemoembolization) [81]	CR +PR 58%, SD 22%	Postembolization syndrome (fever, abdominal pain, nausea) >90%, lasts for 24–72 h
		Uncommon complications including sepsis, hepatorenal syndrome, necrotizing cholecystitis, bleeding peptic ulcers
90Y microspheres [82]	CR 18%, PR 32%	Postembolization syndrome

CR complete response, *RR* response rates, *PR* partial response, *SD* stable disease

(Table 19.7). Of note, these reports include relatively small populations of patients with heterogeneous NET types. However, in general, patients with carcinoid variants of NET fared better with these types of local treatments than patients with other pancreatic islet cell NETs [34].

Systemic Treatment

The role of systemic therapy in the management of NETs is to control hormonal symptoms associated with the disease as well as controlling further spread or progression of the tumor. In this regard, the grade of the tumor becomes important in helping to select optimal management. Low-grade tumors, in general, may require little intervention aside from symptom management and lend themselves well to local interventions or observation. Intermediate- and high-grade tumors may benefit more from systemic interventions aimed at delaying tumor progression. Some high-grade tumors behave very aggressively and can be identified by having a high Ki-67%. These uncommon tumors should be managed as extrapulmonary small cell carcinoma and benefit from aggressive and urgent chemical cytoreduction [35].

Hormonal Therapy

Somatostatins control several glands, including gastrointestinal and pancreatic endocrine/exocrine functions [36]. Somatostatin receptors are highly expressed on pancreatic neuroendocrine cancers. However, native somatostatin peptides have a half-life of only a few minutes; thus, synthetic somatostatin analogs were developed to have more therapeutic relevance. Octreotide, a somatostatin analog, binds to somatostatin 2 receptors, and to a less degree, somatostatin 3 and 5 receptors. Somatostatin type 2 receptors are expressed on nearly all insulinomas, glucagonomas, VIPomas, and nonfunctional NETs. Octreotide is clinically used to relieve symptoms of carcinoid syndrome and delay the time to tumor progression. Kvols and colleagues initially reported octreotide use (150 μg IM three times per day) in 25 patients with metastatic carcinoid NET with carcinoid syndrome [37]. The investigators observed decreases by more than 50% in urine 5-HIAA levels in 18 of 25 treated patients with a median duration of over 12 months (range 1 to >18 months). This was associated with a clinically meaningful reduction in patient flushing and diarrhea. Phase II studies also suggested disease stabilization. Octreotide has thus demonstrated improvement in symptom control and decreased tumor growth in hormone-producing NETs; however, it is not known if the treatment will improve outcomes in nonhormone-producing NETs [38]. The PROMID investigators randomized 90 patients with well-differentiated advanced or metastatic midgut NETs to either octreotide long-acting release (LAR) 30 mg IM every 28 days or placebo until radiographic progression. Patients treated with octreotide LAR had less disease progression (HR, 0.32; 95% CI, 0.19–0.55; $p=0.00015$), an improved median time to tumor progression (14.3 vs. 6.0 months; $p=0.000072$), and a reduced "tumor progression or tumor-related death" event rate (HR,0.24; 95% CI, 0.13–0.45; $p=0.0000036$). Octreotide treatment benefit was noted in both functionally active and inactive tumors. Overall survival, however, did not differ at the time of the data assessment due to low rate of deaths for patients in both arms (HR, 0.81; 95% CI, 0.30–2.18; $p=0.77$). Patients in the octreotide group experienced more fatigue and fevers (8 vs. 2 patients), anemia (5 vs. 1 patients), and bile stones (5 vs. 1 patients) with similar GI toxicity rates (6 vs. 8 patients). The authors concluded that octreotide LAR prolongs time to tumor progression compared to placebo.

A cousin of octreotide, lanreotide was found to offer improved symptoms in the phase III CLARINET trial (Controlled study of Lanreotide Antiproliferative Response In NeuroEndocrine Tumors) [39]. This study randomized 204 patients with well- to moderately differentiated nonfunctioning NETs with Ki-67 index < 10 % and who had not received any tumor-directed treatment in the last 6 months to either lanreotide or placebo. The primary study objective was progression-free survival. Lanreotide (120 mg IM every 4 weeks) or placebo was administered for 96 weeks or until disease progression or death. At 2 years, lanreotide improved progression-free survival compared to placebo

(62% vs. 22%; $p=0.0002$) with no difference in the overall survival between the groups noted at the time of the data analysis (19 deaths vs. 17 deaths; $p=0.8791$). Since these patients had non-functional tumors, more patients in the lanreotide group experienced treatment-related adverse events (50% vs. 28%).

Cardiac assessment for patients with carcinoid syndrome or carcinoid tumors should be undertaken to evaluate for carcinoid heart and valvular disease, even if somatostatin analog use is planned. This is particularly relevant prior to any planned major surgery.

Summary. Hormonal Therapy Use in Metastatic NETs

Octreotide

Improves hormonally mediated symptoms in patients with carcinoid and hormonally active NETs and is relatively well tolerated.

Improves time to tumor progression in hormonally active and inactive tumors.

No benefit demonstrated in overall survival.

Biologic Targeted Therapies

mTOR

Mammalian target of rapamycin (mTOR), Biologic Targeted Therapieswhich regulates cell proliferation and angiogenesis, is felt to contribute to the pathogenesis of NETs [40]. Everolimus, an inhibitor of mTORC2, was studied in patients with advanced NETs. The RADIANT-2 study group randomized 429 patients with low- or intermediate-grade NETs to octreotide (30 mg LAR IM every 28 days) with either everolimus (10 mg orally daily) or placebo [41]. The time to tumor progression favored the everolimus group (16.4 vs. 11.3 months; HR, 0.77; $p=0.026$). Similar to other studies in this patient population, the best overall response—which includes stable disease—was not different between the groups (84% vs. 81%). Patients receiving everolimus had more stomatitis (62% vs. 14%), rash (37% vs. 12%), fatigue (31% vs. 12%), hyperglycemia (12% vs. 2%), thrombocytopenia (14% vs. 0%), diarrhea (27% vs. 16%), and pneumonitis (8% vs. 0%). Despite serious adverse events being frequent in both groups, they were more common in the everolimus arm (57% vs. 35%), which resulted in more dose reductions and/or interruptions (65% vs. 35%) and treatment discontinuation (19% vs. 3%). Although there were more deaths in the everolimus arm, they were not attributed to the medical therapy. The authors concluded that when added to octreotide LAR, everolimus improved progression-free survival, with resultant FDA approval.

The subsequent RADIANT-3 study was conducted to improve the therapy tolerance by testing the elimination of octreotide. The investigators randomized 410 patients with advanced low- or intermediate-grade pancreatic NETs with radiologic progression within the past 12 months to receive everolimus or matching placebo [42]. More than 80% had well-differentiated tumors with hepatic metastases, with 24% of the patients having insulinoma, gastrinoma, glucagonoma, VIPoma, or somastatinoma subtypes. The median progression-free survival was increased in the everolimus group (11 vs. 4.6 months; HR for disease progression or death with everolimus, 0.35; 95% CI, 0.27–0.45; $p<0.001$). The median overall survival was not reached at the time of analysis and was not different compared to placebo (HR, 1.05; 95% CI, 0.71–1.55; $p=0.59$). Similar to RADIANT-2, more dose reductions and/or interruptions (59% vs. 28%) and treatment discontinuation (13% vs. 2%) occurred with everolimus. More patients in the everolimus group died while receiving the study drug (6% vs. 2%), with some of the deaths attributed to disease progression, but a few from atypical infections, including pulmonary tuberculosis, bronchopulmonary aspergillosis, and reactivation of hepatitis B. The authors concluded that everolimus alone prolongs progression-free survival with a low, but notable incidence of severe adverse drug events. Interestingly, in a subgroup analysis of 40 Japanese patients enrolled in the RADIANT-3 study, there was a notable progression-free survival benefit of everolimus compared to placebo (19.4 vs. 2.8 months; 95% CI, 2.46–8.34; $p<0.001$) [43]. The median overall survival was not reached at the time of the analysis; however,

it did not appear different in the Japanese patient subgroup (HR, 0.90; 95% CI, 0.20–4.05; $p=0.45$) from the overall RADIANT-3 population (HR, 0.89; 95% CI, 0.64–1.23). Of note, the Japanese patient treatment group also had a higher incidence of rash (87%), stomatitis (74%), infections (65%), nail disorders (52%), epistaxis (44%), and pneumonitis (44%).

Vascular Endothelial Growth Factor

Since NETs are hypervascular tumors and overexpress both vascular endothelial growth factor (VEGF) and VEGF receptors, inhibitors of this pathway had a biologic rationale to be tested in clinical trials [44]. Sunitinib is an oral inhibitor of several different intracellular tyrosine kinases, including VEGF-R1, VEGF-R2, and VEGF-R3. Based on the results from a promising phase II study demonstrating activity, a phase III study randomized 171 patients with advanced, well-differentiated pancreatic NETs to either sunitinib (37.5 mg orally daily) or placebo [45]. The study was discontinued early after the independent data and safety monitoring committee observed more serious events, including deaths, in the placebo group. The median progression-free survival was prolonged in the sunitinib group (11.4 vs. 5.5 months; HR, 0.42; 95% CI, 0.26–0.66; $p<0.001$) [45]. The objective radiographic response rate was also improved with sunitinib (9.3% vs. 0%). At the time of application submission to the FDA, the overall survival HR appeared to favor sunitinib [46]. However, survival analysis was confounded by a 69% patient crossover rate from placebo to sunitinib after study closure. Grade 3–4 toxicities were uncommon but more likely with sunitinib than placebo, including diarrhea (5% vs. 2%), asthenia (5% vs. 4%), neutropenia (12% vs. 0%), hypertension (10% vs. 1%), palmar and/or plantar erythrodysesthesia (6% vs. 0%), stomatitis (4% vs. 0%), and thrombocytopenia (4% vs. 0%). Two patients receiving sunitinib died of heart failure [46]. The authors concluded that sunitinib increased progression-free survival, overall survival, and objective response rate, leading to FDA approval of this agent.

Bevacizumab is a monoclonal antibody which binds circulating VEGF, thus preventing it from binding to cellular receptors. The activity of bevacizumab was tested in patients receiving octreotide with well- to moderately differentiated NETs [47]. Forty-four patients were randomized to receive either PEG interferon alfa-2b (0.5 μg/kg SQ once per week) or bevacizumab (15 mg/kg IV once every 3 weeks) for 18 weeks. After completion of the 18 weeks or upon progression (whichever occurred first), patients then received both bevacizumab and interferon therapy until progression. Patients who started with bevacizumab had a higher progression-free survival at 18 weeks (95% vs. 68%, $p=0.02$). Given treatment crossover, no survival difference was observed. Most common grade 3–4 toxicities included neutropenia (14%), fatigue (41%), headache (7%), hypertension (43%), myalgia (20%), nausea (9%), rash (5%), stomatitis (5%), and vomiting (5%). The authors concluded that bevacizumab resulted in longer progression-free survival compared to interferon. Ongoing clinical trials are incorporating anti-VEGF strategies in combination with mTOR inhibition or cytotoxic chemotherapy.

Summary. Biologic Targeted Therapies in Advanced NETs

Everolimus

Treatment increases time to progression when added to octreotide or placebo.

May provide modest tumor response, but without a demonstrated survival benefit.

Monitor for GI side effects, infections, and pneumonitis.

Sunitinib

Treatment increases progression-free survival compared to placebo.

May have survival benefit compared to placebo.

May provide minor tumor regression.

Monitor for GI side effects, cytopenias, and hypertension.

Cytotoxic Chemotherapy

Well- to Moderately Differentiated NETs

Given the low incidence of the disease and the typical slow development of symptoms, there

are few historical trials which evaluated chemotherapy benefits in well- to moderately differentiated NETs (which include intermediate-grade tumors with Ki-67 levels < 20 %). However, the trials published do suggest that chemotherapy may provide symptom and survival benefit for these patients. Streptozocin, an analog of *N*-acetylglucosamine, an antitumor antibiotic and alkylating agent isolated from *Streptomyces acromogenes*, was initially developed in the 1970s for its diabetogenic effects in animals [48]. Further studies revealed it had selective pancreatic beta cell toxicity and was thus explored as a treatment for NETs. Moertel et al. enrolled 84 patients with advanced pancreatic islet cell carcinomas to either streptozocin or streptozocin with 5-FU [49]. The combination group had increased response rates (63% vs. 35%) and complete radiographic response rates (33% vs. 12%). However, the study was not powered to demonstrate a survival difference (26 vs. 16.5 months; p=NS). Subsequently, doxorubicin was added to streptozocin in an attempt to improve the objective response rates and overall survival [50]. The investigators randomized 105 patients with advanced islet cell carcinoma into one of three groups: (1) streptozocin (500 mg/m^2) with 5-FU (400 mg/m^2 IV per day for 5 days every 6 weeks); (2) streptozocin (500 mg/m^2) with doxorubicin (50 mg/m^2 IV days 1 and 22 every 6 weeks); and (3) chlorozotocin. The chlorozotocin group was inferior in all measured outcomes. Compared to 5-FU, the addition of doxorubicin to streptozocin improved the objective response rates (69% vs. 45%; p=0.05), time to progression (20 vs. 6.9 months; p=0.001), and median overall survival (2.2 vs. 1.4 years; p=0.004). Nausea and vomiting, alopecia, and heart failure were more common in patients receiving doxorubicin, while stomatitis and diarrhea were more common in those receiving 5-FU. Unfortunately, additional studies failed to reproduce these findings, demonstrating response rates as low as 6%.

The MD Anderson group performed a retrospective review of 84 patients consecutively treated with an intensified treatment regimen consisting of 5-FU (400 mg/m^2 IV days 1–5), doxorubicin (40 mg/m^2 IV on day 1), and streptozocin (400 mg/m^2 IV days 1–5) (FAS) combination therapy every 28 days [51]. The documented radiographic response rate was 39%, with a time to progression of 9.3 months and a median overall survival of 37 months. Radiographic responders had a significantly improved 2-year survival compared to those not responding (97% vs. 55%; p<0.03). Despite the higher response rates, metastatic disease involving >75% of the liver was associated with worse 2-year survival (0% vs. 83%; p<0.0001). Toxicities for all patients included neutropenia (10.7%), fatigue (4.7%), diarrhea (3.5%), and mucositis (4.7%).

Based on in vitro data of synergy and chronomodulation between capecitabine (an oral fluoropyrimidine) and temozolomide (an oral alkylating agent), Strosberg and colleagues treated 30 patients with well- to moderately differentiated pancreatic NETs with these agents in combination [52]. Of note, most patients had previously been treated with octreotide, interferon-alfa, and locoregional therapy including hepatic artery embolization (HAE). Capecitabine (750 mg/m^2 taken orally twice daily for 14 days) and temozolomide (200 mg/m^2 taken orally daily on days 10–14) were administered every 28 days. The regimen resulted in a significantly high objective response rate of 70%, with another 27% achieving stable disease. The estimated overall survival at 2 years was 92%, with a median progression-free survival of 18 months. The oral regimen was well tolerated, with uncommon grade 3–4 toxicities including increased liver function tests (LFTs) (3%) and hematopoietic abnormalities (anemia/thrombocytopenia 3%), although a minor number of patients required dose reductions or delays due to diarrhea or hand–foot syndrome. The high response rate and response duration were replicated in at least two other studies [53–55], making this regimen a popular option for patients requiring cytotoxic regression of disease. Validation in phase III studies is planned.

Poorly Differentiated NETs

In comparison to other NETs, poorly differentiated neuroendocrine cancers (Ki-67% > 50%) commonly behave more like extrapulmonary small cell carcinomas and require treatment with more intensive chemotherapy regimens [2, 31]. Even in the setting of primary surgical resection,

most of these patients relapse with metastatic disease. Thus, similar to small cell lung carcinomas, systemic chemotherapy is recommended [2].

Moertel and colleagues combined etoposide (130 mg/m^2 IV on days 1–3) and cisplatin (45 mg/m^2 IV on days 2 and 3), which is a standard treatment for small cell lung cancer, to treat 45 patients with metastatic pancreatic NETs [56]. The response was poor in the well-differentiated NETs, with only 2 of 27 patients responding. However, among the poorly differentiated NETs, the response was 67% ($n=18$), with a median duration of regression of 8 months. The treatment was associated with toxicities consistent with the prior use of this therapy for other malignancies, including bone marrow suppression, vomiting, alopecia, and neuropathy.

Attempts to further intensify this therapy and improve the response rates and durability of disease control were tested by Hainsworth and colleagues. In a prospective phase II study, 78 patients with poorly differentiated NETs were treated with a combination of carboplatin (AUC of 6 IV on day 1), etoposide (50 mg alternating with 100 mg orally daily on days 1–10), and paclitaxel (200 mg/m^2 IV day 1) repeated every 21 days [57]. More than half of the patients responded, with 29 of 78 achieving a partial response and 12 of 78 achieving a complete response. Unfortunately, 7 of the 12 patients achieving a complete response relapsed at times ranging from 2 to 20 months after treatment. The median overall survival for the 78 patients was 14.5 months, with 14% alive at 5 years. As expected, significant toxicities were common, including treatment-related death from sepsis. The authors concluded that the treatment was too toxic and likely of no benefit compared to the standard platinum and etoposide combination regimen.

Summary

Chemotherapy for well- to moderately differentiated NETs

- Chemotherapy is associated with response rates higher than biologic targeted therapies and may improve survival.
- Streptozocin in combination with 5-FU or doxorubicin are common combinations in use.
- Temozolamide with capecitabine appears very promising, with further validation planned in phase III studies.

Chemotherapy for poorly differentiated NETs

- Systemic therapy is needed even if surgical resection is undertaken.
- Small cell lung cancer–like chemotherapy regimens are recommended.
- Platinum and etoposide combination chemotherapy is the standard palliative treatment with a high initial response rate and variable durability of disease control.

References

1. Cancer facts & figures 2014 [Internet] [cited 2014 Mar 13]. Available from: http://www.cancer.org/research/cancerfactsstatistics/cancerfactsfigures2014/
2. NCCN clinical practice guidelines in oncology [Internet] [cited 2014 May 14]. Available from: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#pancreatic
3. Pancreatic cancer home page [Internet]. National Cancer Institute [cited 2014 May 14]. Available from: http://www.cancer.gov/cancertopics/types/pancreatic
4. Smeenk HG, van Eijck CHJ, Hop WC, Erdmann J, Tran KCK, Debois M, et al. Long-term survival and metastatic pattern of pancreatic and periampullary cancer after adjuvant chemoradiation or observation: long-term results of EORTC trial 40891. Ann Surg. 2007;246(5):734–40.
5. Kalser MH, Ellenberg SS. Pancreatic cancer. Adjuvant combined radiation and chemotherapy following curative resection. Arch Surg. 1985;120(8):899–903.
6. Klinkenbijl JH, Jeekel J, Sahmoud T, van Pel R, Couvreur ML, Veenhof CH, et al. Adjuvant radiotherapy and 5-fluorouracil after curative resection of cancer of the pancreas and periampullary region: phase III trial of the EORTC gastrointestinal tract cancer cooperative group. Ann Surg. 1999;230(6):776–82; discussion 782–4.
7. Neoptolemos JP, Dunn JA, Stocken DD, Almond J, Link K, Beger H, et al. Adjuvant chemoradiotherapy and chemotherapy in resectable pancreatic cancer: a randomised controlled trial. Lancet. 2001;358(9293):1576–85.
8. Neoptolemos JP, Stocken DD, Friess H, Bassi C, Dunn JA, Hickey H, et al. A randomized trial of chemoradiotherapy and chemotherapy after resection

of pancreatic cancer. N Engl J Med. 2004;350(12): 1200–10.
9. Van Laethem J-L, Hammel P, Mornex F, Azria D, Van Tienhoven G, Vergauwe P, et al. Adjuvant gemcitabine alone versus gemcitabine-based chemoradiotherapy after curative resection for pancreatic cancer: a randomized EORTC-40013-22012/FFCD-9203/GERCOR phase II study. J Clin Oncol. 2010;28(29): 4450–6.
10. Burris III HA, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol. 1997; 15(6):2403–13.
11. Regine WF, Winter KA, Abrams RA, Safran H, Hoffman JP, Konski A, et al. Fluorouracil vs gemcitabine chemotherapy before and after fluorouracil-based chemoradiation following resection of pancreatic adenocarcinoma: a randomized controlled trial. JAMA. 2008;299(9):1019–26.
12. Regine WF, Winter KA, Abrams R, Safran H, Hoffman JP, Konski A, et al. Fluorouracil-based chemoradiation with either gemcitabine or fluorouracil chemotherapy after resection of pancreatic adenocarcinoma: 5-year analysis of the U.S. Intergroup/RTOG 9704 phase III trial. Ann Surg Oncol. 2011;18(5):1319–26.
13. Ueno H, Kosuge T, Matsuyama Y, Yamamoto J, Nakao A, Egawa S, et al. A randomised phase III trial comparing gemcitabine with surgery-only in patients with resected pancreatic cancer: Japanese Study Group of Adjuvant Therapy for Pancreatic Cancer. Br J Cancer. 2009;101(6):908–15.
14. Oettle H, Neuhaus P, Hochhaus A, Hartmann JT, Gellert K, Ridwelski K, et al. Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer: the CONKO-001 randomized trial. JAMA. 2013;310(14):1473–81.
15. Oettle H, Post S, Neuhaus P, Gellert K, Langrehr J, Ridwelski K, et al. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. JAMA. 2007;297(3):267–77.
16. Neoptolemos JP, Stocken DD, Bassi C, Ghaneh P, Cunningham D, Goldstein D, et al. Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection: a randomized controlled trial. JAMA. 2010;304(10): 1073–81.
17. Valle JW, Palmer D, Jackson R, Cox T, Neoptolemos JP, Ghaneh P, et al. Optimal duration and timing of adjuvant chemotherapy after definitive surgery for ductal adenocarcinoma of the pancreas: ongoing lessons from the ESPAC-3 study. J Clin Oncol. 2014;32(6):504–12.
18. Quiros RM, Brown KM, Hoffman JP. Neoadjuvant therapy in pancreatic cancer. Cancer Invest. 2007; 25(4):267–73.
19. Abbott DE, Tzeng C-WD, Merkow RP, Cantor SB, Chang GJ, Katz MH, et al. The cost-effectiveness of neoadjuvant chemoradiation is superior to a surgery-first approach in the treatment of pancreatic head adenocarcinoma. Ann Surg Oncol. 2013;20 Suppl 3:S500–8.
20. Callery MP, Chang KJ, Fishman EK, Talamonti MS, William Traverso L, Linehan DC. Pretreatment assessment of resectable and borderline resectable pancreatic cancer: expert consensus statement. Ann Surg Oncol. 2009;16(7):1727–33.
21. Evans DB, Varadhachary GR, Crane CH, Sun CC, Lee JE, Pisters PWT, et al. Preoperative gemcitabine-based chemoradiation for patients with resectable adenocarcinoma of the pancreatic head. J Clin Oncol. 2008;26(21):3496–502.
22. Faris JE, Blaszkowsky LS, McDermott S, Guimaraes AR, Szymonifka J, Huynh MA, et al. FOLFIRINOX in locally advanced pancreatic cancer: the Massachusetts General Hospital Cancer Center experience. Oncologist. 2013;18(5):543–8.
23. Sultana A, Smith CT, Cunningham D, Starling N, Neoptolemos JP, Ghaneh P. Meta-analyses of chemotherapy for locally advanced and metastatic pancreatic cancer. J Clin Oncol. 2007;25(18):2607–15.
24. Moore MJ, Goldstein D, Hamm J, Figer A, Hecht JR, Gallinger S, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol. 2007;25(15):1960–6.
25. Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med. 2013;369(18):1691–703.
26. Conroy T, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med. 2011;364(19):1817–25.
27. Gourgou-Bourgade S, Bascoul-Mollevi C, Desseigne F, Ychou M, Bouché O, Guimbaud R, et al. Impact of FOLFIRINOX compared with gemcitabine on quality of life in patients with metastatic pancreatic cancer: results from the PRODIGE 4/ACCORD 11 randomized trial. J Clin Oncol. 2013;31(1):23–9.
28. Ueno H, Ioka T, Ikeda M, Ohkawa S, Yanagimoto H, Boku N, et al. Randomized phase III study of gemcitabine plus S-1, S-1 alone, or gemcitabine alone in patients with locally advanced and metastatic pancreatic cancer in Japan and Taiwan: GEST study. J Clin Oncol. 2013;31(13):1640–8.
29. Pelzer U, Schwaner I, Stieler J, Adler M, Seraphin J, Dörken B, et al. Best supportive care (BSC) versus oxaliplatin, folinic acid and 5-fluorouracil (OFF) plus BSC in patients for second-line advanced pancreatic cancer: a phase III-study from the German CONKO-study group. Eur J Cancer. 2011;47(11): 1676–81.
30. Capurso G, Fazio N, Festa S, Panzuto F, De Braud F, Delle Fave G. Molecular target therapy for gastroen-

teropancreatic endocrine tumours: biological rationale and clinical perspectives. Crit Rev Oncol Hematol. 2009;72(2):110–24.
31. Ramage JK, Ahmed A, Ardill J, Bax N, Breen DJ, Caplin ME, et al. Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours (NETs). Gut. 2012;61(1):6–32.
32. Basu B, Sirohi B, Corrie P. Systemic therapy for neuroendocrine tumours of gastroenteropancreatic origin. Endocr Relat Cancer. 2010;17(1):R75–90.
33. Modlin IM, Oberg K, Chung DC, Jensen RT, de Herder WW, Thakker RV, et al. Gastroenteropancreatic neuroendocrine tumours. Lancet Oncol. 2008;9(1):61–72.
34. Gupta S, Johnson MM, Murthy R, Ahrar K, Wallace MJ, Madoff DC, et al. Hepatic arterial embolization and chemoembolization for the treatment of patients with metastatic neuroendocrine tumors: variables affecting response rates and survival. Cancer. 2005;104(8):1590–602.
35. Sorbye H, Strosberg J, Baudin E, Klimstra DS, Yao JC. Gastroenteropancreatic high-grade neuroendocrine carcinoma. Cancer. 2014;120:2814–23.
36. Oberg K, Kvols L, Caplin M, Delle Fave G, de Herder W, Rindi G, et al. Consensus report on the use of somatostatin analogs for the management of neuroendocrine tumors of the gastroenteropancreatic system. Ann Oncol. 2004;15(6):966–73.
37. Kvols LK, Moertel CG, O'Connell MJ, Schutt AJ, Rubin J, Hahn RG. Treatment of the malignant carcinoid syndrome. Evaluation of a long-acting somatostatin analogue. N Engl J Med. 1986;315(11):663–6.
38. Rinke A, Müller H-H, Schade-Brittinger C, Klose K-J, Barth P, Wied M, et al. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. J Clin Oncol. 2009;27(28):4656–63.
39. ESMO @ ECC 2013: Phase III trial results favour lanreotide therapy in patients with gastroenteropancreatic neuro-endocrine tumours | ESMO [Internet] [cited 2014 May 14]. Available from: http://www.esmo.org/Conferences/Past-Conferences/European-Cancer-Congress-2013/News/Phase-III-Trial-Results-Favour-Lanreotide-Therapy-in-Patients-with-Gastroenteropancreatic-Neuro-Endocrine-Tumours
40. O'Reilly T, McSheehy PM. Biomarker development for the clinical activity of the mTOR inhibitor everolimus (RAD001): processes, limitations, and further proposals. Transl Oncol. 2010;3(2):65–79.
41. Pavel ME, Hainsworth JD, Baudin E, Peeters M, Hörsch D, Winkler RE, et al. Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): a randomised, placebo-controlled, phase 3 study. Lancet. 2011;378(9808):2005–12.
42. Yao JC, Shah MH, Ito T, Bohas CL, Wolin EM, Van Cutsem E, et al. Everolimus for advanced pancreatic neuroendocrine tumors. N Engl J Med. 2011;364(6):514–23.
43. Ito T, Okusaka T, Ikeda M, Igarashi H, Morizane C, Nakachi K, et al. Everolimus for advanced pancreatic neuroendocrine tumours: a subgroup analysis evaluating Japanese patients in the RADIANT-3 trial. Jpn J Clin Oncol. 2012;42(10):903–11.
44. Kulke MH, Lenz H-J, Meropol NJ, Posey J, Ryan DP, Picus J, et al. Activity of sunitinib in patients with advanced neuroendocrine tumors. J Clin Oncol. 2008;26(20):3403–10.
45. Raymond E, Dahan L, Raoul J-L, Bang Y-J, Borbath I, Lombard-Bohas C, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. N Engl J Med. 2011;364(6):501–13.
46. Blumenthal GM, Cortazar P, Zhang JJ, Tang S, Sridhara R, Murgo A, et al. FDA approval summary: sunitinib for the treatment of progressive well-differentiated locally advanced or metastatic pancreatic neuroendocrine tumors. Oncologist. 2012;17(8):1108–13.
47. Yao JC, Phan A, Hoff PM, Chen HX, Charnsangavej C, Yeung S-CJ, et al. Targeting vascular endothelial growth factor in advanced carcinoid tumor: a random assignment phase II study of depot octreotide with bevacizumab and pegylated interferon alpha-2b. J Clin Oncol. 2008;26(8):1316–23.
48. Konrad RJ, Mikolaenko I, Tolar JF, Liu K, Kudlow JE. The potential mechanism of the diabetogenic action of streptozotocin: inhibition of pancreatic beta-cell O-GlcNAc-selective N-acetyl-beta-D-glucosaminidase. Biochem J. 2001;356(Pt 1):31–41.
49. Moertel CG, Hanley JA, Johnson LA. Streptozocin alone compared with streptozocin plus fluorouracil in the treatment of advanced islet-cell carcinoma. N Engl J Med. 1980;303(21):1189–94.
50. Moertel CG, Lefkopoulo M, Lipsitz S, Hahn RG, Klaassen D. Streptozocin-doxorubicin, streptozocin-fluorouracil or chlorozotocin in the treatment of advanced islet-cell carcinoma. N Engl J Med. 1992;326(8):519–23.
51. Kouvaraki MA, Ajani JA, Hoff P, Wolff R, Evans DB, Lozano R, et al. Fluorouracil, doxorubicin, and streptozocin in the treatment of patients with locally advanced and metastatic pancreatic endocrine carcinomas. J Clin Oncol. 2004;22(23):4762–71.
52. Strosberg JR, Fine RL, Choi J, Nasir A, Coppola D, Chen D-T, et al. First-line chemotherapy with capecitabine and temozolomide in patients with metastatic pancreatic endocrine carcinomas. Cancer. 2011;117(2):268–75.
53. Fine RL, Gulati AP, Krantz BA, Moss RA, Schreibman S, Tsushima DA, et al. Capecitabine and temozolomide (CAPTEM) for metastatic, well-differentiated neuroendocrine cancers: The Pancreas Center at Columbia University experience. Cancer Chemother Pharmacol. 2013;71(3):663–70.

54. Claringbold PG, Price RA, Turner JH. Phase I-II study of radiopeptide 177Lu-octreotate in combination with capecitabine and temozolomide in advanced low-grade neuroendocrine tumors. Cancer Biother Radiopharm. 2012;27(9):561–9.
55. Saif MW, Kaley K, Brennan M, Garcon MC, Rodriguez G, Rodriguez T. A retrospective study of capecitabine/temozolomide (CAPTEM) regimen in the treatment of metastatic pancreatic neuroendocrine tumors (pNETs) after failing previous therapy. J Pancreas. 2013;14(5):498–501.
56. Moertel CG, Kvols LK, O'Connell MJ, Rubin J. Treatment of neuroendocrine carcinomas with combined etoposide and cisplatin. Evidence of major therapeutic activity in the anaplastic variants of these neoplasms. Cancer. 1991;68(2):227–32.
57. Hainsworth JD, Spigel DR, Litchy S, Greco FA. Phase II trial of paclitaxel, carboplatin, and etoposide in advanced poorly differentiated neuroendocrine carcinoma: a Minnie Pearl Cancer Research Network Study. J Clin Oncol. 2006;24(22):3548–54.
58. Boeck S, Hoehler T, Seipelt G, Mahlberg R, Wein A, Hochhaus A, et al. Capecitabine plus oxaliplatin (CapOx) versus capecitabine plus gemcitabine (CapGem) versus gemcitabine plus oxaliplatin (mGemOx): final results of a multicenter randomized phase II trial in advanced pancreatic cancer. Ann Oncol. 2008;19(2):340–7.
59. Colucci G, Giuliani F, Gebbia V, Biglietto M, Rabitti P, Uomo G, et al. Gemcitabine alone or with cisplatin for the treatment of patients with locally advanced and/or metastatic pancreatic carcinoma: a prospective, randomized phase III study of the Gruppo Oncologia dell'Italia Meridionale. Cancer. 2002;94(4):902–10.
60. Colucci G, Labianca R, Di Costanzo F, Gebbia V, Cartenì G, Massidda B, et al. Randomized phase III trial of gemcitabine plus cisplatin compared with single-agent gemcitabine as first-line treatment of patients with advanced pancreatic cancer: the GIP-1 study. J Clin Oncol. 2010;28(10):1645–51.
61. Van Cutsem E, Vervenne WL, Bennouna J, Humblet Y, Gill S, Van Laethem J-L, et al. Phase III trial of bevacizumab in combination with gemcitabine and erlotinib in patients with metastatic pancreatic cancer. J Clin Oncol. 2009;27(13):2231–7.
62. Cunningham D, Chau I, Stocken DD, Valle JW, Smith D, Steward W, et al. Phase III randomized comparison of gemcitabine versus gemcitabine plus capecitabine in patients with advanced pancreatic cancer. J Clin Oncol. 2009;27(33):5513–8.
63. Gonçalves A, Gilabert M, François E, Dahan L, Perrier H, Lamy R, et al. BAYPAN study: a double-blind phase III randomized trial comparing gemcitabine plus sorafenib and gemcitabine plus placebo in patients with advanced pancreatic cancer. Ann Oncol. 2012;23(11):2799–805.
64. Harder J, Ihorst G, Heinemann V, Hofheinz R, Moehler M, Buechler P, et al. Multicentre phase II trial of trastuzumab and capecitabine in patients with HER2 overexpressing metastatic pancreatic cancer. Br J Cancer. 2012;106(6):1033–8.
65. Heinemann V, Quietzsch D, Gieseler F, Gonnermann M, Schönekäs H, Rost A, et al. Randomized phase III trial of gemcitabine plus cisplatin compared with gemcitabine alone in advanced pancreatic cancer. J Clin Oncol. 2006;24(24):3946–52.
66. Herrmann R, Bodoky G, Ruhstaller T, Glimelius B, Bajetta E, Schüller J, et al. Gemcitabine plus capecitabine compared with gemcitabine alone in advanced pancreatic cancer: a randomized, multicenter, phase III trial of the Swiss Group for Clinical Cancer Research and the Central European Cooperative Oncology Group. J Clin Oncol. 2007;25(16):2212–7.
67. Kindler HL, Niedzwiecki D, Hollis D, Sutherland S, Schrag D, Hurwitz H, et al. Gemcitabine plus bevacizumab compared with gemcitabine plus placebo in patients with advanced pancreatic cancer: phase III trial of the Cancer and Leukemia Group B (CALGB 80303). J Clin Oncol. 2010;28(22):3617–22.
68. Kindler HL, Ioka T, Richel DJ, Bennouna J, Létourneau R, Okusaka T, et al. Axitinib plus gemcitabine versus placebo plus gemcitabine in patients with advanced pancreatic adenocarcinoma: a double-blind randomised phase 3 study. Lancet Oncol. 2011;12(3):256–62.
69. Louvet C, Labianca R, Hammel P, Lledo G, Zampino MG, André T, et al. Gemcitabine in combination with oxaliplatin compared with gemcitabine alone in locally advanced or metastatic pancreatic cancer: results of a GERCOR and GISCAD phase III trial. J Clin Oncol. 2005;23(15):3509–16.
70. Moore MJ, Hamm J, Dancey J, Eisenberg PD, Dagenais M, Fields A, et al. Comparison of gemcitabine versus the matrix metalloproteinase inhibitor BAY 12-9566 in patients with advanced or metastatic adenocarcinoma of the pancreas: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol. 2003;21(17):3296–302.
71. Oettle H, Richards D, Ramanathan RK, van Laethem JL, Peeters M, Fuchs M, et al. A phase III trial of pemetrexed plus gemcitabine versus gemcitabine in patients with unresectable or metastatic pancreatic cancer. Ann Oncol. 2005;16(10):1639–45.
72. Philip PA, Benedetti J, Corless CL, Wong R, O'Reilly EM, Flynn PJ, et al. Phase III study comparing gemcitabine plus cetuximab versus gemcitabine in patients with advanced pancreatic adenocarcinoma: Southwest Oncology Group-directed intergroup trial S0205. J Clin Oncol. 2010;28(22):3605–10.
73. Poplin E, Feng Y, Berlin J, Rothenberg ML, Hochster H, Mitchell E, et al. Phase III, randomized study of gemcitabine and oxaliplatin versus gemcitabine (fixed-dose rate infusion) compared with gemcitabine (30-minute infusion) in patients with pancreatic carcinoma E6201: a trial of the Eastern Cooperative Oncology Group. J Clin Oncol. 2009;27(23):3778–85.
74. Reni M, Cordio S, Milandri C, Passoni P, Bonetto E, Oliani C, et al. Gemcitabine versus cisplatin, epirubi-

cin, fluorouracil, and gemcitabine in advanced pancreatic cancer: a randomised controlled multicentre phase III trial. Lancet Oncol. 2005;6(6):369–76.
75. Rougier P, Riess H, Manges R, Karasek P, Humblet Y, Barone C, et al. Randomised, placebo-controlled, double-blind, parallel-group phase III study evaluating aflibercept in patients receiving first-line treatment with gemcitabine for metastatic pancreatic cancer. Eur J Cancer. 2013;49(12):2633–42.
76. Stathopoulos GP, Syrigos K, Aravantinos G, Polyzos A, Papakotoulas P, Fountzilas G, et al. A multicenter phase III trial comparing irinotecan-gemcitabine (IG) with gemcitabine (G) monotherapy as first-line treatment in patients with locally advanced or metastatic pancreatic cancer. Br J Cancer. 2006;95(5):587–92.
77. Modlin IM, Pavel M, Kidd M, Gustafsson BI. Review article: somatostatin analogues in the treatment of gastroenteropancreatic neuroendocrine (carcinoid) tumours. Aliment Pharmacol Ther. 2010;31(2):169–88.
78. Mukherjee JJ, Kaltsas GA, Islam N, Plowman PN, Foley R, Hikmat J, et al. Treatment of metastatic carcinoid tumours, phaeochromocytoma, paraganglioma and medullary carcinoma of the thyroid with (131) I-meta-iodobenzylguanidine [(131)I-mIBG]. Clin Endocrinol (Oxf). 2001;55(1):47–60.
79. Van Essen M, Krenning EP, De Jong M, Valkema R, Kwekkeboom DJ. Peptide receptor radionuclide therapy with radiolabelled somatostatin analogues in patients with somatostatin receptor positive tumours. Acta Oncol. 2007;46(6):723–34.
80. Cwikla JB, Sankowski A, Seklecka N, Buscombe JR, Nasierowska-Guttmejer A, Jeziorski KG, et al. Efficacy of radionuclide treatment DOTATATE Y-90 in patients with progressive metastatic gastroenteropancreatic neuroendocrine carcinomas (GEP-NETs): a phase II study. Ann Oncol. 2010;21(4):787–94.
81. Christante D, Pommier S, Givi B, Pommier R. Hepatic artery chemoinfusion with chemoembolization for neuroendocrine cancer with progressive hepatic metastases despite octreotide therapy. Surgery. 2008;144(6):885–93.
82. King J, Quinn R, Glenn DM, Janssen J, Tong D, Liaw W, Morris DL. Radioembolization with selective internal radiation microspheres for neuroendocrine liver metastases. Cancer. 2008;113(5):921–9.

Endoscopic Therapy: ERCP-Based Therapy

20

Ichiro Yasuda

Endoscopy is becoming increasing popular in the treatment of pancreatic masses. In particular, various endoscopic ultrasound (EUS)-guided techniques have recently been introduced as antitumor therapies or palliative treatments. EUS-guided celiac plexus neurolysis has been attempted to reduce pancreatic cancer pain. Injections of antitumor agents, tumor ablation, fiducial marker placement, and brachytherapy under the guidance of EUS have also been investigated. In contrast, direct antitumor therapies based on the endoscopic retrograde cholangiopancreatography (ERCP) technique have not been reported so far, and the ERCP-based approach is mainly used as a palliative treatment. Although biliary stenting plays a key role in the treatment of patients with obstructive jaundice caused by unresectable pancreatic malignancies, several issues remain unsolved in preoperative biliary drainage. This chapter will summarize the available data on applications of the ERCP-based therapy to the treatment of pancreatic masses.

I. Yasuda (✉)
Department of Gastroenterology,
Teikyo University Mizonokuchi Hospital,
3-8-3 Mizonokuchi, Takatsu-ku, Kawasaki
213-8507, Japan
e-mail: yasudaich@gmail.com

Biliary Stenting as a Palliative Treatment in Unresectable Pancreatic Cancer

Endoscopic biliary stenting was initially described by Soehendra in 1980 [1]. Since then, it has been widely performed as a well-established procedure for treating obstructive jaundice and cholangitis. When this procedure is performed by experienced professionals, the technical success rate can reach 80–90 % [2]. Particularly in cases of unresectable malignant biliary strictures, biliary stenting plays an important role in maintaining the patient's condition and in determining the subsequent prognosis and quality of life.

Around 80 % of pancreatic cancers occur in the head of the pancreas, and pancreatic head cancer is accompanied by biliary obstruction and jaundice in 64–77 % of patients [3]. Such a condition may result in intractable pruritus, progressive liver dysfunction, coagulopathy, and malabsorption. Since only 15–30 % of pancreatic cancer patients are candidates for surgery [3], the control of jaundice and cholangitis constitutes one of the key priorities in the management of individuals with unresectable pancreatic cancer. In such patients, the initial goals of biliary drainage are to palliate the jaundice and normalize the serum bilirubin level prior to systemic chemotherapy. In this context, endoscopic biliary stenting is considered less invasive, safer, and more convenient than surgical bypass.

M.S. Wagh, P.V. Draganov (eds.), *Pancreatic Masses*, DOI 10.1007/978-3-319-19677-0_20

Plastic Stents Vs. Self-Expandable Metallic Stents

Plastic stents (PSs) have been widely used for biliary stenting since the initial report by Soehendra [1] (Fig. 20.1). Several studies have shown that endoscopic stenting with PSs is associated with fewer complications, shorter hospital stays, and lower costs than surgical bypass [4]. A diameter range of 7–11.5 Fr can be used, and a larger diameter is believed to reduce the frequency of stent occlusion [5].

On the other hand, self-expandable metallic stents (SEMSs) are currently gaining popularity owing to the longer duration of patency associated with their use (Fig. 20.2). SEMSs have larger diameters, which reduces the risk of occlusion. Ideally, biliary stents should withstand occlusion or other complications throughout the period of their clinical use. In this regard, SEMSs are expected to be more suitable in cases of unresectable malignant biliary strictures. However, tumor ingrowth through the stent mesh, which may cause early obstruction of the stent, poses a new concern. In addition, it is usually difficult to remove SEMSs after placement, which limits the possibility of reintervention in case of obstruction.

Several studies have compared the efficacy of PSs and SEMSs in patients with distal malignant biliary strictures (Table 20.1) [6–10]. Most of them showed a lower occlusion rate and longer patency for SEMSs compared to PSs. In particular, data of meta-analyses, including seven randomized controlled trials (RCTs) and a total of 724 patients, were reported by Moss et al. in 2007 [11]. Although this study revealed no significant differences in technical success rates, therapeutic

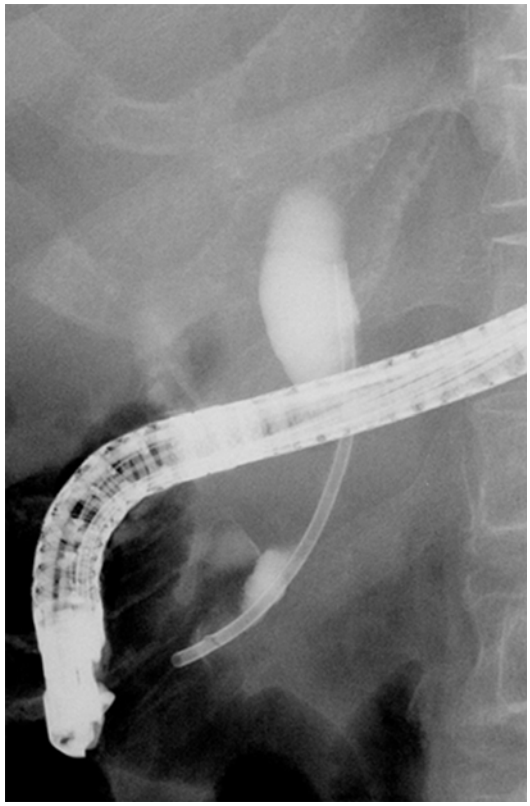

Fig. 20.1 Endoscopic placement of a plastic stent (PS)

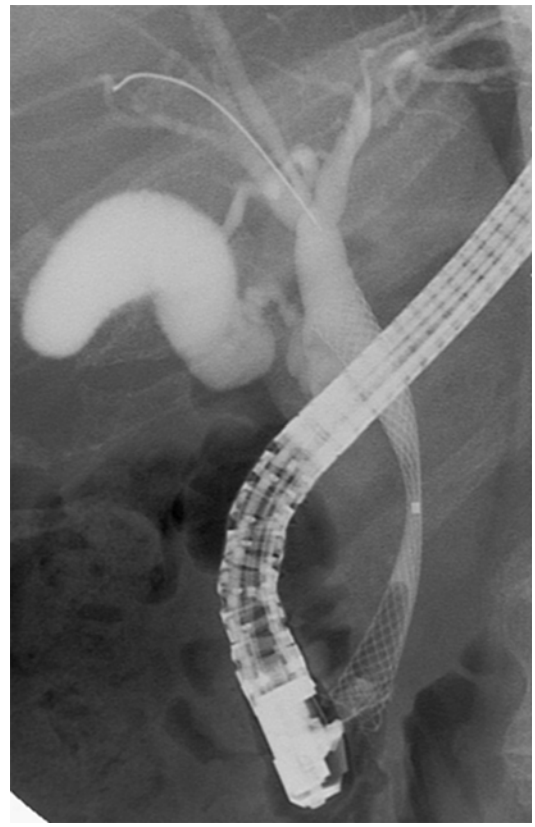

Fig. 20.2 Endoscopic placement of a self-expandable metallic stent (SEMS)

Table 20.1 Summary of published studies comparing the outcomes of the use of PS and SEMS

Author (year)	Stent	No. of patients	Overall stent occlusion	Median stent patency period, months	*P*
Davids et al. (1992) [6]	PS	56	30 (54 %)	4.2	0.006
	SEMS	49	16 (33 %)	9.1	
Knyrim et al. (1993) [7]	PS	31	10 (32 %)[a]	4.6	NR
	SEMS	31	6 (19 %)[a]	6.2	
Prat et al. (1998) [8]	PS	33	NR	3.2	<0.05
	SEMS	34		4.8	
Kaassis et al. (2003) [9]	PS	59	22 (37 %)	5.5	0.007
	SEMS	59	11 (19 %)	Median not reached	
Katsinelos et al. (2006) [10]	PS	24	24 (100 %)	4.1	0.002
	SEMS	23	23 (100 %)	8.5	

PS plastic stent, *SEMS* self-expandable metallic stent, *NR* not reported
[a]30-day occlusion rate

success rates, and 30-day mortality or complication rates, stent occlusion rates at 4 months and the overall risk of obstruction were significantly lower for SEMSs than for PSs. A SEMS was also more cost-effective in cases when the cost of additional ERCP exceeded $1820. Furthermore, Prat et al. [8] and Arguedas et al. [12] suggested that a SEMS is advantageous in terms of cost-effectiveness for patients who survive more than 6 months after the procedure. In another study, Kaassis et al. [9] suggested that a SEMS is cost-effective in patients without liver metastasis owing to their higher median survival time than that in individuals with liver metastasis (5.3 vs. 2.7 months). In addition, Yeoh et al. [13] reported that initial placement of a SEMS is more economically feasible compared to a PS if the cost of a SEMS is less than half of the total ERCP cost. However, these authors also concluded that the use of a PS is preferable for patients surviving less than 4 months.

In conclusion, SEMSs offer longer patency and are more cost-effective than PSs, except in patients with an extremely poor prognosis [4, 6–13].

Covered Self-Expandable Metallic Stents

As mentioned earlier, SEMSs have longer expected patency than PSs, but early obstruction is sometimes caused by tumor ingrowth through the stent mesh. To overcome this difficulty, a SEMS covered with a membrane (covered SEMS: C-SEMS) was developed, which was expected to provide longer patency than uncovered SEMS (U-SEMS) by preventing tumor ingrowth. Isayama et al. [14] conducted an RCT to compare the outcomes of the use of C-SEMSs and U-SEMSs. Their data revealed that stent occlusion occurred in 14 % of patients with a C-SEMS after a mean period of 304 days and in 38 % of patients with a U-SEMS after a mean period of 166 days. Thus, the stent occlusion rate was significantly lower in the C-SEMS group than in the U-SEMS group ($P=0.0032$), whereas the cumulative stent patency period in the C-SEMS group was significantly longer ($P=0.0032$). In subgroup analysis, the cumulative patency of C-SEMS was significantly higher in pancreatic cancer. The authors also suggested theoretical risks of occluding the cystic duct and pancreatic orifice with the cover membrane and causing cholecystitis and pancreatitis. Pancreatitis occurred in 8.7 % of patients of the C-SEMS group and in 1.8 % of patients of the U-SEMS group, whereas the corresponding values for cholecystitis were in 4.8 % and 0 %, respectively. The incidences were not significantly different between the two groups. Moreover, later, a subsequent study investigated the cause of cholecystitis after the C-SEMS placement and concluded that the majority of cases resulted from cystic duct invasion of the tumor and were not caused by the stent itself [15]. Therefore, C-SEMS successfully prevented tumor ingrowth and was

Table 20.2 Summary of published studies comparing the outcomes of the use of uncovered and covered SEMS

Author (year)	Study design	Stent	No. of patients	Stent patency, days	*P*	Complications
Isayama et al. (2004) [14]	RCT	U-SEMS	57	Mean: 161	0.0066	No significant difference between the two groups
		C-SEMS	55	Mean: 304		
Park et al. (2006) [16]	Retro	U-SEMS	108	Mean: 143.5	0.531	Stent migration: 0 % vs. 6.1 % ($P=0.011$)
		C-SEMS	98	Mean: 148.9		
Yoon et al. (2006) [17]	Retro	U-SEMS	36	Mean: 319	0.702	No significant difference between the two groups
		C-SEMS	41	Mean: 398		
Telford et al. (2010) [18]	RCT	U-SEMS	61	Median: 711	0.530	Stent migration: 0 % vs. 12 % ($P=0.0061$)
		C-SEMS	68	Median: 357		
Kullman et al. (2010) [19]	RCT	U-SEMS	200	FQ: 154	0.326	Stent migration: 0 % vs. 3 % ($P=0.030$)
		C-SEMS	200	FQ: 199		
Saleem et al. (2011) [21]	Meta	U-SEMS	386	WMD: 60.56	0.001	Stent migration: U-SEMS < C-SEMS (RR, 8.11)
		C-SEMS	395			
Almadi et al. (2013) [20]	Meta	U-SEMS	356	No differences in patency rates at 6 and 12 months	NR	Stent migration: U-SEMS < C-SEMS (OR, 7.13)
		C-SEMS	365			

RCT randomized controlled trial, *Retro* retrospective study, *Meta* meta-analysis, *SEMS* self-expandable metallic stent, *U-SEMS* uncovered SEMS, *C-SEMS* covered SEMS, *FQ* first quartile stent patency time, *WMD* weighted mean difference, *NR* not reported, *RR* relative risk, *OR* odds ratio

significantly better than U-SEMS for the management of patients with distal malignant stricture, especially caused by pancreatic cancer. It has to be noted, however, that two retrospective studies published after the above report showed similar patency achieved with U-SEMS and C-SEMS [16, 17], whereas two RCTs failed to show the superiority of C-SEMS in terms of stent patency [18, 19]. In addition, they suggested a higher risk of stent migration in cases with C-SEMS than with U-SEMS (Table 20.2). More recently, two meta-analyses with different conclusions were reported. Almadi et al. [20] evaluated data from five fully published articles and four abstracts, comprising a total of 1061 patients. A summary analysis of data from four trials demonstrated no differences in patency between C-SEMS and U-SEMS after 6 and 12 months. Similarly, there were no differences in the rates of pancreatitis, cholecystitis, perforation, bleeding, or cholangitis, length of hospital stay, or number of recurrent biliary obstructions. However, C-SEMS had a higher migration rate (OR, 7.13; 95 % CI, 2.29–22.21). Patients with a C-SEMS had a lower rate of tumor ingrowth (OR, 0.19; 95 % CI, 0.07–0.55) but a higher rate of tumor overgrowth (OR, 1.88; 95 % CI, 1.02–3.45). Therefore, the authors concluded that the use of a C-SEMS offers no clear benefits compared with the use of a U-SEMS. On the other hand, Saleem et al. [21] reported the data of meta-analysis of five fully published RCTs including a total of 781 patients. According to the results, stent dysfunction occurred at a similar rate, but there was a trend toward later obstruction with C-SEMS. Moreover, C-SEMS had a significantly longer duration of patency compared with U-SEMS (weighted mean difference, 60.56 days; $P=0.001$) and demonstrated a significantly lower frequency of dysfunctions secondary to tumor ingrowth [relative risk (RR), 0.23; $P=0.01$]. Additionally, the rates of stent migration, tumor overgrowth, and sludge formation were all significantly higher with the use of C-SEMS (RR 8.11, $P=0.02$; RR 2.03, $P=0.03$; RR 2.89, $P=0.01$, respectively). With regard to adverse effects, no differences in the rates of cholecystitis and pancreatitis were observed between the groups.

In conclusion, the superiority of C-SEMS has not yet been unequivocally proved. Although the design of C-SEMS is intended to reduce tumor ingrowth, it simultaneously prevents stent imbedding and subsequent stent anchoring. Therefore, stent migration is observed more frequently for

C-SEMSs than for U-SEMSs. Although this lack of stent imbedding may seem to be a disadvantage of C-SEMSs, it also brings a benefit of possible reintervention and stent replacement [22]. Overall, the patency of C-SEMS appears to be similar to that of U-SEMS if the stent migration can be prevented.

Preoperative Biliary Drainage

The majority of patients with potentially resectable pancreatic cancer currently undergo preoperative drainage. Hyperbilirubinemia may be a predictor of postoperative complications. Experimental studies have demonstrated the benefits of biliary drainage in terms of improved nutritional status and immune function along with reduced endotoxinemia. In early reports, a correlation was suggested between increased serum bilirubin and a greater incidence of infections, renal and nutritional complications, as well as postoperative mortality [2]. Conversely, several recent studies have suggested that routine preoperative biliary drainage should be avoided in patients with potentially resectable pancreatic cancer because it is associated with increased morbidity [23–25]. In particular, in a multicenter randomized trial, van der Gaag et al. [24] compared the outcomes in a preoperative biliary drainage group of patients with pancreatic head cancer with that of an early surgery group with no preoperative drainage. Preoperative endoscopic biliary drainage was successful in 94 % of the patients, but complications such as stent occlusion and cholangitis occurred in 46 % of the cases. Although the rate of surgery-related complications did not differ between the two groups (47 % vs. 37 %; $P=0.14$), the overall rate of serious complications was significantly higher in the biliary drainage group than in the early surgery group (74 % vs. 39 %; $P<0.001$). In another study, Fang et al. [25] analyzed the results of six RCTs to compare the outcomes of surgery performed for obstructive jaundice with and without preoperative biliary drainage. The results revealed that the proportion of patients who developed serious morbidity was significantly higher in the preoperative drainage group than in the direct surgery group (73.5 % vs. 37.4 %; $P<0.001$) although there were no significant differences in mortality (14.9 % vs. 13.3 %; $P=0.60$) and in the length of hospital stay ($P=0.12$). However, these studies evaluating the role of preoperative drainage included many patients without marked hyperbilirubinemia, and up to 52 % of the patients did not have jaundice (total serum bilirubin level ≤1.8 mg/dL) [23]. For example, the above-mentioned RCT by van der Gaag et al. [24] excluded severely jaundiced patients (total serum bilirubin level >14.6 mg/dL) whose impaired liver function may have benefited the most from preoperative drainage. In addition, up to 32 % of the patients underwent a palliative bypass procedure without pancreatic resection [24]. Therefore, the role of preoperative biliary drainage in patients with marked jaundice remains unclear. If the bilirubin level is markedly elevated, the patient is symptomatic, or surgery needs to be delayed to optimize medical comorbidities or to administer neoadjuvant therapy, preoperative biliary drainage may still be required. In addition, recent studies have shown that neoadjuvant chemo- or chemoradiation therapy results in better postsurgical outcomes for potentially resectable pancreatic cancer [26, 27], and it is becoming popular for borderline resectable patients. Preoperative therapy lasts approximately 3 months and is followed by a 1-month recovery period before surgery. Therefore, patients who have biliary obstruction need drainage while receiving the treatment and waiting to undergo surgery. Effective biliary drainage is essential to prevent liver toxicity caused by chemotherapeutic agents [28].

Choice of Stent

A patient with resectable pancreatic cancer is expected to undergo surgery within 3 months of diagnosis. Therefore, a 7–10 Fr PS has been considered sufficient for the preoperative drainage. However, preoperative drainage using a PS is often associated with problems described above. In addition, with recent studies showing promising outcomes of neoadjuvant therapy, delay of surgery for neoadjuvant treatment is

becoming more common [29]. Therefore, PS may not provide adequate patency in patients receiving neoadjuvant therapy, resulting in interruptions of treatments and further delay of surgery [30]. In such cases, the longer duration of patency makes a SEMS a good candidate. However, the cost of a SEMS is much higher than that of a PS, and the steel mesh of SEMS embeds into the bile duct mucosa, making it impossible to remove the stent after the placement. In addition, the use of SEMS leads to a a hyperplastic reaction and possibly interferes with resection, which may result in more operative complications and compromising of clear surgical margins. However, several small-scale studies have recently shown that the utilization of SEMS does not result in increased operative and postoperative complications [31–36]. For example, Mullen et al. [31] found that 75 of 166 patients (45 %) who had a PS placed during neoadjuvant therapy experienced complications secondary to stent occlusion, compared with only 2 of 29 patients (7 %) with a SEMS. Similarly, Wasan et al. [32] detected stent dysfunction–related cholangitis or cholestasis in 39 of 42 patients (93 %) in the PS group vs. 2 of 13 patients (15 %) in the SEMS group during the neoadjuvant period. Most recently, Cavell et al. [37] performed a retrospective analysis of a larger number of subjects from their database who underwent either attempted or successful pancreaticoduodenectomy with SEMS, PS, or no stent used preoperatively. Of 509 patients with successful pancreaticoduodenectomy, 71 had SEMSs (C-SEMS in 25, U-SEMS in 44, missing data in 2 cases), 149 had PSs, and 289 had no stent. According to the results, having a SEMS did not increase the overall or serious postoperative complications, 30-day mortality, length of hospital stay, biliary anastomotic leak, or positive margin, but was associated with more wound infections and longer operative times. However, the patients in the SEMS group had significantly more comorbidities and were more likely to have received preoperative chemotherapy. Neoadjuvant chemotherapy is generally performed for patients with borderline resectable or locally unresectable tumors. Therefore, it is possible that the SEMS group included more patients with such surgical difficulties, and this may have increased the operative time. Intraoperative determination of local unresectability was also similar between the SEMS group and the other groups. The authors concluded that placement of a SEMS is not contraindicated in patients with resectable pancreatic cancer who require preoperative biliary drainage.

Needless to say, removability of the stent provides additional advantages in case of occlusion. From this perspective, C-SEMS is probably preferable over U-SEMS in potentially resectable cases because it prevents ingrowth of the tumor and hyperplastic tissue and can be removed if required [38–42].

In conclusion, the presented evidence suggests that if surgical resection is planned within 2 months, a plastic stent may be recommended. However, if surgical resection is delayed or neoadjuvant therapy is planned because of borderline resectability, SEMS placement would be advantageous. In addition, C-SEMS may be considered preferable owing to the possibility of stent exchange at a later time.

Conclusions

Among the ERCP-related therapeutic techniques, endoscopic biliary stenting plays a major role in the management of pancreatic cancer. It has been widely performed to control jaundice and cholangitis, and it improves the quality of life in patients with unresectable pancreatic cancer with obstructive jaundice. Whether preoperative biliary drainage is necessary in cases of potentially resectable pancreatic cancer remains controversial. However, the recent popularization of neoadjuvant chemo- or chemoradiation therapy may enhance the role of biliary stenting.

References

1. Soehendra N, Reynders-Frederix V. Palliative bile duct drainage—a new endoscopic method of introducing a transpapillary drain. Endoscopy. 1980;12(1):8–11.
2. Cote GA, Sherman S. Endoscopic palliation of pancreatic cancer. Cancer J. 2012;18(6):584–90.

3. Bonin EA, Baron TH. Preoperative biliary stents in pancreatic cancer. J Hepatobiliary Pancreat Sci. 2011;18(5):621–9.
4. Moss AC, Morris E, MacMathuna P. Palliative biliary stents for obstructing pancreatic carcinoma. Cochrane Database Syst Rev. 2006;2, CD004200.
5. Speer AG, Cotton PB, MacRae KD. Endoscopic management of malignant biliary obstruction: stents of 10 French gauge are preferable to stents of 8 French gauge. Gastrointest Endosc. 1988;34(5):412–7.
6. Davids PH, Groen AK, Rauws EA, Tytgat GN, Huibregtse K. Randomised trial of self-expanding metal stents versus polyethylene stents for distal malignant biliary obstruction. Lancet. 1992;340(8834–8835):1488–92.
7. Knyrim K, Wagner HJ, Pausch J, Vakil N. A prospective, randomized, controlled trial of metal stents for malignant obstruction of the common bile duct. Endoscopy. 1993;25(3):207–12.
8. Prat F, Chapat O, Ducot B, Ponchon T, Pelletier G, Fritsch J, et al. A randomized trial of endoscopic drainage methods for inoperable malignant strictures of the common bile duct. Gastrointest Endosc. 1998;47(1):1–7.
9. Kaassis M, Boyer J, Dumas R, Ponchon T, Coumaros D, Delcenserie R, et al. Plastic or metal stents for malignant stricture of the common bile duct? Results of a randomized prospective study. Gastrointest Endosc. 2003;57(2):178–82.
10. Katsinelos P, Paikos D, Kountouras J, Chatzimavroudis G, Paroutoglou G, Moschos I, et al. Tannenbaum and metal stents in the palliative treatment of malignant distal bile duct obstruction: a comparative study of patency and cost effectiveness. Surg Endosc. 2006;20(10):1587–93.
11. Moss AC, Morris E, Leyden J, MacMathuna P. Do the benefits of metal stents justify the costs? A systematic review and meta-analysis of trials comparing endoscopic stents for malignant biliary obstruction. Eur J Gastroenterol Hepatol. 2007;19(12):1119–24.
12. Arguedas MR, Heudebert GH, Stinnett AA, Wilcox CM. Biliary stents in malignant obstructive jaundice due to pancreatic carcinoma: a cost-effectiveness analysis. Am J Gastroenterol. 2002;97(4):898–904.
13. Yeoh KG, Zimmerman MJ, Cunningham JT, Cotton PB. Comparative costs of metal versus plastic biliary stent strategies for malignant obstructive jaundice by decision analysis. Gastrointest Endosc. 1999;49(4 Pt 1):466–71.
14. Isayama H, Komatsu Y, Tsujino T, Sasahira N, Hirano K, Toda N, et al. A prospective randomised study of "covered" versus "uncovered" diamond stents for the management of distal malignant biliary obstruction. Gut. 2004;53(5):729–34.
15. Isayama H, Kawabe T, Nakai Y, Tsujino T, Sasahira N, Yamamoto N, et al. Cholecystitis after metallic stent placement in patients with malignant distal biliary obstruction. Clin Gastroenterol Hepatol. 2006; 4(9):1148–53.
16. do Park H, Kim MH, Choi JS, Lee SS, Seo DW, Kim JH, et al. Covered versus uncovered wallstent for malignant extrahepatic biliary obstruction: a cohort comparative analysis. Clin Gastroenterol Hepatol. 2006;4(6):790–6.
17. Yoon WJ, Lee JK, Lee KH, Lee WJ, Ryu JK, Kim YT, et al. A comparison of covered and uncovered Wallstents for the management of distal malignant biliary obstruction. Gastrointest Endosc. 2006;63(7): 996–1000.
18. Telford JJ, Carr-Locke DL, Baron TH, Poneros JM, Bounds BC, Kelsey PB, et al. A randomized trial comparing uncovered and partially covered self-expandable metal stents in the palliation of distal malignant biliary obstruction. Gastrointest Endosc. 2010;72(5):907–14.
19. Kullman E, Frozanpor F, Soderlund C, Linder S, Sandstrom P, Lindhoff-Larsson A, et al. Covered versus uncovered self-expandable nitinol stents in the palliative treatment of malignant distal biliary obstruction: results from a randomized, multicenter study. Gastrointest Endosc. 2010;72(5):915–23.
20. Almadi MA, Barkun AN, Martel M. No benefit of covered vs uncovered self-expandable metal stents in patients with malignant distal biliary obstruction: a meta-analysis. Clin Gastroenterol Hepatol. 2013;11(1):27–37. 1.
21. Saleem A, Leggett CL, Murad MH, Baron TH. Meta-analysis of randomized trials comparing the patency of covered and uncovered self-expandable metal stents for palliation of distal malignant bile duct obstruction. Gastrointest Endosc. 2011;74(2):321–7. e1–3.
22. Ho H, Mahajan A, Gosain S, Jain A, Brock A, Rehan ME, et al. Management of complications associated with partially covered biliary metal stents. Dig Dis Sci. 2010;55(2):516–22.
23. Povoski SP, Karpeh Jr MS, Conlon KC, Blumgart LH, Brennan MF. Association of preoperative biliary drainage with postoperative outcome following pancreaticoduodenectomy. Ann Surg. 1999;230(2):131–42.
24. van der Gaag NA, Rauws EA, van Eijck CH, Bruno MJ, van der Harst E, Kubben FJ, et al. Preoperative biliary drainage for cancer of the head of the pancreas. N Engl J Med. 2010;362(2):129–37.
25. Fang Y, Gurusamy KS, Wang Q, Davidson BR, Lin H, Xie X, et al. Pre-operative biliary drainage for obstructive jaundice. Cochrane Database Syst Rev. 2012;9, CD005444.
26. Evans DB, Varadhachary GR, Crane CH, Sun CC, Lee JE, Pisters PW, et al. Preoperative gemcitabine-based chemoradiation for patients with resectable adenocarcinoma of the pancreatic head. J Clin Oncol. 2008;26(21):3496–502.
27. Varadhachary GR, Wolff RA, Crane CH, Sun CC, Lee JE, Pisters PW, et al. Preoperative gemcitabine and cisplatin followed by gemcitabine-based chemoradiation for resectable adenocarcinoma of the pancreatic head. J Clin Oncol. 2008;26(21):3487–95.

28. Singh A, Lee JH. Self-expanding metal stents for preoperative biliary drainage in patients receiving neoadjuvant therapy for pancreatic cancer. J Gastrointest Oncol. 2012;3(4):304–5.
29. Abrams RA, Lowy AM, O'Reilly EM, Wolff RA, Picozzi VJ, Pisters PW. Combined modality treatment of resectable and borderline resectable pancreas cancer: expert consensus statement. Ann Surg Oncol. 2009;16(7):1751–6.
30. Boulay BR, Gardner TB, Gordon SR. Occlusion rate and complications of plastic biliary stent placement in patients undergoing neoadjuvant chemoradiotherapy for pancreatic cancer with malignant biliary obstruction. J Clin Gastroenterol. 2010;44(6):452–5.
31. Mullen JT, Lee JH, Gomez HF, Ross WA, Fukami N, Wolff RA, et al. Pancreaticoduodenectomy after placement of endobiliary metal stents. J Gastrointest Surg. 2005;9(8):1094–104. discussion 104–5.
32. Wasan SM, Ross WA, Staerkel GA, Lee JH. Use of expandable metallic biliary stents in resectable pancreatic cancer. Am J Gastroenterol. 2005;100(9):2056–61.
33. Lawrence C, Howell DA, Conklin DE, Stefan AM, Martin RF. Delayed pancreaticoduodenectomy for cancer patients with prior ERCP-placed, nonforeshortening, self-expanding metal stents: a positive outcome. Gastrointest Endosc. 2006;63(6):804–7.
34. Singal AK, Ross WA, Guturu P, Varadhachary GR, Javle M, Jaganmohan SR, et al. Self-expanding metal stents for biliary drainage in patients with resectable pancreatic cancer: single-center experience with 79 cases. Dig Dis Sci. 2011;56(12):3678–84.
35. Decker C, Christein JD, Phadnis MA, Wilcox CM, Varadarajulu S. Biliary metal stents are superior to plastic stents for preoperative biliary decompression in pancreatic cancer. Surg Endosc. 2011;25(7):2364–7.
36. Aadam AA, Evans DB, Khan A, Oh Y, Dua K. Efficacy and safety of self-expandable metal stents for biliary decompression in patients receiving neoadjuvant therapy for pancreatic cancer: a prospective study. Gastrointest Endosc. 2012;76(1):67–75.
37. Cavell LK, Allen PJ, Vinoya C, Eaton AA, Gonen M, Gerdes H, et al. Biliary self-expandable metal stents do not adversely affect pancreaticoduodenectomy. Am J Gastroenterol. 2013;108(7):1168–73.
38. Enya M, Yasuda I, Mukai T, Shinoda T, Otsuji K, Iwasa J, et al. Endoscopic treatment for benign biliary strictures: can placement of a covered metallic stent be an option in refractory cases? Dig Endosc. 2003;16(1):12–20.
39. Kahaleh M, Tokar J, Le T, Yeaton P. Removal of self-expandable metallic Wallstents. Gastrointest Endosc. 2004;60(4):640–4.
40. Familiari P, Bulajic M, Mutignani M, Lee LS, Spera G, Spada C, et al. Endoscopic removal of malfunctioning biliary self-expandable metallic stents. Gastrointest Endosc. 2005;62(6):903–10.
41. Shin HP, Kim MH, Jung SW, Kim JC, Choi EK, Han J, et al. Endoscopic removal of biliary self-expandable metallic stents: a prospective study. Endoscopy. 2006;38(12):1250–5.
42. Kahaleh M, Behm B, Clarke BW, Brock A, Shami VM, De La Rue SA, et al. Temporary placement of covered self-expandable metal stents in benign biliary strictures: a new paradigm? (with video). Gastrointest Endosc. 2008;67(3):446–54.

Endoscopic Therapy: EUS-Based Therapy

21

Takao Itoi

Introduction

A linear array echoendoscope enables not only the diagnosis of pancreatic masses by fundamental imaging but also tissue sampling using a fine needle. In fact, endoscopic ultrasonography (EUS)-guided fine-needle aspiration biopsy (EUS-FNA) is currently the most essential modality for histocytological diagnosis of pancreatic solid masses by carrying out tissue sampling because of its high diagnostic ability (4766 pooled patients: pooled sensitivity, 87 %; pooled specificity, 96 % [1]) [1–5].

Among the pancreatic solid masses, pancreatic cancer is the fourth or fifth leading causes of cancer death in most developed countries [6], with a global annual incidence rate of approximately 8/100,000 persons [7]. Pancreatic solid masses are usually unresectable at the time of diagnosis despite recent progress in imaging modalities. The prognosis of advanced and metastatic pancreatic carcinomas is in fact dismal because the 5-year survival rate is less than 6 % [8]. Thus, salvage therapy for unresectable pancreatic cancers in combination with or without standard chemoradiation therapy has been highly anticipated. Recently, EUS-guided advanced interventions have emerged based on the EUS-FNA technique. This chapter reviews the current status of EUS-guided therapy for pancreatic solid masses, including experimental studies.

T. Itoi, M.D., Ph.D., F.A.S.G.E. (✉)
Department of Gastroenterology and Hepatology, Tokyo Medical University, 6-7-1 Nishishinjuku, Shinjuku, Tokyo 160-0023, Japan
e-mail: itoi@tokyo-med.ac.jp

EUS-Guided Interventions for Pancreatic Solid Masses

To date, several investigators have reported animal studies involving normal pancreas and clinical studies involving pancreatic solid masses as follows: (1) injection therapy using alcohol, antitumor agents, and immunoreactive agents; (2) ablation therapy using radiofrequency, photodynamic therapy, a neodymium:yttrium aluminum garnet (ND:YA) laser therapy, and high-intensity focused ultrasound; (3) implantation using iodine-125 radioactive seeds, fiducial markers, and marking ink (Table 21.1).

Injection Therapy

Direct injection of chemical and antitumor agents into pancreatic masses under EUS guidance may be one of the suboptimal therapies for pancreatic cancers because of their hypovascular nature (Fig. 21.1). However, the effects of this type of therapy are limited to pancreatic masses without metastatic lesions. On the other hand, immunotherapy theoretically may increase therapeutic

M.S. Wagh, P.V. Draganov (eds.), *Pancreatic Masses*, DOI 10.1007/978-3-319-19677-0_21

Table 21.1 EUS-guided Antitumor Therapy

	Human	Animal
Therapy		
1. Injection therapy		
(a) Ethanol	Yes (P-NET)	Yes
(b) Gemcitabine	Yes	No
(c) Paclitaxel (OncoGel)	No	Yes
(d) Oncolytic adenovirus (ONYX-015)	Yes	No
(e) Immunoreactive agents		
• Cytoimplants	Yes	No
• Dendritic cells	Yes	No
• TNFerade	Yes	No
2. Ablation therapy		
(a) Radiofrequency ablation	Yes	Yes
(b) Photodynamic therapy	No	Yes
(c) ND:YAG laser	No	Yes
(d) High-intensity focused ultrasound	No	Yes
3. Implantation therapy		
(a) Fiducial maker	Yes	No
(b) Brachytherapy	Yes	No
(c) Tattooing	Yes	Yes

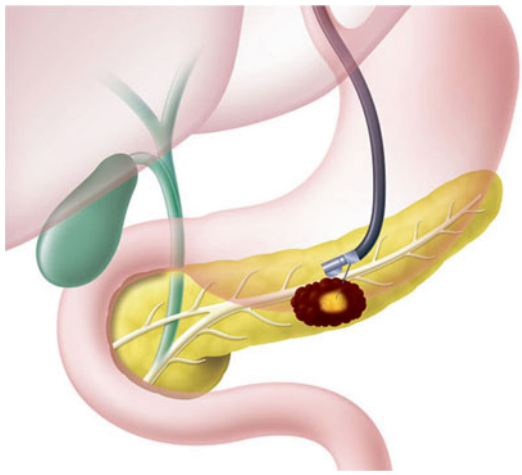

Fig. 21.1 Schema of EUS-guided injection therapy in the pancreas

efficacy even in metastatic pancreatic cancers because of the induction of tumor antigen-specific cytotoxic T lymphocytes.

Ethanol

The mechanism of ethanol ablation mainly involves cell death by causing cell membrane lysis, protein denaturation, and vascular occlusion [9]. Several investigators have shown that ethanol injection can be safely performed in normal pancreatic tissues in a pig model [10, 11]. To date, EUS-guided ethanol injection has been performed in pancreatic neuroendocrine tumors (PNETs) [12–17]. High concentrations of ethanol (95–98 %) were used for tumor ablation. The sizes of the targeted PNETs ranged from 7 to 20 mm. The amount of ethanol injected ranged from 0.1 to 8.5 mL. In terms of procedure-related complications, abdominal pain, elevation of pancreatic enzyme level, and duodenal ulcers were observed, but no fatal and serious complications were present.

Although there is as yet no report on ethanol injection in pancreatic cancer, a previous study described EUS-guided ethanol injection in a metastatic liver mass derived from pancreatic cancer [18]. The study showed that ethanol injection decreased the size of the liver mass without causing significant complications except for a transient low fever.

Gemcitabine

A short report previously described the clinical trial of EUS-guided intratumoral gemcitabine injection in patients with locally advanced and metastatic pancreatic cancers without causing any complications [19]. Six-months survival and 1-year survival were achieved in 76 % and 46 % of the patients, respectively, and curative operation could be performed in three patients.

Paclitaxel (OncoGel)

OncoGel is an intralesional injectable formulation of the chemotherapeutic drug based on paclitaxel bound to a thermosensitive gel carrier [20]. Matthes and colleagues [20] reported that OncoGel injection under EUS guidance was safely performed without inducing any complications in normal pancreas in eight pigs, and achieved high and sustained localized concentrations of paclitaxel.

Oncolytic Adenovirus (ONYX-015)

ONYX-015 (dl1520) is a 55-kDa protein from the E1B-region of the adenovirus that binds to and inactivates the p53 gene, which is mutated in half of human cancers. Hecht and colleagues [21] performed a clinical trial in 21 patients with locally advanced or metastatic pancreatic cancers. In eight sessions, ONYX-015 was delivered into the primary pancreatic cancer over a period of 8 weeks. The final four treatments were given in combination with gemcitabine. Finally, the patients received 2×10^{10} ($n=3$) or 2×10^{11} ($n=18$) virus particles/treatment. After the combination therapy, 2 patients had partial regressions of the injected tumor, 2 had minor responses, 6 had stable disease, and 11 had progressive disease or had to go off study because of treatment toxicity. No clinical pancreatitis occurred despite mild, transient elevations in the lipase level in a minority of patients.

Immunoreactive Agents

Recently, novel agents targeting tumor-specific pathways using immunotherapy have been developed and investigated as single agents or adjuncts to conventional chemotherapy. These agents have been found to contribute to the improvement of prognosis in unresectable pancreatic cancers [22].

Cytoimplants

Chang and colleagues [23] reported the clinical trial of an EUS-guided cytoimplant, which is an allogeneic mixed-lymphocyte culture in eight patients with an unresectable pancreatic cancer (four patients in stage II, three in stage III, and one in stage IV). This is discussed in further detail elsewhere (Chap. 24) in this book.

Dendritic Cells

Immunotherapy using dendritic cells (DCs) attempts to harness the power and specificity of the individual's immune system to treat cancers (Fig. 21.2a–c). To date, two clinical studies have been reported in terms of EUS-guided DC injection in patients with unresectable pancreatic cancers [24, 25]. This is discussed in further detail elsewhere (Chap. 24) in this book.

Fig. 21.2 EUS-guided dendritic cells injection. (**a**) Frozen dendritic cells are solved just before injection. (**b**) Solved dendritic cells are aspirated using a disposable syringe. (**c**) Injection under EUS guidance using a 22-gauge FNA needle

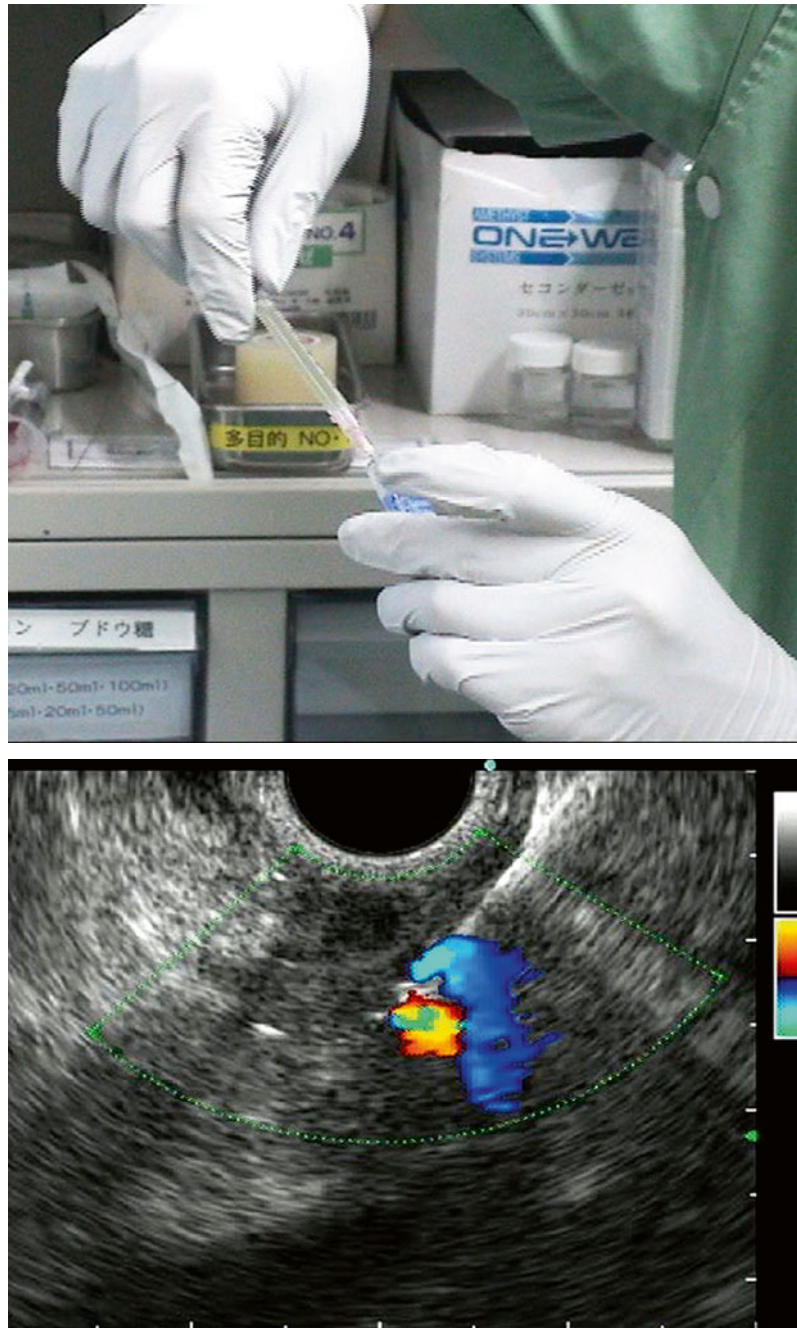

Fig. 21.2 (continued)

TNFerade

TNFerade biologic is a novel means of delivering tumor necrosis factor (TNF) alpha regulated by a radiation-inducible promoter to tumor cells by gene transfer. Details about this modality are included elsewhere (Chap. 24) in the book.

Ablation Therapy

To date, EUS-guided ablation therapy for unresectable pancreatic solid tumors has been attempted by interventional endoscopists.

Radiofrequency

Radiofrequency current is emitted from the exposed portion of the electrode, and this current translates into ion agitation within the surrounding tissue, which is converted by friction into heat and induces cellular death by coagulation necrosis [26]. This is discussed in further detail elsewhere (Chap. 24) in this book.

Photodynamic Therapy

Photodynamic therapy is a treatment involving the production of a form of oxygen that kills adjacent cells with a specific type of light after the administration of a photosensitizer. To date, this form of therapy has been applicable in several types of cancers [27]. In terms of the application of interventional EUS for the pancreas, Chan and colleagues [28] first reported the feasibility and safety of EUS-guided photodynamic therapy with intravenous low-dose porfimer sodium (Photofilin) at 1 mg/kg for 24 h before the procedure in normal pancreas as well as in the liver, kidney, and spleen in a pig model. Yusuf and colleagues also demonstrated the feasibility and safety of EUS-guided photodynamic therapy with intravenous verteporfin in normal pancreas in a pig model. Localized tissue necrosis within the pancreatic tail (range, 6.6–30.5 mm in diameter) was observed in all pigs without any procedure-related complications. To date, however, there has been no study for human pancreatic cancers.

Nd:YAG Laser Therapy

Laser ablation with the Nd:YAG laser can achieve a high rate of complete tissue necrosis and has been applied as a minimally invasive, palliative option for the treatment of human cancers [29]. Di Matteo and his colleagues [29] demonstrated the feasibility and safety of Nd:YAG laser therapy under EUS guidance in a pig model. In their study, a 1.064-nm wavelength Nd:YAG laser therapy was successfully administered with an output power of 2 and 3 W and a total delivered energy of 500 and 1000 J in the continuous mode in all pigs without causing any complications at 24 h. The volume of ablation tissue ranged from a mean of 314–483 mm^3. The ablation area ranged from a mean of 49–80 mm^2.

High-Intensity Focused Ultrasound

High-intensity focused ultrasound (HIFU) is one of the available minimally invasive salvage treatments for pancreatic cancers. Ultrasound is emitted from a transrectal transducer and is focused so that it causes coagulation and necrosis of the target tissue [30]. Hwang and colleagues [31] developed a newly designed HIFU transducer, which is attached to a linear echoendoscope with a spherically curved PZT element (radius of curvature, 35 mm; frequency, 3.9 MHz). In their ex vivo study, the focal distance was measured as 35 mm from the surface of the transducer with focal dimensions of 2 mm (diameter) × 10 mm (axial). The transducer successfully created lesions in gel phantoms and ex vivo bovine livers with a focal acoustic intensity of 250 W/cm^2. On the other hand, in vivo studies demonstrated that ablation was feasible in the porcine pancreas and liver).

Implantation Therapy

Radiation therapy with or without chemotherapy is one of the options for the treatment of unresectable locally advanced pancreatic cancers. Recently, EUS-guided fiducial marker implantation for stereotactic body radiation therapy (SBRT) and radioactive seeds for brachytherapy have emerged.

Fiducial Marker Placement

The advantages of SBRT in the treatment of pancreatic cancer are attributed to its ability to increase the radiation dose delivered to the target tumor while decreasing the irradiation of the surrounding normal tissues. This may result in improved local treatment and normal tissue protection. Fiducial markers are radiopaque spheres, coils, or seeds that are implanted in or near the tumor to demarcate its borders and facilitate image-guided radiation therapy. Pishvaian and colleagues first reported the EUS-guided fiducial maker implantation for SBRT in pancreatic cancers in 2006 [32]. Since then, several investigators have demonstrated the feasibility and usefulness of SBRT in unresectable pancreatic cancers [33–40]. Fiducials are placed using a 19-gauge or 22-gauge needle, with a technical success rate ranging from 85 to 100 % without serious complications except for minor bleeding and mild pancreatitis and cholangitis. Although the interfiducial distance is often debatable for accurate radiotherapy, a recent study has shown that an ideal geometry might not be as important as previously assumed [40]; that is, in most patients, the interfiducial distance was less than 2 cm and image-guided radiation therapy was still possible [41].

Brachytherapy

Brachytherapy provides a means to further escalate the local dose; it has been used in an effort to improve long-term results in men with high-risk disease [42]. Sun and colleagues first reported the clinical trial of brachytherapy in 15 patients with unresectable pancreatic cancer using iodine-125 under EUS guidance in combination with gemcitabine [43]. A mean number of 22 radioactive seeds per patient were implanted into the tumors. The mean total implanted activity was 20 mCi. The minimum peripheral dose was 14,000 cGy. The mean volume of the implants was 52 cm^3. The partial response and stable disease rates were 27 % and 33 %, respectively. Clinical benefit was demonstrated in 30 % of the patients, mostly due to pain reduction. Local complications such as pancreatitis and pseudocyst formation occurred in three patients and grade III hematologic toxicity occurred in three patients without serious clinical sequelae. On the other hand, Jin and colleagues described a prospective pilot study of EUS-guided implantation of iodine 125-seeds combined with chemotherapy in 22 patients with unresectable pancreatic cancer [44]. The median 10 seeds and the maximum 30 seeds were placed without any complications. The partial response rate and the stable disease rate were 13.6 % and 45.5 %, respectively. The estimated median survival time was 9 months. The visual analog scale pain score significantly dropped, from 5.07 ± 2.63 to 1.73 ± 1.91 ($p < 0.01$) 1 week after brachytherapy but significantly increased again, to 3.53 ± 1.51, 1 month later ($p < 0.05$ vs. baseline). Both studies revealed that EUS-guided brachytherapy regardless of the combined chemotherapy may be effective for pain relief but not survival time. In fact, the follow-up outcome of the patients sustained the same conclusion [45].

Tatooing

With small pancreatic masses, it may be time-consuming or at times difficult for a surgeon to detect the lesion perioperatively even when using high-resolution intraoperative ultrasound. To enhance the ease of perioperative tumor detection, the preoperative localization of tumors, so-called tatooing using India ink, carbon particles, indocyanine green, or methylene blue, has been attempted under EUS guidance [46–49]. Although the timing of injection is debatable and it depends on the type of ink, Lennon and colleagues [49] suggested that if carbon particles are available, EUS-guided tatooing does not need to be performed immediately before surgery because the tattoo was visible on laparoscopy in all 13 patients, and the tattoos were durable for up to 69 days despite the small lesion size. Larsen and colleagues [50] described an alternative technique to tattooing in which they inserted a 5-mm × 0.8-mm pin within a pancreatic tumor using a 19-gauge needle under EUS guidance.

Conclusions

EUS-guided injection therapy, ablation therapy, and implantation therapy have been reported as novel and salvage techniques for the treatment of pancreatic solid tumors, mainly pancreatic cancers. Although their feasibility and safety have been demonstrated in many studies and their promising outcomes have produced enthusing echoendosonographers, there are several limitations in interventional EUS for pancreatic solid tumors because previous investigations were mostly retrospective and nonrandomized studies involving a small number of cases except for TNFerade injection. Large prospective and randomized controlled trials are needed to fully investigate optimal options regarding their efficacy over the standard treatment in pancreatic solid tumors.

Acknowledgment Thanks are due to Dr. Edward Barroga for reviewing and editing this chapter.

References

1. Puli SR, Bechtold ML, Buxbaum JL, Eloubeidi MA. How good is endoscopic ultrasound-guided fine-needle aspiration in diagnosing the correct etiology for a solid pancreatic mass?: A meta-analysis and systematic review. Pancreas. 2013;42:20–6.
2. Vilmann P, Jacobsen GK, Henriksen FW, Hancke S. Endoscopic ultrasonography with guided fine needle aspiration biopsy in pancreatic disease. Gastrointest Endosc. 1992;38:172–3.
3. Harewood GC, Wiersema MJ. Endosonography-guided fine needle aspiration biopsy in the evaluation of pancreatic masses. Am J Gastroenterol. 2002;97:1386–91.
4. Varadarajulu S, Tamhane A, Eloubeidi MA. Yield of EUS-guided FNA of pancreatic masses in the presence or the absence of chronic pancreatitis. Gastrointest Endosc. 2005;62:728–36.
5. Itoi T, Tsuchiya T, Itokawa F, et al. Histological diagnosis by EUS-guided fine-needle aspiration biopsy in pancreatic solid masses without on-site cytopathologist: a single-center experience. Dig Endosc. 2011;23 Suppl 1:34–8.
6. Ferlay J, Shin HR, Bray F, et al. GLOBOCAN 2008, cancer incidence and mortality worldwide: IARC cancer base no. 10. Lyon: International Agency for Research on Cancer. 2010. http://www.globocan.iarc.fr. Accessed May 2011.
7. Raimondi S, Maisonneuve P, Lowenfels AB. Epidemiology of pancreatic cancer: an overview. Nat Rev Gastroenterol Hepatol. 2009;6:699–708.
8. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. Cancer J Clin. 2013;63(1):11–30.
9. Gelczer RK, Charboneau JW, Hussain S, Brown DL. Complications of percutaneous ethanol ablation. J Ultrasound Med. 1998;17:531–3.
10. Aslanian H, Salem RR, Marginean C, Robert M, Lee JH, Topazian M. EUS-guided ethanol injection of normal porcine pancreas: a pilot study. Gastrointest Endosc. 2005;62:723–7.
11. Matthes K, Mino-Kenudson M, Sahani DV, Holalkere N, Brugge WR. Concentration-dependent ablation of pancreatic tissue by EUS-guided ethanol injection. Gastrointest Endosc. 2007;65:272–7.
12. Jürgensen C, Schuppan D, Neser F, Ernstberger J, Junghans U, Stölzel U. EUS-guided alcohol ablation of an insulinoma. Gastrointest Endosc. 2006;63:1059–62.
13. Muscatiello N, Salcuni A, Macarini L, Cignarelli M, Prencipe S, di Maso M, Castriota M, D'Agnessa V, Ierardi E. Treatment of a pancreatic endocrine tumor by ethanol injection guided by endoscopic ultrasound. Endoscopy. 2008;40 Suppl 2:E258–9.
14. Muscatiello N, Nacchiero M, Della Valle N, Di Terlizzi F, Verderosa G, Salcuni A, Macarini L, Cignarelli M, Castriota M, D'Agnessa V, Ierardi E. Treatment of a pancreatic endocrine tumor by ethanol injection (PEI) guided by endoscopic ultrasound. Endoscopy. 2008;40 Suppl 2:E83.
15. Deprez PH, Claessens A, Borbath I, Gigot JF, Maiter D. Successful endoscopic ultrasound-guided ethanol ablation of a sporadic insulinoma. Acta Gastroenterol Belg. 2008;71:333–7.
16. Vleggaar FP, Bij de Vaate EA, Valk GD, Leguit RJ, Siersema PD. Endoscopic ultrasound-guided ethanol ablation of a symptomatic sporadic insulinoma. Endoscopy. 2011;43(Suppl 2) UCTN: E328–E329.
17. Levy MJ, Thompson GB, Topazian MD, Callstrom MR, Grant CS, Vella A. US-guided ethanol ablation of insulinomas: a new treatment option. Gastrointest Endosc. 2012;75:200–6.
18. Hu YH, Tuo XP, Jin ZD, Liu Y, Guo Y, Luo L. Endoscopic ultrasound (EUS)-guided ethanol injection in hepatic metastatic carcinoma: a case report. Endoscopy. 2010;42 Suppl 2:E256–7.
19. Levy MJ, Alberts SR, Chari ST, et al. EUS guided intra-tumoral gemcitabine therapy for locally advanced and metastatic pancreatic cancer. Gastrointest Endosc. 2011;73:AB144–5.
20. Matthes K, Mino-Kenudson M, Sahani DV, et al. EUS-guided injection of paclitaxel (OncoGel) provides therapeutic drug concentrations in the porcine pancreas (with video). Gastrointest Endosc. 2007;65:448–53.
21. Hecht JR, Bedford R, Abbruzzese JL, et al. A phase I/II trial of intratumoral endoscopic ultrasound injection of ONYX-015 with intravenous gemcitabine in

unresectable pancreatic carcinoma. Clin Cancer Res. 2003;9:555–61.
22. Brennan GT, Relias V, Saif MW. Novel agents for the treatment of pancreatic cancer. J Pancreas. 2014;15: 110–3.
23. Chang KJ, Nguyen PT, Thompson JA, et al. Phase I clinical trial of allogeneic mixed lymphocyte culture (cytoimplant) delivered by endoscopic ultrasound-guided fine-needle injection in patients with advanced pancreatic carcinoma. Cancer. 2000;88:1325–35.
24. Irisawa A, Takagi T, Kanazawa M, et al. Endoscopic ultrasound- guided fine-needle injection of immature dendritic cells into advanced pancreatic cancer refractory to gemcitabine: a pilot study. Pancreas. 2007;35:189–90.
25. Hirooka Y, Itoh A, Kawashima H, et al. A combination therapy of gemcitabine with immunotherapy for patients with inoperable locally advanced pancreatic cancer. Pancreas. 2009;38:e69–74.
26. Cosman ER, Nashold BS, Ovelman-Levitt J. Theoretical aspects of radiofrequency lesions in the dorsal root entry zone. Neurosurgery. 1984;15:945–50.
27. Dolmans DE, Fukumura D, Jain RK. Photodynamic therapy for cancer. Nat Rev Cancer. 2003;3(5): 380–7.
28. Chan HH, Nishioka NS, Mino M, et al. EUS-guided photodynamic therapy of the pancreas: a pilot study. Gastrointest Endosc. 2004;59:95–9.
29. Di Matteo F, Martino M, Rea R, et al. EUS-guided Nd:YAG laser ablation of normal pancreatic tissue: a pilot study in a pig model. Gastrointest Endosc. 2010;72:358–63.
30. Rukstalis DB. Treatment options after failure of radiation therapy: a review. Rev Urol. 2002;4 Suppl 2:S12–7.
31. Hwang J, Farr N, Morrison K, et al. Development of an EUS-guided high-intensity focused ultrasound endoscope. Gastrointest Endosc. 2011;73:AB155.
32. Pishvaian AC, Collins B, Gagnon G, Ahlawat S, Haddad NG. EUS-guided fiducial placement for CyberKnife radiotherapy of mediastinal and abdominal malignancies. Gastrointest Endosc. 2006;64:412–7.
33. Varadarajulu S, Trevino JM, Shen S, Jacob R. The use of endoscopic ultrasound-guided gold markers in image-guided radiation therapy of pancreatic cancers: a case series. Endoscopy. 2010;42:423–5.
34. Park WG, Yan BM, Schellenberg D, et al. EUS-guided gold fiducial insertion for image-guided radiation therapy of pancreatic cancer: 50 successful cases without fluoroscopy. Gastrointest Endosc. 2010;71:513–8.
35. DiMaio CJ, Nagula S, Goodman KA, et al. EUS-guided fiducial placement for image-guided radiation therapy in GI malignancies by using a 22-gauge needle (with videos). Gastrointest Endosc. 2010;71: 1204–10.
36. Sanders MK, Moser AJ, Khalid A, et al. EUS-guided fiducial placement for stereotactic body radiotherapy in locally advanced and recurrent pancreatic cancer. Gastrointest Endosc. 2010;71:1178–84.
37. Ammar T, Coté GA, Creach KM, et al. Fiducial placement for stereotactic radiation by using EUS: feasibility when using a marker compatible with a standard 22-gauge needle. Gastrointest Endosc. 2010;71:630–3.
38. Khashab MA, Kim KJ, Tryggestad EJ, et al. Comparative analysis of traditional and coiled fiducials implanted during EUS for pancreatic cancer patients receiving stereotactic body radiation therapy. Gastrointest Endosc. 2012;76:962–71.
39. Choi JH, Seo DW, Park DH, Lee SK, Kim MH. Fiducial placement for stereotactic body radiation therapy under only endoscopic ultrasonography guidance in pancreatic and hepatic malignancy: practical feasibility and safety. Gut Liver. 2014;8:88–93.
40. Dávila Fajardo R, Lekkerkerker SJ, van der Horst A, Lens E, Bergman JJ, Fockens P, Bel A, van Hooft JE. EUS-guided fiducial markers placement with a 22-gauge needle for image-guided radiation therapy in pancreatic cancer. Gastrointest Endosc. 2014;79:851. doi:10.1016/j.gie.2013.12.027. pii: S0016-5107(13)02710-7.
41. Majumder S, Berzin TM, Mahadevan A, et al. Endoscopic ultrasound guided pancreatic fiducial placement: how important is ideal fiducial geometry? Pancreas. 2013;42:692–5.
42. Taira AV, Merrick GS, Butler WM, Galbreath RW, Lief J, Adamovich E, Wallner KE. Long-term outcome for clinically localized prostate cancer treated with permanent interstitial brachytherapy. Int J Radiat Oncol Biol Phys. 2011;79:1336–42.
43. Sun S, Xu H, Xin J, et al. Endoscopic ultrasound-guided interstitial brachytherapy of unresectable pancreatic cancer: results of a pilot trial. Endoscopy. 2006;38:399–403.
44. Jin Z, Du Y, Li Z, et al. Endoscopic ultrasonography-guided interstitial implantation of iodine 125-seeds combined with chemotherapy in the treatment of unresectable pancreatic carcinoma: a prospective pilot study. Endoscopy. 2008;40:314–20.
45. Du Y, Jin Z, Meng H, Zou D, Chen J, Liu Y, Zhan X, Wang D, Liao Z, Li Z. Long-term effect of gemcitabine-combined endoscopic ultrasonography-guided brachytherapy in pancreatic cancer. J Interv Gastroenterol. 2013;3:18–24.
46. Gress FG, Barawi M, Kim D, Grendell JH. Preoperative localization of a neuroendocrine tumor of the pancreas with EUS-guided fine needle tattooing. Gastrointest Endosc. 2002;55(4):594–7.
47. Ashida R, Yamao K, Okubo K, Sawaki A, Mizuno N, Nakamura T, Tajika M, Kawai H, Shimizu Y. Indocyanine green is an ideal dye for endoscopic ultrasound-guided fine-needle tattooing of pancreatic tumors. Endoscopy. 2006;38(2):190–2.

48. Farrell JJ, Sherrod A, Parekh D. EUS-guided fine-needle tattooing for preoperative localization of early pancreatic adenocarcinoma. Gastrointest Endosc. 2009;69(1):176–7.
49. Lennon AM, Newman N, Makary MA, Edil BH, Shin EJ, Khashab MA, Hruban RH, Wolfgang CL, Schulick RD, Giday S, Canto MI. EUS-guided tattooing before laparoscopic distal pancreatic resection (with video). Gastrointest Endosc. 2010;72(5):1089–94.
50. Larsen MH, Fristrup CW, Mortensen MB. Endoscopic ultrasound-guided fine-needle marking of a small pancreatic tumor. Endoscopy. 2009;41 Suppl 2:E175–6.

Endoscopic Therapy of Gastric Outlet Obstruction

22

Emmanuel C. Gorospe, Barham Abu-Dayyeh, and Louis M. Wong Kee Song

Introduction

Upper gastrointestinal malignancy has supplanted peptic stricture as the most common cause of gastric outlet obstruction (GOO) in the era of effective medical therapy for acid suppression and *H. pylori* infection [1]. Presently, 80 % of cases of GOO are due to advanced upper gastrointestinal cancers [2]. Malignant GOO usually occurs late in the course of the disease as a result of mechanical obstruction of the gastric outlet and is thus a sign of locally advanced and often unresectable malignancy [3]. Patients with pancreatic cancer, especially when located in the pancreatic head, may develop biliary obstruction, duodenal obstruction, or both. Approximately 15–25 % of patients with pancreatic cancer will develop GOO in the course of their disease [4, 5].

Previously, palliative surgical bypass in the form of a gastrojejunostomy was the main treatment modality. However, surgical intervention carries significant morbidity, complicated by the patient's advanced malignancy and poor quality of life. The advent of self-expandable metal stents (SEMSs) offered a minimally invasive alternative at restoring the patient's ability to tolerate oral intake and relieving obstructive symptoms. Truong et al. were the first to report on the endoscopic placement of SEMSs for malignant GOO in 1992 [6]. Since then, endoscopic stent placement has become a major strategy for palliation of GOO in the setting of advanced pancreatic cancer [7]. Several studies have demonstrated that SEMS placement is associated with faster resumption of oral intake, shorter postprocedural hospital stay, lesser morbidity, and lower costs when compared to gastrojejunostomy [8–10].

Herein, the evaluation and management of GOO due to pancreatic malignancy are highlighted, with emphasis on duodenal SEMS placement for palliation of GOO. The concomitant management of biliary obstruction via endoscopic retrograde cholangiopancreatography (ERCP) is addressed in a separate chapter (see Chap. 20).

Combined Duodenal and Biliary Obstruction in Pancreatic Cancer

Combined duodenal and biliary obstruction is often a complication of pancreatic cancer. In a series of 64 patients with combined obstruction, 84 % of cases had primary pancreaticobiliary malignancy [11]. To a lesser extent, other gastrointestinal malignancies, such as ampullary cancer, distal cholangiocarcinoma, primary duodenal

E.C. Gorospe, M.D., M.P.H., F.A.C.P.
B. Abu-Dayyeh, M.D., M.P.H.
L.M. Wong Kee Song, M.D., F.R.C.P.C., F.A.S.G.E. (✉)
Division of Gastroenterology and Hepatology, Department of Medicine, Mayo Clinic College of Medicine, 200 First Street SW, Rochester, MN 55905, USA
e-mail: wong.louis@mayo.edu

M.S. Wagh, P.V. Draganov (eds.), *Pancreatic Masses*, DOI 10.1007/978-3-319-19677-0_22

cancer, and metastatic disease in the pancreatic head, may result in combined duodenal and biliary obstruction. The concurrent luminal and biliary obstruction can present a challenge in the palliation of malignant GOO.

Early recognition of impending biliary and/or duodenal obstruction in cases of pancreatic malignancy is essential in planning for SEMS placement. Often, the development of concomitant duodenal and biliary obstruction predicts poor overall survival, and the median survival time was only 81 days in a series of 64 patients with combined obstruction [11]. Based on the relationship of the duodenal obstruction with the major papilla, combined duodenal and biliary obstruction can be classified into three types [11]. Type I involves obstruction in the duodenal bulb without involvement of the major papilla. Type II involves concurrent obstruction of the second duodenum and major papilla. Type III encompasses an obstruction in the third portion of the duodenum distal to the papilla. The recommended management strategy varies according to the different types of anatomic involvement causing GOO.

Proximal Duodenal Obstruction Without Major Papilla Involvement

With regard to Type I obstruction, the approach and sequence to duodenal and biliary stent placement depend on whether the obstruction is traversable by the endoscope. The technical details regarding biliary stent placement are discussed in a separate chapter.

As a general rule, placement of the biliary stent is recommended as the first step, followed by duodenal stent placement if the duodenoscope can be advanced beyond the duodenal obstruction to the major papilla [12, 13]. Endoscope advancement beyond the duodenal stenosis may require initial balloon dilation of the narrowed lumen. If the duodenoscope still cannot traverse the obstruction after dilation, a duodenal stent can be deployed as the initial step, with the distal flange of the stent preferably positioned proximal to the major papilla. The duodenal stent will then serve as a conduit and access to the major papilla for biliary stent placement.

In some cases, advancement of a duodenoscope beyond the stented stricture may not be feasible despite successful deployment of the duodenal stent. A wait period of 2–3 days may allow for full expansion of the stent, thus facilitating subsequent passage of the duodenoscope. Another approach involves immediate balloon dilation of the duodenal stent [12], although this method should be performed with caution due to the risk of perforation [11, 14]. If both approaches are unsuccessful and biliary drainage is required, endoscopic ultrasound (EUS)-guided hepaticogastrostomy or percutaneous access of the biliary system are both acceptable alternatives (Fig. 22.1).

Obstruction at the Second Duodenum with Major Papilla Involvement

Type II obstruction is the most challenging scenario. It involves simultaneous involvement of the second portion of the duodenum and the major papilla. In addition, a large tumor mass may preclude visualization or successful cannulation of the major papilla. Deployment of a biliary SEMS is first attempted whenever feasible [13]. Plastic biliary stents are not recommended as they are likely to become occluded in a short time interval and are difficult to replace once a duodenal SEMS has been deployed across the ampulla. After successful biliary stent placement, a duodenal SEMS is deployed across the luminal stricture (Figs. 22.2, 22.3, and 22.4).

In locally advanced disease, the major papilla may become deeply imbedded in the obstructing tumor without any viable access for cannulation via ERCP. If biliary access fails, potential options include either placement of a percutaneous biliary drain or EUS-guided biliary drainage via a hepaticogastrostomy or choledochoduodenostomy approach. With the recent approval of a short, fully covered lumen-apposing stent

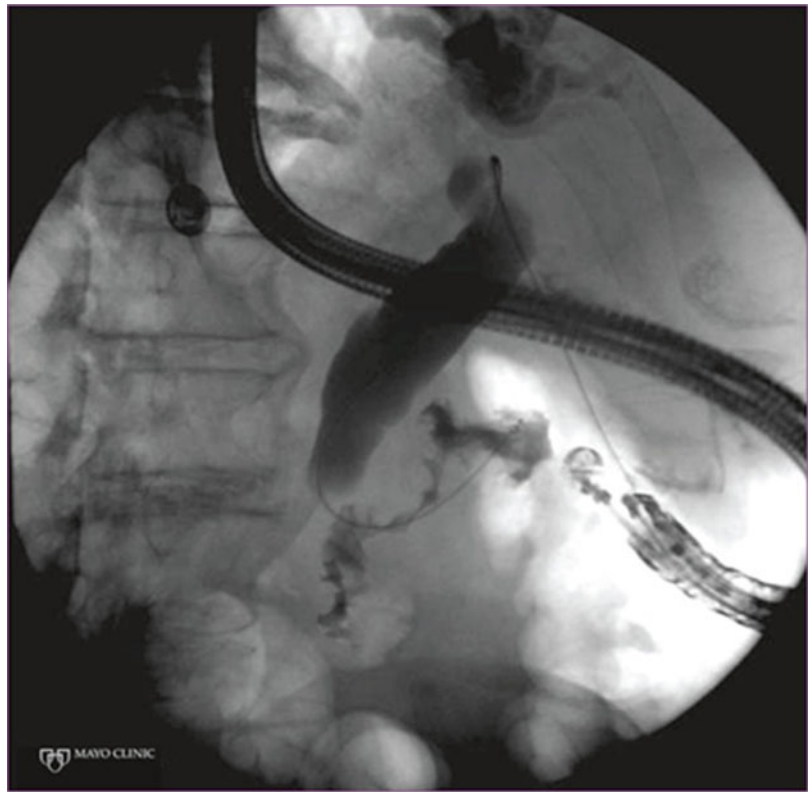

Fig. 22.1 EUS-guided biliary access via a transhepatic (hepaticogastrostomy) approach. A guidewire was passed via a EUS-guided needle through the gastric wall into a dilated left intrahepatic duct and maneuvered distally to coil in the duodenum through the major papilla

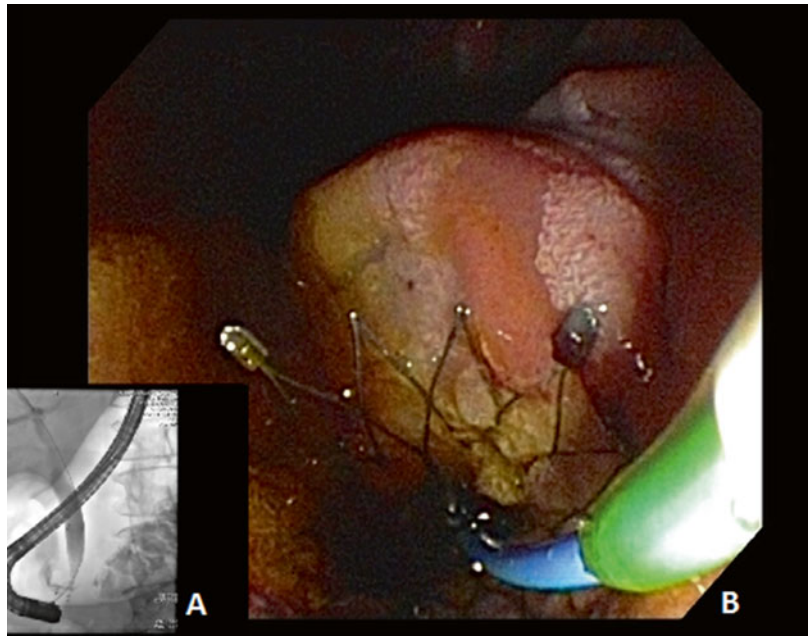

Fig. 22.2 ERCP and biliary SEMS placement. (**a**) Cholangiogram; (**b**) endoscopic view with deployed SEMS

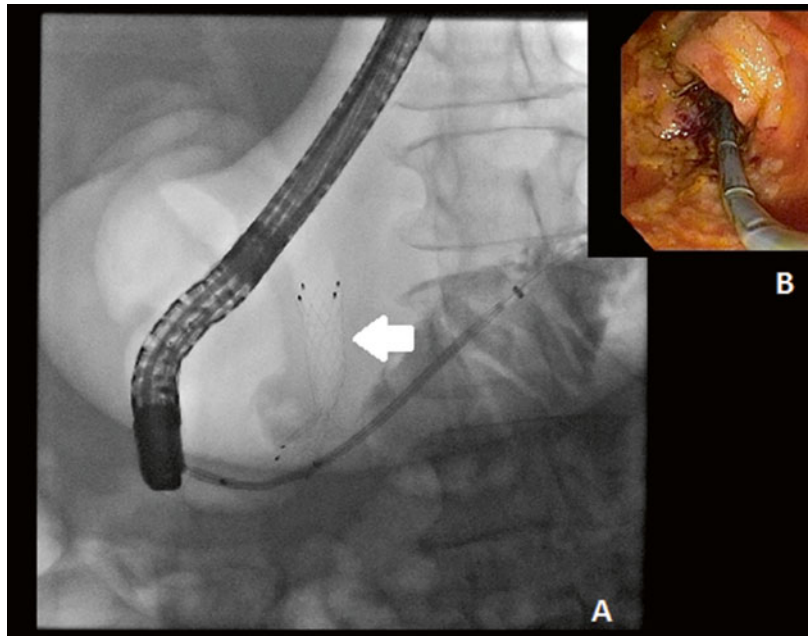

Fig. 22.3 Duodenal SEMS placement. (**a**) Fluoroscopic view showing relationship of the duodenal SEMS to the biliary SEMS (*arrow*); (**b**) endoscopic view showing passage of the duodenal SEMS delivery catheter through the luminal obstruction

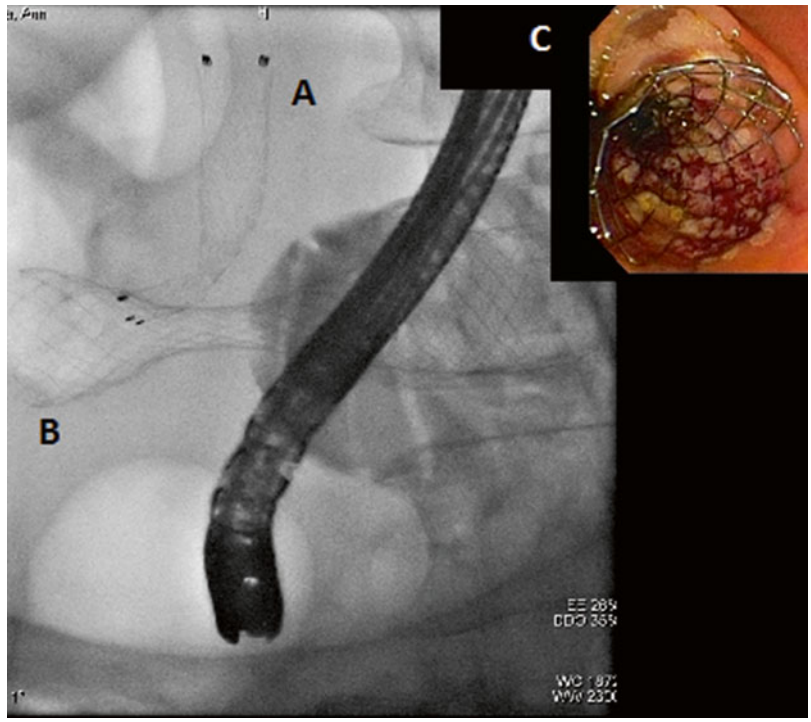

Fig. 22.4 Successful deployment of duodenal SEMS. (**a**) Biliary SEMS; (**b**) duodenal SEMS; (**c**) endoscopic view showing deployed duodenal SEMS through the luminal obstruction

(AXIOS, Xlumena, Mountain View, CA), a choledochoduodenostomy approach is preferable to minimize the risk of bile peritonitis (Fig. 22.5). Percutaneous biliary access is an acceptable and often more readily accessible option when therapeutic EUS expertise is not available [15].

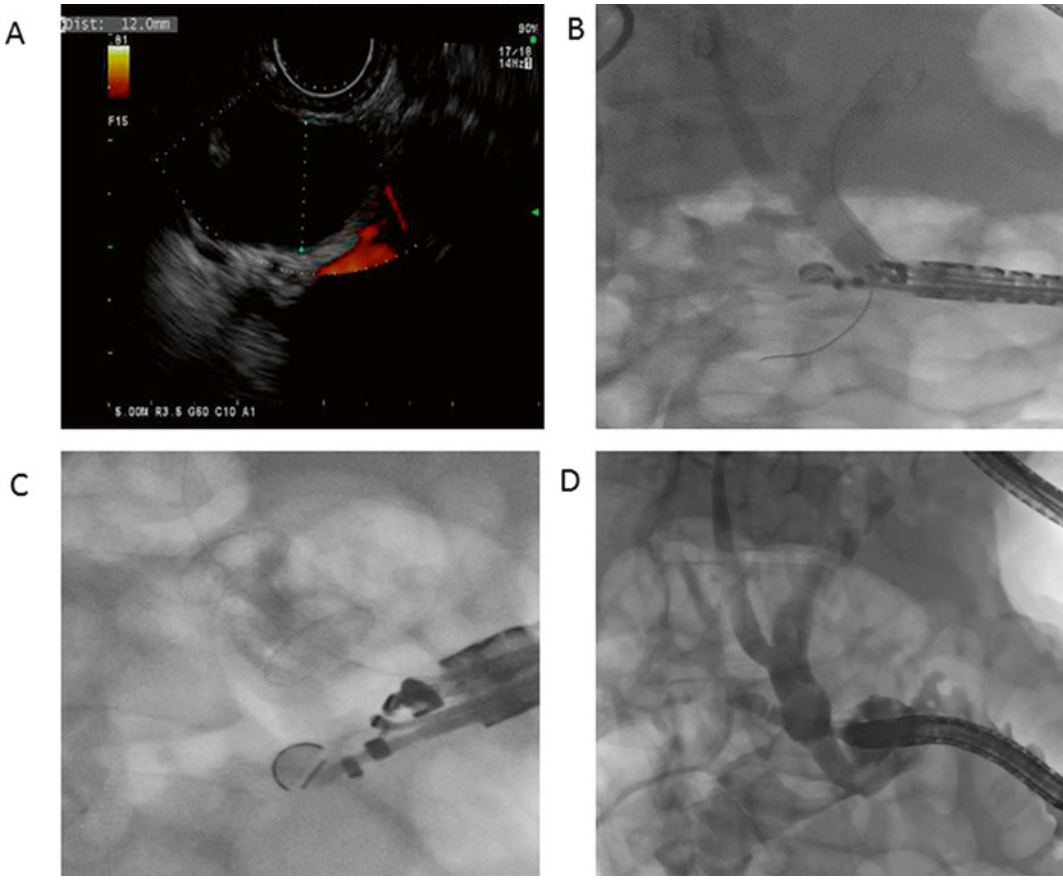

Fig. 22.5 EUS-guided biliary access via an extrahepatic (choledochoduodenostomy) approach. (**a**) Dilated bile duct identified by EUS from the duodenum above the distal biliary obstruction; (**b**) guidewire was passed via an EUS-guided needle through the duodenal bulb into the dilated common bile duct and left hepatic duct; (**c**) placement of a fully covered lumen-apposing stent to create the choledochoduodenostomy; (**d**) contrast injection showing excellent drainage through the choledochoduodenostomy

Distal Duodenal Obstruction Without Major Papilla Involvement

Type III obstruction is the least common scenario of combined duodenal and biliary obstruction. It is also the least technically demanding for stent placement since the duodenal obstruction is in the third portion of the duodenum, distal to the major papilla. The sequence of duodenal and biliary stent placement is not critical in this setting. Placement of the duodenal stent is likely to be straightforward since obstruction is in the distal duodenum in a fairly straight path and more readily accessible. In rare instances where the proximal end of the duodenal stricture approaches the major papilla, it is advised to place the biliary stent first to prevent the major papilla from being shrouded by a proximally positioned duodenal stent [12].

Self-Expandable Metal Stents

Equipment

Table 22.1 lists commercially available enteral stents in the United States, which can be used for the management of GOO from duodenal

Table 22.1 Selected enteral self-expandable metal stents[a]

Name	Company	Material	Covering	Stent length (cm)	Body diameter (mm)	Flared end diameter (mm)	Delivery system diameter (Fr)
Bonastent	EndoChoice	Nitinol	Covered	3-5-7	20	n/a	10
Bonastent	EndoChoice	Nitinol	Uncovered	6-8-10	20	n/a	10
Evolution	Cook Medical	Nitinol	Uncovered	6-9-12	22	27	10
Hanarostent (NCN)	M.I.Tech	Nitinol	Partially covered	6-8-11-14-17	18	20	10.2
Hanarostent (NNN)	M.I.Tech	Nitinol	Uncovered	6-8-11-14-17	18	20	10.2
Niti-S	Taewoong Medical	Nitinol	Uncovered	6-8-10-12-14-15	18-20-22-24	n/a	10.5
Wallflex	Boston Scientific	Nitinol	Uncovered	6-9-12	22	27	10

[a]*Source:* From DiMaio CJ. Chapter 9: Gastroduodenal stents. In: Adler DG, ed. Self-expanding stents in gastrointestinal endoscopy. SLACK incorporated, 2012.

obstruction. Specific stents and additional equipment required for the treatment of biliary obstruction are discussed in a separate chapter (see Chap. 20). At present, duodenal SEMSs are deployed using a through-the-scope, over-the-wire technique. Most stents that are utilized for palliation of duodenal obstruction are uncovered, composed of nitinol, and come with a 10 F introducer system. Therapeutic channel upper endoscopes and duodenoscopes are suitable for the deployment of these SEMSs. In most cases, the use of a duodenoscope enables both biliary and duodenal stent placement without the need to change endoscopes. On occasion, a forward-viewing therapeutic channel endoscope may facilitate luminal stent placement, particularly across the duodenal bulb and apex, where stenting through a side-viewing endoscope may be technically more challenging.

Endoscopic placement of SEMSs for malignant GOO requires fluoroscopic assistance, and the endoscopy suite should be equipped adequately with biliary and duodenal stents. Several items, including water-soluble radiographic contrast, biliary balloon catheters, and hydrophilic guidewires, should be readied prior to starting the procedure.

Preprocedure Evaluation and Preparation

Prior abdominal CT with oral and intravenous contrast provides essential information in planning for SEMS deployment. The finding of a transition point enables anatomic localization prior to endoscopy, although this may not be evident initially. Other findings, such as the presence of multifocal obstruction, necrotic tumor, and free air, will dictate the suitability of SEMSs in these settings.

Preprocedural preparation on part of the patient requires fasting and, in some circumstances, prolonged *nil per os* to reduce the risk of aspiration. In our practice, we do not routinely perform gastric evacuation of food residue via a nasogastric tube prior to endoscopy. Gastric evacuation, however, may be required in cases where a completely obstructed gastric outlet with a large amount of retained material precludes adequate endoscopic visualization. More importantly, general anesthesia with endotracheal intubation for airway protection is highly recommended when performing SEMS placement for malignant GOO.

Contraindications to enteral SEMS placement for GOO are few and include (1) uncorrected

coagulopathy, (2) multiple intrinsic and extrinsic stenoses not amenable to luminal stenting, such as in the case of peritoneal carcinomatosis, (3) inability to advance a guidewire across the stricture, (4) bowel ischemia, and (5) sepsis [16].

Duodenal Stent Deployment

As previously mentioned, the sequence of duodenal and biliary stent placement depends on the type of obstruction encountered. This section will focus on the technical aspects of duodenal SEMS placement for GOO due to pancreatic malignancy.

The initial assessment consists of determining the length of the duodenal stricture. This is readily accomplished if the endoscope can traverse the obstruction. In the situation where the endoscope cannot pass through a partially obstructing lesion, fluoroscopic contrast injection aids in estimating the length of the stricture. For a very tight, complex stricture with near-complete obstruction and limited contrast delineation, successful cannulation of the stricture can usually be achieved using a biliary balloon-occluding catheter loaded onto a flexible hydrophilic guidewire (e.g., Glidewire, Boston Scientific Inc., Marlborough, MA). With the biliary occlusion balloon apposed against the orifice of the stricture, the guidewire is manipulated and negotiated past the luminal obstruction under fluoroscopic view, followed by advancement of the balloon-occluding catheter well beyond the stricture. Once past the stricture, the flexible guidewire can be exchanged for a stiffer 0.035-in. guidewire (e.g., Jagwire, Boston Scientific Inc., Marlborough, MA) that will serve as a rail for passage of the stent's delivery system. Under fluoroscopic imaging, contrast can be injected through the balloon-inflated catheter, which is slowly retracted until resistance is encountered, thus marking the distal extent of the stricture and providing a fluoroscopic estimate of the length of the stricture. Further contrast injection may also allow adequate imaging to rule out additional distal strictures prior to stent deployment.

Following assessment of the proximal and distal margins of the stricture, the appropriate stent size and length can be selected. The stent chosen should be of sufficient length to extend at least 2 cm beyond the stricture at both ends. Occasionally, internal (e.g., endoscopic clips and submucosal contrast injection) and external (e.g., paper clips and coins) fluoroscopic markers can be used to delineate both the proximal and distal margins of the stricture. With experience, however, the combined endoscopic and fluoroscopic visualization is more than adequate in accomplishing satisfactory stent positioning and deployment. Since duodenal SEMS are deployed via a distal-release mechanism, fluoroscopic guidance is required to ensure that the distal end of the stent is optimally positioned. Under continuous endoscopic and fluoroscopic monitoring, backward tension on the stent introducer during SEMS deployment will minimize the risk of distal migration and malposition of the stent. The delivery systems of most enteral stents enable a partially deployed stent to be recaptured if its initial location is not satisfactory.

For strictures in the proximal portion of the duodenal sweep, we recommend that the proximal flare of the stent be deployed in the prepyloric stomach to prevent abutment of the flare against the wall of the duodenal bulb, which may result in partial obstruction and/or flange-induced pressure ulceration into tissue. A liquid diet may be initiated as soon as 24 h post–stent placement, with gradual advancement to a low-residue diet as tolerated.

Clinical Outcomes

Procedural success pertains to the technical success in placing the SEMS, whereas clinical success is defined as symptomatic improvement and resumption of oral intake. Adler and Baron proposed a simplified scoring system (Table 22.2) to facilitate standardized reporting of clinical improvement in patients with GOO [3].

Although there is substantial literature on SEMS placement for GOO, most studies are retrospective in nature. These reports also included

Table 22.2 Adler & Baron gastric outlet obstruction scoring system [3]

Oral intake	Score
None	0
Liquids only	1
Soft diet	2
Low residue to full diet	3

patients with GOO associated with various malignant diseases as well as heterogeneity regarding the type and size of SEMSs utilized and the experience of the endoscopist.

Procedural success regarding SEMS deployment ranges from 91 to 100 % [3, 9, 17–21]. In a systematic review encompassing 1046 patients, the technical success for stent placement in GOO was approximately 96 % [22]. Technical failures included inability to deploy the stent, immediate stent dislocation, and perforation.

In a meta-analysis of 32 studies, the pooled clinical success rate was 89 % [23]. All patients reported resumption of oral intake after SEMS placement, with the majority (87 %) being able to advance to a score of 2–3 on the Adler and Baron GOO scoring system.

Stent Patency

Due to the short survival associated with pancreatic cancer–related GOO, most SEMSs placed for palliative therapy remain patent until the time of death. The median stent patency ranges from 146–385 days [3, 11, 20, 24–26]. The rate of patency does not appear to differ among the various stents utilized. Similar to other luminal stents, food impaction, stent migration, and tumor ingrowth or overgrowth are the main causes of stent occlusion. Although chemotherapy may potentially deter tumor ingrowth or overgrowth, an improvement in SEMS patency was not demonstrated in a retrospective analysis of patients with malignant GOO from pancreatic cancer. In the 49 patients who initially achieved resolution of GOO with SEMSs, the stents remained patent in 84 %, 54 %, and 41 % of patients at 2, 3, and 6 months, respectively [27]. From a dietary standpoint, it is important to avoid high-residue food items to prevent stent occlusion from food debris.

Adverse Events

The adverse events related to SEMS deployment in malignant GOO can be immediate or delayed. Immediate adverse events include abdominal pain, perforation, stent malposition, bleeding, and aspiration. Delayed adverse events include perforation, stent migration, and occlusion. The overall reported rates of adverse events range from 11–43 % [24, 28].

Abdominal pain may be a prominent feature during the first few days postdeployment as the stent expands further [29]. It usually resolves and can be treated effectively with analgesics [30–32]. A more serious adverse event is perforation, which can be life-threatening. The risk for bowel perforation is often due to the erosion and pressure necrosis of the metallic flare of the stent through tissue. The reported risk is approximately 1 % [23, 26]. Perforation often requires surgical repair, which carries high morbidity in a generally poor surgical candidate. In a multicenter study on the palliation of malignant GOO, the risk of perforation increased with the administration of chemotherapy following SEMS placement. Another potentially serious adverse event is hemorrhage from the trauma sustained during SEMS deployment. This occurs in less than 1 % of reported cases [5, 23].

Stent migration is less likely to occur with uncovered SEMSs, which are generally used for palliation of GOO. In a randomized trial comparing uncovered vs. covered SEMSs for the management of GOO, stent migration occurred in 26 % of patients with covered SEMSs as opposed to 3 % in the uncovered group [33]. The administration of chemotherapy and radiation therapy after SEMS deployment also seems to be a risk factor for stent migration [26].

Stent occlusion is the most common delayed adverse event [34]. This can be caused by impaction of food residue, compression of the stent by expanding tumor, and tissue ingrowth or overgrowth. Stent obstruction from food material can

be managed with endoscopic disimpaction [26, 35]. In such cases, it is important to reiterate to the patient the need to maintain a low-residue diet to prevent future episodes of stent-related food impaction. Obstruction from tumor ingrowth or overgrowth can usually be managed by deploying a new stent through the indwelling occluded stent [23, 34].

Comparison with Surgery

With increasing experience in the use of SEMS, palliative stent placement has superseded surgical bypass with regard to the management of malignant GOO. However, the success of endoscopic stenting is largely dependent on available local expertise. In the hands of experienced endoscopists, stent placement for malignant GOO, even with concomitant biliary obstruction, is highly successful, with a low rate of adverse events. Based on published data, there is consensus that SEMS placement is more advantageous than palliative surgical bypass in patients with short life expectancies (<2–3 months). For patients who are expected to survive beyond several months and who are good surgical candidates, surgical palliation with gastrojejunostomy is favored by some [7]. In a prospective randomized trial, palliative gastrojejunostomy showed better long-term outcomes than SEMS placement in terms of recurrent symptoms and reinterventions [8]. A retrospective study by No et al. reported a median survival of 293 days in patients who underwent gastrojejunostomy as opposed to 189 days in the stent placement group ($p = 0.003$). The median patency duration was shorter for stent placement than for gastrojejunostomy (125 vs. 282 days, $p = 0.001$) [36]. However, this study was conducted in patients with unresectable gastric cancer, which may differ in its disease course compared with pancreatic cancer.

In our practice, SEMS placement is the first-line treatment for unresectable malignant GOO. SEMS placement offers a less invasive strategy, especially in nutritionally debilitated patients with advanced disease. If stent patency becomes an issue, repeat stent placement (stent-in-stent) is a viable option and offers the opportunity to relieve the obstruction in the few patients who are still alive due to a protracted course of their advanced pancreatic malignancy.

Conclusion

The minimally invasive approach of SEMS placement has become the primary treatment modality for the palliation of symptomatic GOO in the setting of advanced pancreatic malignancy. Several trials have demonstrated favorable outcomes relative to surgical gastrojejunostomy or palliative placement of venting tubes. The biggest technical challenge in the placement of SEMS for pancreatic mass-associated GOO is the presence of concurrent duodenal and biliary obstruction. The technical success for endoscopic SEMS placement to relieve malignant GOO is high, with relatively few adverse events. Duodenal SEMS placement is of benefit in patients with unresectable disease, limited life expectancy, and absence of multifocal small bowel obstructions distally.

References

1. Shone DN, Nikoomanesh P, Smith-Meek MM, Bender JS. Malignancy is the most common cause of gastric outlet obstruction in the era of H_2 blockers. Am J Gastroenterol. 1995;90:1769–70.
2. Tendler DA. Malignant gastric outlet obstruction: bridging another divide. Am J Gastroenterol. 2002; 97:4–6.
3. Adler DG, Baron TH. Endoscopic palliation of malignant gastric outlet obstruction using self-expanding metal stents: experience in 36 patients. Am J Gastroenterol. 2002;97:72–8.
4. Watanapa P, Williamson RC. Surgical palliation for pancreatic cancer: developments during the past two decades. Br J Surg. 1992;79:8–20.
5. Lopera JE, Brazzini A, Gonzales A, Castaneda-Zuniga WR. Gastroduodenal stent placement: current status. Radiographics. 2004;24:1561–73.
6. Truong S, Bohndorf V, Geller H, Schumpelick V, Gunther RW. Self-expanding metal stents for palliation of malignant gastric outlet obstruction. Endoscopy. 1992;24:433–5.
7. Goldberg EM. Palliative treatment of gastric outlet obstruction in terminal patients: SEMS. Stent every

malignant stricture! Gastrointest Endosc. 2014;79: 76–8.
8. Jeurnink SM, Steyerberg EW, van Hooft JE, van Eijck CH, Schwartz MP, Vleggaar FP, et al. Surgical gastrojejunostomy or endoscopic stent placement for the palliation of malignant gastric outlet obstruction (SUSTENT study): a multicenter randomized trial. Gastrointest Endosc. 2010;71:490–9.
9. Tringali A, Didden P, Repici A, Spaander M, Bourke MJ, Williams SJ, et al. Endoscopic treatment of malignant gastric and duodenal strictures: a prospective, multicenter study. Gastrointest Endosc. 2014;79: 66–75.
10. Ly J, O'Grady G, Mittal A, Plank L, Windsor JA. A systematic review of methods to palliate malignant gastric outlet obstruction. Surg Endosc. 2010;24: 290–7.
11. Mutignani M, Tringali A, Shah SG, Perri V, Familiari P, Iacopini F, et al. Combined endoscopic stent insertion in malignant biliary and duodenal obstruction. Endoscopy. 2007;39:440–7.
12. Baron TH. Optimizing endoscopic placement of expandable stents throughout the GI tract. Expert Rev Gastroenterol Hepatol. 2008;2:399–409.
13. Baron TH. Management of simultaneous biliary and duodenal obstruction: the endoscopic perspective. Gut Liver. 2010;4 Suppl 1:S50–6.
14. Maire F, Hammel P, Ponsot P, Aubert A, O'Toole D, Hentic O, et al. Long-term outcome of biliary and duodenal stents in palliative treatment of patients with unresectable adenocarcinoma of the head of pancreas. Am J Gastroenterol. 2006;101:735–42.
15. Shami VM, Kahaleh M. Endoscopic ultrasound-guided cholangiopancreatography and rendezvous techniques. Dig Liver Dis. 2010;42:419–24.
16. Katsanos K, Sabharwal T, Adam A. Stenting of the upper gastrointestinal tract: current status. Cardiovasc Intervent Radiol. 2010;33:690–705.
17. Telford JJ, Carr-Locke DL, Baron TH, Tringali A, Parsons WG, Gabbrielli A, et al. Palliation of patients with malignant gastric outlet obstruction with the enteral Wallstent: outcomes from a multicenter study. Gastrointest Endosc. 2004;60:916–20.
18. Yim HB, Jacobson BC, Saltzman JR, Johannes RS, Bounds BC, Lee JH, et al. Clinical outcome of the use of enteral stents for palliation of patients with malignant upper GI obstruction. Gastrointest Endosc. 2001;53:329–32.
19. Kaw M, Singh S, Gagneja H. Clinical outcome of simultaneous self-expandable metal stents for palliation of malignant biliary and duodenal obstruction. Surg Endosc. 2003;17:457–61.
20. van Hooft JE, Uitdehaag MJ, Bruno MJ, Timmer R, Siersema PD, Dijkgraaf MG, et al. Efficacy and safety of the new WallFlex enteral stent in palliative treatment of malignant gastric outlet obstruction (DUOFLEX study): a prospective multicenter study. Gastrointest Endosc. 2009;69:1059–66.
21. Shaw JM, Bornman PC, Krige JE, Stupart DA, Panieri E. Self-expanding metal stents as an alternative to surgical bypass for malignant gastric outlet obstruction. Br J Surg. 2010;97:872–6.
22. Jeurnink SM, van Eijck CH, Steyerberg EW, Kuipers EJ, Siersema PD. Stent versus gastrojejunostomy for the palliation of gastric outlet obstruction: a systematic review. BMC Gastroenterol. 2007;7:18.
23. Dormann A, Meisner S, Verin N, Wenk Lang A. Self-expanding metal stents for gastroduodenal malignancies: systematic review of their clinical effectiveness. Endoscopy. 2004;36:543–50.
24. Masci E, Viale E, Mangiavillano B, Contin G, Lomazzi A, Buffoli F, et al. Enteral self-expandable metal stent for malignant luminal obstruction of the upper and lower gastrointestinal tract: a prospective multicentric study. J Clin Gastroenterol. 2008;42: 389–94.
25. van Hooft J, Mutignani M, Repici A, Messmann H, Neuhaus H, Fockens P. First data on the palliative treatment of patients with malignant gastric outlet obstruction using the WallFlex enteral stent: a retrospective multicenter study. Endoscopy. 2007;39: 434–9.
26. Kim JH, Song HY, Shin JH, Choi E, Kim TW, Jung HY, et al. Metallic stent placement in the palliative treatment of malignant gastroduodenal obstructions: prospective evaluation of results and factors influencing outcome in 213 patients. Gastrointest Endosc. 2007;66:256–64.
27. Cha BH, Lee SH, Kim JE, Yoo JY, Park YS, Kim JW, et al. Endoscopic self-expandable metallic stent placement in malignant pyloric or duodenal obstruction: does chemotherapy affect stent patency? Asia Pac J Clin Oncol. 2013;9:162–8.
28. Nassif T, Prat F, Meduri B, Fritsch J, Choury AD, Dumont JL, et al. Endoscopic palliation of malignant gastric outlet obstruction using self-expandable metallic stents: results of a multicenter study. Endoscopy. 2003;35:483–9.
29. Moon JH, Choi HJ, Ko BM, Koo HC, Hong SJ, Cheon YK, et al. Combined endoscopic stent-in-stent placement for malignant biliary and duodenal obstruction by using a new duodenal metal stent (with videos). Gastrointest Endosc. 2009;70:772–7.
30. Maetani I, Isayama H, Mizumoto Y. Palliation in patients with malignant gastric outlet obstruction with a newly designed enteral stent: a multicenter study. Gastrointest Endosc. 2007;66:355–60.
31. Tang T, Allison M, Dunkley I, Roberts P, Dickinson R. Enteral stenting in 21 patients with malignant gastroduodenal obstruction. J R Soc Med. 2003;96: 494–6.
32. Song HY, Shin JH, Yoon CJ, Lee GH, Kim TW, Lee SK, et al. A dual expandable nitinol stent: experience in 102 patients with malignant gastroduodenal strictures. J Vasc Interv Radiol. 2004;15:1443–9.

33. Kim CG, Choi IJ, Lee JY, Cho SJ, Park SR, Lee JH, et al. Covered versus uncovered self-expandable metallic stents for palliation of malignant pyloric obstruction in gastric cancer patients: a randomized, prospective study. Gastrointest Endosc. 2010;72:25–32.
34. Kim JH, Song HY, Shin JH. Malignant gastric outlet obstructions: treatment with self-expandable metallic stents. Gut Liver. 2010;4 Suppl 1:S32–8.
35. Khullar SK, DiSario JA. Gastric outlet obstruction. Gastrointest Endosc Clin N Am. 1996;6:585–603.
36. No JH, Kim SW, Lim CH, Kim JS, Cho YK, Park JM, et al. Long-term outcome of palliative therapy for gastric outlet obstruction caused by unresectable gastric cancer in patients with good performance status: endoscopic stenting versus surgery. Gastrointest Endosc. 2013;78:55–62.

Management of Cystic Lesions of the Pancreas

23

Raymond S. Tang and Thomas J. Savides

Introduction

Pancreatic cystic lesions (PCLs) have been increasingly diagnosed due to the more widespread use of crossing-sectional imaging [1]. In recent studies from referral centers in the United States and Europe, the prevalence of incidental PCLs in patients undergoing cross-sectional abdominal imaging for nonpancreatic indications ranges from 2.4 to 13.5 % [2–4]. While many PCLs are discovered as incidental lesions, PCLs have attracted clinical attention because a subgroup may progress and undergo malignant transformation.

The management of PCLs continues to evolve as more data on the natural history of PCLs become available. In particular, there has been growing evidence that certain cystic neoplasms with lower malignant potential, such as branch-duct intraductal papillary mucinous neoplasms (BD-IPMNs) without high-risk stigmata or worrisome features, may be managed conservatively [5]. The decision making on the management of various PCLs can be challenging because their behaviors may range from completely benign to overtly malignant. This chapter aims to review the key issues in the management of PCLs.

Classification of Pancreatic Cystic Lesions

PCLs can be divided into two main categories: nonneoplastic cystic lesions and cystic neoplasms. A list of commonly encountered PCLs is included in Table 23.1. Because the morphological and imaging features of various PCLs were already discussed in another chapter of this book (see Chap. xx), the following discussions will be focused on the epidemiology, natural history, evaluation, and management of PCLs.

Evaluation of Cystic Lesions of the Pancreas

In the management of PCLs, the following questions often concern clinicians the most:

1. The nature of the cystic lesion: serous lesions vs. mucinous lesions vs. cystic degeneration of other solid lesions
2. Whether the cystic lesion contains a malignancy

R.S. Tang, M.D. (✉)
Institute of Digestive Disease, Prince of Wales Hospital, The Chinese University of Hong Kong, Room 94020, 7/F, Clinical Science Building, Shatin, New Territories, Hong Kong, China
e-mail: rtang01@yahoo.com; raymondtang@cuhk.edu.hk

T.J. Savides, M.D.
Division of Gastroenterology, University of California–San Diego, La Jolla, CA, USA

M.S. Wagh, P.V. Draganov (eds.), *Pancreatic Masses*, DOI 10.1007/978-3-319-19677-0_23

Table 23.1 Major types of pancreatic cystic lesions

Nonneoplastic cysts
Pseudocyst
True cyst
Lymphoepithelial cyst
Neoplastic cysts
Serous cystic neoplasm
Serous cystadenoma (SCA)
Serous cystadenocarcinoma
Mucinous cystic neoplasm (MCN)
Mucinous cystadenoma
Mucinous cystic neoplasm with moderate dysplasia
Mucinous cystadenocarcinoma
Intraductal papillary mucinous neoplasm (IPMN: MD, BD, or mixed type)
Intraductal papillary mucinous adenoma
Intraductal papillary mucinous neoplasm with moderate dysplasia
Intraductal papillary mucinous carcinoma
Solid pseudopapillary tumor (SPT)
Cystic pancreatic endocrine tumor (PET)
Cystic pancreatic ductal adenocarcinoma

MD, main duct; *BD,* branch duct

3. The risk of malignant transformation if no overt malignancy is detected
4. Whether the cystic lesion should be resected or can be managed conservatively

Symptoms Related to the Cystic Lesion

In the initial evaluation of a PCL, the clinician should identify whether there are cyst-related symptoms (e.g., history of pancreatitis, abdominal pain, jaundice, weight loss, etc.). Incidentally found PCLs on imaging performed for nonpancreatobiliary indications are not uncommon [2–4]. In a young patient with a symptomatic cystic neoplasm, resection of the lesion is often preferred. On the other hand, if an elderly patient with multiple comorbidities is found to have an incidental PCL, conservative management of such an asymptomatic lesion would be a better option.

Cross-Sectional Imaging

In the evaluation of PCL, cross-sectional imaging is often the initial diagnostic modality. This is discussed in detail elsewhere in this book.

Endoscopic Ultrasound (EUS)

With its high-resolution imaging and the capability to perform real-time ultrasound-guided fine-needle aspiration (FNA) sampling for cyst fluid analysis and cytology, endoscopic ultrasound (EUS) is a valuable tool in evaluating PCLs. EUS imaging alone may be inadequate in predicting the histopathologic type of a PCL. In a large multicenter study, EUS morphology alone is only about 51 % accurate in the diagnosis of mucinous PCLs [6]. In a study comparing computed tomography (CT) and EUS for the detection of mural nodules, EUS was found to be more sensitive than CT, with a sensitivity of 75 % and 24 %, respectively [7].

Differentiation between mucus and a mural nodule can sometimes be difficult with EUS. The following EUS features have been reported to be more suggestive of mucus inside a PCL: a smooth-edged hypoechoic focus, a hyperechoic rim, lack of Doppler flow, and mobile upon change of patient position [5, 7]. Recently, the use of contrast-enhanced harmonic endoscopic ultrasound (CEH-EUS) to differentiate between mural nodule and mucus has been reported. The presence of contrast-enhanced fine blood vessels inside an intracystic echogenic focus supports the diagnosis of a mural nodule [8].

Cyst Fluid Cytology

Multiple studies have shown that EUS-guided FNA cytology of PCLs has a high specificity, ranging from approximately 80–100 % [6, 9, 10]. However, the sensitivity of EUS-FNA cytology is suboptimal, ranging from 30 to 50 % only [6, 9, 10]. Hence, a negative EUS-FNA cytology result does not completely rule out malignancy or a mucinous lesion.

Cyst Fluid Chemistry and Tumor Marker Analysis

Amylase and various tumor markers (e.g., CEA, CA 19-9, CA 72-4, CA 125, CA 15-3) have been evaluated to distinguish between mucinous and

nonmucinous PCLs. A high cyst fluid amylase level is usually found in pseudocysts and IPMNs because of communication of the cyst with the pancreatic duct [6, 10–13]. CEA is one of the most widely studied tumor markers in pancreatic cyst fluid analysis. In an early study from the 1990s using percutaneous FNA, a CEA <5 ng/mL was 100 % sensitive and 86 % specific for serous cystadenomas (SCAs) [14]. A CEA cutoff of 192 ng/mL has been shown in a large multicenter study to provide a sensitivity of 73 % and a specificity of 84 % for differentiating mucinous cystic lesions from nonmucinous counterparts [6]. Thus, a CEA level much greater than 192 ng/mL is most suggestive of a mucinous lesion, but a CEA level <192 ng/mL does not completely rule out a mucinous lesion. In a recent meta-analysis of 12 studies, cyst fluid amylase <250 U/L was suggestive of an SCA or a mucinous lesion (MCN) with a sensitivity of 44 % and a specificity of 98 %, while cyst fluid CEA <5 ng/mL was suggestive of an SCA or pseudocyst with a sensitivity of 50 % and a specificity of 95 % [15]. However, cyst fluid CEA was not found to accurately differentiate malignant from benign mucinous lesions [16].

Cyst Fluid DNA and Mutation Analysis

Cyst fluid DNA analysis has been evaluated to predict the malignant potential of PCLs [17, 18]. K-ras mutation analysis from cyst fluid obtained by EUS-FNA alone was reported to be 45 % sensitive and 96 % specific for a mucinous lesion in a recent multicenter study [18]. Based on the study result, a high cyst fluid DNA level, a high allelic loss amplitude, and a specific mutation acquisition sequence (K-ras mutation followed by allelic loss) were indicators of malignancy [18]. However, another study comparing CEA to DNA analysis in patients who underwent EUS-FNA for pancreatic cyst found poor agreement between CEA and DNA analysis for classification of mucinous lesions [19]. When CEA and DNA analysis were combined, these two tests were complementary and identified all mucinous cysts in the study [19]. Recently, mutations in guanine nucleotide binding protein, alpha stimulating complex locus (GNAS) have been evaluated for the diagnosis of IPMN of the pancreas [20, 21]. In a small study with 25 patients with PCLs including nine IPMNs, cyst fluid GNAS mutations for the diagnosis of IPMN was reported to have a sensitivity of 44 %, a specificity of 100 %, and a diagnostic accuracy of 80 % [21]. One hundred percent of the IPMNs were found to have either GNAS or K-ras mutation or both [21].

At this time, the optimal clinical indications of cyst fluid DNA and mutation analysis have not been well established. They are probably best used in cases when cyst fluid cytology and CEA testing yield indeterminate results for malignancy.

Emerging Diagnostic Technologies

Because conventional diagnostic modalities such as cross-sectional imaging and EUS with or without FNA for cyst fluid analysis may not always be accurate in making a specific diagnosis of PCLs, new technologies are being evaluated for their use in the characterization of PCLs. EUS-guided needle-based confocal laser endomicroscopy (nCLE) is among such emerging technologies. In a multicenter study of 66 patients with PCLs, the detection of epithelial villous structures on nCLE was associated with a pancreatic cystic neoplasm, with a sensitivity of 59 %, a specificity of 100 %, a positive predictive value (PPV) of 100 %, and a negative predictive value (NPV) of 50 % [22]. Complications such as pancreatitis, transient abdominal pain, and intracystic bleeding were reported in 9 % of patients [22].

Natural History and Management of Pancreatic Cystic Lesions

Pancreatic Pseudocyst

In patients with a history of pancreatitis, pseudocysts account for up to 50 % of the PCLs [23]. Pseudocysts with internal debris due to necrosis or infection may sometimes mimic cystic neoplasms.

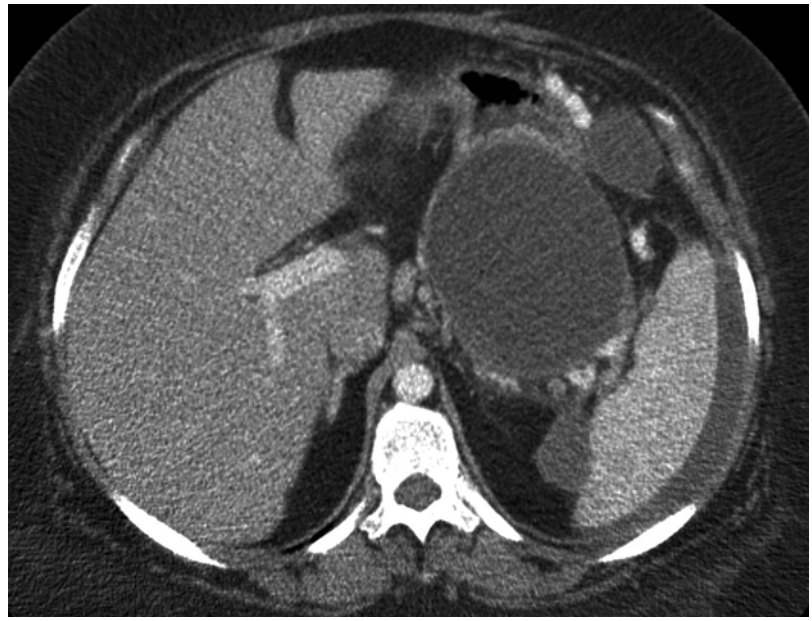

Fig. 23.1 CT appearance of a pancreatic pseudocyst

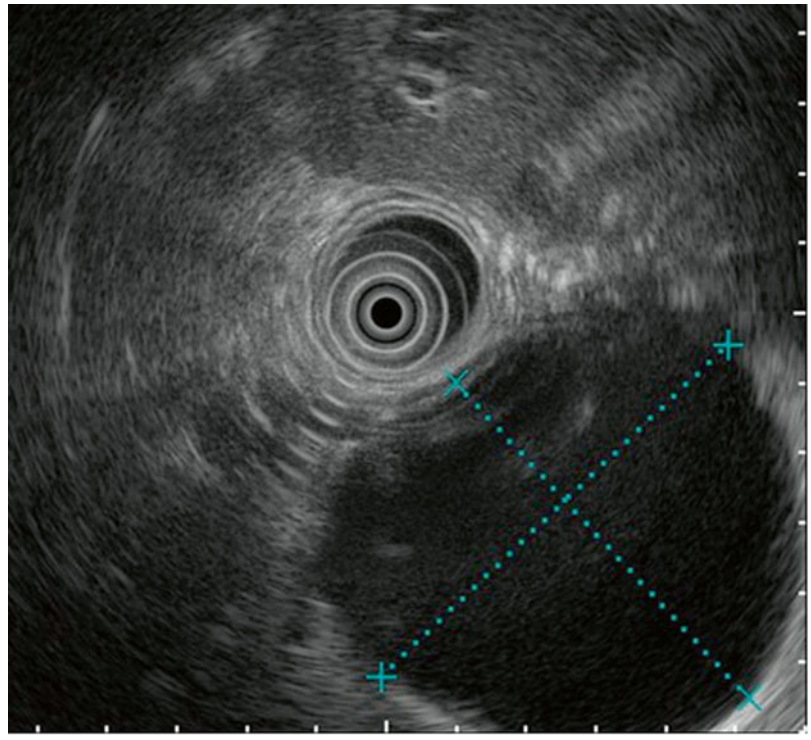

Fig. 23.2 EUS appearance of a pancreatic pseudocyst

Conversely, up to 40 % of the PCLs may be initially misdiagnosed as pseudocysts [24]. In most cases, pancreatic pseudocysts are associated with acute or chronic pancreatitis, with an incidence of 2–3 % and 20–40 %, respectively [25].

In general, a diagnosis of pseudocyst can be made when a PCL with typical radiological features is observed with a preceding history of acute or chronic pancreatitis (Figs. 23.1 and 23.2). While some patients with a pseudocyst

may not have overt symptoms, persistent abdominal pain and anorexia combined with possible abdominal distension 4–6 weeks after an episode of pancreatitis raises the possibility of pancreatic pseudocyst formation [12]. In patients with a history of recent acute pancreatitis who present with fever and clinical deterioration, an infected pseudocyst should be considered [12].

If diagnostic uncertainty remains after cross-sectional imaging, EUS with or without FNA of cyst fluid can be helpful, but unnecessary FNA should be avoided given the risk of infecting the pseudocyst.

Up to 60 % of pancreatic pseudocysts resolve with no intervention. Thus, serial cross-sectional imaging can be used to monitor the pseudocyst in the initial management [25]. If the pseudocyst does not resolve over time (usually more than 6 weeks) and/or becomes symptomatic, then drainage can be considered. While pseudocyst drainage can be done endoscopically, surgically, or percutaneously by interventional radiology, endoscopic drainage is the preferred method in suitable patients. When endoscopic drainage is performed, EUS-guided drainage is preferred since it has been shown to have a higher technical success rate when compared to drainage by esophagogastroduodenoscopy (EGD) in a randomized study [26]. In a retrospective study of 211 patients who underwent endoscopic drainage of pancreatic pseudocysts, abscesses, or necrosis, an overall treatment success rate of 85.3 % and an overall complication rate of 8.5 % were reported [27]. The treatment success rate was highest in the pseudocyst group (93.5 %), while the complication rate was highest in the necrosis group (15.8 %) [27]. In a randomized study comparing endoscopic versus surgical cystogastrostomy in 40 patients with pseudocysts, endoscopic drainage was shown to have equal efficacy when compared to surgical drainage, with no pseudocyst recurrence in the endoscopic drainage group during a 24-month follow-up [28]. Endoscopic drainage has been associated with a shorter hospital stay and lower cost [28]. Nevertheless, surgical management should be considered for pseudocysts with a large amount of necrotic debris or infection.

Serous Cystic Neoplasms

Pancreatic serous cystic neoplasms, which can be categorized into serous cystadenomas (SCAs) and the extremely rare serous cystadenocarcinomas, represent approximately 30 % of primary pancreatic cystic neoplasms [11, 25]. SCAs are usually found incidentally on cross-sectional imaging performed for other indications [29]. SCAs can be seen in up to 70 % of patients with von Hippel–Lindau syndrome, who often present with multiple SCAs in the pancreas [11, 30].

The majority of the SCAs are microcystic, with an individual cyst less than 5 mm in size, giving it a honeycomb appearance [31], but the macrocystic variant of SCA (individual cysts >5 mm) may sometimes be confused with mucinous cystic neoplasms on imaging. SCAs are often detected as multicystic lesions with septa enhancement and small cysts in a honeycomb appearance on CT (Fig. 23.3) [30, 32]. The typical honeycomb appearance of microcystic SCA can be easily seen on EUS, which is considered diagnostic and thus makes FNA rarely necessary (Fig. 23.4) [33]. They also may have central calcification (“stellate scar”). Surgical pathology is characterized by cuboidal glycogen-rich epithelial cells which produce serous fluid.

SCAs are generally considered to be benign lesions [11, 32, 34]. Pancreatic serous cystadenocarcinomas are extremely rare and represent less than 3 % of all serous cystic neoplasms of the pancreas [24, 34]. Serous cystadenocarcinomas are unique in a sense that malignancy is diagnosed by aggressive behavior such as local invasion or metastasis, but not by histology, because the histology of the malignant lesions generally lacks the expected cytologic atypia [34]. Small asymptomatic SCAs in an elderly patient can usually be managed conservatively given the largely benign and indolent course of SCAs. However, some SCAs do grow over time and become symptomatic [30, 32]. In a surgical series of 257 patients with SCAs, large tumor size and location in the pancreatic head were found to be independent predictors of malignant behaviors [35]. Surgical resection should be

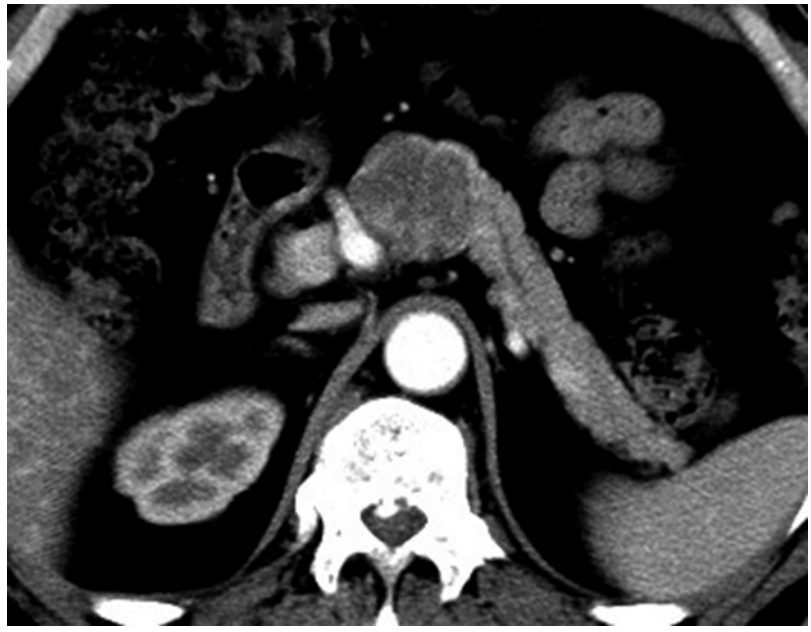

Fig. 23.3 CT appearance of a serous cystadenoma

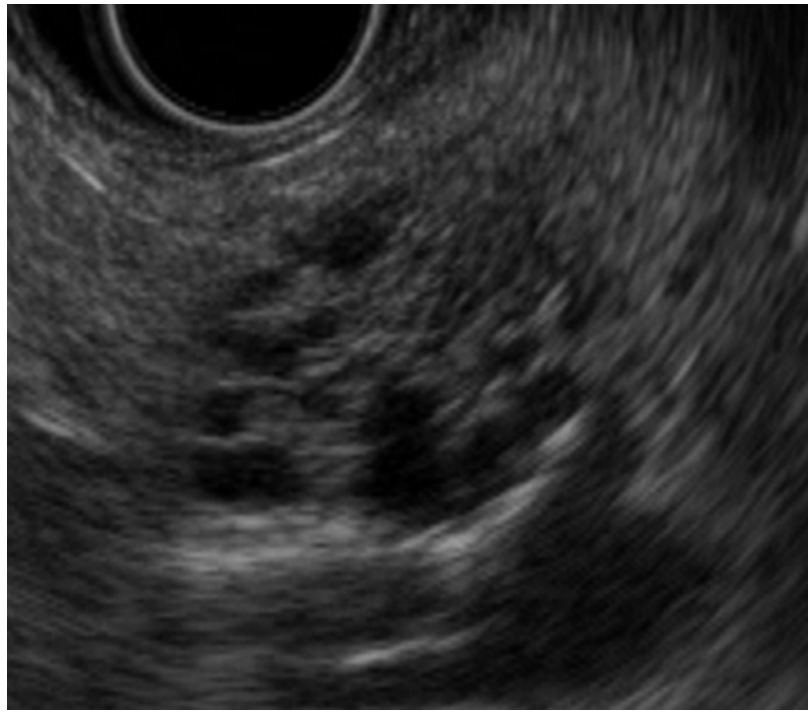

Fig. 23.4 EUS appearance of a serous cystadenoma

considered in patients with symptoms or rapidly growing SCAs, who are physically fit for surgery [32, 35].

Mucinous Cystic Neoplasms

MCNs are mucinous lesions with variable malignant potential and account for approximately one third of cystic neoplasms in the pancreas [36–38]. About 95 % of MCNs occur in females and are usually diagnosed between the fifth and seventh decades of life [36–38]. Small MCNs are usually asymptomatic, but patients with larger MCNs may present with abdominal complaints such as epigastric pain or fullness or a palpable mass [37, 38]. In patients with large MCNs, the development of weight loss, jaundice, abdominal pain, and pancreatic insufficiency should raise the concern for malignant transformation [36–38].

MCNs are usually unilocular lesions with or without septations that occur in the body or tail of the pancreas [38]. They occasionally have peripheral calcification. Surgical pathology reveals cysts lined with mucin-producing epithelium associated with ovarian-type stroma. Figure 23.5 shows a unilocular MCN on EUS. At times, small septated MCNs may be difficult to distinguish from branch-duct IPMNs on CT or EUS. Cyst fluid aspirate is generally slightly viscous to thick, with an elevated carcinoembryonic antigen (CEA) level [6, 33]. Mucin and columnar epithelial cells with or without atypia may be seen on cyst fluid cytology [6, 33].

The natural history of small MCNs in asymptomatic patients is not fully known [37, 38]. In a surgical series of 163 patients, the risk of malignancy in resected MCNs was reported to be 17.5 %, with all malignant MCNs being greater than 4 cm with the presence of mural nodules [39]. Surgical resection has been recommended by the 2006 and 2012 international consensus guidelines for all MCNs in surgically fit patients regardless of lesion size given the risk of malignant transformation, relatively younger age of most patients, and the common locations of MCNs in the pancreatic body or tail [5, 40]. However, small incidentally found MCNs may be managed conservatively. Emerging data from studies on small incidental asymptomatic cystic lesions of the pancreas suggest a low risk of malignancy during follow-up, and the nonsurgical management of selected lesions without high-risk features (e.g., mural nodules, wall thickening, or size > 4 cm) has been proposed [41–46]. This strategy may be most appropriate in elderly patients who are not surgically fit.

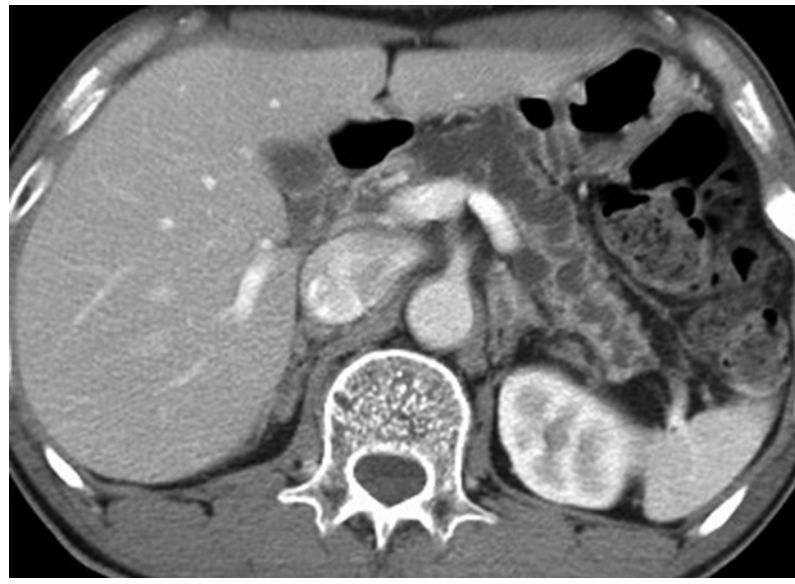

Fig. 23.5 CT appearance of a main-duct intraductal papillary mucinous neoplasm (MD-IPMN)

Intraductal Papillary Mucinous Neoplasms

Intraductal papillary mucinous neoplasms (IPMNs) represent a spectrum of mucinous cystic lesions involving the pancreatic ductal system with highly variable malignant potential [13, 25]. IPMNs represent approximately 25 % of pancreatic cystic neoplasms and 1 % of all pancreatic neoplasms [13, 47].

IPMNs can be categorized into main-duct IPMN (MD-IPMN), branch-duct IPMN (BD-IPMN), or mixed type with both main-duct and branch-duct involvement [13]. Four distinct histopathological subtypes of papillary structures (gastric, intestinal, pancreatobiliary, and oncocytic) have been described, which appear to correlate with the behavior of the IPMN [13, 48]. The intestinal subtype has a high rate of malignant transformation and is most commonly seen in MD-IPMN [48]. The gastric subtype seems to have a lower rate of malignant transformation and is the most common variant found in BD-IPMN [48]. The oncocytic subtype in general follows a noninvasive course [48].

IPMNs are usually diagnosed in the seventh decade of life, with an equal distribution in males and females [13, 32]. The age of diagnosis of malignant IPMNs is generally older than that of nonaggressive IPMNs [5, 13]. The time of progression to invasive disease in MD-IPMN was reported to range from 5–7 years [49]. Clinically, up to 40 % of patients with IPMNs are asymptomatic (mostly patients with BD-IPMN) [50–52]. When symptomatic (more common with MD-IPMN), patients may present with abdominal pain or symptoms of pancreatitis [50–52]. Weight loss, new-onset jaundice, new-onset diabetes, and steatorrhea are more commonly seen in IPMNs with malignant transformation [50]. Figure 23.5 shows the typical CT appearance of an MD-IPMN with a dilated main pancreatic duct. Figure 23.6a, b demonstrate a large mural nodule/solid component in an MD-IPMN on conventional EUS and CEH-EUS suggestive of malignant transformation. Figures 23.7 and 23.8 show the typical appearance of BD-IPMN on CT and EUS, respectively.

While IPMNs are generally considered a premalignant lesion given their mucinous nature, they represent a spectrum of lesions with variable malignant potential. MD-IPMNs have been reported to have a high risk of malignant degeneration, with a mean frequency of malignancy of 61.6 % (range, 36–100 %) [5, 49, 50, 52–64]. However, the natural history of BD-IPMN is less well established. Based on studies of surgically resected BD-IPMN, the mean frequency of malignancy is 25.5 % (range, 6.3–46.5 %) [5, 49–67]. Recently, multiple natural history studies of BD-IPMNs reported a lower risk of malignancy (0–5.8 %), thus providing evidence for conservative management of small, incidentally found BD-IPMNs [68–70].

Management of IPMN patients can be challenging given limited knowledge on the natural history of these lesions (especially BD-IPMN). In 2006, the working group of the International Association of Pancreatology published the Sendai international consensus guidelines for management of IPMNs and MCNs of the pancreas [40]. The international consensus guidelines were subsequently revised in 2012, which have become known as the Fukuoka guidelines [5].

In the 2006 Sendai guidelines, surgical resection is recommended for all MD-IPMN, BD-IPMN that are symptomatic or greater than 3 cm, BD-IPMN less than 3 cm with "worrisome features" such as cyst-related symptoms, main pancreatic duct (MPD) dilation greater than 6 mm, or presence of mural nodule in patients who are surgically fit [40]. Surveillance with crossing-sectional imaging and EUS has been recommended for BD-IPMNs less than 3 cm without worrisome features [40]. Evaluation of the operating characteristics of the 2006 Sendai guidelines in surgically resected BD-IPMN cohorts showed that the guidelines have a high NPV (capturing all high-risk lesions for resection), but a low PPV (many of the resected lesions were not advanced lesions) [51, 55, 71, 72].

In the 2012 Fukuoka guidelines, all MD-IPMNs are still recommended for surgical resection [5]. The major revisions are in the indications for resection of BD-IPMNs. Symptomatic cysts should undergo further evaluation or be

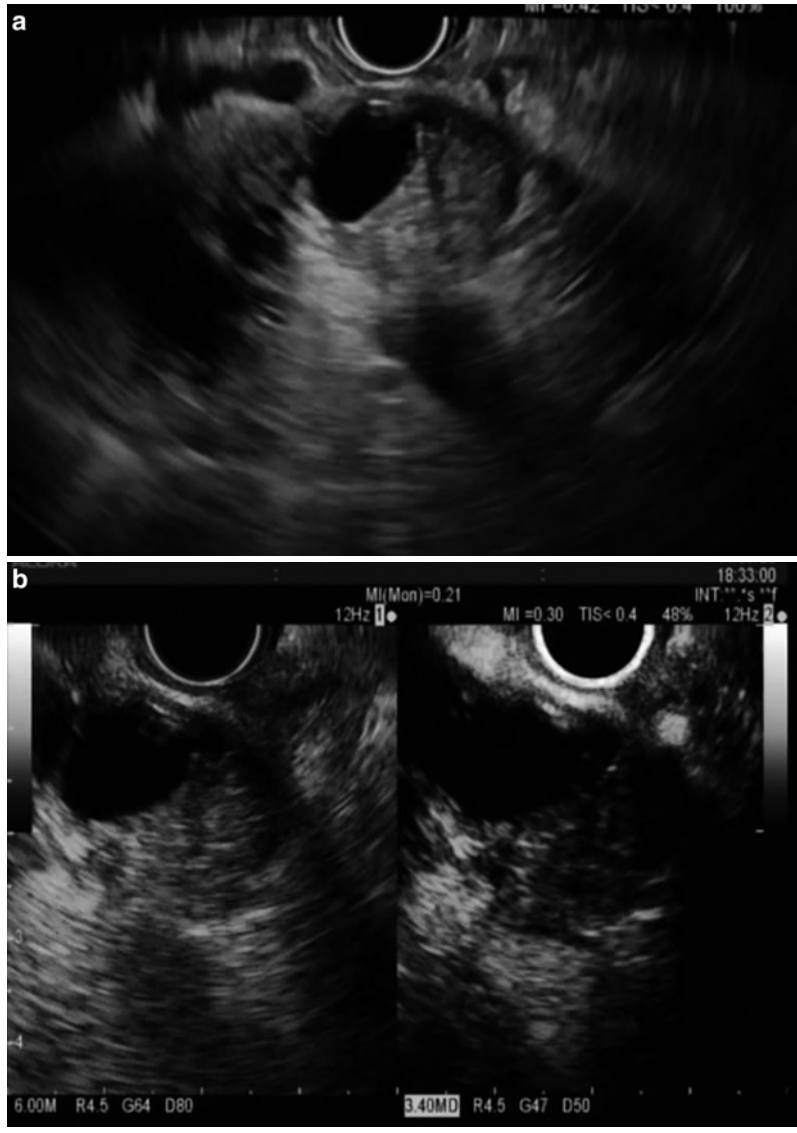

Fig. 23.6 (**a**) A large mural nodule/solid component in an MD-IPMN detected on conventional EUS. (**b**) On contrast-enhanced harmonic EUS (CEH-EUS), the large mural nodule/solid component was shown to be hypoenhanced with internal fine vessels, suggestive of malignant transformation

considered for resection. Resection has been recommended for all BD-IPMNs with any of the "high-risk stigmata of malignancy": a pancreatic head BD-IPMN causing obstructive jaundice; the presence of an enhancing solid component within a cyst; or MPD dilation ≥10 mm [5]. In the revised guidelines, cyst size >3 cm by itself is no longer a recommended absolute indication for resection since it is thought to be a weaker predictor of malignancy [5]. In BD-IPMNs with "worrisome features" such as cyst size ≥ 3 cm, thickened enhanced cyst walls, MPD size of 5–9 mm, nonenhanced mural nodules, abrupt change in the MPD caliber with distal pancreatic atrophy, or lymphadenopathy, EUS was recommended to further evaluate the BD-IPMN [5]. If EUS confirms the presence of a definite mural nodule, MPD involvement, or suspicious/positive

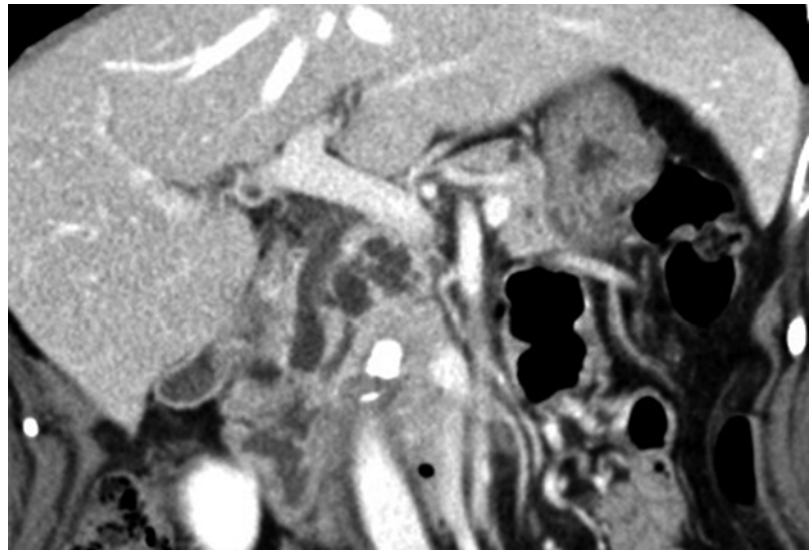

Fig. 23.7 CT appearance of a branch-duct intraductal papillary mucinous neoplasm (BD-IPMN)

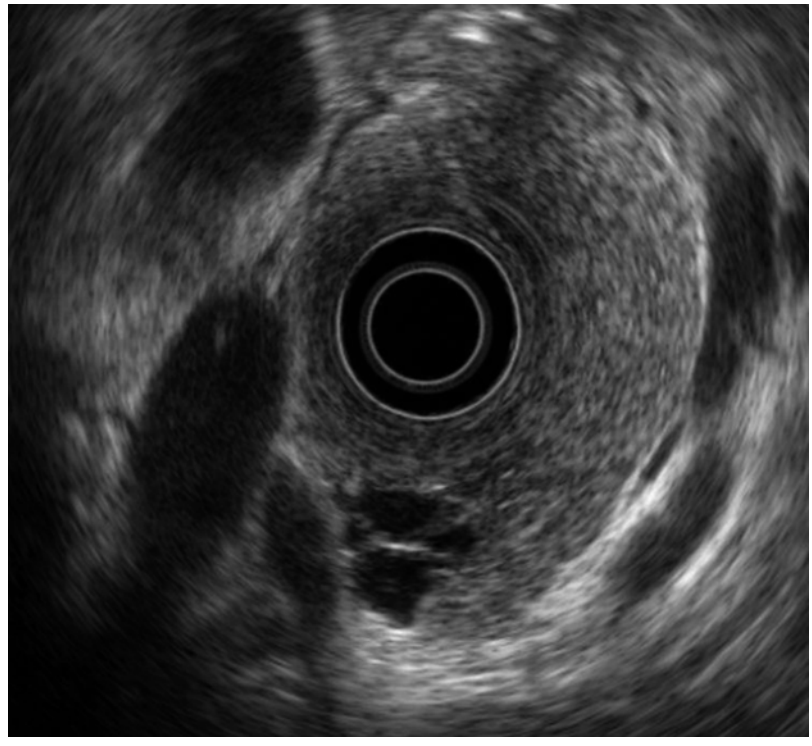

Fig. 23.8 EUS appearance of a BD-IPMN

cytology for malignancy, resection is recommended [5]. In patients with cyst size >3 cm but without "worrisome features" or "high-risk stigmata," EUS is also useful for further risk stratification and surveillance. Surveillance with cross-sectional imaging (e.g., CT, MRI) with or without EUS is recommended for cysts <3 cm without "worrisome features," with surveillance intervals being dictated by the cyst size and patients' life expectancy [5].

While not specifically included in the Fukuoka guidelines, a rapid increase in cyst size and the

presence of high-grade atypia on cytology were reported to be additional risk factors for malignancy [73–76]. Lesions with such findings should also be considered for resection in young patients who may otherwise require long-term close surveillance.

There has been growing evidence to support the concept of "field defect" (all pancreatic ductal epithelial cells are at risk for the development of dysplasia or new adenocarcinoma) in patients with IPMNs since 25–41 % of BP-IPMNs are multifocal and because malignancy in other parts of the pancreas uninvolved by the original IPMN has been observed [51, 54, 68–70, 73]. Thus, surveillance by cross-sectional imaging with or without EUS should be considered for conservatively managed IPMN and post-IPMN resection in patients with a reasonably long life expectancy.

While the updated consensus guidelines serve as a good framework to guide the management of IPMNs, the decision to resect or conservatively manage an IPMN should be individualized, taking into account the patient's overall health, life expectancy, and the risk of malignancy in the lesion.

Solid Pseudopapillary Tumor

Accounting for 1–2 % of exocrine pancreatic tumors, a solid pseudopapillary tumor (SPT) is a rare neoplasm with malignant potential and is predominantly diagnosed in females during the second and third decades of life [11, 32].

While SPTs are generally large tumors with average size ranging from 6 to 10 cm, surgical resection should be considered for SPTs that can often be cured by extended resections [11, 32, 77].

Cystic Pancreatic Endocrine Tumor

Pancreatic endocrine tumors (PETs) represent approximately 1–2 % of all pancreatic neoplasms and are often diagnosed between the third and sixth decades, with a slightly higher prevalence in males [78–81]. Up to 10 % of PETs demonstrate cystic changes [82, 83]. The symptoms related to PETs depend on the size, location, and functional status of the tumor. While patients with functional tumors may present with various hormonal syndromes, data from the past two decades have found that up to 90 % of PETs are actually nonfunctional [78–81]. Thus, these patients are commonly found without tumor-related symptoms or have symptoms related to bulky disease [78–81]. Insulinomas, glucagonomas, gastrinomas (as in Zollinger–Ellison syndrome), VIPomas, and somatostatinomas make up the classic functional PETs [78–80]. PETs can be associated with four major genetic syndromes: multiple endocrine neoplasia Type 1 (MEN-1), von Hippel–Lindau (VHL) disease, neurofibromatosis Type 1 (NF-1), and tuberous sclerosis (TS) [78–80].

Functional PETs were reported to have better outcomes than the nonfunctional counterpart in a series of 1483 patients with PETs, with age, advanced stage, and higher tumor grade being associated with worse prognosis [80]. Surgical resection should be offered if possible, while locoregional therapies (e.g., transarterial embolization, radiofrequency ablation) and systemic therapies (e.g., somatostatin analog, chemotherapy, or target therapies) are options for inoperable diseases or candidates not surgically fit [80].

Investigational Therapy

Recent studies have evaluated EUS-guided cyst ablation for PCLs in patients who are not surgically fit or have declined surgery. In a randomized study, EUS-guided ethanol lavage of pancreatic cysts achieved complete cyst resolution in 33 % of patients by follow-up imaging [84]. Persistent cyst resolution by follow-up imaging (majority of lesions were MCNs) was demonstrated in another study with median follow-up of 26 months after initial successful cyst ablation [85]. In a Korean study of 14 patients, EUS-guided ethanol lavage with paclitaxel injection achieved complete cyst resolution in 11 patients [86]. Complications such as acute pancreatitis, abdominal pain, infection, or intracystic bleeding have been reported [84–86]. At this time, EUS-guided cyst ablation remains mostly experimental and more long-term data would be needed to define the optimal role of this therapy.

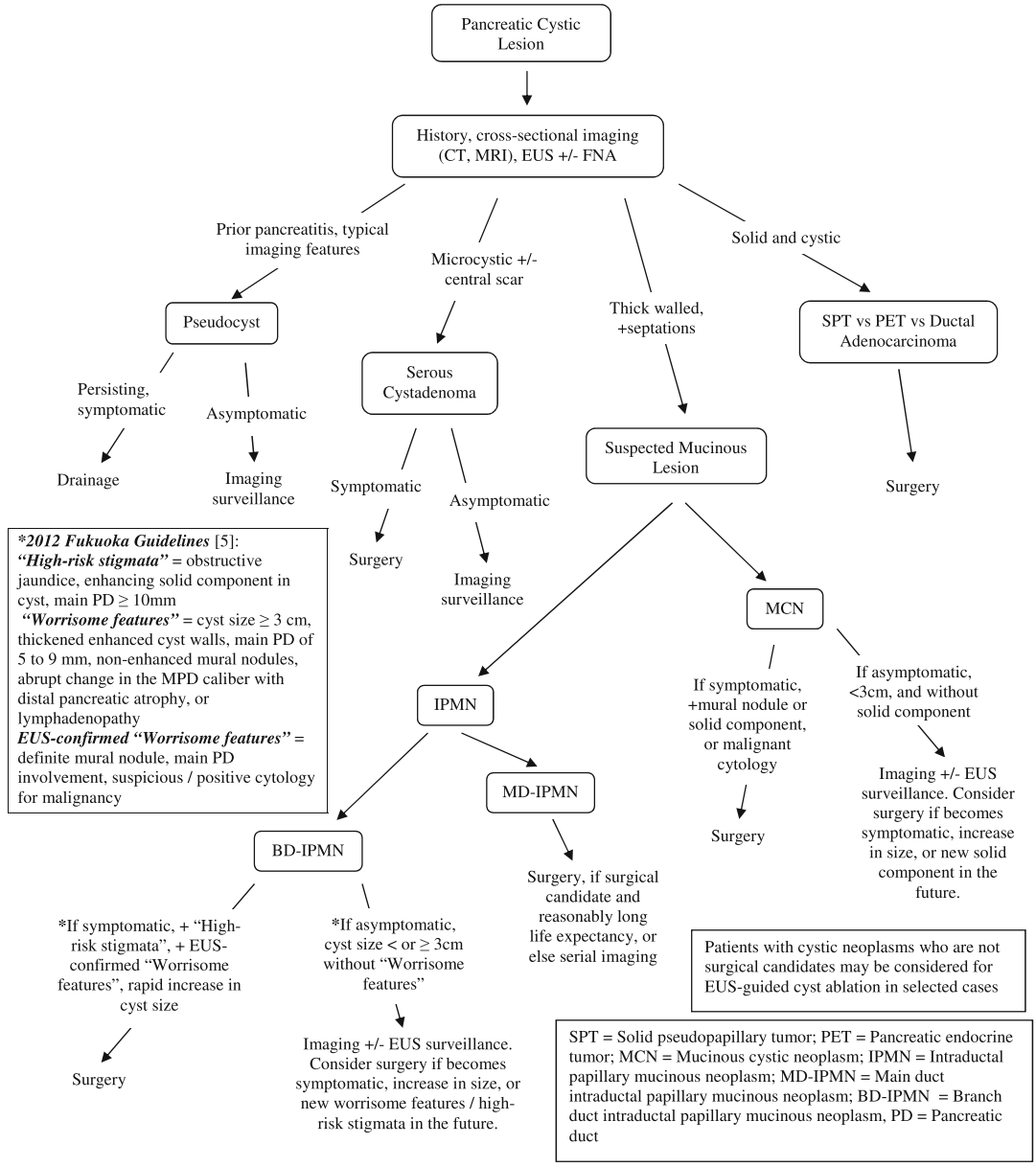

Fig. 23.9 Suggested algorithm for the management of pancreatic cystic lesions

Summary

PCLs causing symptoms or showing features of malignant transformation are best managed surgically if the patient is surgically fit. The optimal management of small incidental pancreatic cystic neoplasms continues to evolve as clinicians gain knowledge on the natural history of these lesions. The final management decision should be individualized, taking into consideration the risk of malignancy in the PCL and the patient's overall health. Figure 23.9 provides a suggested algorithm for management of PCLs.

References

1. Spinelli KS, Fromwiller TE, Daniel RA, et al. Cystic pancreatic neoplasms: observe or operate. Ann Surg. 2004;239(5):651.
2. de Jong K, Nio CY, Hermans JJ, et al. High prevalence of pancreatic cysts detected by screening magnetic resonance imaging examinations. Clin Gastroenterol Hepatol. 2010;8(9):806–11.
3. Lee KS, Sekhar A, Rofsky NM, et al. Prevalence of incidental pancreatic cysts in the adult population on MR imaging. Am J Gastroenterol. 2010;105(9): 2079–84.
4. Laffan TA, Horton KM, Klein AP, et al. Prevalence of unsuspected pancreatic cysts on MDCT. Am J Roentgenol. 2008;191:802–7.
5. Tanaka M, Fernandez-del Castillo C, Adsay V, et al. International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas. Pancreatology. 2012;12:183–97.
6. Brugge WR, Lewandrowski K, Lee-Lewandrowski E, et al. Diagnosis of pancreatic cystic neoplasms: a report of the cooperative pancreatic cyst study. Gastroenterology. 2004;126:1330–6.
7. Zhong N, Zhang L, Takahashi N, et al. Histologic and imaging features of mural nodules in mucinous pancreatic cysts. Clin Gastroenterol Hepatol. 2012;10: 192–8.
8. Kitano M, Sakamoto H, Komaki T, et al. New techniques and future perspective of EUS for the differential diagnosis of pancreatic malignancies: contrast harmonic imaging. Dig Endosc. 2011;23 Suppl 1:46–50.
9. Brandwein SL, Farrell JJ, Centeno BA, et al. Detection and tumor staging of malignancy in cystic, intraductal, and solid tumors of the pancreas by EUS. Gastrointest Endosc. 2001;53:722–7.
10. Linder JD, Geenen JE, Catalano MF. Cystic fluid analysis obtained by EUS-guided FNA in the evaluation of discrete cystic neoplasms of the pancreas: a prospective single-centre study. Gastrointest Endosc. 2006;64:703–4.
11. Hamilton SR, Aaltonen LA. World Health Organization classification of tumours. Pathology and genetic of tumours of the digestive system. France: IARC Press; 2010.
12. Brun A, Agarwal N, Pitchumoni CS, et al. Fluid collections in and around the pancreas in acute pancreatitis. J Clin Gastroenterol. 2011;45(7):614–25.
13. Fernandez-del Castillo C, Adsay NV. Intraductal papillary mucinous neoplasm of the pancreas. Gastroenterology. 2010;139:708–13.
14. Hammel P, Levy P, Voitot H, et al. Preoperative cyst fluid analysis is useful for the differential diagnosis of cystic lesions of the pancreas. Gastroenterology. 1995;108:1230–5.
15. Van DerWaaij LA, van Dullemen HM, Porte RJ. Cyst fluid analysis in the differential diagnosis of pancreatic cystic lesions: a pooled analysis. Gastrointest Endosc. 2005;62:383–9.
16. Cizginer S, Turner B, Bilge AR, et al. Cyst fluid carcinoembryonic antigen is an accurate diagnostic marker of pancreatic mucinous cysts. Pancreas. 2011;40(7):1024–8.
17. Tateishi K, Tada M, Yamagata M, et al. High proportion of mutant K-ras gene in pancreatic juice of patients with pancreatic cystic lesions. Gut. 1999; 45:737–40.
18. Khalid A, Zahid M, Finkelstein SD, et al. Pancreatic cyst fluid DNA analysis in evaluating pancreatic cysts: a report of the PANDA study. Gastrointest Endosc. 2009;69:1095–102.
19. Sawhney MS, Devarajan S, O'Farrel P, et al. Comparison of carcinoembryonic antigen and molecular analysis in pancreatic cyst fluid. Gastrointest Endosc. 2009;69:1106–10.
20. Kanda M, Knight S, Topazian M, et al. Mutant GNAS detected in duodenal collections of secretin-stimulated pancreatic juice indicates the presence or emergence of pancreatic cysts. Gut. 2013;62(7):1024–33.
21. Siddiqui AA, Kowalski TE, Kedika R, et al. EUS-guided pancreatic fluid aspiration for DNA analysis of KRAS and GNAS mutations for the evaluation of pancreatic cystic neoplasia: a pilot study. Gastrointest Endosc. 2013;77(4):669–70.
22. Konda VJ, Meining A, Jamil LH, et al. A pilot study of in vivo identification of pancreatic cystic neoplasms with needle-based confocal laser endomicroscopy under endosonographic guidance. Endoscopy. 2013;45(12):1006–13.
23. Fernández-del Castillo C, Targarona J, Thayer SP, et al. Incidental pancreatic cysts: clinicopathologic characteristics and comparison with symptomatic patients. Arch Surg. 2003;138(4):427.
24. Visser BC, Muthusamy VR, Yeh BM, et al. Diagnostic evaluation of cystic pancreatic lesions. HPB (Oxford). 2008;10:63–9.
25. Spence R, Dasari B, Love M, et al. Overview of the investigation and management of cystic neoplasms of the pancreas. Dig Surg. 2011;28:386–97.
26. Varadarajulu S, Christein JD, Tamhane A, et al. Prospective randomized trial comparing EUS and EGD for transmural drainage of pancreatic pseudocysts (with videos). Gastrointest Endosc. 2008;68(6): 1102–11.
27. Varadarajulu S, Bang JY, Phadnis MA, et al. Endoscopic transmural drainage of peripancreatic fluid collections: outcomes and predictors of treatment success in 211 consecutive patients. J Gastrointest Surg. 2011;15(11):2080–8.
28. Varadarajulu S, Bang JY, Sutton BS, et al. Equal efficacy of endoscopic and surgical cystogastrostomy for pancreatic pseudocyst drainage in a randomized trial. Gastroenterology. 2013;145(3):583–90.
29. Brugge WR. The incidental pancreatic cyst on abdominal imaging computerized tomography imaging: diagnosis and management. Clin Gastroenterol Hepatol. 2008;6:140–4.
30. Pyke CM, van Heerden JA, Colby TV, et al. The spectrum of serous cystadenoma of the pancreas. Clinical,

pathologic, and surgical aspects. Ann Surg. 1992;215: 132–9.
31. Warshaw AL, Compton CC, Lewandrowski K, et al. Cystic tumors of the pancreas. New clinical, radiologic, and pathologic observations in 67 patients. Ann Surg. 1990;212:432–43.
32. Khalid A, Brugge WR. ACG practice guidelines for the diagnosis and management of neoplastic pancreatic cysts. Am J Gastroenterol. 2007;102:2339–49.
33. Levy MJ, Clain JE. Evaluation and management of cystic pancreatic tumors: emphasis on the role of EUS-FNA. Clin Gastroenterol Hepatol. 2004;2: 639–53.
34. Strobe O, Z'Graggen K, Schmitz-Winnenthal FH, et al. Risk of malignancy in serous cystic neoplasms of the pancreas. Digestion. 2003;68:24–33.
35. Khashab MA, Shin EJ, Amateau S, et al. Tumor size and location correlate with behavior of pancreatic serous cystic neoplasms. Am J Gastroenterol. 2011;106(8):1521–6.
36. Brugge WR, Lauwers GY, Sahani D, et al. Cystic neoplasms of the pancreas. N Engl J Med. 2004;351: 1218–26.
37. Zamboni G, Scarpa A, Bogina G, et al. Mucinous cystic tumors of the pancreas: clinicopathological features, prognosis, and relationship to other mucinous cystic tumors. Am J Surg Pathol. 1999;23:410–22.
38. Reddy RP, Smyrk TC, Zapiach M, et al. Pancreatic mucinous cystic neoplasm defined by ovarian stroma: demographics, clinical features, and prevalence of cancer. Clin Gastroenterol Hepatol. 2004;2:1026–31.
39. Crippa S, Silvia R, Warshaw AL, et al. Mucinous cystic neoplasm of the pancreas is not an aggressive entity: lesions from 163 resected patients. Ann Surg. 2008;247:571–9.
40. Tanaka M, Chari S, Adsay V, et al. International consensus guidelines for management of intraductal papillary mucinous neoplasms and mucinous cystic neoplasms of the pancreas. Pancreatology. 2006;6:17–32.
41. Allen PJ, D'Angelica M, Gonen M, et al. A selective approach to the resection of cystic lesions of the pancreas: results from 539 consecutive patients. Ann Surg. 2006;244:572–82.
42. Goh BK, Tan YM, Chung YF, et al. A review of mucinous cystic neoplasms of the pancreas defined by the ovarian-type stroma: clinicopathological features of 344 patients. World J Surg. 2006;30:2236–45.
43. Cameron JL, Riall TS, Coleman J, et al. One thousand consecutive pancreaticoduodenectomies. Ann Surg. 2006;244(1):10–5.
44. Gaujoux S, Brennan MF, Gonen M, et al. Cystic lesions of the pancreas: changes in the presentation and management of 1,424 patients at a single institution over a 15-year time period. J Am Coll Surg. 2011;212(4):590–600.
45. Lahav M, Maor Y, Avidan B, et al. Nonsurgical management of asymptomatic incidental pancreatic cysts. Clin Gastroenterol Hepatol. 2007;5:813–7.
46. Pausawasdi N, Heidt D, Kwon R, et al. Long-term follow-up of patients with incidentally discovered pancreatic cystic neoplasms evaluated by endoscopic ultrasound. Surgery. 2010;147(1):13–20.
47. Yamaguchi K, Tanaka M. Intraductal papillary mucinous tumor of the pancreas: a historical review of the nomenclature and recent controversy. Pancreas. 2001; 23:12–9.
48. Furukawa T, Hatori T, Fujita I, et al. Prognostic relevance of morphological types of intraductal papillary mucinous neoplasms of the pancreas. Gut. 2011; 60:509–16.
49. Sohn TA, Yeo CJ, Cameron JL, et al. Intraductal papillary mucinous neoplasms of the pancreas: an updated experience. Ann Surg. 2004;239:788–99.
50. Salvia R, Fernandez-del Castillo C, Bassi C, et al. Main-duct intraductal papillary mucinous neoplasms of the pancreas: clinical predictors of malignancy and long-term survival following resection. Ann Surg. 2004;239:678–85.
51. Rodriguez JR, Salvia R, Crippa S, et al. Branch-duct intraductal papillary mucinous neoplasms: observations in 145 patients who underwent resection. Gastroenterology. 2007;133:72–9.
52. Levy P, Jouannaud V, O'Toole D, et al. Natural history of intraductal papillary mucinous tumors of the pancreas: actuarial risk of malignancy. Clin Gastroenterol Hepatol. 2006;4:460–8.
53. Serikawa M, Sasaki T, Fujimoto Y, et al. Management of intraductal papillary-mucinous neoplasm of the pancreas: treatment strategy based on morphologic classification. J Clin Gastroenterol. 2006;40:856–62.
54. Schmidt CM, White PB, Waters JA, et al. Intraductal papillary mucinous neoplasms: predictors of malignant and invasive pathology. Ann Surg. 2007;246: 644–51.
55. Nagai K, Doi R, Kida A, et al. Intraductal papillary mucinous neoplasms of the pancreas: clinicopathologic characteristics and long-term follow-up after resection. World J Surg. 2008;32:271–8.
56. Hwang DW, Jang JY, Lee SE, et al. Clinicopathologic analysis of surgically proven intraductal papillary mucinous neoplasms of the pancreas in SNUH: a 15-year experience at a single academic institution. Langenbecks Arch Surg. 2012;397:93–102.
57. Mimura T, Masuda A, Matsumoto I, et al. Predictors of malignant intraductal papillary mucinous neoplasm of the pancreas. J Clin Gastroenterol. 2010;44: 224–9.
58. Sugiyama M, Izumisato Y, Abe N, et al. Predictive factors for malignancy in intraductal papillary-mucinous tumours of the pancreas. Br J Surg. 2003;90:1244–9.
59. Suzuki Y, Atomi Y, Sugiyama M, et al. Cystic neoplasm of the pancreas: a Japanese multiinstitutional study of intraductal papillary mucinous tumor and mucinous cystic tumor. Pancreas. 2004;28:241–6.
60. Lee SY, Lee KT, Lee JK, et al. Long-term follow up results of intraductal papillary mucinous tumors of pancreas. J Gastroenterol Hepatol. 2005;20:1379–84.
61. Schnelldorfer T, Sarr MG, Nagorney DM, et al. Experience with 208 resections for intraductal papil-

lary mucinous neoplasm of the pancreas. Arch Surg. 2008;143:639–46.
62. Kim SC, Park KT, Lee YJ, et al. Intraductal papillary mucinous neoplasm of the pancreas: clinical characteristics and treatment outcomes of 118 consecutive patients from a single center. J Hepatobiliary Pancreat Surg. 2008;15:183–8.
63. Ohno E, Hirooka Y, Itoh A, et al. Intraductal papillary mucinous neoplasms of the pancreas: differentiation of malignant and benign tumors by endoscopic ultrasonography findings of mural nodules. Ann Surg. 2009;249:628–34.
64. Nara S, Onaya H, Hiraoka N, et al. Preoperative evaluation of invasive and noninvasive intraductal papillarymucinous neoplasms of the pancreas: clinical, radiological, and pathological analysis of 123 cases. Pancreas. 2009;38:8–16.
65. Bournet B, Kirzin S, Carrere N, et al. Clinical fate of branch duct and mixed forms of intraductal papillary mucinous neoplasia of the pancreas. J Gastroenterol Hepatol. 2009;24:1211–7.
66. Jang JY, Kim SW, Lee SE, et al. Treatment guidelines for branch duct type intraductal papillary mucinous neoplasms of the pancreas: when can we operate or observe? Ann Surg Oncol. 2008;15:199–205.
67. Sadakari Y, Ienaga J, Kobayashi K, et al. Cyst size indicates malignant transformation in branch duct intraductal papillary mucinous neoplasm of the pancreas without mural nodules. Pancreas. 2010;39:232–6.
68. Sawai Y, Yamao K, Bhatia V, et al. Development of pancreatic cancers during long-term follow-up of side-branch intraductal papillary mucinous neoplasms. Endoscopy. 2010;42:1077–84.
69. Tanno S, Nakano Y, Nishikawa T, et al. Natural history of branch duct intraductal papillary-mucinous neoplasms of the pancreas without mural nodules: long-term follow-up results. Gut. 2008;57(3):339–43.
70. Tanno S, Nakano Y, Sugiyama Y, et al. Incidence of synchronous and metachronous pancreatic carcinoma in 168 patients with branch duct intraductal papillary mucinous neoplasm. Pancreatology. 2010;10(2–3):173–8.
71. Pelaez-Luna M, Chari ST, Smyrk TC, et al. Do consensus indications for resection in branch duct intraductal papillary mucinous neoplasm predict malignancy? A study of 147 patients. Am J Gastroenterol. 2007;102:1759–64.
72. Tang RS, Weinberg B, Dawson DW, et al. Evaluation of the guidelines for management of pancreatic branch-duct intraductal papillary mucinous neoplasm. Clin Gastroenterol Hepatol. 2008;6:815–9.
73. Arlix A, Bournet B, Otal P, et al. Long-term clinical and imaging follow-up of nonoperated branch duct form of intraductal papillary mucinous neoplasms of the pancreas. Pancreas. 2012;41:295–301.
74. Kang MJ, Jang JY, Kim SJ, et al. Cyst growth rate predicts malignancy in patients with branch duct intraductal papillary mucinous neoplasms. Clin Gastroenterol Hepatol. 2011;9:87–93.
75. Rautou PE, Levy P, Vullierme MP, et al. Morphologic changes in branch duct intraductal papillary mucinous neoplasms of the pancreas: a midterm follow-up study. Clin Gastroenterol Hepatol. 2008;6:807–14.
76. Pitman MB, Genevay M, Yaeger K, et al. High-grade atypical epithelial cells in pancreatic mucinous cysts are a more accurate predictor of malignancy than "positive" cytology. Cancer Cytopathol. 2010;118: 434–40.
77. Butte JM, Brennan MF, Gonen M, et al. Solid pseudopapillary tumors of the pancreas. Clinical features, surgical outcomes, and long-term survival in 45 consecutive patients from a single center. J Gastrointest Surg. 2011;15:350–7.
78. Asa SL. Pancreatic endocrine tumors. Mod Pathol. 2011;24 Suppl 2:S66–77.
79. Klimstra DS, Modlin IR, Coppola D, et al. The pathologic classification of neuroendocrine tumors: a review of nomenclature, grading, and staging systems. Pancreas. 2010;39(6):707–12.
80. Halfdanarson TR, Rabe KG, Rubin J, et al. Pancreatic neuroendocrine tumors (PNETs): incidence, prognosis and recent trend toward improved survival. Ann Oncol. 2008;19(10):1727–33.
81. Bruns WR, Edil BH. Neuroendocrine pancreatic tumors: guidelines for management and update. Curr Treat Options Oncol. 2012;13:24–34.
82. Kongkam P, Al-Haddad M, Attasaranya S, et al. EUS and clinical characteristics of cystic pancreatic neuroendocrine tumors. Endoscopy. 2008;40:602–5.
83. Baker MS, Knuth JL, DeWitt J, et al. Pancreatic cystic neuroendocrine tumors: preoperative diagnosis with endoscopic ultrasound and fine-needle immunocytology. J Gastrointest Surg. 2008;12:450–6.
84. DeWitt J, McGreevy K, Schmidt CM, et al. EUS-guided ethanol versus saline solution lavage for pancreatic cysts: a randomized, double-blind study. Gastrointest Endosc. 2009;70:710–23.
85. DeWitt J, DiMaio CJ, Brugge WR. Long-term follow-up of pancreatic cysts that resolve radiologically after EUS-guided ethanol ablation. Gastrointest Endosc. 2010;72:862–6.
86. Oh HC, Seo DW, Lee TY, et al. New treatment for cystic tumors of the pancreas: EUS-guided ethanol lavage with paclitaxel injection. Gastrointest Endosc. 2008;67:636–42.

Part IV

Recent Advances

Recent Advances and Novel Treatments of Pancreatic Masses

24

Jason B. Samarasena and Kenneth J. Chang

Endoscopic Ultrasound–Guided Radiofrequency Ablation

Image-guided radiofrequency ablation (RFA) is a well-recognized minimally invasive treatment modality in oncology, one that utilizes the generation of high-frequency electrical alternating current through target tissue to induce ion agitation and tissue friction, ultimately leading to thermal injury and consequent coagulative necrosis. Effective ablation is achieved by optimizing heat production and minimizing heat loss with the objective of generating a clear tumor ablation margin while reducing potential side effects. The availability, safety, efficacy, and low cost of percutaneous RFA have facilitated its common utilization, in conjunction with ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI) guidance, in the management of a variety of solid tumors, most commonly hepatocellular carcinoma, renal cell carcinoma, non-small cell lung cancer, and osteoid osteoma.

RFA has also been used to treat pancreatic cancer in an exploratory laparotomy or laparoscopy; a recent systemic review identified five studies including 158 such patients with a median survival after RFA of 3–33 months, a mortality of 0–19 %, an overall morbidity of 10–43 %, and an RFA-related morbidity of 4–37 %, much of which was related to collateral injury to adjacent tissues [1]. Given its minimally invasive nature and superior imaging capabilities of the pancreas, EUS potentially provides an ideal vehicle for delivering RFA in the setting of pancreatic cancer as well as other percutaneously inaccessible tumors.

Animal Studies

Seven studies, five utilizing porcine models, of EUS-guided RFA have been conducted to date (Table 24.1). Using a modified 19-gauge needle electrode connected to a monopolar RF generator, the study by Goldberg et al. in 1999 was the first to demonstrate the feasibility of EUS-guided RFA of the pancreas in 13 pigs [2]. The maximum diameter of the ablated area in this study was 10–15 mm at EUS and 12 mm at histology. Complications included three transmural gastric wall burns, an intestinal serosal burn, and an asymptomatic pancreatic fluid collection. Correlation between EUS or CT and gross pathologic findings was excellent for all lesions larger than 5 mm; and lesion size at pathologic examination was within 2 mm of that at imaging.

In an attempt to improve ablation efficiency while reducing collateral thermal injury, Carrara

J.B. Samarasena, M.D.
K.J. Chang, M.D., F.A.S.G.E., F.A.C.G. (✉)
Division of Gastroenterology and Hepatology,
H.H. Chao Comprehensive Digestive Disease Center,
University of California, Irvine Medical Center,
101 The City Drive, Bldg. 22C, Orange, CA, USA
e-mail: kchang@uci.edu

M.S. Wagh, P.V. Draganov (eds.), *Pancreatic Masses*, DOI 10.1007/978-3-319-19677-0_24

Table 24.1 Summary of studies evaluating endoscopic ultrasound-guided radiofrequency ablation in human trials and animal models

Reference	Year	Probe design/technique	Subjects	Target organ	Maximum diameter/area of ablated area at EUS	Maximum diameter/area of ablated area at histology	Complications	**Follow up**
Goldberg [2]	1999	Monopolar 19-gauge needle electrode	13 pigs	Pancreas (tail)	10–15 mm	12 mm	Transmural gastric wall burns ($n=3$)	Variable; up to 14 days
							Intestinal serosal burn ($n=1$)	
							Asymptomatic pancreatic fluid collection ($n=1$)	
Carrara [3]	2008	Hybrid bipolar RFA-carbon dioxide cryoprobe	14 pigs	Pancreas (body)	900 mm^2	4000 mm^2	Necrotic pancreatitis with peritonitis ($n=1$)	Variable; up to 14 days
							Asymptomatic pancreatitis ($n=1$)	
							Gastric wall burn ($n=1$)	
							Adhesion between the pancreas and gut ($n=4$)	
Petrone [5]	2010	Hybrid bipolar RFA-carbon dioxide cryoprobe; ultrasound-guided	16 humans with pancreatic adenocarcinoma (ex vivo)	Pancreas	Not stated	10–20 mm (depending on application time)	N/A	N/A
Gaidhane [7]	2012	1 Fr monopolar probe deployed through a 19-gauge needle	5 pigs	Pancreas (head)	Not stated	Not stated	Asymptomatic histologic pancreatitis ($n=5$)	6 days
Kim [8]	2012	18-gauge electrode with saline pump cooling	10 pigs	Pancreas (body and tail)	14.5 mm	23 mm	Asymptomatic retroperitoneal fibrosis ($n=1$)	7 days
							Asymptomatic adhesions between pancreas and stomach or bowel ($n=2$)	
Arcidiacono [9]	2012	Hybrid bipolar RFA-carbon dioxide cryoprobe	22 humans with unresectable stage III pancreatic adenocarcinoma	Pancreas	Uncertain	Uncertain	Failed probe deployment ($n=6$)	Uncertain; at least 15 months
							Mild abdominal pain ($n=3$); 1 with pancreatitis	
							Duodenal bleed ($n=1$)	
							Obstructive jaundice ($n=2$)	
							Duodenal stricture ($n=1$)	
							Asymptomatic pancreatic cystic collection ($n=1$)	
Pai [10]	2013	1.2 mm Monopolar EUS-RFA catheter	Seven humans with unresectable pancreatic adenocarcinoma	Pancreas	Uncertain	Uncertain	Mild pancreatitis ($n=1$)	

et al. used a hybrid cryotherm (CT) probe (ERBE Electromedizin, Tubingen, Germany) combining bipolar RF current with carbon dioxide cryotherapy to ablate the body of the pancreas in 14 pigs; they were able to achieve a larger ablation zone (18 mm vs. 10 mm) during a 300-s application than that obtained with a 360-s application of the monopolar system utilized by Goldberg et al. [3]. However, similar side effects, most reflecting the longer application duration, were encountered, including two cases of pancreatitis (one necrotizing and the other asymptomatic), a gastric wall burn, and four cases of adhesions between the pancreas and the gut. The CT probe was used by the same group to demonstrate the feasibility of EUS-guided RFA of the liver and spleen in porcine models, where no complications were reported [4], and that of ultrasound-guided RFA in a human ex vivo study of 16 pancreatic tumors with a mean diameter of 29 mm, where ablation zone diameters of 10–20 mm were achieved [5].

Varadarajulu et al. used an EUS-guided umbrella-shaped retractable monopolar electrode array to ablate five porcine livers, generating ablation zone diameters of 23 mm at EUS and 26 mm at histology without any complications [6]. Gaidhane et al. deployed a 1 Fr RFA probe through a 19-gauge needle to ablate five porcine pancreas without complications; only histological evidence of focal pancreatitis could be documented [7]. Kim et al. used an 18-gauge saline pump-cooled RFA electrode to ablate the body or tail of the pancreas of 10 pigs; ablation zone diameters of 14.5 mm at EUS and 23 mm at histology were achieved [8]. Complications included three cases of asymptomatic retroperitoneal fibrosis or pancreato-gastric adhesions.

Human Studies

Human study employing EUS-guided RFA is limited. Arcidiacono et al. ablated 16 unresectable stage III pancreatic cancers with a mean diameter of 35.7 mm using the CT probe; RFA could not be deployed in 6 additional patients because of gastroduodenal wall or tumor stiffness. Complications included mild abdominal pain in three patients, one of whom had pancreatitis; a duodenal bleed requiring endotherapy; two cases of obstructive jaundice requiring stenting; a duodenal stricture treated with stenting; and an asymptomatic pancreatic cystic collection. The median postablation survival time was 6 months. CT imaging could clearly define the tumor margins in only 6 of 16 ablated patients, whereby reduction or no change in tumor size, albeit insignificant, could be seen for up to 78 days [9]. Pai et al. conducted a study on seven patients with unresectable pancreatic adenocarcinoma where EUS-guided RFA was performed using the monopolar radiofrequency catheter (1.2 mm Habib EUS-RFA catheter, Emcision Ltd, London). The tumor was shown to decrease in size in all cases, and only one patient developed mild pancreatitis [10].

Conclusion

At present, EUS-guided RFA remains a research tool that requires further assessment, refinement, and validation of its safety and efficacy in well-designed randomized controlled studies before it can be formally recommended for use in clinical practice. In particular, future studies will need to address the development of a sharper probe design possibly equipped with cutting current to facilitate transluminal access, the appropriate radiologic modality and time interval for assessing tumor response, in addition to the optimal settings for treatment duration, generator power, and gas coolant pressure for effective ablation of pancreatic cancer as opposed to healthy pancreatic tissue.

Endoscopic Ultrasound-Guided Antitumor Agents

EUS-guided fine-needle injection (FNI) has received attention as a method for antitumor agent delivery, particularly for intratumoral and combination therapy against pancreatic cancer. The evidence supporting the feasibility of EUS-FNI of antitumor agents has been expanding; however, finding the most effective local agent for EUS-guided delivery is still a work in progress.

The concept of EUS-FNI for antitumor agent delivery has been studied largely in pancreatic

cancer treatment mainly due to its accessible anatomic location and the dismal prognosis of this cancer. Various organs and major vessels surrounding the pancreas make access to it difficult for modalities such as CT, with EUS providing excellent access to all regions of the pancreas. Despite extensive basic and clinical research, the prognosis of pancreatic cancer is still dismal and surgical resection represents the only possibility of cure. One of the reasons for the poor response to chemotherapy in pancreatic cancer is because of poor drug delivery due to abundant desmoplasia and the hypovascular nature of the tumor. By injecting antitumor agents directly into the tumor under EUS guidance, these hurdles can be overcome less invasively.

Early Experience

Our first study testing the concept of EUS-FNI for antitumor agent delivery involved injection of allogenic mixed-lymphocyte culture (cytoimplant) into pancreatic tumors. Despite the early termination of a randomized controlled trial employing EUS-guided cytoimplant vs. conventional therapy, this experience clearly demonstrated the feasibility of EUS-FNI as a delivery method for an antitumor agent [11].

Studies that followed included EUS-FNI of "gene therapy" with ONYX-015 [12, 13], a gene-deleted replication-selective adenovirus that preferentially replicates in and kills malignant cells. A phase I/II trial testing the feasibility, tolerability, and efficacy of EUS-FNI of ONYX-015 into unresectable pancreatic carcinomas was evaluated in 21 patients. Objective partial regressions were seen in only two patients, but this study again further supported the feasibility and safety of EUS-FNI antitumor therapy and moreover set the stage for more advanced gene therapy studies as discussed below.

TNFerade Gene Therapy

Tumor necrosis factor-α (TNF-α) has potent antitumor properties through its effect on tumor vasculature and direct cytotoxic effect. TNF-α may also function as a radiosensitizer by increasing levels of hydroxyl radicals, thereby enhancing the oxidative damage produced by radiation. Clinical studies with TNF-α have been limited due to severe systemic toxicity. TNFerade was constructed as a second-generation adenovector, which expresses the complementary DNA (cDNA) encoding human TNF as a novel means of selective delivery of TNF to tumor cells that uses gene transfer [14]. To optimize local effectiveness and minimize systemic toxicity, the radiation-inducible immediate response early growth response (Egr)-1 promotor was placed upstream of the transcriptional start site of the human TNF cDNA. This vector was engineered to ensure that maximal gene expression and subsequent TNF secretion are constrained in space and time by radiation therapy. Human clinical trials have been performed in pancreatic, esophageal, and rectal cancers.

In patients with pancreatic cancer, long-term results of phase I/II study of EUS or percutaneous transabdominal delivery of TNFerade with chemoradiation were reported in patients with locally advanced pancreatic cancer [14]. TNFerade was injected into locally advanced pancreatic carcinomas once a week for 5 weeks together with 50.4 Gy of radiation and 5-fluorouracil (5-FU) 200 mg/m^2 daily over 5.5 weeks. Dose levels from 4×10^9 to 1×10^{12} particle units (PU) were studied. TNFerade was delivered with a single needle pass by the percutaneous transabdominal approach, whereas up to four injections were given by EUS (Figs. 24.1, 24.2, and 24.3 show TNFerade patient pre- and posttreatment). Fifty patients completed this dose-escalation study with 27 patients undergoing EUS-guided injection. Dose-limiting toxicities (DLTs) occurred in three EUS patients at 1×10^{12} PU (two patients with pancreatitis and one patient with cholangitis). Major grade-3 and -4 adverse events were gastrointestinal bleeding, deep vein thrombosis and pulmonary emboli, pancreatitis, and cholangitis. The median time to tumor progression was 108 days (95 % CI, 67–198 days) and the median overall survival (OS) was 297 days (95 % CI, 201–316 days). The best median survival was seen in the 4×10^{11} PU cohort of 332 days (95 % CI, 154–316). Seven patients underwent surgical resection after treatment and

six had negative surgical margins, with one patient demonstrating a complete pathologic response. Given the high rate of pathologically negative surgical resection after downstaging, this treatment seemed to be promising.

Subsequently, a phase II/III randomized controlled trial of standard of care (SOC—chemoradiation therapy) with and without TNFerade was conducted [15]. In this study 198 patients were assigned to the TOC + TNFerade and 90 to SOC. The median overall survival (OS) was 10.0 months for patients in both the SOC+TNFerade and SOC arms (hazard ratio, 0.90; 95 % CI, 0.66–1.22; $p=0.26$). The median progression-free survival (PFS) was 6.8 months for SOC + TNFerade vs. 7.0 months for SOC (HR, 0.96; 95 % CI, 0.69–1.32; $p=0.51$). Patients in the SOC + TNFerade arm experienced more grade-1 and -2 fevers and chills than those in the SOC arm ($p<0.001$), but both arms had similar rates of grade-3 and -4 toxicities. Although overall results did not show a difference in survival, a subgroup analysis showed patients with T1 to T3 tumors and cancer antigen (CA) 19–9 U/mL levels <1000 had longer survival with the addition of TNFerade (10.9 vs. 9.0 months; $p=0.04$) [16]. Thus, patient selection may be especially important with TNFerade therapy (Figs. 24.1, 24.2, and 24.3).

Endoscopic Ultrasound–Guided Immunotherapy

EUS-guided immunotherapy has been considered an attractive option, especially in patients with pancreatic cancer, which is usually refractory to conventional chemotherapy. Tumor antigen-loaded dendritic cells (DCs) have been considered a therapeutic vaccine for inducing tumor-specific immunity because DCs are the most potent antigen-presenting cells.

Irisawa and colleagues reported a pilot trial of EUS-FNI of unpulsed immature DCs in seven patients with unresectable pancreatic cancer refractory to gemcitabine [17]. Five of the seven patients received irradiation before the initial EUS-FNI of DCs to induce apoptosis and necrosis. Patients received intratumoral injection of ten billion or more immature DCs at 2–3 sites on days 1, 8, and 15. The cycles were repeated every 28 days. No complication with EUS-FNI was noted. The CA 19–9 level decreased in three patients and three had a mixed response defined as regression in the main tumor, with other lesions remaining stable or progressing.

Subsequently, Hirooka and colleagues performed a pilot trial of combination therapy of gemcitabine and immunotherapy using OK432-pulsed

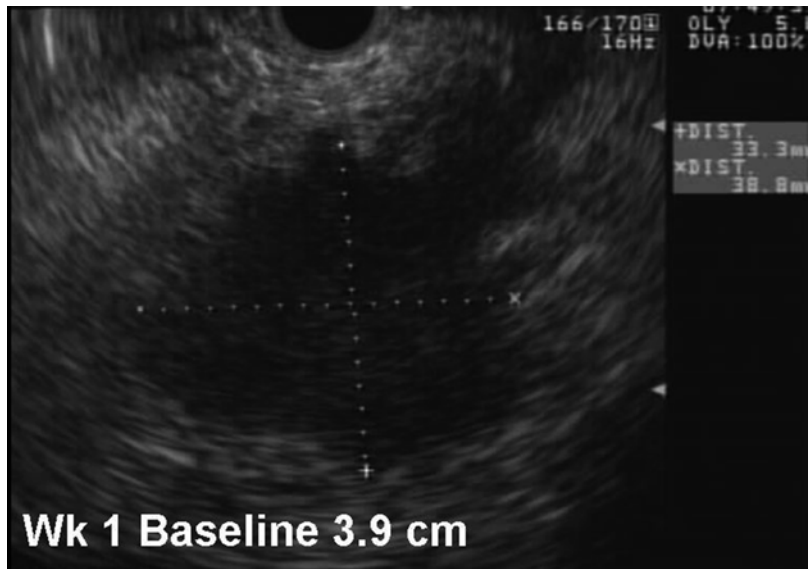

Fig. 24.1 A 71 year old man with T4 adenocarcinoma in the neck of the pancreas. Pretreatment tumor size was 3.9×3.3 cm

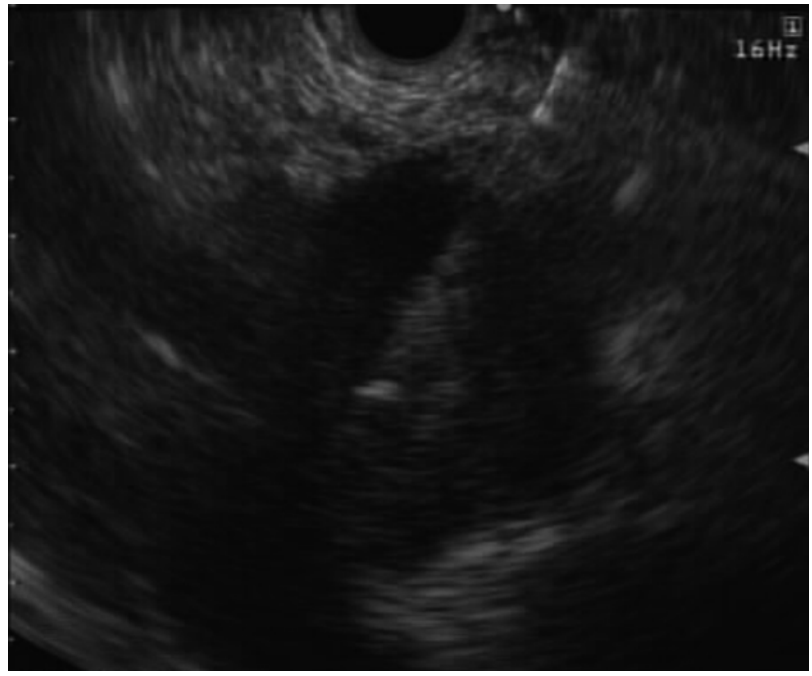

Fig. 24.2 EUS-guided fine-needle injection of TNFerade

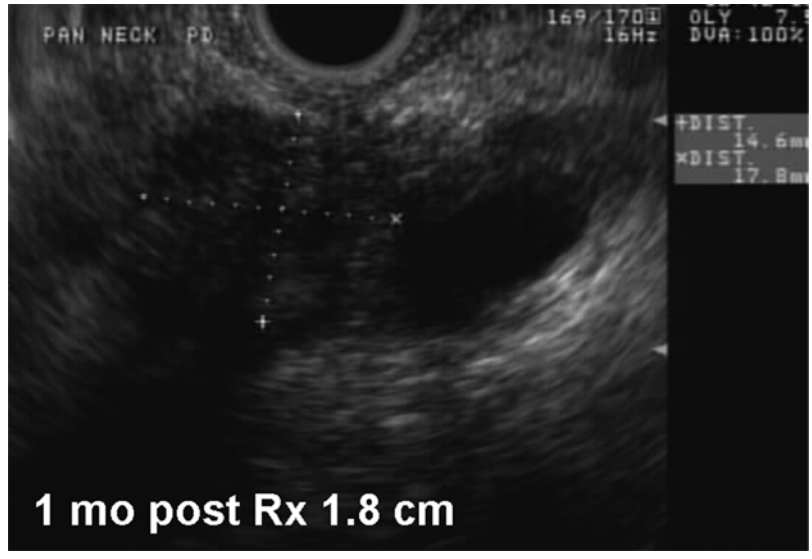

Fig. 24.3 EUS at 4 weeks from EUS-FNI showed a marked decrease of tumor size to 1.8 cm × 1.5 cm

DCs in five patients with inoperable locally advanced pancreatic cancer. OK432 is a widely used maturation stimulus for DCs. In this trial, patients received gemcitabine IV administration at 1000 mg/m^2 (day 1) and EUS-FNI of OK432-pulsed DCs into a tumor, followed by IV infusion of lymphokine-activated killer cells stimulated with anti-CD3 monoclonal antibody (day 4) at 2-week intervals. No serious treatment-related adverse events were observed. One patient had a partial response and two had sustained stable disease for more than 6 months.

These studies, despite being small study populations, suggest that immunotherapy via intratumoral injection of DCs under EUS guidance should be further explored in larger clinical trials.

Future Directions

Many of the clinical studies mentioned are still experimental with small study populations. Prospective randomized controlled trials with large study populations are necessary to confirm the role of EUS-FNI in cancer treatment. Unlike systemic chemotherapy, EUS-FNI of an antitumor agent only exerts antitumor effects locally. Therefore, appropriate patient selection with truly local disease is important. For pancreatic cancer, EUS-FNI antitumor therapy cannot be offered as monotherapy but can be part of a combination treatment including systemic therapy.

In conclusion, although EUS-FNI of antitumor agent has not yet been established as a standard option in cancer treatment, its feasibility and safety have been proven in both animal and human studies. The task at hand is to develop effective biologic and nonbiologic local therapies. Once these agents are identified, large prospective randomized controlled trials will be needed to prove efficacy over standard therapy. We remain optimistic that EUS-FNI will play in important role in future pancreatic cancer therapy.

Photodynamic Therapy

Photodynamic therapy (PDT) involves the administration of a tumor-localizing photosensitizer, exposure of the target tissue to light of an appropriate wavelength, and the generation of a highly cytotoxic oxygen species termed *singlet oxygen* [18]. Antitumor effects of PDT result from direct cytotoxic effects, damage to the tumor vasculature, and induction of inflammatory reaction leading to the development of system immunity [19]. It leads to a predictable zone of ablation within a tumor. To date, light has been delivered via small optic fibers which largely have been positioned percutaneously under image guidance (e.g., CT).

The first Phase 1 trial of PDT in locally advanced pancreatic cancer was conducted in 2002 by Bown and colleagues. In this study, 16 patients with inoperable pancreatic adenocarcinoma of the head of the pancreas were studied. Patients were photosensitized intravenously with 0.15 mg/kg meso-tetrahydroxyphenyl chlorin (mTHPC), which notably has a long half-life; to avoid skin photosensitivity, patients had to avoid daylight for 7 days and bright sunlight for 1 month. Three days after photosensitization, under CT guidance, up to six 19-G needles were inserted into the deepest part of the tumor by a radiologist. The light source was diode laser delivering red light at 652 nm. All patients had substantial tumor necrosis on scans after treatment. Two patients with tumor involving the gastroduodenal artery had significant gastrointestinal bleeding that was controlled endoscopically and with transfusion. Three patients developed duodenal obstruction during follow-up that may have been related to treatment. There was no treatment-related mortality, and the median survival time after PDT was 9.5 months [20].

A more recent Phase I/II study by Huggett and colleagues studied 15 inoperable patients with locally advanced pancreatic adenocarcinoma who were sensitized with 0.4 mg/kg verteporfin, a photosensitizer with a relatively short half-life of 4 h and a duration of photosensitivity of only 24 h. After 60–90 min, laser light using a diode 690-nm laser was delivered via single (13 patients) or multiple (two patients) fibers positioned percutaneously under CT guidance. The light dose was escalated, initially at 5J and doubled, until the target size of necrosis (12 mm) was achieved in each group of patients. In all patients, 12-mm lesions were consistently seen at 40J but with considerable variation of necrosis volume. Minor, self-limiting side effects were observed, including mild to moderate abdominal pain shortly after PDT and diarrhea. No adverse interactions were seen in patients given chemotherapy or radiotherapy before or after PDT. After PDT, one patient underwent an R0 Whipple's pancreaticoduodenectomy [21].

Given that the PDT optic fibers' size allows passage through a 19-G needle, the concept of PDT administration into pancreatic tumors under EUS guidance has been of interest. A pilot study of EUS-guided PDT using the photosensitizer verteporfin on porcine pancreas was reported in 2008. In this study six pigs were randomly divided into three groups with two pigs in each group; the first was exposed to 10 min of 689-nm wavelength laser light at 150 J/cm^2, the second group to 15 min, and the third group 20 min. Serum amylase, lipase, renal and liver function tests were obtained at baseline and 4 days after the EUS-PDT. An abdominal CT with contrast was performed on day 4 to evaluate the pancreas for tissue effect. The mean diameter of the lesion after 10, 15, and 20 min of laser light exposure on CT was 6.6 mm, 9.4 mm, and 26.3 mm, respectively. Histology revealed a well-defined solitary lesion that included areas of fat necrosis, granulation tissue, inflammation, and fibrosis. There were no complications encountered except for a mild increase in serum amylase in one pig without clinical evidence of pancreatitis [22].

In summary, photodynamic therapy appears to be a relatively feasible and safe local therapy for pancreatic adenocarcinoma. The low adverse event profile suggests that alongside systemic therapy, there is a role for further studies of PDT for the treatment of pancreatic adenocarcinoma and likely other focal pancreatic neoplasms.

Conclusion

The advent of linear echoendoscopic ultrasound has transformed EUS from a purely diagnostic modality to a platform for therapeutic applications including delivery of various ablative agents, antitumor agents, and miniature devices. Given the ease of access to the pancreas with EUS-FNA, the treatment of pancreatic tumors using this modality has been a logical choice. As just described, over the past 15 years a number of attempts have been made to use EUS in a novel manner to treat pancreatic tumors. Although none of the described modalities has proven to be completely effective, each holds promise for future refinement and further gains in efficacy of tumor destruction with improved safety.

References

1. Fegrachi S, et al. Radiofrequency ablation for unresectable locally advanced pancreatic cancer: a systematic review. HPB (Oxford). 2014;16(2):119–23.
2. Goldberg SN, et al. EUS-guided radiofrequency ablation in the pancreas: results in a porcine model. Gastrointest Endosc. 1999;50(3):392–401.
3. Carrara S, et al. Endoscopic ultrasound-guided application of a new hybrid cryotherm probe in porcine pancreas: a preliminary study. Endoscopy. 2008;40(4):321–6.
4. Carrara S, et al. Endoscopic ultrasound-guided application of a new internally gas-cooled radiofrequency ablation probe in the liver and spleen of an animal model: a preliminary study. Endoscopy. 2008;40(9):759–63.
5. Petrone MC, et al. US-guided application of a new hybrid probe in human pancreatic adenocarcinoma: an ex vivo study. Gastrointest Endosc. 2010;71(7):1294–7.
6. Varadarajulu S, Jhala NC, Drelichman ER. EUS-guided radiofrequency ablation with a prototype electrode array system in an animal model (with video). Gastrointest Endosc. 2009;70(2):372–6.
7. Gaidhane M, et al. Endoscopic ultrasound-guided radiofrequency ablation (EUS-RFA) of the pancreas in a porcine model. Gastroenterol Res Pract. 2012;2012:431451.
8. Kim HJ, et al. EUS-guided radiofrequency ablation of the porcine pancreas. Gastrointest Endosc. 2012;76(5):1039–43.
9. Arcidiacono PG, et al. Feasibility and safety of EUS-guided cryothermal ablation in patients with locally advanced pancreatic cancer. Gastrointest Endosc. 2012;76(6):1142–51.
10. Pai M, et al. Endoscopic ultrasound guided radiofrequency ablation (EUS- RFA) for pancreatic ductal adenocarcinoma. Gut. 2013;62:A153.
11. Chang KJ, et al. Phase I clinical trial of allogeneic mixed lymphocyte culture (cytoimplant) delivered by endoscopic ultrasound-guided fine-needle injection in patients with advanced pancreatic carcinoma. Cancer. 2000;88(6):1325–35.
12. Mulvihill S, et al. Safety and feasibility of injection with an E1B-55 kDa gene-deleted, replication-selective adenovirus (ONYX-015) into primary carcinomas of the pancreas: a phase I trial. Gene Ther. 2001;8(4):308–15.
13. Hecht JR, et al. A phase I/II trial of intratumoral endoscopic ultrasound injection of ONYX-015 with intravenous gemcitabine in unresectable pancreatic carcinoma. Clin Cancer Res. 2003;9(2):555–61.
14. Hecht JR, et al. EUS or percutaneously guided intratumoral TNFerade biologic with 5-fluorouracil and radiotherapy for first-line treatment of locally advanced pancreatic cancer: a phase I/II study. Gastrointest Endosc. 2012;75(2):332–8.

15. Herman JM, et al. Randomized phase III multi-institutional study of TNFerade biologic with fluoro-uracil and radiotherapy for locally advanced pancreatic cancer: final results. J Clin Oncol. 2013;31(7):886–94.
16. Nakai Y, Chang KJ. Endoscopic ultrasound-guided antitumor agents. Gastrointest Endosc Clin N Am. 2012;22(2):315–24. x.
17. Irisawa A, et al. Endoscopic ultrasound-guided fine-needle injection of immature dendritic cells into advanced pancreatic cancer refractory to gem-citabine: a pilot study. Pancreas. 2007;35(2):189–90.
18. Dougherty TJ, et al. Photodynamic therapy. J Natl Cancer Inst. 1998;90(12):889–905.
19. Agostinis P, et al. Photodynamic therapy of cancer: an update. CA Cancer J Clin. 2011;61(4):250–81.
20. Bown SG, et al. Photodynamic therapy for cancer of the pancreas. Gut. 2002;50(4):549–57.
21. Huggett MT, et al. Phase I/II study of verteporfin photodynamic therapy in locally advanced pancreatic cancer. Br J Cancer. 2014;110(7):1698–704.
22. Yusuf TE, Matthes K, Brugge WR. EUS-guided photodynamic therapy with verteporfin for ablation of normal pancreatic tissue: a pilot study in a porcine model (with video). Gastrointest Endosc. 2008;67(6):957–61.
23. Hirooka Y, Itoh A, Kawashima H, Hara K, Nonogaki K, Kasugai T, Ohno E, Ishikawa T, Matsubara H, Ishigami M, Katano Y, Ohmiya N, Niwa Y, Yamamoto K, Kaneko T, Nieda M, Yokokawa K, Goto H. A combination therapy of gemcitabine with immunotherapy for patients with inoperable locally advanced pancreatic cancer. Pancreas. 2009;38(3):e69–74.

Index

M.S. Wagh, P.V. Draganov (eds.), *Pancreatic Masses*, DOI 10.1007/978-3-319-19677-0