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

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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].

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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.

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