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## 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.

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## 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].

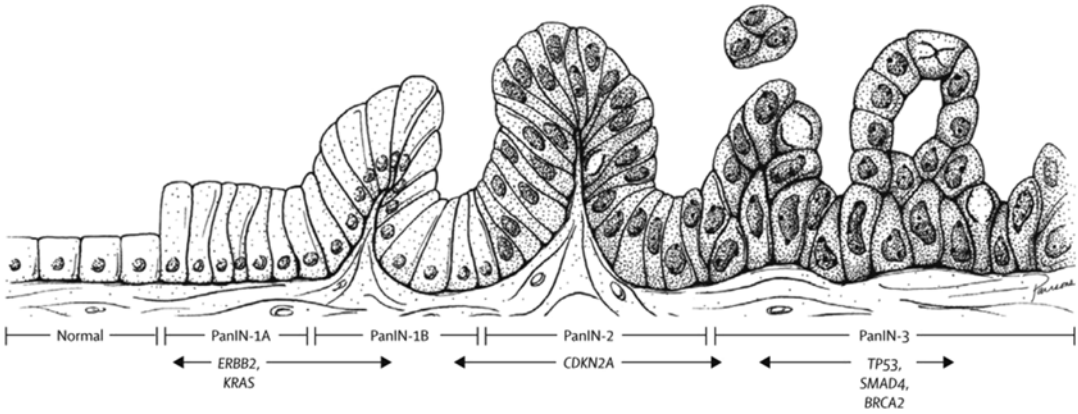
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## Biology

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,

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**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 constitutively 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.

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## 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 choloria (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 ade-

nocarcinoma, 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.

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## 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 clinically 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 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



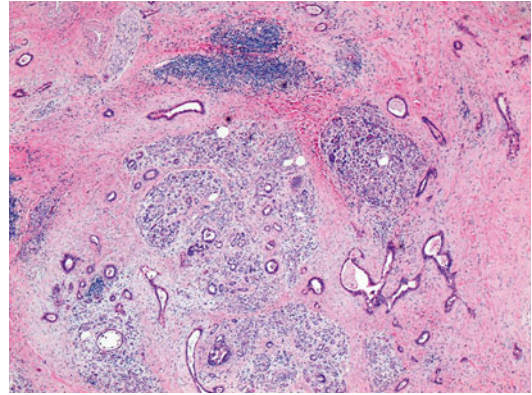
approximately 80 %, are less useful in the management of pancreatic adenocarcinoma, and not routinely used in clinical practice [54, 55]. In the future, newer technologies such as posttranscriptional gene regulation and next-generation gene sequencing will likely produce more promising, clinically relevant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

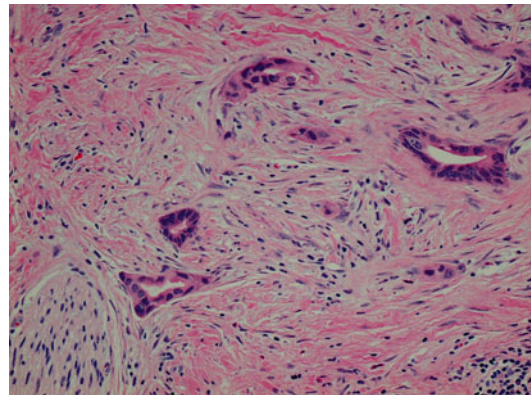
pressure induces vascular collapse and is thought to reduce perfusion to the tumor [58]. Reduced perfusion, in turn, has been implicated as a potential barrier to the adequate delivery of chemotherapeutic agents. On immunohistochemistry, pancreatic cancers may express CEA, cytokeratin, CA 19-9, B72.3 (TAG-72), CA 125, DUPAN2, as well as a number of mucins [56, 57].



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



**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. 2.4** 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:  $\times 200$ ) (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

**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 <sup>a</sup>		
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

<sup>a</sup>This includes lesions classified as PanInIII classification

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].

## 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.

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