

Intraductal Papillary Mucinous Neoplasm of the Pancreas



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KEYWORDS

- Intraductal papillary mucinous neoplasm • Pancreas • Biology
- Clinical management

KEY POINTS

- Intraductal papillary mucinous neoplasms (IPMNs) of the pancreas are categorized as main-duct (MD) and branch-duct (BD) lesions, with MD-IPMNs associated with a higher risk of malignancy and warranting surgical resection.
- Most BD-IPMNs are biologically indolent, with obstructive jaundice and radiographic features, such as presence of mural nodule or main pancreatic duct dilation greater than 10 mm, indicating higher risks lesions that should prompt consideration for resection.
- IPMN is a disease associated with a field defect. For multilesion disease, every cyst should be risk-stratified individually, and cyst-specific segmental resection performed when indicated. Follow-up after resection should be pursued, even if it was for benign IPMNs, given the risk of recurrence in the remnant gland.
- There are no high-level data supporting the use of adjuvant chemotherapy or radiation for invasive IPMNs. However, IPMNs with even small foci of invasion are associated with lymph node metastasis that poses a significant recurrence risk, suggesting the use of adjuvant therapy is appropriate in selected settings.

INTRODUCTION

The incidence of intraductal papillary mucinous neoplasms (IPMNs) of the pancreas has been on a rise in the past 2 decades, driven mainly by the widespread use of cross-sectional imaging.^{1,2} IPMNs are defined as intraductal mucin-producing neoplasms that involve the main pancreatic duct or its side branches and lack the ovarian stroma typically seen in mucinous cystic neoplasms. Most IPMNs are discovered incidentally and remain asymptomatic, making it difficult to estimate their true prevalence, which has been described to be as low as 0.0008%, and as high as 10% in patients

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older than 70 years.^{3,4} IPMNs follow a classic spectrum of dysplastic changes and can be classified as low, moderate, or high-grade dysplasia and invasive cancer. Based on experience and clinical evidence from the past 30 years, the International Association of Pancreatology (IAP) released consensus guidelines in 2006 and 2012 providing clinical algorithms based on IPMN features and risk of malignancy.^{5,6} In this article, we review the different classifications of IPMNs, their natural history, and clinical management and address recent controversies in the literature.

BIOLOGY OF INTRADUCTAL PAPILLARY MUCINOUS NEOPLASMS

Duct Involvement

IPMNs are morphologically classified into 2 main subtypes based on the location of pancreatic duct involvement: main duct (MD) and branch duct (BD). This morphologic classification has important biologic implications; MD-IPMNs have been associated with a malignancy rate of 57% to 92%, whereas BD-IPMNs have a more indolent natural history, with a malignancy risk ranging from 6% to 46%.^{7–14} However, these malignancy rates are based solely on resected lesions, suggesting that the true malignancy risk is lower for both MD-IPMNs and particularly so for BD-IPMNs.

There is a third group, IPMNs with mixed-duct involvement, which historically has been treated akin to MD involvement with regard to its malignancy risk. This concept has recently been challenged, with the Heidelberg group demonstrating that 29% (n = 512) of suspected BD-IPMNs revealed histologic involvement of the MD that was not evident on preoperative imaging.¹⁵ However, in an analysis of our own data at the Massachusetts General Hospital (n = 404), we found that the risk of high-grade dysplasia and invasive carcinoma in these minimal-mixed IPMNs was 11% and 6%, respectively, which more closely resembles the natural history of BD-IPMNs.¹⁶ This subset of minimal-mixed IPMNs is clearly biologically different from those with grossly mixed involvement, which has been reported to have malignancy rates of up to 72% (Fig. 1).¹⁷

Histologic and Cytologic Classification

In recent years, IPMNs have been further classified into the following categories based on their histologic characteristics and specific mucin expression: intestinal, pancreatobiliary, gastric, and oncocytic subtype (Fig. 2). When IPMNs progress to invasive cancer, they can be of the tubular or colloid subtype, and rarely oncocytic.^{18–21} These subtypes have important implications and show that IPMN is a heterogeneous disease.

BD-IPMNs have been shown to be most commonly associated with the gastric subtype, which has the least likelihood of tumor invasion (10%) and tumor recurrence (9%) among all subtypes. However, when carcinoma does occur, they are usually of the tubular subtype, which is associated with an increased risk of vascular invasion, perineural invasion, and nodal metastasis, portending a poorer prognosis similar to that of conventional ductal adenocarcinoma.^{18,21} Conversely, MD-IPMNs more commonly exhibit intestinal-type epithelium, which has a high likelihood of progressing to carcinoma but generally is of the biologically less aggressive colloid type.²¹ The pancreatobiliary and oncocytic subtypes are both less common but very contrasting in their biological behavior. IPMNs exhibiting pancreatobiliary epithelium are associated with the highest rate of tumor invasion (68%) and transformation to tubular carcinoma (82%).^{18,21} Oncocytic IPMNs, on the other hand, have a very indolent biology. In a review of 18 patients with oncocytic IPMN, Marchegiani and colleagues²² reported that most patients (67%) were asymptomatic, and although they had a 10-year recurrence

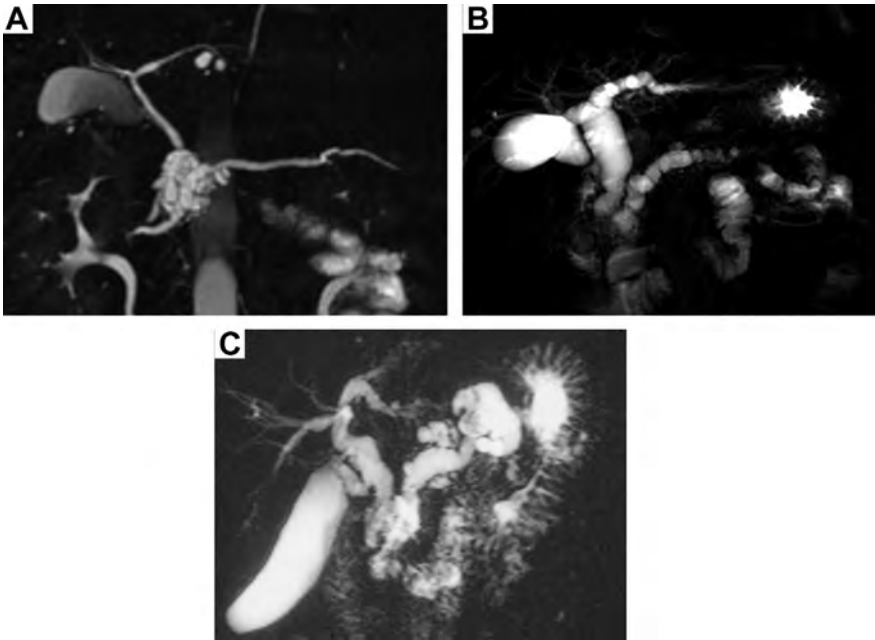


Fig. 1. Radiographic appearance of (A) BD, (B) MD, and (C) mixed-type IPMNs. (Adapted from Tanaka M. International consensus on the management of intraductal papillary mucinous neoplasm of the pancreas. *Ann Transl Med* 2015;3:286; with permission.)

rate of 46% (of which half underwent completion total pancreatectomy) there was no disease-specific death at a median follow-up of 7 years.

Field-Defect Concept

IPMNs are increasingly recognized as a disease associated with a “field defect” because of their propensity toward multifocality, which places the entire pancreatic gland at risk for neoplasia. The rate of synchronously occurring IPMN lesions has been reported to be as high as 83%,²³ and the risk of developing clinically significant metachronous lesions is approximately 8%.²⁴ Each lesion should be individually risk stratified, and cyst-specific segmental resection performed when indicated. More importantly, the rate of concomitantly occurring ductal adenocarcinoma has been reported to be approximately 4% and that of metachronous development of ductal adenocarcinoma as high as 11%. Although these rates are lower than that of invasive cancer arising from IPMNs, they have implications for postoperative surveillance and risk stratification (**Table 1**).^{25–30} It is also important to differentiate pancreatic ductal adenocarcinoma occurring concomitantly with IPMN (also known as distinct) from carcinoma arising within an IPMN for risk stratification studies; the former is reflective of the risk of the entire pancreatic gland, and the latter defines the malignancy risk of BD-IPMNs, which guides recommendations for resection based on the cyst characteristics.

DIAGNOSIS

Imaging

The focus of diagnostics in IPMNs is in detecting specific cyst characteristics that are predictive of malignancy, specifically MD involvement and presence of mural nodule.

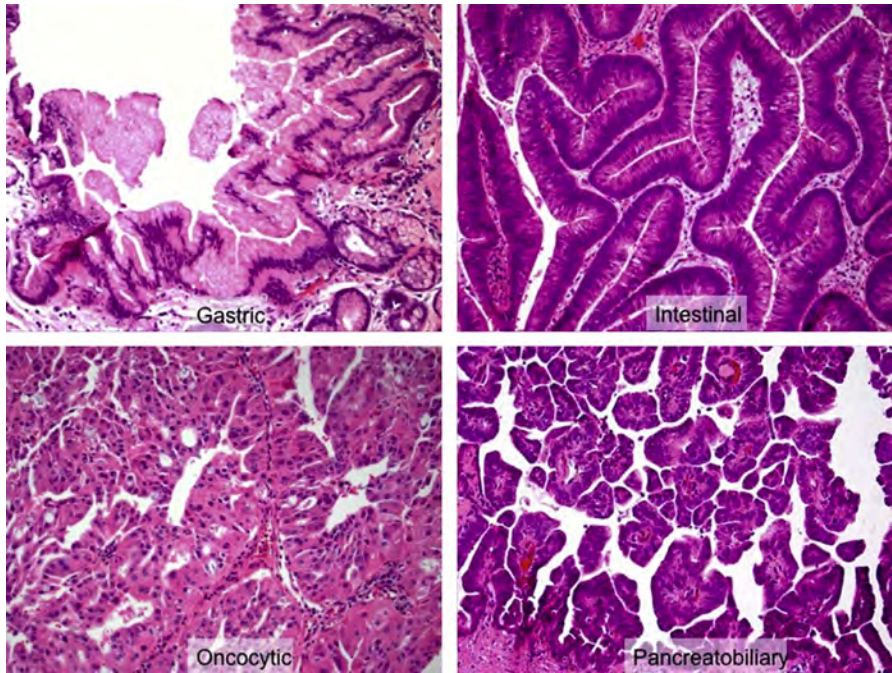


Fig. 2. High-power magnifications of IPMN histologic subtypes (hematoxylin-eosin, original magnification $\times 200$). (Adapted from Fong ZV, Ferrone CR, Lillemoe KD, et al. Intraductal papillary mucinous neoplasm of the pancreas: current state of the art and ongoing controversies. *Ann Surg* 2016;263(5):908–17; with permission.)

Mural nodule, a solid protrusion of the internal lining of the cyst, is challenging to identify, as mucin globules can frequently mimic its appearance. Although there are no studies correlating the size of mural nodule with the risk of malignancy, the generally accepted size threshold used in the literature is 5 mm.^{31–33} Most IPMNs are discovered incidentally when patients are imaged for an unrelated indication. Historically, a pancreas-protocol computed tomography (CT) scan or gadolinium-enhanced MRI with magnetic resonance cholangiopancreatography (MRCP) are the modalities of choice, with studies demonstrating similar diagnostic performance in detecting suspicious cyst features that guides clinical management.³⁴ However, MRI is preferred in practice, given its superior contrast resolution in delineating MD involvement and detecting mural nodules (Fig. 3), and it avoids repeated radiation exposure for patients requiring long-term surveillance. Although more invasive, endoscopic ultrasound (EUS) has a higher sensitivity and better detects mural nodules within IPMNs. However, it is less specific, and often picks up mucin globules, which may inadvertently lead to unnecessary resections.³⁵ Contrast-enhanced EUS, on the other hand, is better able to distinguish between both entities by detecting blood flow signals that are present in mural nodules, and has a specificity of more than 90%.³⁶

Cyst Fluid Analysis

EUS also provides the opportunity for fine-needle aspiration (FNA) to sample the cyst fluid for analysis. This should be reserved for centers with appropriate local expertise, because the aspirated cyst fluid is often insufficient for accurate cytopathologic

Table 1
Summary of studies in the literature reporting on recurrence after resection of benign intraductal papillary mucinous neoplasm

First Author, Year	n	Median Follow-up, mo	Recurrence Rate, %	Recurrence Rate with Invasion, %	Time to Recurrence, mo	5-y Survival, %
Chari et al, ⁶⁷ 2002	60	37	8.3	3.3	40	85
Sohn et al, ¹⁴ 2004	84	—	8.3	5.9	—	77
Wada et al, ⁶⁸ 2005	75	—	1.3	0	—	100
Salvia et al, ⁶⁹ 2009	80	31	1.0	0	—	100
Raut et al, ⁷⁰ 2006	28	34	0	0	—	100
White et al, ⁷¹ 2007	78	40	7.7	5.1	22	87
Fujii et al, ⁷² 2010	103	—	9.7	7.8	—	—
Miller et al, ⁷³ 2011	191	—	20	2	35	83
He et al, ⁶⁰ 2013	130	38	17	4	46	81
Kang et al, ⁵⁹ 2014	298	44	5.4	2.3	47	—
Marchegiani et al, ²⁸ 2015	316	58	9	5	48	—

Data from Refs. ^{14,28,59,60,67–73}

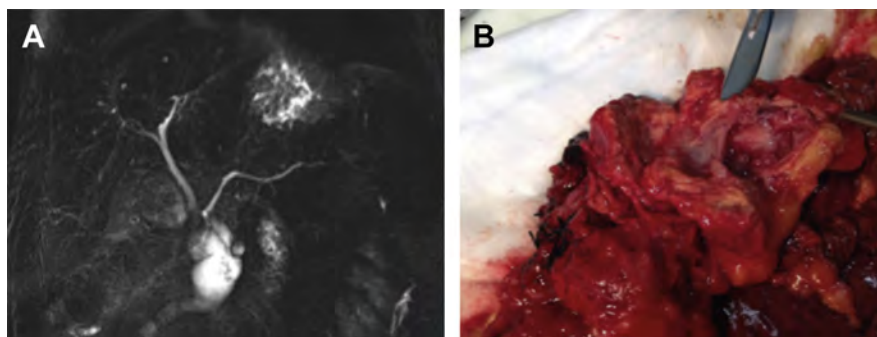


Fig. 3. (A) MRCP showing a large BD-IPMN associated with a mural nodule, with the (B) correlating specimen after surgical resection.

analysis and the specimen is often contaminated by cells from the gastric or duodenal wall. However, when performed well, cyst fluid analysis can differentiate mucinous from nonmucinous cysts with a sensitivity and specificity of 67% to 80% and 85% to 88%, respectively.^{37–39} The most commonly used cyst fluid marker has been carcinoembryonic antigen (CEA), with studies suggesting a cutoff of 192 ng/mL was most accurate in the diagnosis of IPMN, although it cannot distinguish benign from malignant cysts.⁴⁰ Additionally, it is also equally elevated in mucinous cystic neoplasms (MCNs) and is low in approximately 30% of cases.⁴¹ The 2 most common mutations tested for, KRAS and GNAS, are still investigational. KRAS can be found in approximately 50% of IPMNs but is also present in MCNs. GNAS is specific to IPMNs and is found in approximately 60% of cases. Both KRAS and GNAS also cannot differentiate benign from malignant disease.^{42–44} Other promising biomarkers and mutations currently being investigated include monoclonal antibodies Das-1, SMAD4, TP53, P16, and BRAF.⁴⁵

CLINICAL MANAGEMENT

The International Association of Pancreatology Guidelines

Given that we still are unable to reliably determine extent of MD involvement preoperatively, the current IAP guidelines recommend surgical resection for both MD-IPMNs and mixed-type IPMNs. Location-dependent segmental resection (pancreaticoduodenectomy for head lesions, distal pancreatectomy for body and tail lesions) should be performed, with lymph node dissection. Recently, parenchymal-sparing resections, such as enucleation and middle pancreatectomy, have been increasingly used. They are associated with a greater short-term complication rate, but preserve pancreatic exocrine and endocrine function.^{46,47} This is especially appealing to younger patients who are better able to tolerate upfront morbidity for a longer-term benefit. Conversely, there also have been suggestions that total pancreatectomy should be recommended for younger patients with multifocal disease given their higher cumulative lifetime risk of malignancy; this should be balanced against the morbidity of a total pancreatectomy and the metabolic consequences of an apancreatic state.

The management of BD-IPMNs embraces a more tailored approach, given their indolent natural history. The 2006 IAP guidelines recommend that BD-IPMNs that are symptomatic, asymptomatic but larger than 3 cm, with main pancreatic duct dilatation to greater than 6 mm, or presence of a mural nodule be resected, given that

these features represent harbingers for malignancy.^{5,48} However, subsequent evaluation of the guideline has found that although these criteria yield a high negative predictive value, they have a low positive predictive value, indicating that resection is overused.^{49–51} The IAP has since revised the guidelines, liberalizing the size threshold for resection and introduced 2 new categories: “high-risk stigmata,” which is an indication for resection, and “worrisome features,” which recommends further investigation (**Fig. 4**).⁶ A review of 563 patients with BD-IPMNs at our institution revealed that liberalization of the size criteria with the new IAP guideline would have doubled the rate of missed high-grade dysplasia (8.8%) and would have missed one case of invasive cancer.⁵² Other studies corroborate the concerns, reporting a higher risk of malignancy with increasing cyst size on interval follow-up imaging.^{53,54} To further address this concern, Crippa and colleagues⁵⁵ reviewed 281 patients with worrisome features or high-risk stigmata who did not undergo surgical resection secondary to physician recommendation, patients’ personal choice, or comorbidities precluding surgery. At a median follow-up of 51 months, invasive cancer developed in 12% of patients; the 5-year disease-free survival was 95%. Taken together, although the new IAP guidelines are safe, caution should be exercised in younger patients, given their higher cumulative lifetime risk of progression. Conversely, conservative management in elderly, frail patients is appropriate and should be offered as a treatment option.

The American Gastroenterology Association Guidelines

In 2015, the American Gastroenterology Association (AGA)’s Clinical Practice Guideline Committee released their official guidelines on the management of asymptomatic neoplastic pancreatic cysts (**Box 1**).⁵⁶ The guidelines were based on an extensive review of 1500 articles on the topic, and notably recommended the following: (1) surgery for an asymptomatic patient only if a cyst has 2 of the 3 concerning features (presence of nodule, size >3 cm, or duct dilation) and EUS shows malignancy, (2) surveillance interval of 2 years regardless of size of the cyst, and (3) discontinuation of surveillance after 5 years of no significant change or after resection of the cyst. These recommendations contradict the IAP’s guidelines and take a drastically more conservative approach. The basis of their recommendations is their analysis of the Surveillance, Epidemiology, and End Results (SEER) database that revealed only 1137 identified cases of mucinous pancreatic adenocarcinoma amidst an estimated 3.5 million cysts in the population, suggesting an exceedingly low risk of cancer. However, mucinous adenocarcinoma arises from MCNs and is indeed a rare entity; invasive cancer arising from IPMN is indistinguishable from the coded pancreatic cancer and is impossible to be identified from the SEER database. Additionally, their recommendations ignore a decade’s long evidence of IPMNs being a disease with a field defect, disregarding the risks of metachronously occurring IPMNs and ductal adenocarcinomas, as detailed in **Table 1**. The current criteria for resection and surveillance set by the IAP represent possibly the only chance of early intervention in pancreatic cancer, and in our opinions, the AGA guidelines need to be further vetted before they can be safely recommended to practitioners.

FOLLOW-UP STRATEGY

Surveillance of the Nonresected Intraductal Papillary Mucinous Neoplasm

Given that all MD-IPMNs should be resected, this section pertains to patients with BD-IPMNs. The intensity of surveillance depends on the initial size and feature of the IPMN and the interval progression of the lesion. In smaller lesions (0–2 cm), it is recommended that imaging (CT or MRCP) be performed every 2 years, and interval can be

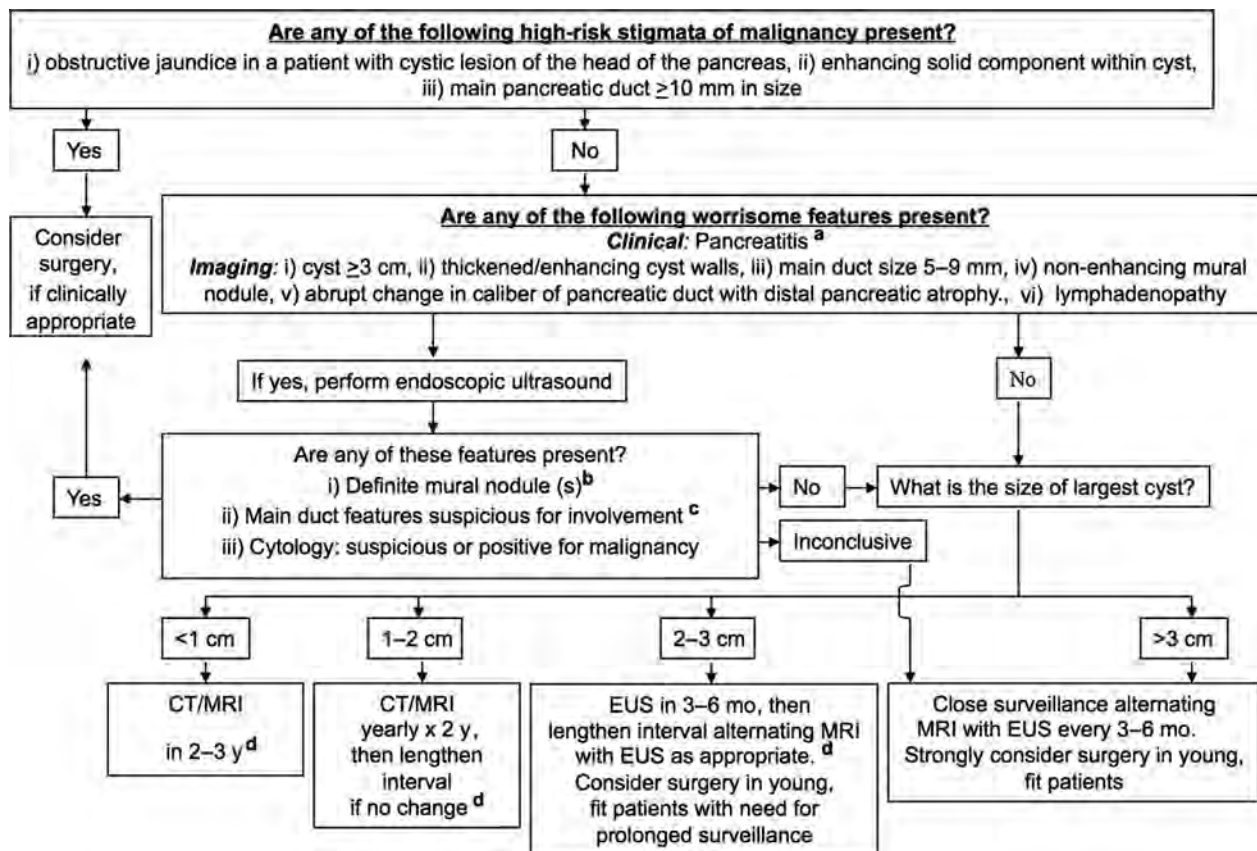


Fig. 4. Clinical algorithm put forth in 2012 by the IAP for the management of BD-IPMNs. ^a Pancreatitis may be an indication for surgery for relief of symptoms. ^b Differential diagnosis includes mucin. Mucin can move with change in patient position, may be dislodged on cyst lavage and does not have doppler flow. Features of true tumor nodule include lack of mobility, presence of doppler flow and FNA of nodule showing tumor tissue. ^c Presence of any one of thickened walls, intraductal mucin or mural nodules is suggestive of main duct involvement. In their absence main duct involvement is inconclusive. ^d Studies from Japan suggest that on follow-up of subjects with suspected BD-IPMN there is increased incidence of pancreatic ductal adenocarcinoma unrelated to malignant transformation of the BD-IPMN(s) being followed. However, it is unclear if imaging surveillance can detect early ductal adenocarcinoma, and, if so, at what interval surveillance imaging should be performed.

Box 1**Recommendations put forth by the American Gastroenterology Association (AGA) on the diagnosis and management of patients with intraductal papillary mucinous neoplasms***Recommendations from the AGA Guidelines*

1. Before starting any pancreatic cyst surveillance program, patients should have a clear understanding of the risks and benefits.
2. Patients with pancreatic cysts smaller than 3 cm without a solid component or dilated pancreatic duct undergo MRI for surveillance in 1 year followed by every 2 years for a total of 5 years.
3. Pancreatic cysts with at least 2 high-risk features, such as size ≥ 3 cm, a dilated main pancreatic duct, or the presence of an associated solid component, should be examined with endoscopic ultrasound–fine-needle aspiration (EUS-FNA).
4. Patients without concerning EUS-FNA results should undergo MRI surveillance after 1 year and then every 2 years to ensure no change in risk of malignancy.
5. Significant changes in the characteristics of the cyst (solid component, increasing size of pancreatic duct, and/or diameter ≥ 3 cm) are indications for EUS-FNA.
6. Recommend against continued surveillance of pancreatic cysts if there has been no significant change in the characteristics of the cyst after 5 years of surveillance or if the patient is no longer a surgical candidate.
7. Patients with both a solid component and a dilated pancreatic duct and/or concerning features on EUS-FNA should undergo surgery to reduce the risk of mortality from carcinoma.
8. If surgery is considered, patients are referred to a center with demonstrated expertise in pancreatic surgery.
9. Patients with invasive cancer/dysplasia in a cyst that has been resected should undergo MRI surveillance of any remaining pancreas every 2 years.
10. Recommend against routine surveillance of pancreatic cysts without high-grade dysplasia or malignancy at surgical resection.

Adapted from Vege SS, Ziring B, Jain R, et al. American Gastroenterological Association institute guideline on the diagnosis and management of asymptomatic neoplastic pancreatic cysts. *Gastroenterology* 2015;148(4):819–22; [quiz: 12–3]; with permission.

lengthened if a pattern of stability has been established. In lesions larger than 2 cm, imaging along with EUS is recommended every 3 to 6 months, and lengthening of interval alternating MRCP with EUS if there has been no change on follow-up.⁶ It should be noted that the degree of interval lengthening is entirely subjective, given that these recommendations are based on expert consensus. The degree of interval lengthening probably does not matter as much as the consistency; patients should be referred to and enrolled in a dedicated pancreatic cyst clinic with an established surveillance program and followed in a standardized manner. Surveillance of patients with low-risk IPMNs also can cause patient anxiety and poses a significant burden on health care cost and resources. Hence, physicians should exercise clinical judgment in balancing continued surveillance against the patients' accumulative lifetime risk of malignancy and fitness for surgery.

Follow-up of the Resected Intraductal Papillary Mucinous Neoplasm

For patients with invasive cancer arising from their resected IPMN, postoperative surveillance should follow that of ductal adenocarcinoma, given the similarly overwhelming risk of systemic and local recurrence.^{57,58} The recurrence pattern for

resected benign IPMNs is different and would be a reflection of the risk of synchronous, low-risk lesions left behind and the development of metachronous lesions in the healthy remnant gland as a result of the field defect with which IPMNs are associated.

The rate of synchronous disease has been reported to be as high as 83%,²³ and the risk of developing metachronous disease is approximately 8%.²⁴ Of patients undergoing resection for benign IPMNs, the recurrence rate ranges from 5.4% to 9.0%, of which 2.3% to 5.0% are invasive recurrences, occurring from 22 to 46 months from the index surgery (see [Table 1](#)).^{28,59} The Johns Hopkins group analyzed 130 patients who underwent resection for benign IPMNs and reported 1-year, 5-year, and 10-year risks of developing invasive cancer being 0%, 7%, and 38%, respectively. At a median follow-up of 60 months, those patients who underwent completion pancreatectomy for recurrent invasive disease remained alive with no evidence of recurrent disease. These data imply that long-term surveillance is necessary, as recurrence can occur up to 4 years after resection of benign IPMNs, further reaffirming the danger of the AGA guidelines that would potentially deprive patients of the opportunity at early surgical intervention that has a positive impact on long-term survival.

Better understanding cohorts at higher risk of developing recurrences can guide postoperative surveillance strategies and maximize efficiency. A family history of pancreatic cancer has been shown to be associated with a higher likelihood of developing recurrence (23% vs 7%, $P < .05$),⁶⁰ concurrently occurring ductal adenocarcinoma (11.1% vs 2.9%, $P = .02$), and extrapancreatic malignancies (35.6% vs 20.1%, $P = .03$) after resection of benign IPMNs.⁶¹ Patients with a positive margin have been shown to have a significantly higher rate of recurrence (25% vs 14%, $P = .008$) and a positive margin was the strongest independent predictor of survival (hazard ratio 2.6, $P = .0046$).¹⁷ Finally, high-grade dysplasia in the primary lesion, despite negative margins, also has been shown to be a strong predictor of recurrence, portending an eightfold increase in the risk of developing invasive recurrence.⁶²

The current IAP guidelines recommend performing a history/physical examination and MRCP surveillance at 2 years and 5 years after resection of noninvasive IPMNs, with a gradual lengthening of the follow-up interval once a pattern of stability has been determined.⁶ Based on the evidence presented previously, the guidelines may not be sufficient. Caution must be exercised, particularly in patients with a family history of pancreatic cancer or high-grade dysplasia found in the primary lesion or surgical margin. For selected elderly patients with significant comorbidities in whom life expectancy is short or who cannot tolerate a pancreatectomy, follow-up could potentially be avoided altogether, especially if the aforementioned risk factors are absent.

ADJUVANT THERAPY

The role of adjuvant chemotherapy and radiation in patients with invasive IPMNs has not been well defined. Current studies in the literature are retrospective reviews confounded by patient selection,^{63–65} and a randomized controlled trial is not feasible given the heterogeneity of the morphologic and histopathological subtypes. In a recent analysis of patients with IPMNs with small (<2 cm) invasive components, 19% were found to have lymph node metastases, which was highly predictive of recurrence rates (24%) and overall survival.⁶⁶ This suggests that IPMNs associated with invasive cancer should be treated similarly to conventional pancreatic adenocarcinoma, but the implication of malignancy morphology (tubular vs colloid) is still unknown. There are currently no formal recommendations regarding the use of

adjuvant therapy in patients with invasive IPMN, but treatment certainly would be appropriate in the right context.

SUMMARY

It has been 3 decades since the initial discovery of IPMNs, and our understanding of the disease is still evolving. Although it may represent the only window of opportunity of early intervention in pancreatic cancer, we must be cautious and strike a judicious balance to prevent overutilization of surgical resection and avoid unnecessary morbidity and mortality. Presently, the IAP guidelines are safe and should be used as the gold standard for the management of patients with IPMNs, and clinical judgment should be exercised when treating younger and older/frail patients depending on their cumulative lifetime risk of progression. Efforts focusing on the development of serum and cyst fluid biomarkers that can better distinguish benign from malignant lesions and guide clinical management are under way.

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