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REVIEW

Clinical approach to incidental pancreatic cysts

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Abstract

The approach to incidentally noted pancreatic cysts is constantly evolving. While surgical resection is indicated for malignant or higher risk cysts, correctly identifying these highest risk pancreatic cystic lesions remains difficult. Using parameters including cyst size, presence of solid components, and pancreatic duct involvement, the 2012 International Association of Pancreatology (IAP) and the 2015 American Gastroenterological Association (AGA) guidelines have sought to identify the higher risk patients who would benefit from further evaluation using endoscopic ultrasound (EUS). Not only can EUS help further assess the presence of solid component and nodules, but also fine needle aspiration of cyst fluid aids in diagnosis by obtaining cellular, molecular, and genetic data. The impact of new endoscopic innovations with novel methods of direct visualization including confocal endomicroscopy require further validation. This review also highlights the differences between the 2012 IAP and 2015 AGA guidelines, which include the thresholds for sending patients for EUS and surgery and methods, interval, and duration of surveillance for unresected cysts.

Key words: Pancreatic cysts; Intraductal papillary mucinous neoplasms; Pancreatic cystic neoplasms; Endoscopic ultrasound; Mucinous cystic neoplasm; Serous cystadenoma

Core tip: The approach to incidentally noted pancreatic cysts is constantly evolving. While surgical resection is indicated for malignant or higher risk cysts, correctly identifying these highest risk pancreatic cystic lesions remains difficult. Using parameters including cyst size, presence of solid components, and pancreatic duct involvement, the 2012 International Association of Pancreatology and the 2015 American Gastroenterological Association guidelines have sought to identify the higher risk patients who would benefit from further evaluation using endoscopic ultrasound.

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INTRODUCTION

Pancreatic cysts are identified in up to 20% of magnetic resonance imaging (MRI) and 3% of computed tomography (CT) scans[1,2]. The greater detection of incidental pancreatic cysts is likely in part due to increasing use of CT and MRI from less than 10 to over 30 per 100 persons in recent years and improved resolution of imaging studies[3]. Not only have more incidental cysts been discovered over the past decade, but when identified, they are also smaller[4]. Given the malignant potential of some pancreatic cystic lesions, these incidental findings should be considered carefully. In fact, incidental pancreatic cysts on CT or MRI demonstrated a hazard ratio (HR) of 1.40 [confidence interval (CI): 1.13-1.74] for mortality in patients less than 65 years old compared with a HR of 0.97 in those without cysts; pancreatic adenocarcinoma (not including non-adenocarcinoma neoplasms) conferred a hazard ratio of 3.0[5]. A recent American Gastroenterological Association (AGA) technical review reported the estimated incident risk of malignancy of incidental pancreatic cysts at 0.24% per year with a prevalent malignant risk of 0.25% at the time of cyst diagnosis[6].

Cystic lesions in the pancreas can range from entirely non-neoplastic (*e.g.*, pseudocysts, retention cysts, benign epithelial cysts, mucinous non-neoplastic cysts, lymphoepithelial cysts) to necrotic degeneration of solid tumors. This review focuses on pancreatic cystic neoplasms, some of which carry malignant potential. Most pancreatic cystic neoplasms are asymptomatic though some lesions may present with pancreatitis [especially if there is invasion into or mucus plugging of the pancreatic duct as with intraductal papillary mucinous neoplasms (IPMN)], abdominal pain, nausea, vomiting, and/or jaundice.

The 2000 WHO histological classification of pancreatic cystic neoplasms outlines four general categories: serous cystic tumor, mucinous cystic neoplasm (MCN), IPMN, and solid pseudopapillary neoplasm (SPEN)[7]. Serous cystic tumors include serous cystadenomas (SCAs), which often have a microcystic or honeycomb appearance on imaging with the pathognomonic central scar or sunburst calcification occurring in up to 20% of these lesions (Figure 1). Serous cystadenomas consist of cuboidal epithelial cells that stain positive for glycogen (Figure 2), and more importantly only very rarely carry malignant potential. CT is only 23% accurate, but diffusion-weighted MRI has 100% sensitivity and 97% specificity in differentiating SCA from mucinous cysts[8,9].

On the other hand, MCN and IPMN are premalignant mucinous lesions. Main duct IPMNs (MD-IPMN), defined as diffuse or segmental dilatation of the main pancreatic duct (MPD) to > 5 mm from a cystic tumor producing mucus within the duct (Figure 3), has a reported 62% frequency of malignancy[10]. Branch duct IPMNs (BD-IPMN) are cysts arising within the side branches of the pancreatic duct with a nondilated MPD (Figure 4) and carry up to 26% frequency of malignancy[10]. The recent AGA review reported an approximately 3% risk of developing malignancy during surveillance of BD-IPMN[6]. MD-IPMNs more commonly present as the intestinal histologic type whereas BD-IPMNs demonstrate more gastric differentiation[11]. Mixed type IPMNs have features of

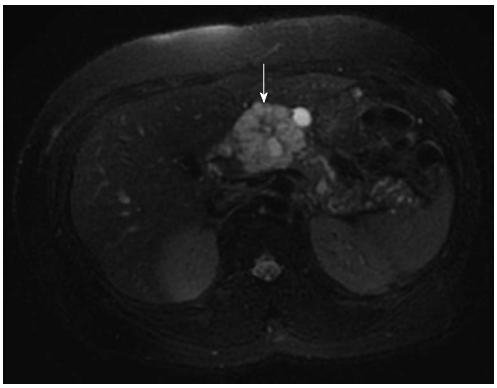

Figure 1 Magnetic resonance imaging of microcystic serous cystadenoma (arrow) in body of pancreas.

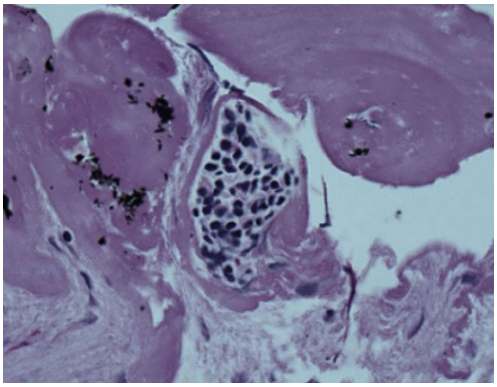

Figure 2 Cytology of serous cystadenoma with cuboidal epithelial cells containing glycogen staining for periodic acid-Schiff.

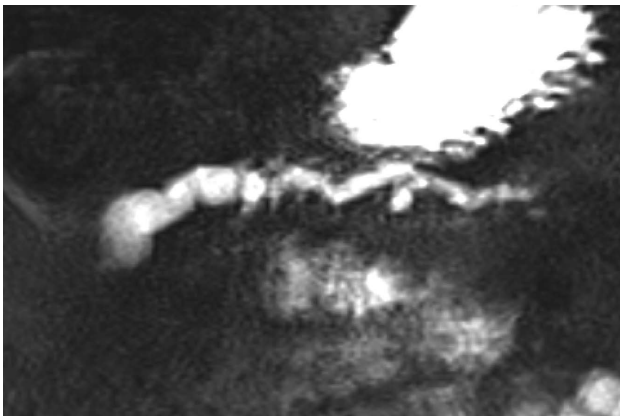

Figure 3 Magnetic resonance cholangiopancreatography of main duct intraductal papillary mucinous neoplasms.

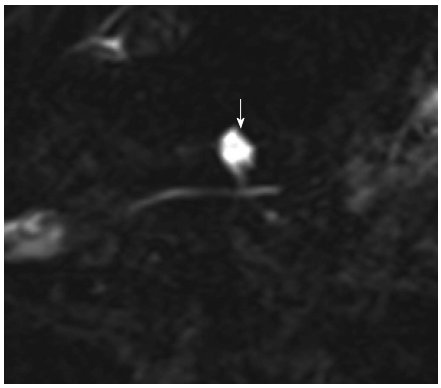

Figure 4 Magnetic resonance cholangiopancreatography of branch duct intraductal papillary mucinous neoplasms (arrow) communicating with nondilated main pancreatic duct.

both MD-IPMN and BD-IPMN with approximately 20% to 30% of BD-IPMN ultimately proven to be mixed type IPMN on surgical pathology[12]. The malignant potential of mixed type IPMN is more comparable to MD-IPMN although different subtypes of mixed type IPMN may carry different malignant potential[13]. Risk factors for malignant IPMNs include solid component, main pancreatic duct dilation > 3 cm, cyst size > 3 cm, and nodule[6]. MCNs are also mucinous cysts, but are defined by the presence of ovarian-like stroma and thus almost exclusively occur in women. On imaging, MCNs are usually characterized by unilocular cysts in the body and/or tail (Figure 5). Approximately 15% of resected MCNs contain invasive cancer with risk factors for malignancy including size > 6 cm and nodule[6]. Less than 0.4% of MCNs that are smaller than 3 cm without a nodule harbor high-grade dysplasia or invasive cancer[14]. Solid pseudopapillary neoplasms also carry malignant potential with characteristic pseudopapillae and cystic spaces containing hemorrhage and cholesterol clefts in myxoid stroma alternating with solid tissue. Thus these lesions appear as solid and cystic masses, typically in young women (Figure 6).

APPROACHING THE INCIDENTAL PANCREATIC CYST

The key questions to consider when evaluating incidental pancreatic cysts include the following: (1) what type of cyst is it as malignant potential varies with different cysts. In particular, is the cyst mucinous or nonmucinous given the malignant potential of mucinous cysts; (2) is the cyst currently malignant; and (3) if not, what is the malignant potential of the cyst[15,16]? The latter issue is most relevant to young, surgically fit patients with long life expectancies while the risk of prevalent cancer is most concerning to the elderly or those with multiple comorbidities with more limited longevity. Defining the best approach to managing incidental pancreatic cysts could potentially spare patients unnecessary testing, radiation, and surgery and also confer global cost benefit. Currently, the diagnosis of pancreatic cystic neoplasms is based upon both radiologic imaging and cyst fluid analyses. All patients with pancreatic cysts should undergo a good quality MRI of the pancreas with magnetic resonance cholangiopancreatography in 1.5 or 3 tesla with T1, T2, 3-D, fat-saturated, gradient-echo T1 gadolinium-enhanced sequences[10,17]. MRI is most accurate for diagnosing malignant and mucinous cysts (76%-91% and 80%, respectively) while it is only 50% accurate for diagnosing the specific type of cyst[16,18]. If MRI cannot be performed, pancreatic protocol CT with contrast-enhanced images during the pancreatic and portal venous phases allowing 3D analysis should be obtained. The findings on MRI or CT will guide the decision to pursue endoscopic ultrasound-guided fine needle aspiration (EUS-FNA), surgery, or surveillance.

To date three consensus guidelines have been proposed to manage pancreatic cystic lesions beginning with the original 2006 Sendai guideline which was revised in 2012 by the International Association of Pancreatology (IAP) in Fukuoka and the recent AGA guideline (Table 1)[10,19,20]. The Sendai guideline was updated in 2012 to improve its positive predictive value while maintaining its negative predictive value, however, the revised guideline still suffers from low positive predictive value (21%-63%)[21,22]. The AGA guideline increased the threshold for sending a patient

Table 1 Key differences between 2012 International Association of Pancreatology and 2015 American Gastroenterological Association guidelines for the management of pancreatic cysts[10,20]

Specifics of guidelines	2012 IAP	2015 AGA
Patient population targeted by guideline	Suspected MCN and IPMN	All incidental pancreatic cysts
Recommended imaging modality	Pancreatic protocol CT or MRI	MRI pancreas with MRCP
Threshold for recommending EUS and/or surgery	1 risk factor	At least 2 risk factors
Surveillance recommendations in unresected cysts	Frequent surveillance based on cyst size	MRI in 1 yr and then every 2 yr
Stopping surveillance	No explicit recommendation to stop in unresected cysts Following resection of serous cystadenoma and MCN without invasive cancer	After 5 yr of stable unresected cyst without development of high risk features Surgically unfit patients Select resected cysts including BD-IPMN with no, low or moderate-grade dysplasia

IAP: International Association of Pancreatology; AGA: American Gastroenterological Association; MRI: Magnetic resonance imaging; EUS: Endoscopic ultrasound; MCN: Mucinous cystic neoplasm; IPMN: Intraductal papillary mucinous neoplasms; MRCP: Magnetic resonance cholangiopancreatography; CT: Computed tomography.

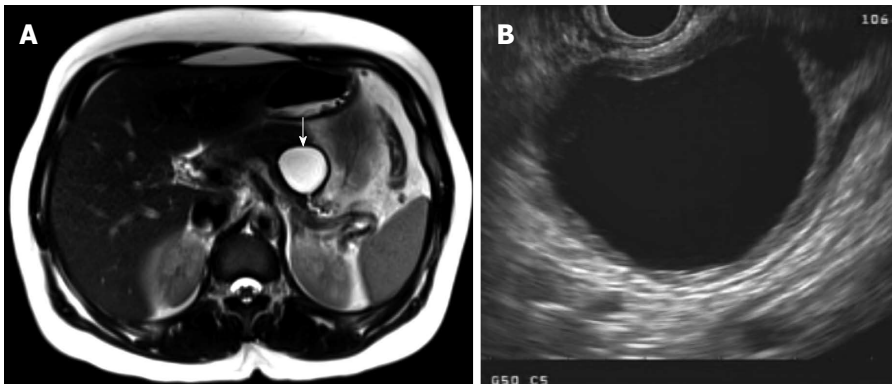

Figure 5 Mucinous cystic neoplasm seen on magnetic resonance imaging (A, arrow pointing to mucinous cystic neoplasm) and endoscopic ultrasound (B), with unilocular appearance and thick wall.

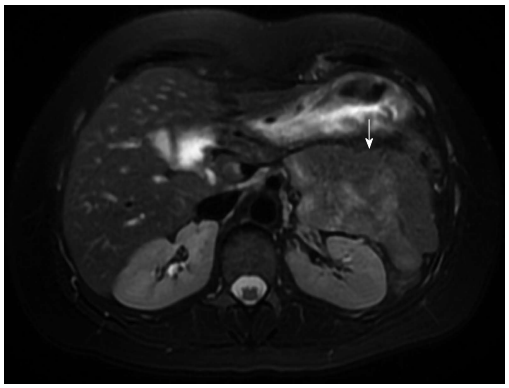

Figure 6 Magnetic resonance imaging of solid pseudopapillary neoplasm (arrow).

to EUS-FNA as well as surgery from one to at least two risk factors. While this may be expected to decrease the unnecessary resection of benign, albeit larger cysts, the impact on the negative predictive value remains to be determined. In addition, while the IAP guideline supports surveillance intervals based on cyst size without an explicit recommendation to stop surveillance, the AGA guideline endorses a simplified surveillance regimen for 5 years followed by stopping if the cyst remains stable without developing any high risk features and in nonsurgical candidates. The impact of these recommendations to stop surveillance after 5 years in stable cysts as well as a "one size fits all" approach to surveillance intervals is controversial and remains to be evaluated.

ENDOSCOPIC DIAGNOSTIC MODALITIES

EUS

EUS may allow diagnosis of malignant cysts and identification of cysts at high risk for becoming malignant. The IAP and AGA guidelines offer guidance on whom to select for EUS-FNA. The 2012 IAP guideline for suspected MCN and IPMN recommends EUS for patients with any one of these clinical or radiologic "worrisome features" (pancreatitis, size ⩾ 3 cm, thickened enhanced cyst wall, nodule, MPD 5-9 mm, abrupt change in MPD diameter with upstream parenchymal atrophy, or lymphadenopathy). The goal of EUS would be to confirm presence of nodules, detect features of main duct involvement (thickened wall, intraductal mucin or nodule), and identify suspicious or positive cytology[10]. On the other hand, the AGA guideline suggests EUS-FNA only for cysts with two of the following high risk imaging features (size ⩾ 3 cm, solid component, or dilated MPD) or if significant changes develop in the cyst during surveillance[20]. However, it seems reasonable to perform EUS-FNA in certain situations even with a single risk factor such as a solid component or significantly dilated MPD given the relatively high risk of malignancy associated with these features. Furthermore, the implications of the greater dependence on MRI findings in the AGA guideline need further evaluation as the interobserver agreement between EUS and MRI has been reported as poor to fair[23]. EUS-FNA is also helpful in differentiating mucinous from nonmucinous cysts when imaging is indeterminate and in diagnosing suspected cystic neuroendocrine tumors and SPENs[18].

In addition to identification of nodules or ductal involvement, EUS also allows further evaluation of cyst size, septations, cyst contour (lobular *vs* smooth), wall thickness, communication of cyst with the pancreatic duct, and pancreatic duct caliber (< 5 mm defined as normal, 5-9 mm considered a "worrisome feature" and ⩾ 10 mm a "high-risk stigma" per IAP)[10,18]. Endoscopists can predict the presence of nodules and mucus by comparing the echogenicity relative to adjacent tissue and assessing the mobility of structures with patient repositioning and probing with the needle[24]. Nodules appear as iso- or hypoechoic structures without a smooth edge or hyperechoic rim compared with mucus which have a smooth-edge hyperechoic rim around a hypoechoic center. EUS can further aid in diagnosis with direct visualization using Spyglass technology (Boston Scientific, Marlborough, MA) and needle confocal laser endomicroscopy (Mauna Kea Technologies, Paris,

Table 2 Recommended cyst fluid studies[28,33,34,40]

Cyst fluid test	Test characteristics	Diagnosis
String sign ≥ 1 cm, ≥ 1 s	95% specificity, 94% positive predictive value	Mucinous
Cyst fluid cytology	63% sensitivity	Mucinous or malignant
Cyst wall cytology	29% increased diagnostic yield	Mucinous or malignant
CEA > 192 ng/mL	75% sensitivity, 84% specificity	Mucinous
CEA < 5 ng/mL	50% sensitivity, 95% specificity	Serous cystadenoma, pseudocyst, cystic neuroendocrine tumor
Amylase < 250 U/L	44% sensitivity, 98% specificity	Excludes pseudocyst

France), which involves passing a probe through a 19 gauge needle to obtain real-time microscopic imaging of the cyst wall[25,26]. Identifying a vascular network pattern representing subepithelial capillary vascularization using endomicroscopy could help discern a serous cystadenoma with reported accuracy, sensitivity, specificity, positive predictive value, and negative predictive value of 87%, 69%, 100%, 100%, 82% respectively[25]. Further validation studies are necessary to assess the value of these diagnostic tools.

The utility of EUS was suggested by a study of 154 surgically resected cysts, where the sensitivity for neoplastic disease was 76% with EUS, as compared to 48% and 34% for CT and MRI, respectively. However, there may be bias toward EUS (with or without FNA) given that only surgically resected cysts were studied[27]. Some limitations to EUS imaging alone include lower sensitivity, specificity, and accuracy (56%, 45%, 51%, respectively) for the diagnosis of mucinous cysts[28]. Moreover, among expert endosonographers there remains wide variation in interobserver agreement of neoplastic features[29,30]. Agreement is reportedly best for nodules, moderate for solid component and cystic communication with PD, and fair for suspicion of malignancy[29].

Cyst fluid analysis

EUS allows sampling of cyst fluid from cysts greater than 1 cm typically using a 22 or 25 gauge needle, though larger bore 19 gauge needles may be useful for bigger cysts with thicker fluid. FNA is performed with the goal of aspirating the cyst to complete collapse and sampling solid components or nodules. Although EUS-FNA of pancreatic cysts has proven to be safe, a single dose of an intravenous fluoroquinolone antibiotic is recommended with a short course of oral antibiotics thereafter for prophylaxis[31,32].

Before sending fluid for analysis (Table 2), it should be evaluated for string sign, defined as cyst fluid extending from the tip of the needle for at least 1 cm and 1 second. This can also be assessed by placing a drop of fluid between two fingers and separating them. The string sign is highly specific (95%) for a mucinous cyst[33].

Cyst fluid for cytology typically has low diagnostic yield with less than 50% sensitivity for mucinous lesions, however, it is helpful when positive for a specific diagnosis. Cytology is useful if malignancy is detected with its high positive predictive value and 90% specificity. Cyst fluid cytology is only 60% sensitive for malignancy[20,34]. Fluid cytology carries 70%-75% accuracy for SPEN and 71% diagnostic yield for cystic neuroendocrine tumors[35-38]. Cyst fluid from a pancreatic lymphangioma has a characteristic chylous appearance, elevated triglyceride levels, and numerous benign lymphocytes[39]. Improved diagnostic yield for mucinous or malignant cysts by 29% has been reported with cyst wall cytology, obtained by repeatedly passing the needle back and forth through the collapsed cyst wall[40]. Therefore, cyst wall cytology may be preferred over fluid alone, unless copious fluid is available for cytology.

Tumor markers from cyst aspirates may help diagnose certain pancreatic cystic neoplasms. While carcinoembryonic antigen (CEA) is not predictive of malignancy, it remains the most widely used and accurate tumor marker for differentiating mucinous from non-mucinous pancreatic cysts[41]. However, it does not distinguish IPMN from MCN. The threshold of CEA elevation to suggest a mucinous lesion is debated, but CEA values greater than 192 ng/mL confer a 73% sensitivity and 84% specificity for mucinous cysts[28]. A low CEA of < 5 ng/mL yields 50% sensitivity and 95% specificity for SCA, pseudocyst, or cystic neuroendocrine tumor[42]. An existent challenge is that CEA assays are validated for serum but not for cyst fluid, and there could be significant CEA variation among different assays[43]. Other markers such as amylase is helpful in excluding pseudocysts if less than 250 U/L[42]. DNA analysis of cyst aspirates may be helpful especially when less than 0.5cc of fluid is available as this precludes the usual chemistry and tumor marker analyses. Identification of KRAS mutations has 54% sensitivity and 100% specificity for mucinous differentiation in a study of 142 surgically resected cysts[44]. The presence of both elevated CEA and KRAS mutation increased sensitivity to 83% but specificity dropped to 85% for mucinous cysts[45]. Presence of both KRAS mutations and loss of heterozygosity mutations is highly specific (94%-96%) for malignant cysts with 25%-37% sensitivity[21,46,47]. The addition of DNA analysis does not appear to improve diagnostic yield for malignant cysts beyond the 2012 IAP guideline[47].

Given that most cyst fluid markers suffer from poor sensitivity, tremendous efforts in translational research have attempted to identify more accurate biomarkers. Of the numerous DNA, RNA, and protein-based studies, guanine nucleotide binding protein alpha stimulating activity polypeptide 1 (GNAS) is one of the more promising. Mutation of either KRAS or GNAS was found in 95% of IPMNs[48]. Similarly, targeted sequencing also showed 96% of IPMNs having

either the KRAS or GNAS mutation, with frequency of either at 79% and 50% of lesions, respectively[49]. GNAS mutations have been associated with IPMN in not only cyst fluid, but also tissue pathology and pancreatic juice[50]. Our own pathology-based study found GNAS mutations in 42% of IPMNs compared with 10% in SCA and none in MCN and pancreatic ductal adenocarcinoma[21]. Whole-exome sequencing of mucinous pancreatic cysts has also found that IPMNs are more commonly characterized by mutations in *KRAS*, *GNAS*, *RNF43*, *TP53*, *p16/CDKN2A* and *SMAD4* genes whereas MCNs demonstrate *KRAS*, *RNF43*, *TP53*, *p16/CDKN2A* and *SMAD4* gene mutation profile[48]. Similarly, microRNA (miRNA) profiles have been explored to differentiate mucinous from non-mucinous lesions and MCN from BD-IPMN with a reported 85%-100% sensitivity and 100% specificity[51].

More investigational methods to interpret cyst fluid include a proteomic approach, analyzing the mucin for certain glycoproteins to discern premalignant from malignant lesions. Some have argued superiority of this method compared to CEA and cytology to detect malignant lesions, and expression of certain markers has been studied to define specific IPMN histologic subtypes (gastric, intestinal, or pancreaticobiliary) and ascertain the degree of dysplasia[52,53]. Higher expression of specific cytokines such as IL-1beta, IL-5, and IL-8 has also been linked to high-grade dysplasia or malignancy[54]. Various cytokines may help differentiate mixed type from BD-IPMN as well as BD-IPMN from inflammatory cysts[55,56]. Elevated cyst fluid vascular endothelial growth factor-A (VEGF-A) > 8500 pg/mL has 100% sensitivity and 97% specificity for SCA[57]. In addition, a reduction in certain metabolites such as glucose and kynurenine has been seen in mucinous as opposed to non-mucinous cysts[58]. While all these biomarkers appear promising, they require further validation as well as delineation of their role within the currently accepted cyst fluid markers. A recent study promoted a panel of DNA markers and assessment of aneuploidy as yielding 100% sensitivity and 91%-100% specificity for serous cystadenoma and SPEN while these markers were 76%-100% sensitive and 75%-97% specific for mucinous cysts[59]. A composite of clinical and molecular markers improved sensitivity and specificity for MCN and IPMN to 90%-94% and 84%-97%, respectively. Despite promising results, larger prospective histology-based validation studies are necessary before clinical application.

SURGICAL RESECTION

The recommendation to resect certain pancreatic cystic neoplasms largely rests on the malignant potential of the lesion. Serous cystadenomas carry the least malignant potential (1% rate of malignancy) and therefore are not recommended to undergo resection unless symptomatic or large[60,61]. How large remains to be clarified with some suggesting a 4 cm threshold[16]. SPENs are considered premalignant with 2%-15% incidence of local invasion or metastatic disease[36]. Although there are no concrete guidelines about SPENs, given their malignant potential and favorable post-resection outcomes, referral for surgical resection is also appropriate. MCNs have invasive cancer in 15% of surgically resected cysts with 3 and 5 year survival rates of 44% and 26%, respectively[6,62]. MD-IPMN and mixed-type IPMN have the greatest malignant potential of all pancreatic cystic neoplasms at 40%-70%. As a result, the 2012 IAP guidelines recommend surgical resection for MCNs and MD-IPMNs. Resection is recommended for BD-IPMN if any one of the "high-risk stigmata" or "worrisome features" is present. High-risk stigmata include: obstructive jaundice with a cyst in the head of the pancreas, a solid component, or MPD $\geqslant$ 1 cm[10]. In addition, presence of nodules, features of main duct involvement (thickened wall, intraductal mucin or nodule), and suspicious or positive cytology on EUS-FNA are also deemed indications for surgery[10].

The AGA technical review identified the following as the greatest risk factors for malignancy in incidental pancreatic cysts: solid component with the highest odds ratio (OR) 7.7, cyst size > 3 cm (OR = 3), and dilated MPD (OR = 2.4); presence of a solid component in the cyst was also the most specific feature with a specificity of 91%[20,63]. One caveat is that the included studies used various definitions for dilated MPD ranging from $\geqslant$ 3 mm to > 6 mm, and others suggested that the degree of MPD dilation may portend varying risks of malignancy[64]. Regarding cyst size, a study including 563 resected and radiologically diagnosed BD-IPMN noted that 18% of cysts > 3 cm had high-grade dysplasia or invasive cancer, while no malignancy was detected in cysts < 2 cm and no high-grade dysplasia was noted in lesions < 1 cm[65]. The assessment of cyst size and nodules may vary depending on the imaging modality[66]. EUS was more sensitive for detecting nodules than CT (75% *vs* 24%, respectively) although this disparity is expected to diminish when compared with MRI[24].

In the AGA review, invasive malignancy was present in 15% of resected pancreatic cyst specimens while prevalence of high-grade dysplasia was not evaluated[6]. Of surgically resected IPMNs, 25% had invasive malignancy while 42% carried either high-grade dysplasia and/or invasive malignancy[6]. Whether resecting benign lesions or IPMN with low-grade dysplasia in 58% of cases is acceptable can be debated, but to improve the positive predictive value for resecting potentially malignant pancreatic cysts, the AGA guideline increased the threshold for surgery to presence of both solid component and dilated MPD and/or concerning features on EUS-FNA[20]. This will likely be most helpful when assessing the risk and benefits of surgery in patients who are elderly and/or with multiple comorbidities. In young healthy patients with longer life expectancies, the more relevant issue

Table 3 Recommended surveillance modalities and intervals for unresected pancreatic cysts according to 2012 International Association of Pancreatology guideline[10]

Size	Modality	Interval
< 1 cm	CT/MRI	2-3 yr
1-2 cm	CT/MRI	1 yr (lengthen if no change after 2 yr)
2-3 cm	EUS, MRI	EUS in 3-6 mo, then lengthen interval thereafter alternating MRI and EUS
> 3 cm	EUS, MRI	Alternate MRI and EUS every 3-6 mo

MRI: Magnetic resonance imaging; EUS: Endoscopic ultrasound; CT: Computed tomography.

is the risk of malignancy over their lifetime, which may require adjusting the threshold for sending a patient to surgery. Any decision to pursue surgical resection should take into account not only cyst characteristics but also the patient's comorbidities and other risks associated with surgery. The ongoing challenge remains identifying signs predictive of malignancy to allow early referral for resection in the hope of improving long-term survival while sparing low risk patients the morbidity and mortality of pancreatic surgery.

The decision of how much pancreas to resect must take into consideration the type of lesion in relation to the patient's life expectancy from their other medical conditions. This is of particular relevance to patients with MD-IPMN where before proceeding with total pancreatectomy, it is paramount to consider how well the patient will tolerate brittle diabetes or exocrine insufficiency postoperatively. The goal of surgery is to resect the entire tumor with negative margins although whether this includes low and moderate-grade dysplasia is debated[10]. The extent of disease or invasion can be assessed intraoperatively with frozen sections as well as novel preoperative methods including pancreatoscopy, intraductal ultrasound (IDUS), or irrigation cytology (aspiration of saline injected into pancreatic duct). Irrigation cytology was shown in 17 patients with IPMNs to have 100% sensitivity and specificity for malignancy[62]. Small Japanese case series have suggested the utility of pancreatoscopy with IDUS in mapping IPMNs preoperatively[67-69].

SURVEILLANCE

Patients with low risk for malignancy and following resection of certain cysts should undergo surveillance. This includes patients with cysts < 3 cm, nondilated MPD, and no nodule, solid component, or concerning EUS-FNA findings. MRI is the preferred imaging modality over CT for surveillance to reduce radiation exposure. Even without gadolinium, non-contrast MRI scans have demonstrated similar efficacy to contrast-enhanced MRI in discerning benign from malignant disease[70]. Surveillance is recommended at various intervals for unresected pancreatic cystic neoplasms depending on size by the 2012 IAP guideline (Table 3)[10,20]. The interval of surveillance can be lengthened if there are no concerning features or changes found over repeated testing. According to the AGA guideline, surveillance recommendations were simplified to repeating MRI in 1 year followed by every 2 years thereafter for 5 years if no changes were demonstrated in the cyst[20]. While the IAP guideline does not explicitly recommend stopping surveillance, the AGA guideline supports this in surgically unfit patients and after 5 years of surveillance without any significant changes to the cyst[10,20]. This is perhaps the most controversial aspect of the AGA guideline which requires further evaluation.

After surgical resection of SCA or MCN without invasive features, surveillance is not necessary as resection is considered curative. This is because no recurrence of MCN without invasive cancer was noted in patients after nearly 5 years[62]. For IPMNs with negative surgical margins, the 2012 IAP guideline recommends repeat imaging at 2 and 5 years after resection and every 6 mo if dysplasia was noted[10]. Those with resected invasive cancer should continue surveillance as per patients with pancreatic ductal adenocarcinoma. The AGA guideline supports postoperative surveillance only following resection of high-grade dysplasia or invasive cancer with MRI every 2 years[20]. A concern with this recommendation is that early recurrences, especially in patients with invasive cancer, may be missed.

Several questions remain with regards to surveillance including the optimal surveillance interval and duration in unresected cysts. How to perform surveillance of IPMNs in those at higher risk with a family history of pancreatic adenocarcinoma remains unclear. Moreover, the need to screen for extrapancreatic malignancies in those with IPMNs is also not fully defined.

CONCLUSION

Approaching the incidental pancreatic cyst begins with performing good quality MRI imaging of the pancreas to identify malignant and mucinous cysts. Both the 2012 IAP and the 2015 AGA guidelines strive to identify patients with higher risk cysts for EUS-FNA and surgical resection. Based on the relatively low risk of prevalent and incident malignancy in these incidental pancreatic cysts, the AGA guideline overall raises the threshold for sending patients to further procedures, increases the surveillance interval, and even proposes stopping surveillance. While the huge economic burden of providing serial MRI imaging to all patients with pancreatic cysts must be appreciated, this also needs to be weighed against the individual patient. Further high quality studies are necessary to uncover better diagnostic markers, to improve risk stratification of patients, and to evaluate the impact of the AGA guideline.

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