Cystic Neoplasms of the Pancreas

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Abstract

Cystic neoplasms of the pancreas are being identified at an increasing frequency largely due to the increased use of abdominal cross-sectional imaging. These neoplasms represent a heterogeneous group of tumors with various genetic alterations, molecular features, and risks of malignancy. Despite the use of high-resolution radiographic studies, endoscopic evaluation, cyst fluid analysis, and novel molecular diagnostics, many of these lesions remain difficult to classify without operative resection. These diagnostic challenges are coupled with an improving but limited understanding of the natural history of these neoplasms. Treatment of pancreatic cystic neoplasms therefore remains controversial but consists largely of a selective tumor-specific approach to surgical resection. Future research remains necessary to better discriminate the biological behavior of these tumors in order to more appropriately select patients for operative intervention.

INTRODUCTION

PCN: pancreatic cystic neoplasm

SCA: serous cystadenoma

MCN: mucinous cystic neoplasm

IPMN: intraductal papillary mucinous neoplasm

Cystic neoplasms of the pancreas are an increasingly common clinical entity, and the growth in incidence is attributable to the increasing use of abdominal cross-sectional imaging. Both computed tomography (CT) and magnetic resonance imaging (MRI) examinations suggest a 2.5–5.0% prevalence of cysts (1–3), with rates as high as 25% in autopsy series (4). Older data suggest that the majority of cystic lesions represent non-neoplastic inflammatory pancreatic pseudocysts; cystic neoplasms thus represent only 15–20% of all pancreatic cysts (5, 6). Other non-neoplastic entities include congenital cysts, lymphoepithelial cysts, enterogenous cysts, retention cysts, and mucinous non-neoplastic cysts (5).

Together, pancreatic cystic neoplasms (PCNs) are a heterogeneous group of tumors with a broad histologic differential. Kloppel and colleagues (5) have characterized this diverse group as outlined in **Figure 1**. Neoplastic cysts can be classified according to their malignant potential as benign, premalignant, or malignant (7). Reports of patients who have undergone resection suggest that the most common entities are serous cystadenomas (SCAs), mucinous cystic neoplasms (MCNs), and intraductal papillary mucinous neoplasms (IPMNs), each of which is covered here. In a large French series of resected lesions from 73 institutions, these three histologies comprised 87% of all cystic lesions (8). It is important to note that there are also cystic variants of carcinomas (including neuroendocrine carcinoma and pancreatic ductal adenocarcinoma) that can mimic the more common entities radiographically.

EPIDEMIOLOGY AND RISK FACTORS

Cystic lesions of the pancreas are commonly pancreatic pseudocysts that have no malignant potential (9). These pseudocysts are named as such because they are fluid collections that lack an epithelial lining and are typically rich in amylase. Pseudocysts generally occur in patients with a history of acute pancreatitis; risk factors therefore include gallstones, a history of alcohol use, other biliary pathology, trauma, or a personal or family history of pancreatic pathology. In the clinical evaluation of a cystic pancreatic lesion, these aspects of the history are crucial.

By contrast, cystic neoplasms of the pancreas have few definable risk factors. MCNs almost exclusively occur in women and histologically feature an ovarian-type stroma. Whether the hormonal milieu in women potentiates the subsequent development of MCNs remains unknown. The development of IPMNs, in particular, may be associated with age. This is suggested by evidence that 10% of individuals over the age of 70 have pancreatic cysts (10). It is believed that the majority of these neoplastic lesions represent small branch-duct-type IPMNs (BD-IPMNs), suggesting that age may be a risk factor in this disease.

PATHOGENESIS AND CLINICAL PRESENTATION

Serous Cystadenomas

First characterized by Compagno & Oertel (11, 12) in 1978, SCAs are glycogen-rich lesions arising from cuboidal epithelium that account for ~16% of all resected PCNs (13). Typically, these lesions are described as "microcystic" as they generally feature small cysts (measured in millimeters) with characteristic septations and thick fibrous walls that may confer a honeycomb appearance on gross examination. Whereas MCNs and IPMNs have thick, mucinous material within the cystic component, SCAs have a clear thin fluid, often in innumerable small cysts. Ten percent of cases have an oligo- or macrocystic appearance that can make them difficult to distinguish from MCNs. A genetic predisposition to the development of SCAs is conferred by the von Hippel–Lindau

Epithelial	Non-neoplastic		Congenital cyst (in malformation syndromes) Lymphoepithelial cyst Mucinous non-neoplastic cyst Enterogenous cyst Retention cyst Periampullary duodenal wall cyst Endometrial cyst
	Neoplastic	Benign	Serous adenoma (microcystic) Serous adenoma (oligocystic, ill-demarcated) Acinar cell cystadenoma Dermoid cyst Cystic hamartoma Von Hippel–Lindau-associated cystic neoplasm
		Pre-malignant	Mucinous cystic neoplasm Intraductal papillary mucinous neoplasm
		Malignant	Solid pseudopapillary tumor Mucinous cystic neoplasm–associated carcinoma Intraductal papillary mucinous neoplasm–associated carcinoma Ductal adenocarcinoma, cystic Serous cystadenocarcinoma Pancreatoblastoma, cystic Cystic metastatic epithelial neoplasm Neuroendocrine carcinoma, cystic
Non-epithelial	Non-neoplastic		Pseudocyst Parasitic cyst
	Neoplastic	Benign	Lymphangioma
		Malignant	Sarcoma with cystic degeneration

Figure 1

Classification of pancreatic cysts (adapted from Reference 60 with permission).

syndrome; SCAs are observed in 15% of patients with this syndrome (14). In addition, sporadic SCAs have been recently found to feature somatic mutations in the *VHL* gene in 50% of cases (15).

SCAs are generally benign, indolent neoplasms predominating in women (~75% of cases) (16), and they may occur anywhere in the pancreas. Malignancy in SCAs, namely serous cystadenocarcinoma, is limited to approximately 25–30 case reports in the worldwide literature, representing <1% of all SCAs (17). The average age of patients undergoing resection in large US and European series has ranged from 52 to 62 years (8, 18, 19). Most SCAs are discovered as an incidental finding but, depending on size and location, may cause symptoms such as abdominal pain, early satiety, jaundice, or pancreatitis.

Mucinous Cystic Neoplasms

MD-IPMN: main-duct intraductal papillary mucinous neoplasm

BD-IPMN: branch-duct intraductal papillary mucinous neoplasm

PDAC: pancreatic ductal adenocarcinoma

Mucinous cystic neoplasms (MCNs), which represent 25% of all resected PCNs, are cystic tumors featuring the production of mucin that only recently have been recognized as a distinct clinicopathologic entity apart from IPMNs (13). Unlike IPMNs, MCNs lack communication with the pancreatic duct, whether it be the main duct or its side branches. These lesions are typically solitary and unilocular, and they most commonly occur in the tail of the pancreas. MCNs are lined by columnar epithelium supported by an ovarian-like stroma, features that make them histologically quite distinct from SCAs. This ovarian stroma is a pathognomonic finding that is invariably associated with MCNs; it is no surprise, then, that MCNs are almost universally found in women, as the stroma will stain variably for estrogen receptor (ER)/progesterone receptor (PR) and beta-human chorionic gonadotropin (β-HCG). In two large case series, the average age at presentation was 45 and 48 years, respectively (20, 21), with 95% of cases occurring in women. Like SCAs, MCNs are variably symptomatic; only 20% of patients present with either acute pancreatitis or a palpable mass.

MCNs harbor a risk of malignancy, with estimates ranging from 10% to 50%. The pathogenesis of MCNs and their malignant transformation remains poorly understood. *KRAS* mutations are observed in benign, borderline, and malignant MCNs with increasing frequency correlating with the extent of dysplasia, whereas *p53* overexpression is typically only seen in invasive MCNs (22). More recently, investigators have shown loss of *DPC4* in 85% of invasive MCN specimens but none of the benign MCNs examined (23).

Intraductal Papillary Mucinous Neoplasms

It was not until 1996, with the development of the first classification published by the World Health Organization, that IPMNs were recognized as a distinct clinicopathologic entity (24). Prior to this, IPMNs were variably described as mucinous ductal ectasia, papillary carcinoma, and/or villous adenoma. Unlike SCAs and MCNs, IPMNs are found in men and women equally, with an increased prevalence in older individuals and a peak incidence in those between 60 and 70 years of age (3).

The pathogenesis of IPMNs involves the dilation of the main pancreatic duct and/or its side branches with the associated accumulation of mucin produced by a proliferative epithelium with papillary projections. As such, IPMNs are classified radiographically as either main-duct (MD-IPMN), branch-duct (BD-IPMN), or mixed-type. Mucin is typically found within the cytoplasm of epithelial cells as well as within the acellular fluid matrix. Originating from the cells of the pancreatic ductal system, IPMNs may be localized, diffuse, or multifocal, with one-third found in the head/uncinate process, one-third in the body, and the remaining third in the tail of the pancreas (25). IPMNs encompass a spectrum of precursor lesions ranging from adenoma to varying grades of dysplasia to frank carcinoma (26).

MD-IPMNs typically involve dilatation and frequent ectasia of the main pancreatic duct, often to >10 mm diameter. In one-third of patients, the dilatation of the main duct involves the entirety of the gland. Although there may be a focal mucinous cystic growth limited to a portion of the gland, IPMNs are thought to represent a "field defect" in which the whole pancreas is at risk for the development of malignancy. This is supported by data showing that BD-IPMNs can frequently be associated with concomitant pancreatic ductal adenocarcinoma (PDAC) that does not arise from the radiographically detected IPMN itself. The risk of malignancy with BD-IPMN has been extensively studied; 25% of these neoplasias progress to at least high-grade dysplasia and 17% have at least some invasive component (27–31). It has been reported that 30% of patients with

BD-IPMN who develop invasive carcinoma will develop an invasive carcinoma elsewhere in the gland, lending credence to the notion of a field defect (32). MD-IPMNs are associated with much higher rates of malignancy, with 45% harboring an invasive component and an additional 20% with high-grade dysplasia at the time of resection (25, 28, 33). Mixed-type IPMNs, which feature a branch-duct and main-duct component, have been reported to have malignancy rates averaging that of BD-IPMNs and MD-IPMNs.

Recent histopathologic analysis has enabled new insight into the pathogenesis of IPMNs. Histopathologically, IPMNs can be classified by oncocytic subtype: gastric, intestinal, pancreatobiliary, or intraductal (34, 35). The gastric type is typically seen in patients with BD-IPMNs and is associated with low-grade biological behavior. *MUC5AC* and *MUC6* are characteristically expressed in gastric-type IPMNs and feature abundant cytoplasmic mucin and basally located nuclei (36). By contrast, MD-IPMNs largely have either pancreatobiliary or intestinal subtype, carry some degree of dysplasia, and overexpress *MUC5AC* and *MUC2* with weak expression of *MUC6* (37). Malignant transformation in intestinal-type IPMNs is usually of the colloid-type adenocarcinoma, which portends a better prognosis. Pancreatobiliary-type IPMNs can be either BD-IPMNs or MD-IPMNs, and they generally progress to tubular-type adenocarcinoma that carries both the histologic findings and poor prognosis associated with conventional PDAC (38, 39).

IPMNs are probably the most heterogeneous of the PCNs. The median age at diagnosis is 66 years (27), although this may continue to increase given the association of IPMNs with age. Typical symptoms include abdominal pain (55%), weight loss (45%), jaundice (17%), and acute pancreatitis (15%). Approximately 20% of patients describe a history of symptoms suggestive of acute and/or chronic pancreatitis; however, 25% of patients are asymptomatic (40). This number is likely increasing as well, given the growing frequency of incidentally discovered small BD-IPMNs, which generally do not lead to jaundice, pancreatitis, or abdominal pain.

MDCT: multidetector computed tomography

MRCP: magnetic resonance cholangiopancreatography

DIAGNOSTIC EVALUATION

Radiographic Studies

The diagnostic evaluation of a patient with a cystic lesion of the pancreas depends on high-quality cross-sectional imaging (41). At our institution, we typically employ multidetector computed tomography (MDCT) with thin-section imaging of the pancreas. Whether CT or MRI is used, high-resolution imaging can carefully delineate both the cystic lesion itself and the adjacent pancreatic parenchyma. It is not infrequent for a retention cyst to be present adjacent to an otherwise radiographically occult pancreatic neuroendocrine tumor or PDAC. The presence of septations, mural nodules, and calcifications in the cyst itself can help distinguish between PCNs and help calibrate the risk for malignancy. Thick septations and mural nodules are predictors of malignant behavior among IPMNs. Together, the data suggest that MDCT can correctly predict the malignant behavior of pancreatic cystic lesions in 56–75% of cases (42). Magnetic resonance cholangiopancreatography (MRCP) can also be used to define ductal anatomy and cyst morphology. Where the distinction between MCN and BD-IPMN is difficult, MRCP may be useful in delineating a communication with a ductal side branch, which is characteristic of the latter and always absent in the former.

Frequently, these imaging modalities alone can readily enable diagnosis of the PCN in question, with key features summarized in **Table 1**. SCAs are typically characterized by a spherical, microcystic lesion with central stellate calcification, often with a solid component. Oligocystic

Table 1 Characteristics of common pancreatic cystic neoplasms (adapted from Reference 60 with permission)

Cystic neoplasm	Age (years)	Gender ratio F:M	Gross features	Macroscopic features	Imaging	Cyst fluid findings	Cyst fluid cytology
Serous cystadenoma	61–65	7:3	Variable size Microcystic Stellate scar	Clear cytoplasm Well-defined borders, uniform nuclei Glycogen-rich cells	Microcystic Honeycomb pattern Stellate scar No ductal involvement	Viscosity low CEA low Amylase low	Cuboidal cells Clear glycogen-rich cytoplasm
Mucinous cystic neoplasm	45–55	>10:1	Large size Multilocular Thick walled	Tall columnar mucin-producing epithelial ovarian-type stroma	Macrocystic Body/tail location Does not communicate with duct Peripheral calcifications	Viscosity high CEA high Amylase low	Variable cellularity with columnar cells with or without atypia
Intraductal papillary mucinous neoplasm	65–75	1:1	Variable size Multilocular Involves main or branch ducts	Mucin-producing epithelium with papillae	Macrocystic Ductal involvement	Viscosity high CEA high Amylase high	Variable cellularity with columnar cells with or without atypia
Solid pseudopapillary neoplasm	25	9:1	Irregular cystic cavities with hemorrhage	Solid sheets of variable cells Hyaline globules Neuroendocrine features	Macrocystic Areas of hemorrhage	Bloody necrotic debris	Polygonal cells Eosinophilic cytoplasm
Ductal adenocarcinoma with cystic degeneration	60–80	1:1.3	Mass with cystic degeneration	Ductal adenocarcinoma	Cyst with solid component Ductal dilatation	Bloody necrotic debris	Malignant cells
Pseudocyst	Variable	1:1	Fibrous thick-walled capsule	No epithelial lining	Unilocular Associated with pancreatitis	Viscosity low CEA low CA 19–9 high Amylase high	Inflammatory cells No mucin Epithelial cells

SCAs may be difficult to distinguish from MCNs. MCNs are typically macrocystic and lack mural nodules, and they occur in a characteristic demographic population (i.e., middle-aged women). These neoplasms can be quite large, several centimeters in diameter, and contain peripheral (so-called "eggshell") calcifications.

Main pancreatic duct ectasia and dilatation are characteristic of MD-IPMNs and are not generally seen in SCAs or MCNs. Any focal mass or solid component within an IPMN lesion should raise significant suspicion for malignancy. BD-IPMNs that are multifocal show multiple cystic lesions in the absence of main-duct involvement; however, unifocal BD-IPMNs may be exceedingly difficult to distinguish from MCNs (or oligocystic SCAs), as an MRCP may not clearly show ductal communication. Although single-institution studies suggest MDCT with or without MRI

can classify cystic neoplasms as mucinous or nonmucinous with an accuracy of 82–85% (42, 43), there often remains a need for further testing. Small BD-IPMNs lacking septations, a solid component, or mural nodularity pose the greatest diagnostic challenge, as these can be easily confused with retention cysts, MCNs, small cystic neuroendocrine tumors, or even pseudocysts.

EUS: endoscopic ultrasound

CEA: carcinoembryonic antigen

Endoscopic Ultrasound

As cross-sectional imaging does not reliably establish the diagnosis of a PCN, endoscopic ultrasound (EUS) is frequently employed to assist in the initial evaluation. In our experience, EUS is most commonly employed for lesions of intermediate size (2–4 cm) without concerning features that are radiographically indeterminate. EUS, though operator dependent, is useful because it can frequently demonstrate ductal communication of a pancreatic cyst; however, when prospectively compared to MRI, EUS has been shown to be equivalent in its ability to detect such communications (44). The advantages of EUS lie in its ability to describe cyst morphology, including the presence of mural nodules in the cyst wall, which are correlated with risk of malignancy, and its ability to perform cyst fluid sampling. Prospective evaluation of the ability of MRI/MRCP versus EUS to detect mural nodules has suggested that these modalities are equivalent to each other but superior to CT (31, 45, 46). With the detection of mural nodules limited in part by the presence of mucin globules within cystic lesions, there is not yet evidence to support the superiority of EUS imaging over high-quality MDCT or MRI.

Cyst Fluid Analysis

The additional value of EUS lies largely in the ability to analyze fluid from a cystic lesion of the pancreas. Cyst fluid analysis has been extensively studied as a diagnostic tool in the assessment of PCNs, and a number of markers have been evaluated, including CA 19–9, carcinoembryonic antigen (CEA), CA 15–3, specific MUC proteins, K-ras, and amylase. Amylase is crucial in excluding a pancreatic pseudocyst in patients with a vague history of pancreatitis, with elevations to >250 U/L characteristic of a pseudocyst (47). As MCNs and SCAs have no communication with the pancreatic ductal system, there should be no amylase present.

One of the earliest lines of evidence to support the use of cyst fluid in the diagnosis of PCNs was the landmark study by Brugge et al. (48), in which a cyst fluid CEA >192 ng/ml could accurately predict a mucinous lesion in 79% of cases. Coupled with the presence of extracellular mucin, the positive predictive value of CEA is as high as 85%, far exceeding that of CA 15–3, CA 19–9, and CA 72–4. The absence of CEA in the fluid of SCAs and retention cysts helps exclude these largely benign lesions. CEA is therefore useful in determining a PCN is mucinous; however, the extent of CEA elevation does not serve to distinguish between noninvasive and invasive mucinous lesions.

Cytology on pancreatic cyst fluid is of limited use, as the cellularity is often quite low. The observation of atypical cells in an EUS-FNA (fine-needle aspiration) image of a cystic lesion is a relatively specific (83%) but not sensitive finding. The presence of extracellular mucin or mucin-producing cells in the aspirate would be of use were it not for contamination from the stomach and duodenum that often limits the reliability of these observations. Studies attempting to quantify the accuracy of cyst fluid cytology have largely shown it to be inferior to CEA alone, with accuracy rates of ~50% (47, 48). Key findings in cyst fluid analysis are summarized in **Table 1**.

Molecular Diagnostics

Over the last 10 years, commercially available molecular testing has gained widespread use in the analysis of cyst fluid and the evaluation of PCNs. These tests reflect the increased understanding

of the key molecular events leading to neoplastic cyst formation, including *KRAS* mutation, *p53* mutation, and loss of *p16* and *SMAD4* (49). A multi-institutional prospective analysis—the Pancreatic Cyst DNA Analysis (PANDA) study—showed excellent specificity (96%) but very limited sensitivity (50). Additional single-institution efforts have yet to offer specific clinical circumstances where molecular diagnostics offer a sensitivity greater than that of CEA alone (51, 52).

More recently, activating mutations have been found in *GNAS* in malignant IPMNs, and these mutations have been found to be associated with colloid-type carcinoma. Overall, *GNAS* mutations were found in ~50% of all IPMNs and did not predominate in low-grade, high-grade, or invasive lesions (38). *KRAS* mutations, which frequently are associated with tubular-type invasive IPMNs, appear to identify a largely distinct population. As currently available molecular diagnostic testing relies in part on detection of *KRAS* mutation, the hope is that the addition of *GNAS* testing—which identifies a separate population with IPMNs—could help elevate the sensitivity of these tests. A recent single-institution study that performed cyst fluid analysis for both *GNAS* and *KRAS* in the preoperative setting showed that a mutation in either gene had 98% specificity and 84% sensitivity for the detection of IPMNs (53). Further evaluation is needed to validate these results, but the early data are encouraging.

Next-generation sequencing (NGS) of cyst fluid has been recently evaluated as a tool in the classification of PCNs. One recent study examined 92 cysts in 79 patients for mutations in a panel of 39 cancer-related genes, and found that NGS identified mutations in 60% of cysts (54). Although mutations were largely identified in *KRAS* and *GNAS*, 13% of cysts harbored mutations in other genes in the set, namely *CDKN2A*, *TP53*, and *SMAD4*. In the limited set of patients ($n = 18$) for whom pathologic data were available, NGS was found to have only 75% specificity and 86% sensitivity for the detection of mucinous neoplasia, demonstrating limited superiority over *GNAS* and *KRAS* evaluation alone. Because mutations outside of *GNAS* and *KRAS* in PCNs are quite rare, any role for additional sequencing has yet to be defined.

MANAGEMENT

Serous Cystadenomas

Where the diagnostic evaluation reveals an SCA, whether by typical radiographic features or by cyst fluid analysis revealing the absence of CEA, initial surgical resection is reserved for those patients who are symptomatic. In the absence of symptoms, most centers advocate surveillance consisting of MDCT every 12 months. If there is significant interval growth in the lesion, the concern for malignancy remains low, but the need for more extensive operative intervention generally mandates resection when feasible. SCAs that are asymptomatic and do not grow over time can typically continue on indefinite surveillance, as the risk of malignant transformation (<1%) is exceeded by the mortality of pancreatic resection (~2% in high-volume centers). SCAs can be expected to grow ~0.5 cm year^{-1} with no clear association between size and the rate of growth (55). Therefore, asymptomatic patients can be observed irrespective of lesion size unless the extent of resection is altered.

Mucinous Cystic Neoplasms

Mucinous cystic neoplasms are considered precancerous, and typically resection is recommended. Resection is favored over surveillance because these lesions typically occur in the tail of the pancreas in young women, and resection of a benign lesion should be considered curative. As these lesions are most commonly located in the body and tail of the pancreas, the operation of choice is often a

distal pancreatectomy. At most high-volume centers, a laparoscopic approach is undertaken for all but the largest of lesions. Splenic preservation is frequently possible. In the absence of mucinous cystadenocarcinoma, patients do not require surveillance following surgical resection as the pancreatic remnant has not been found to be at any increased risk of developing pancreatic cancer. Outcomes following resection of noninvasive MCNs are uniformly excellent; however, distant recurrence is common in patients with invasive MCNs, and five-year disease-specific survival is reported to be ~57% (20).

Several groups have recently advocated a selective approach to MCNs, partly because of data suggesting that size ≥4 cm and mural nodularity were found in all invasive MCNs (20). Thus, small lesions without concerning radiographic features could theoretically undergo observation. At our institution, we favor surgical resection for lesions >3 cm with mural nodularity or a solid component, given the extremely low rate of malignancy in any mucinous lesion under 3 cm (55).

Intraductal Papillary Mucinous Neoplasms

Main-duct and mixed-type IPMNs. When cross-sectional imaging and endoscopic evaluation reveal an IPMN with main-duct involvement, operative resection is the primary modality of treatment. This approach is warranted because of the high incidence of high-grade dysplasia or invasive disease (~60%) in this population (56). Because those patients who do not harbor high-grade dysplasia or invasive carcinoma at the time of presentation are likely to progress to malignancy, there is no need for extensive sampling of the cystic lesions involving the main duct. However, the potentiality for invasive carcinoma necessitates considering the resectability of any solid component, as one would for conventional PDAC.

The debate surrounding the management of patients with main-duct or mixed-type IPMNs is not about whether resection is indicated, but rather about the appropriate extent of resection. Generally, the aim of resection is to remove the high-risk disease while preserving endocrine function of the pancreas when possible. For IPMNs with limited main-duct involvement, the operation of choice is therefore a partial pancreatectomy (either pancreaticoduodenectomy or distal pancreatectomy + splenectomy) that removes all of the radiographically involved ducts. A frozen section of the pancreatic margin should be evaluated intraoperatively to confirm that no high-grade dysplasia is present at the site of transection. Studies have found the presence of high-grade dysplasia to be a significant predictor of recurrence in the remaining pancreas (57).

Where a diagnosis of invasive carcinoma is made, usually by preoperative biopsy of a superimposed solid component, a partial pancreatectomy should again be the operation of choice, even if ductal dilatation diffusely involves the entire gland. Pancreatectomy should be planned so as to remove the invasive disease and not necessarily all of the IPMN. The presence of invasive carcinoma in the resected pancreas diminishes the need to clear all premalignant disease in the remnant gland; this is largely because long-term survival depends less on progression of IPMN in the remnant and more on recurrence of the index carcinoma at distant sites. The need for a frozen section free of high-grade dysplasia is therefore diminished in this setting. Additionally, total pancreatectomy should be avoided when the diagnostic evaluation suggests an invasive cancer in the setting of IPMN.

The management of MD-IPMN involving the entire gland without an invasive component is less clear. The presence of diffuse main-duct dilatation itself does not mean the whole gland is involved—frequently, proximal pancreatic ductal obstruction by a clinically inapparent lesion may dilate the upstream pancreatic duct. In this clinical scenario, there is no way to determine if a proximal or distal pancreatectomy is preferred. In these carefully identified patients, a total pancreatectomy may be an option, but its benefit must be balanced with the increased morbidity and

mortality of this operation and quality-of-life issues related to diabetes mellitus. In our institution, we favor partial pancreatectomy whenever possible, with the understanding that a completion pancreatectomy may be necessitated by progression of disease in the remnant gland.

Branch-duct IPMNs. As discussed above, BD-IPMNs carry a lower risk of malignancy than do MD- or mixed-type IPMNs. High-grade dysplasia or invasive disease is reported in 12–30% of patients undergoing resection (27, 30). However, several features of BD-IPMNs correlate with the presence of malignancy; these include size >3 cm, mural nodules, solid component, septation, or symptomatology. These factors serve as the basis of the Sendai criteria for operative resection of BD-IPMNs (56, 58). Most centers have adopted this selective approach to resection of BD-IPMNs, with partial pancreatectomy performed when resection is appropriate.

Retrospective studies indicate that these criteria are highly sensitive but are limited in specificity, such that many noninvasive and low-risk lesions continue to be resected (30). In a large series at our institution of nearly 1,500 patients, among those patients selected for surveillance who subsequently underwent operative resection for interval development of symptoms or growth in the cystic lesion, only 11% were found to have malignancy, representing <2% of all those initially selected for surveillance (59). This risk of malignancy was equivalent to the risk of mortality from pancreatic resection, suggesting that nonoperative management is indeed appropriate in this carefully selected cohort. At our institution, we have therefore consolidated our management of all mucinous lesions, whether they are MCNs or IPMNs, selecting only those patients with lesion size >3 cm, mural nodules, solid component, or symptomatology for initial resection.

Nonoperative management in the remaining patients with mucinous lesions consists of close surveillance, with high-quality cross-sectional imaging every six months for two years and annually thereafter. Close attention is paid to the entire pancreas, as 30% of malignancies identified in patients undergoing initial surveillance are remote from the index cyst (28). Resection is typically recommended if there is development of concerning radiographic features or symptoms.

CONCLUSIONS

Pancreatic cystic neoplasms are a diverse clinicopathologic entity of growing importance owing to their increased detection on cross-sectional imaging. Clinical presentation is highly variable, and the diagnostic evaluation is limited by an ongoing inability to distinguish benign lesions from those with malignant potential. Current management consists of the use of high-quality cross-sectional imaging with judicious use of EUS and cyst fluid CEA analysis when needed. Surgical intervention remains the mainstay of treatment, with continued refinement of selection criteria based on the risk of malignancy in the resected and remnant gland. As our understanding of the molecular features of MCNs, SCAs, and IPMNs continues to grow, identification of those patients appropriate for surveillance or operative resection should become increasingly clear.

DISCLOSURE STATEMENT

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