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Current Management of Intraductal Papillary Mucinous Neoplasms

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KEYWORDS
• Pancreas • Pancreatic cystic neoplasms • Intraductal papillary mucinous neoplasms

KEY POINTS

- Pancreatic cystic neoplasms represent a diverse group of lesions, with intraductal papillary mucinous neoplasms (IPMNs) being the most prevalent.
- For most patients diagnosed with a suspected branch-duct IPMN, the primary approach is surveillance.
- Deciding on surgical intervention primarily relies on clinical and radiological findings though there is an evolving role for molecular markers indicating malignant progression.
- When surgery is necessary, the recommended procedure is a standard pancreatic resection with lymphadenectomy. Intraoperative frozen section may be performed for margin assessment of main duct tumors.

CLASSIFICATION

Pancreatic cystic neoplasms (PCNs) are a heterogeneous group of lesions with varying biological behaviors. The prevalence of PCNs in the general population ranges between 3% and 75% [1]. Outside of rare cystic neuroendocrine tumors and pancreatic pseudocysts, PCNs can be divided into serous histologies, including serous cystadenoma that is invariably benign, and premalignant mucinous histologies that include intraductal papillary mucinous neoplasms (IPMNs) and mucinous cystic neoplasms (MCNs). IPMNs and MCNs exhibit a spectrum of dysplasia ranging from low-grade dysplasia (LGD) to high-grade dysplasia (HGD) and invasive cancer (IC). IPMN, the most prevalent PCN, affects approximately 2% of the general population, with its prevalence increasing to 12% among individuals over 80 years of age [2]. Significantly higher incidences have been reported from autopsy studies. They are defined as grossly visible, predominantly papillary, noninvasive mucin-producing epithelial neoplasms arising in the main pancreatic duct (MPD) or branch ducts [3]. Both IPMNs and MCNs with HGD are considered precursors of pancreatic cancer, along with PanIN-3. However, while PanIN lesions are not detectable through radiological means, the diagnosis and surveillance of PCNs, particularly IPMNs, provide an opportunity for early detection and potential pancreatic cancer prevention.

IPMNs can be classified based on their radiological appearance and the involvement of the MPD into (1) branch-duct IPMN (BD-IPMN), when there is no involvement of the MPD; (2) main-duct IPMN (MD-IPMN), when it involves the MPD; and (3) mixed-type IPMN (MT-IPMN) as a combination of both (Fig. 1A–D). Beyond their radiological appearance, further discussed in the following sections, the involvement of the MPD is associated with a higher risk of a diagnosis of HGD or IC and therefore warrants a different clinical management. Additionally, IPMNs are divided into 3 distinct histologic subtypes [4]:

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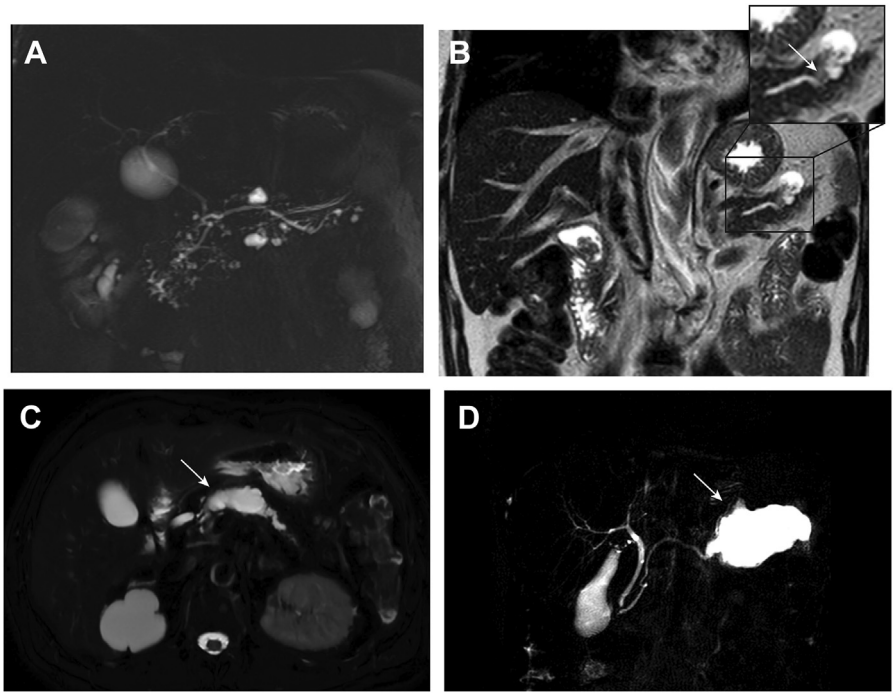

FIG. 1 (**A**) An MRCP image displaying a multifocal BD-IPMN without worrisome features or high-risk stigmata. (**B**) T2 MRI image of a BD-IPMN located in the pancreatic tail, connected to the MPD. (**C**) T2 image depicting an MD-IPMN in the pancreatic body. (**D**) Image of a large MD-IPMN located in the pancreatic tail. BD-IPMN, branch-duct intraductal papillary mucinous neoplasm; MD-IPMN, main-duct intraductal papillary mucinous neoplasm; MPD, main pancreatic duct; MRCP, MRI with cholangiopancreatography. Pointing to the lesion (*Arrows* in *B-D*).

- Gastric
- Intestinal
- Pancreatobiliary

This classification is primarily based on morphologic characteristics and immunohistochemical mucin staining. Histologic classification is closely associated with distinct clinical behaviors [5] which partly account for the differences between BD-IPMN and MD-IPMN. Notably, gastric IPMN typically exhibits LGD and primarily involves side branches, whereas intestinal IPMN often presents with HGD and affects the MPD, resulting in dilation and mucin accumulation. It is worth noting that gastric IPMNs can progress to HGD and may lead to the development of tubular adenocarcinoma, characterized by a poor prognosis. Conversely, intestinal IPMN typically leads to the formation of associated colloid carcinoma, which generally has a more favorable prognosis when compared to pancreatic ductal adenocarcinoma (PDAC) [6,7]. It is believed that there are multiple pathways of accumulating mutations within dysplastic lesions to progress to invasive disease.

Intraductal oncocytic papillary neoplasms (previously classified as oncocytic IPMNs) and intraductal tubular papillary neoplasms are separate and rare entities beyond the scope of this article.

Clinical Assessment

The vast majority of PCNs are asymptomatic and are typically discovered incidentally during radiological examinations performed for other reasons. However, when symptoms do occur, patients may experience nonspecific abdominal pain, weight loss, reduced appetite, pancreatitis, new-onset diabetes mellitus, or jaundice [8]. It's important to note that aside from pancreatitis, diabetes, and jaundice, which are specific to pancreatic issues, caution should be exercised when interpreting other symptoms as they may be related to more common underlying etiologies. While the presence of symptoms in general warrant further evaluation, the presence of pancreatitis or jaundice (caused by the IPMN) should prompt consideration for surgical resection [9,10].

Radiology

The initial assessment of IPMNs typically involves computed tomography (CT) or MRI with cholangiopancreatography (MRCP). While MRI/MRCP exhibits a higher sensitivity for detecting pancreatic cysts compared to CT, they share relatively low specificity for diagnosing specific cystic tumors.

In addition to the classification of IPMNs based on their involvement of the MPD as discussed earlier, IPMNs can manifest with various radiological presentations. They may appear as solitary cystic lesions or as multifocal cysts, exhibiting either a unilocular or multilocular morphology. Moreover, different cysts within the same patient can exhibit varying appearances. In cases where a clear communication with the MPD is not documented, the differential diagnosis may include serous cystadenoma or MCNs. The overlapping radiological characteristics of these lesions pose a significant challenge for clinicians, resulting in a relatively high rate of preoperative misdiagnosis, ranging from 30% to 60%, and in fact, multiple difference types of PCNs can coexist [11–13].

A set of radiological features that may be utilized to evaluate patients affected by an IPMN are termed worrisome features (WFs) and high-risk stigmata (HRS) as defined by the International Association of Pancreatology guidelines [10]. While they have been associated with the diagnosis of HGD and IC, not all WFs and HRS carry the same level of risk [14]. The most relevant suspect features are the presence of mural nodules, defined as a contrast-enhanced solid nodule growing within the cystic lesion, and the dilation of the MPD. The categorization of these features as either WFs or HRS depends on their size (Table 1) [15].

Molecular Diagnosis

In recent years, several publications have explored new biomarkers to improve the diagnosis and risk stratification of IPMNs [16]. These studies have focused on markers in close proximity to the lesion from cyst fluid [17–20] and from distant tissues like peripheral blood [21] and urine [22]. The tasks that need to be addressed by the introduction of novel biomarkers are the diagnosis of IPMNs and the diagnosis of HGD [23].

Markers that have already been integrated into clinical practice include cyst fluid carcinoembryonic antigen (CEA) and serum cancer antigen 19-9 (CA19-9). CEA is a glycoprotein that is utilized for the diagnosis of mucinous cysts. An elevated cyst fluid CEA ($\geq$192 ng/mL) is indicative of the presence of a mucinous cyst. However, it is not possible to differentiate between IPMNs and MCNs and identify cysts harboring HGD using CEA alone [24]. CA19-9 is also utilized in the assessment of IPMNs. The International guidelines consider an elevated serum CA19-9 (>37 U/ml) level as one of the WFs necessitating further evaluation [10]. However, it's important to note that an elevated CA19-9 is linked to the diagnosis of an IPMN with an associated IC rather than the diagnosis of HGD [25]. Consequently, its application in surveillance should be guided by the existing evidence, and even in cases of a negative result, surgery should not be ruled out.

Other markers have been proposed for the diagnosis of PCNs and the identification of HGD [1]. Some research groups have suggested employing sequencing-based assays on cyst fluid samples to detect key mutations associated with distinct cystic entities and their level of dysplasia [18,20]. Another approach involves assessing the expression of inflammatory molecules and several microribonucleic acids to detect IPMNs with HGD [17]. While these tests have demonstrated better performance than guidelines alone, their adoption in clinical practice remains limited. This delay in their integration into clinical practice reflects the complexity of the field, where the substantial heterogeneity among different entities and their subtypes presents challenges in relying on a single diagnostic test to evaluate PCNs.

A new area of research involving IPMNs concerns the study of the tumor immune microenvironment (TIME). Notably, as IPMN progresses from LGD to IC, a shift in the composition of the TIME becomes apparent, transitioning from a proinflammatory microenvironment in low-grade lesions to an immunosuppressive one in tumors that have developed an invasive component [26]. While the research in this area is still in its early phase, we are encouraged by the potential to yield new biomarkers and potentially novel therapeutic avenues for IPMNs in the future.

SURVEILLANCE

Introduction

The objective of surveillance is 2-fold: to enhance the selection of patients who require surgery, thereby reducing the number of resections performed for benign lesions, and to avoid delaying intervention until an associated invasive adenocarcinoma has developed. Ideally, the goal is to identify patients whose IPMN has progressed or is likely to progress to HGD before

TABLE 1
Comparison of the Indications of the Main Guidelines Regarding the Management of Intraductal Papillary Mucinous Neoplasms

	2015 American Gastroenterological Association (AGA) Guidelines	2017 International Association of Pancreatology (IAP)–Revised Fukuoka Guidelines	2018 European Study Group on Cystic Tumors of The Pancreas Guidelines
Preoperative cyst diagnosis	*N/A*	MRI is preferred over CT; EUS-FNA (cytology/cyst fluid analysis) performed for better diagnosis	MRI is preferred over CT; EUS-FNA (cytology/cyst fluid analysis) performed for better diagnosis
Biomarkers	*N/A*	CA 19-9, CEA, amylase, molecular biomarkers (ie, KRAS, GNAS)	CA 19–9, CEA, amylase, molecular biomarkers (ie, KRAS, GNAS)
Nonoperative Surveillance	MRI/CT at 1 y then every 2 y for 5 y total	*<1 cm*: CT/MRI in 6 mo, then every 2 y if no changes *1–2 cm*: CT/MRI in 6 mo for 1 y, then in 1 y for 2 y, then every 2 y *2–3 cm*: EUS in 3–6 mo then alternating EUS and MRI annually *>3 cm*: MRI alternating with EUS every 3–6 mo	EUS and/or MRI every 6 mo for 1 y then annually as long as surgically fit
Indications for surgery	Dilated main pancreatic duct, solid cystic component, cytology with high-grade dysplasia or invasive carcinoma	*Surgery* *High-risk stigmata*: Jaundice (mass related), enhancing mural nodule $\geq$ 5 mm, main pancreatic duct $\geq$ 10 mm *Proceed with EUS*	*Absolute indications*: Cytology with high-grade dysplasia or invasive carcinoma, main pancreatic duct dilatation>10 mm, mural nodule>5 mm, solid mass, jaundice (mass related) *Consider surgery*

		Worrisome features: Pancreatitis, cyst $\geq$ 3 cm, enhancing mural nodule<5 mm, thickened/ enhancing cyst walls, main duct size 5–9 mm, abrupt change in caliber of the pancreatic duct with distal pancreatic atrophy, lymphadenopathy, increased serum level of CA 19–9, cyst growth rate $\geq$ 5 mm/2 y	*Relative indications*: growth rate>5 mm/year, CA 19-9 > 37 U/mL, main pancreatic duct dilatation 5–9 mm, cyst diameter>4 cm, symptoms of new-onset diabetes and acute pancreatitis, mural nodule<5 mm
Frozen section	*N/A*	*Recommended*: If margin positive for invasive cancer or high-grade dysplasia, additional resection is warranted to obtain negative margin. If low-grade dysplasia is present at margin, further resection is not necessary	*Recommended*: If margin positive for invasive cancer or high-grade dysplasia, additional resection is warranted to obtain negative margin. If low-grade dysplasia is present at margin, further resection is not necessary
Postoperative follow-up	*Invasive cancer or high-grade dysplasia:* MRI every 2 y *No high-grade dysplasia or invasive cancer:* no additional surveillance required	*No increased risk for malignancy*: CT/MRI every 6–12 mo *Higher risk for malignant progression*: CT/MRI at least 2 times/year *Invasive IPMN*: same follow-up strategy as PDAC	*Low-grade dysplasia*: EUS and/or MRI every 6 mo for 1 y then annually as long as surgically fit *High-grade dysplasia or MD-IPMN*: EUS and/or MRI every 6 mo for first 2 y, then annual surveillance *Invasive IPMN*: same follow-up strategy as PDAC

Abbreviations: CA 19-9, cancer antigen 19-9; CEA, carcinoembryonic antigen; CT, computed tomography; EUS, endoscopic ultrasound; FNA, fine-needle aspiration; IPMN, intraductal papillary mucinous neoplasm; MD-IPMN, main-duct intraductal papillary mucinous neoplasm; PDAC, pancreatic ductal adenocarcinoma.

From Pollini T, Wong P, Maker AV. The Landmark Series: Intraductal Papillary Mucinous Neoplasms of the Pancreas-From Prevalence to Early Cancer Detection. Ann Surg Oncol. 2023;30(3):1453-1462.

the onset of an invasive component. Unfortunately, despite recent advances, we continue to overtreat patients. In fact, a majority of those who undergo resection are subsequently found to have an IPMN with LGD [27].

To define who should be surveilled, we rely on the available clinical guidelines, particularly on the International and European guidelines. According to the International [10] and European [9] guidelines, patients with a presumed IPMN without any suspect features are candidates for surveillance. Suspect features are categorized as WFs and HRS in the International guidelines, while the European guidelines define them as relative and absolute indications (see Table 1). Notably, when the MPD is dilated without other causes of obstruction, it has been associated with HGD and IC, leading to a general recommendation for surgery in all MD-IPMN cases with an MPD $\geq$ 10 mm. For cases where the MPD measures between 5 and 9 mm in diameter (considered a WF or a relative indication for surgery), surgical resection may be considered. In fact, MPD dilation between 5 and 9 mm has also been associated with the diagnosis of HGD and IC in surgical series [28,29]. Nevertheless, findings from surgical series should be interpreted cautiously, as they may be influenced by a selection bias where conclusions are drawn from a nonrepresentative group of patients chosen for surgery [30].

The publication of the American Gastroenterological Association (AGA) guidelines [31] in 2015 sparked a controversial debate on surveillance discontinuation. The AGA guidelines suggested that surveillance could be discontinued after 5 years when no significant changes were documented. However, several series have reported malignant progression of pancreatic cysts under surveillance is in fact more common after 5 years of stability.

When Should We Stop Surveillance?

Once a patient is enrolled in a surveillance program, it should generally be surveilled as long as the patient remains fit for surgery. However, given the increasing number of individuals with PCNs and IPMNs under surveillance, coupled with rising life expectancies, maintaining lifelong surveillance is a considerable challenge for most health care systems. As previously mentioned, a lively debate is ongoing regarding the opportunity to suspend surveillance after 5 years if no changes are observed. Several medical centers have reported in their observational cohorts that even after 5 years of stability (ie, no development of WFs or HRS), suspect features and/or pancreatic cancer did emerge in some patients [32–36].

The occurrence of suspect features or pancreatic cancer, even after 5 years of stability, implies that there is no specific time threshold at which the risk of developing a pancreatic malignancy drops to zero. However, it's important to note that the incidence of pancreatic cancer in the general population has increased significantly in the last 30 years, especially in the aging population in high-income countries [37]. Increasing age is strongly associated with a substantially elevated risk of developing pancreatic cancer; for instance, males between the ages of 50 and 54 have an incidence of 11.5 per 100,000 people per year, while individuals aged 70 and 74 have an incidence of 62 per 100,000 people per year in the United States and Europe [38]. Therefore, when assessing the risk associated with an IPMN diagnosis, it's crucial to consider that even in the general population without a pancreatic cyst, the risk increases significantly with age.

Following this approach a recent international retrospective study identified subsets of patients with a presumed BD-IPMN under surveillance where the risk of developing pancreatic cancer was comparable to that of the matched general population [38]. Specifically, patients with presumed BD-IPMNs who did not develop any WFs or HRS during the first 5 years of surveillance (referred to as 'trivial BD-IPMN') and were 75 years or older had a standardized incidence ratio (SIR) of 1.12 (95% confidence interval [CI] 0.23–3.39). Similarly, those with trivial BD-IPMN, whose diameter remained $\leq$ 15 mm after 5 years of surveillance and were 65 years or older, had a SIR of 0.95 (95% CI 0.11–3.42). The SIR represents the ratio between the observed cases of pancreatic cancer in the BD-IPMN patient group under surveillance and the expected number of cases in an age-standardized control group from the same countries during the same period. Therefore, an SIR of 1 indicates no difference in risk between the BD-IPMN patients under surveillance and the control group. Notably, as a comparison, the SIR of pancreatic cancer for chronic pancreatitis has been reported to be 22.61 (95% CI, 14.42–32.720) [39]. While further studies are necessary to validate these findings, this subgroup of patients might be candidates for discontinuing surveillance, based on the rationale that their risk of developing pancreatic cancer, although greater than zero, does not differ significantly from that of the general population.

Ultimately the decision to discontinue surveillance should be the subject of thorough discussion with our patients. Given that there is no definitive answer regarding an individual's risk of developing pancreatic cancer, the choice to discontinue surveillance in cases of presumed BD-IPMNs must be meticulously considered. It is important to take into account both the financial cost and the

psychological burden of ongoing surveillance. In fact, it has been reported that patients with an IPMN under surveillance experience higher rates of depression and anxiety compared to patients undergoing surgery [40]. Nevertheless, considering the grim prognosis associated with pancreatic malignancies, surveillance may still be the preferred option for a significant proportion of patients.

SURGERY

Introduction

A minority of patients with an IPMN will undergo surgery during their lifetime. The issue of selecting patients for surgery is similar to that of selecting patients for surveillance. Especially considering the risks associated with pancreatic surgery, only lesions that have, or will progress to, HGD should be resected. Pancreaticoduodenectomies (PDs) even in high volume centers still carry a 2% to 3% mortality and approximately 20% risk of severe complications, particularly postoperative pancreatic fistula [41,42]. Furthermore, when considering the longer postoperative survival compared to patients with a PDAC, there are significant implications for long-term endocrine and exocrine insufficiency [43].

Type of Resection

Once a patient is selected for surgery, a standard oncological resection with lymphadenectomy should be performed, though it should be mentioned that some groups advocate for more limited resections when purposely performed for low-risk lesions [44]. The rationale for an oncologic resection lies on the basis that surgery is currently considered when a lesion shows signs of potential malignant progression. Depending on the location, a PD, distal pancreatectomy, or total pancreatectomy (TP) might be indicated. In cases of multifocal disease, where not all lesions show signs of progression, surgery should target the lesion(s) presenting the features that have triggered surgery and the type of surgery should be planned accordingly.

Recently, researchers have discussed the role of TP for IPMNs. Indeed, the management of postoperative type 3c diabetes has significantly improved, leading to a quality of life that is similar to that of patients undergoing a high-risk PD [45,46]. As a consequence, the indications for TP are broadening, though still controversial, and potential candidates for TP may include [47] IPMNs with diffuse MPD involvement not allowing partial pancreatectomy, young healthy patients with diffuse high-risk IPMNs, or patients with HGD or IC at a positive surgical margin.

Intraoperative Management

Frozen section should be performed in case of a partial pancreatectomy for MD-IPMNs to confirm the extent of the resection. HGD or IC at the margin warrants an extension of the resection, whereas LGD does not [48]. Special consideration should be given to the finding of a denuded epithelium. While the absence of an epithelium does not allow for a diagnosis, it has been associated with a higher rate of recurrence and therefore may require an extension of the resection [49].

Recently the notion of skip lesions and the search for a tailored approach have propelled the use of intraoperative pancreatoscopy. Pancreatoscopy, either peroral (generally performed preoperatively) or intraoperative enables the direct visualization of the MPD, allowing for a visual inspection of the IPMN or the remnant pancreas. It can be performed both during open or minimally invasive resections, with a low rate of reported adverse effects [50,51]. The use of intraoperative pancreatoscopy increases the sensitivity and specificity for the detection of pathologic tissue in the remnant pancreas compared to frozen section alone to 86% and 92%, respectively [50]. Furthermore, a recent systematic review and meta-analysis showed that intraoperative pancreatoscopy altered the surgical approach in 13% to 62% of cases [52]. Additional prospective studies are currently ongoing (NCT03062124 and NCT03729453) and may potentially expand the indications for intraoperative pancreatoscopy in the context of IPMNs.

FOLLOW-UP

Patients with a resected IPMN are at increased risk of developing additional IPMNs in the remnant pancreas, including dilation of the MPD, development of a new cyst, or increased size of existing cysts in the remnant pancreas [53]. Furthermore, patients with a resected IPMN with HGD have a higher risk of developing a PDAC in the remnant pancreas compared to patients with a low-grade IPMN [54–56]. These data support the indication to continue extended, if not lifelong, postoperative follow-up [9,10].

CLINICS CARE POINTS

- panceatic cystic neoplasms of the pancreas can be challenging to classify based on radiographic features alone, and are often misdiagnosed
- IPMN are one of the only radiographic precursors to pancreatic cancer, and thus represent an opportunity

for early diagnosis and curative intent surgery/treatment for an otherwise deadly disease
- There is an evolving an important role for molecular diagnostics
- The majority of resected lesions are low-risk on final surgical pathology, thus guidelines for resection and surveillance continue to evolve

DISCLOSURE

A.V. Maker is an inventor of record on the following pending or issued patents: WO2018183603A1 (US11732305B2) nationalized in the United States, Canada, European Patent Office, Australia, China, and Japan, and patent #9,757,457. Shorenstein Foundation and Inner Child Foundation. T. Pollini and P. Wong have no conflicts of interest to disclose.

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