Intraductal papillary mucinous neoplasm of the pancreas (IPMN): Evaluation and management

AUTHORS: Sunil G Sheth, MD, Tara S Kent, MD, FACS
SECTION EDITOR: David C Whitcomb, MD, PhD
DEPUTY EDITOR: Shilpa Grover, MD, MPH, AGAF

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INTRODUCTION

Intraductal papillary mucinous neoplasms (IPMNs) of the pancreas are potentially malignant intraductal epithelial neoplasms that are grossly visible (typically >10 mm) and are composed of mucin-producing columnar cells. The lesions show papillary proliferation, cyst formation, and varying degrees of cellular atypia [1,2].

IPMNs may involve the main pancreatic duct, the branch ducts, or both. Whereas patients with branch-duct lesions are at lower risk for developing malignancy (approximately 20 percent at 10 years), patients with IPMNs involving the main duct are at high risk (approximately 70 percent). As a result, these lesions need to be accurately diagnosed and characterized so that appropriate treatment can be recommended. (See "Intraductal papillary mucinous neoplasm of the pancreas (IPMN): Pathophysiology and clinical manifestations", section on 'Classification' and "Intraductal papillary mucinous neoplasm of the pancreas (IPMN): Pathophysiology and clinical manifestations", section on 'Pancreatic malignancy'.)

This topic will review the evaluation and management of IPMNs. The pathophysiology and clinical manifestations of IPMNs and an overview of the diagnostic approach to pancreatic cystic neoplasms are discussed separately. (See "Intraductal papillary mucinous neoplasm of the pancreas (IPMN): Pathophysiology and clinical manifestations" and "Classification of pancreatic cysts" and "Pancreatic cystic neoplasms: Clinical manifestations, diagnosis, and management".)

DIAGNOSIS

The approach to the diagnosis of pancreatic cystic neoplasms typically starts with cross-sectional imaging (magnetic resonance imaging with magnetic resonance cholangiopancreatography or computed tomography). Additional evaluation with endoscopic ultrasound with fine-needle aspiration may be needed to confirm a diagnosis or to assess for malignant features. The diagnostic approach to pancreatic cystic neoplasms is discussed separately. (See "Pancreatic cystic neoplasms: Clinical manifestations, diagnosis, and management".)

EVALUATION FOR MALIGNANCY

The evaluation of a patient with an intraductal papillary mucinous neoplasm (IPMN) aims to determine if the patient has or is at high-risk of developing a malignancy [3]. Resection is typically recommended for IPMNs with high-grade dysplasia (carcinoma in situ), IPMNs that have progressed to invasive carcinoma (also referred to as invasive IPMN or malignant IPMN), and IPMNs with features concerning for malignancy or that are at high risk for developing malignancy. IPMNs not meeting these criteria are typically followed with surveillance imaging. (See 'Management' below.)

While the approach to evaluating IPMNs is similar to the initial evaluation of pancreatic cystic neoplasms (PCNs), additional testing is often indicated because IPMNs have known malignant potential (as opposed to PCNs in general, which may or may not have malignant potential based on the cyst type). (See "Pancreatic cystic neoplasms: Clinical manifestations, diagnosis, and management", section on 'Diagnostic approach'.)

Cross-sectional imaging — Magnetic resonance imaging with magnetic resonance cholangiopancreatography (MRCP) or a pancreatic protocol computed tomography (CT) scan are typically the first imaging tests used to diagnose and characterize IPMN (image 1 and image 2). The studies can assess the neoplasm and its relationship to surrounding structures, may suggest there is lymph node involvement (scans can show enlargement, which suggests lymph node involvement, but they cannot confirm that nodes are involved), and can detect metastatic disease [4-7].

Both MRCP and CT are capable of detecting mural nodules. A CT scan finding of mural nodules within an IPMN or the duct is highly suggestive of malignancy [8]. Compared with endoscopic retrograde cholangiopancreatography (ERCP), MRCP is more sensitive for differentiating mural nodules from mucin globs since mucin has the same signal intensity as pancreatic fluid [4,8-11].

MRCP is also superior for demonstrating the internal architecture of the main duct and the extent of IPMN. However, MRCP is inferior to ERCP in demonstrating peripheral ductal abnormalities [12] and in the ability to obtain tissue or perform therapeutic interventions. The most sensitive test for the detection of mural nodules is an endoscopic ultrasound. (See 'Endoscopic ultrasound with fine-needle aspiration' below.)

Indications for additional evaluation — Additional evaluation with endoscopic ultrasound (EUS) with fine-needle aspiration (FNA) may **not** be needed if there are clear indications for surgery demonstrated on cross-sectional imaging, such as IPMN with a main pancreatic duct diameter ≥10 mm, an enhancing solid component within the IPMN, or if the patient has obstructive jaundice or other symptoms attributable to the IPMN (algorithm 1 and algorithm 2). (See 'Management' below.)

For patients without an indication for surgery, additional evaluation with EUS-FNA is needed if there are concerning findings on cross-sectional imaging such as:

- IPMN size ≥30 mm
- Thickened or enhancing cyst walls on imaging
- Presence of a non-enhancing mural nodule
- Associated pancreatitis
- A dilated main pancreatic duct that is 5 to 9 mm in diameter
- An abrupt change in the caliber of the pancreatic duct with distal pancreatic atrophy

These criteria are more conservative than those suggested by the American Gastroenterological Association (AGA) guideline for the evaluation of PCNs in general [13] (see "Pancreatic cystic neoplasms: Clinical manifestations, diagnosis, and management"). The AGA guideline recommends patients undergo further evaluation only if a cyst has two or more specific worrisome features (size ≥3 cm, a solid component, or a dilated main pancreatic duct). However, the AGA guideline points out that there is insufficient evidence to make definitive recommendations and that the approach may need to be individualized on a case-by-case basis. In addition, some data now suggest that if the AGA guidelines are applied, many IPMNs with adenocarcinoma or high-grade dysplasia will be missed [14] (see "Pancreatic cystic neoplasms: Clinical manifestations, diagnosis, and management"). We use a more conservative approach when recommending additional evaluation because IPMNs have known malignant potential.

The optimal approach to evaluating IPMNs ≥10 mm but <30 mm in size with no other concerning features is unclear. Our approach is to offer patients the option of undergoing additional evaluation with EUS-FNA if the patient is particularly concerned about malignancy. If additional evaluation is not performed, we follow the patient with surveillance imaging. For

IPMNs that are <10 mm in size, we suggest surveillance imaging. (See 'IPMN without confirmed malignancy or high-grade dysplasia' below.)

Additional evaluation also is typically required for patients with signs of invasive carcinoma on cross-sectional imaging to confirm the diagnosis and to stage the malignancy. (See "Clinical manifestations, diagnosis, and staging of exocrine pancreatic cancer".)

Endoscopic ultrasound with fine-needle aspiration — EUS-FNA provides high-quality imaging of the pancreas and the opportunity to sample pancreatic lesions for cytology and cyst fluid analysis.

Sonographic findings — Certain EUS features suggest malignancy, although their sensitivity and specificity have not been well established. These findings include [15-19]:

- A main pancreatic duct ≥7 mm in main-duct (MD) IPMN
- Cystic lesion >30 mm with an irregular, thick septum in branch-duct (BD) IPMN
- Mural nodules >10 mm for both MD- and BD-IPMN

Pancreatic and cyst fluid analysis — Sampling of fluid within the pancreatic duct and FNA of cyst fluid and mural nodules can be performed for cytologic evaluation to look for atypical or malignant cells. However, 50 to 60 percent of fluid samples are nondiagnostic or acellular, and the absence of atypical or malignant cells does **not** exclude the presence of malignant IPMN [20]. (See "Endoscopic ultrasound-guided fine needle aspiration in the gastrointestinal tract".)

The cyst fluid can also be analyzed for the presence of carcinoembryonic antigen (CEA), which, when elevated, indicates that the cyst is mucinous. Mucinous cysts, including both IPMN and mucinous cystadenoma, have malignant potential, depending on their features, but this risk does not correlate with the level of CEA in cyst fluid [21]. CEA levels are not currently used to decide which patients should undergo resection, but they can be used to differentiate patients with mucinous neoplasms from those with other lesions. (See "Pancreatic cystic neoplasms: Clinical manifestations, diagnosis, and management", section on 'Cyst fluid analysis'.)

Pancreatic secretions can also be tested for molecular markers such as *KRAS*, P53, and telomerase activity. These markers can be helpful for detecting malignant IPMN [22-24].

Studies are variable regarding the ability of tumor markers in the cyst fluid to differentiate malignant from benign IPMN:

- In one study, a CEA level >200 ng/mL had a sensitivity and specificity for malignant IPMN of 90 and 71 percent, respectively [25].

- A second study found that neither CEA nor carbohydrate antigen 19-9 (CA 19-9) were useful for distinguishing malignant from benign IPMN [17].

- In a third study with 40 patients, mean mucin-2 (MUC2) and MUC4 cyst fluid concentrations were elevated in patients with high-grade dysplasia or carcinoma compared with patients with low-grade or moderate dysplasia (10 versus 4.4 ng/mL and 20.6 versus 4.5 ng/mL, respectively) [26,27].

- A fourth study found that microRNA (miR)-21 and miR-221 were associated with malignant cysts [15,28].

Careful selection of patients who should undergo EUS-FNA is necessary as the risk of postprocedural complications, especially pancreatitis, may be higher than originally believed. A multicenter study that reviewed complications found an incidence of pancreatitis of 8 percent following EUS-FNA of BD-IPMN, which was higher than seen with EUS-FNA performed on other cyst types (1.3 percent) [29].

Other tests — If after EUS-FNA there is still concern about possible malignancy, or if the extent of the IPMN is unclear and is needed for preoperative staging, additional testing may be done. Testing may include ERCP with aspiration of the pancreatic duct contents or brushing of the pancreatic duct, pancreatoscopy, intraductal ultrasonography, positron emission tomography (PET), or assessment of serum tumor markers.

- **ERCP** – ERCP can be performed to obtain cytology by aspiration of the duct contents or brushings. In addition, therapeutic maneuvers can be performed to help clear the tenacious mucin from the pancreatic duct.

  Cytologic examination may reveal mucin and floating epithelial cells with varying degrees of atypia. Pancreatic duct lavage cytology using the cell block method is another approach that has been tested for detecting malignant cells. In a series of 44 patients with BD-IPMN and mural nodules, the sensitivity and specificity of pancreatic duct lavage cytology for detecting malignancy were 92 and 100 percent [30]. (See "Pancreatic cystic neoplasms: Clinical manifestations, diagnosis, and management", section on 'Diagnostic approach'.)

- **Pancreatoscopy** – The patulous pancreatic orifice can be cannulated easily with a pancreatoscope during ERCP, permitting direct visualization of the pancreatic duct (image 3 and picture 1). Pancreatoscopy can help determine the extent of IPMN, especially if skip lesions are present, which may aid preoperative staging [31]. Features suggesting malignancy include spotty or linear red markings, "fish-egg-like" lesions, villous

proliferations (picture 2), and vegetative-type lesions [32-34]. (See "Cholangioscopy and pancreatoscopy", section on 'Suspected pancreatic neoplasm'.)

The sensitivity of pancreatoscopy was illustrated in a study of 60 patients with IPMN in which 57 (95 percent) patients were correctly identified as IPMN [33]. In another report of patients with IPMN, the presence of "fish-egg-like," villous, and prominent mucosal protrusions had a sensitivity of 68 percent and a specificity of 87 percent for malignancy [34]. The sensitivity was lower for BD-IPMN compared with lesions of the main pancreatic duct.

Advances in "baby" scope technology using complementary metal-oxide semiconductor (CMOS) chips and small charge-coupled devices (CCDs) have resulted in much better visualization, which may permit more determination of the extent of IPMN than previously available (picture 3), but comparisons to MRCP and EUS are needed. Finally, the risks of postprocedural pancreatitis at present are unclear, demanding caution [35].

- **Intraductal ultrasound** – Intraductal ultrasonography using high-frequency ultrasound catheter probes can be helpful for determining tumor extent in MD-IPMN (image 4). However, intraductal ultrasonography has a limited ability to detect lesions more than a few millimeters away from the main pancreatic duct due to poor penetration of the high-frequency waves [36]. (See "Intraductal ultrasound for evaluating the pancreaticobiliary ductal system".)

- **PET** – PET scanning is not routinely performed in patients with IPMN but it can be used to detect a malignancy in an IPMN [26,37-39]. A study of 162 patients with MD- or BD-IPMN examined the ability of PET scanning to detect malignancy [39]. The study compared PET scanning with either histology (81 patients) or the results of surveillance (62 patients; median follow-up 21 months). Follow-up/histologic data were not available for 19 patients. The sensitivity and specificity for PET scanning were 83 and 100 percent, respectively. (See "Clinical manifestations, diagnosis, and staging of exocrine pancreatic cancer", section on 'Positron emission tomography scanning'.)

- **Serum tumor markers** – Determination of serum levels of CA 19-9 and CEA may aid in the differentiation of IPMNs that have progressed to invasive carcinoma from noninvasive IPMNs. In a study of 142 patients undergoing surgical resection for IPMN, patients with invasive carcinoma had higher CA 19-9 and CEA levels compared with patients with noninvasive IPMN [40]. Eighty percent of patients with invasive carcinoma had one or both markers elevated, compared with 18 percent of patients with noninvasive IPMN. Using a cutoff of 37 units/mL, CA 19-9 was 74 percent sensitive and 86 percent specific for invasive

carcinoma. The sensitivity and specificity for CEA at a cutoff of 5 mcg/L were 40 and 92 percent, respectively. Taken together (ie, CA 19-9 and/or CEA positive), the tests had a sensitivity of 80 percent and a specificity of 82 percent. (See "Clinical manifestations, diagnosis, and staging of exocrine pancreatic cancer", section on 'Role of tumor markers'.)

Mucin-5AC (MUC5AC) serum levels may help differentiate high-risk IPMN from low-risk IPMN. A study found elevated MUC5AC levels in patients with high-grade dysplasia or carcinoma compared with patients with lesser degrees of dysplasia (20 versus 2 ng/mL) [27].

MANAGEMENT

This discussion deals with the management of patients with a diagnosis of intraductal papillary mucinous neoplasm (IPMN). This approach differs from the management of pancreatic cystic neoplasms for which a definitive diagnosis has not been made. The evaluation and management of uncharacterized pancreatic cystic neoplasms are discussed separately. (See "Pancreatic cystic neoplasms: Clinical manifestations, diagnosis, and management", section on 'Mucinous cyst, specific type unknown'.)

High-grade dysplasia or invasive cancer

Surgical therapy — Surgery is the only treatment option in patients with IPMN of the pancreas with high-grade dysplasia or IPMNs that have progressed to invasive carcinoma. Preoperative staging using a combination of endoscopic retrograde cholangiopancreatography (ERCP), pancreatoscopy, endoscopic ultrasound (EUS), and intraductal ultrasonography may be beneficial [10,34,41,42]. Invasive cancer arising from IPMN is staged using the tumor-node-metastasis system (table 1). (See "Clinical manifestations, diagnosis, and staging of exocrine pancreatic cancer", section on 'Staging system and the staging workup'.)

Surgical series have described a variety of operations for IPMN, including total pancreatectomy (figure 1), pancreaticoduodenectomy (figure 2 and figure 3), distal pancreatectomy (figure 4 and figure 5), and segmental resection of the tumor [43-48]. The choice of surgery will be determined by the location of the tumor and the extent of involvement of the gland. It is not clearly established that multifocality corresponds to a higher risk of invasive cancer, and in most cases with more than one lesion, the dominant or concerning lesion(s) are resected and the other(s) are observed with follow-up imaging [49]. (See 'IPMN without confirmed malignancy or high-grade dysplasia' below.)

However, some data suggest that patients with multiple (≥4) IPMNs may have high-grade dysplasia or invasive carcinoma in the absence of worrisome computed tomography (CT) scan findings [50]. In a study of 43 patients with ≥4 IPMNs and no solid pancreatic mass who underwent surgical resection, 18 (42 percent) had either IPMN with high-grade dysplasia or invasive carcinoma. Importantly, seven patients (16 percent) lacked worrisome CT findings but were found to have high-grade dysplasia or invasive carcinoma. However, the results of this study should be viewed in light of the fact that it was a retrospective series and that the indications for surgery were not discussed. Therefore, the study is at risk for bias with regard to which patients underwent surgery. In addition, the study only used CT scans for diagnosis and not EUS (which may detect smaller cysts missed by CT), so the study results and conclusions should be viewed with caution.

Resection of the tumor (IPMN with high-grade dysplasia or an invasive carcinoma) can be attempted in patients with no imaging or endoscopic evidence of local vascular invasion or distant metastases. The most common operation is pancreaticoduodenectomy (70 percent) because most tumors are in the head of the pancreas. Examination of frozen sections of the resection margins during surgery can determine tumor extent and the need for further surgical resection, bearing in mind that, given the "field defect" nature of IPMN, a negative surgical margin does not preclude the presence of neoplasia in the remnant pancreas [47,51]. Intraoperative pancreatoscopy may also be helpful in determining tumor extent [32]. (See "Pylorus-preserving pancreaticoduodenectomy" and "Surgical resection of lesions of the body and tail of the pancreas".)

Surgical resection of the entire pancreas may be appropriate for patients with multiple symptomatic lesions or with IPMNs that have concerning radiologic or endoscopic features, though the risk of malignancy needs to be carefully weighed against the issues that arise in patients who do not have a pancreas. Additional long-term studies of outcomes in patients with multiple asymptomatic IPMNs are needed before recommending total pancreatectomy in this setting.

Adjuvant therapy — For patients with invasive ductal adenocarcinoma of the pancreas, postresection adjuvant therapy improves survival, even in patients with positive margins or involved lymph nodes. There is controversy as to the best adjuvant strategy. (See "Treatment for potentially resectable exocrine pancreatic cancer".)

In a study using the National Cancer Data Base, outcomes were evaluated in 1220 patients with invasive IPMN [52]. Overall survival was worse among patients who were treated with surgery alone compared with those who received adjuvant therapy (chemotherapy with or without radiotherapy; hazard ratio 1.36, 95% CI 1.17-1.58). On stratified analysis, adjuvant therapy was

associated with improved survival in patients with TNM stage II or III/VI disease, positive lymph node status, positive resection margins, or poorly differentiated tumors. Adjuvant therapy was not associated with a survival advantage for patients with stage I disease and lymph node-negative disease.

The benefit of adjuvant therapy for patients with invasive carcinoma arising from IPMN was also examined in a retrospective series with 70 patients. Forty patients received adjuvant chemoradiotherapy (mostly external beam radiotherapy with concomitant infusional fluorouracil, followed by fluorouracil chemotherapy alone), while 30 patients had resection only [53]. Invasive carcinoma was present at the resection margin in 16 percent of cases, and 50 percent had involved lymph nodes. Despite the fact that patients receiving adjuvant therapy were more likely to have adverse prognostic features (nodal metastases, perineural invasion, and stage II or III rather than stage I disease), the two-year survival rate after surgery with chemotherapy was similar to that seen in those who did not receive chemoradiotherapy (56 versus 59 percent). In multivariable analysis after adjusting for major confounders, adjuvant chemoradiotherapy was associated with a 57 percent reduction in mortality after pancreaticoduodenectomy.

While it appears reasonable to offer postresection adjuvant therapy to patients with IPMNs that have progressed to invasive carcinoma, the identification of the specific subgroups that benefit from postoperative therapy and the optimal treatment strategy (chemoradiotherapy versus chemotherapy alone) is undefined. (See "Treatment for potentially resectable exocrine pancreatic cancer".)

IPMN without confirmed malignancy or high-grade dysplasia — The treatment of main-duct (MD) and branch-duct (BD) IPMN without known malignancy or high-grade dysplasia depends on whether the lesion has a high risk of harboring malignancy.

The approach that follows is generally consistent with that outlined in the 2006 and 2012 Sendai consensus guidelines [49,54] for the management of IPMN and a 2015 guideline from the American Gastroenterological Association (AGA) for the management of pancreatic cystic neoplasms [13]. However, our approach differs in that:

- Our indications for resection are in keeping with the Sendai consensus guidelines, but are slightly broader than those in the AGA guideline.
- Our approach to surveillance is largely in line with the AGA guideline, though it is slightly more conservative because of the known malignant potential of IPMNs; conversely, our surveillance approach is less aggressive than that suggested by the Sendai Consensus guidelines, which suggest surveillance up to every three to six months for some patients.

Main-duct IPMN — The management of MD-IPMN depends on the degree of ductal dilation (algorithm 1).

- ≥10 mm – If the duct is ≥10 mm in diameter, resection of MD-IPMN is recommended for patients who are good surgical candidates with reasonable life expectancy. This recommendation is based on the high rate of malignancy in MD-IPMN (approximately 70 percent) [49].

- 5 to 9 mm – If the duct is 5 to 9 mm in diameter, additional evaluation (EUS with fine-needle aspiration [FNA]) is recommended. Surgery is then indicated if there is evidence of thickened walls, intraductal mucin, or mural nodules on EUS, or if cytology is suspicious or positive for malignancy. If there is no evidence of thickened walls, intraductal mucin, or mural nodules in a patient with MD-IPMN, the results of the EUS are considered to be inconclusive.

  In such patients, we suggest resection of the IPMN if the patient is surgically fit and has a life expectancy of at least 10 years. This is because the association of malignancy with this degree of pancreatic duct dilation has not been well characterized [55]. One study that included 156 patients who underwent surgery for MD-IPMN with a main pancreatic duct diameter of 5 to 9 mm found high-grade dysplasia or carcinoma in 59 percent of patients [56]. However, this study may overestimate the risk since the patients included were those with indications for surgery. For patients not undergoing surgery, we obtain a magnetic retrograde cholangiopancreatography (MRCP) or CT scan in one year. Surgery should again be considered if the duct increases in size or if intramural nodules develop. If the duct is stable on repeat imaging, we lengthen the surveillance interval to every two years and continue it as long as the patient is a good surgical candidate.

- <5 mm – If the duct is <5 mm in diameter, we obtain a follow-up MRCP or CT in two years. As with other IPMNs, surgery is indicated if the duct increases in size or if intramural nodules develop. If the duct is stable on repeat imaging, we lengthen the surveillance interval to every two to three years and continue surveillance as long as the patient remains a good surgical candidate.

In addition to performing surgery for the reasons noted above, resection is indicated if the patient has symptoms attributable to the IPMN (eg, pancreatitis) regardless of the degree of ductal dilation.

However, because of the significant morbidity and mortality associated with pancreaticoduodenectomy or distal pancreatectomy, the decision to recommend surgery should take into account not only the degree of ductal dilation, but also factors such as the

patient's age and general health, the malignant risk of the lesion, and the suspicion for malignancy.

Branch-duct IPMN — Patients with BD-IPMN that has signs of malignant transformation or that is at high-risk for developing malignancy are typically managed with surgical resection. As with MD-IPMN, the decision to recommend surgery should take into account factors such as the patient's age and general health, the malignant risk of the lesion, and the suspicion for malignancy. The criteria for proceeding with surgery are the same for patients with single and multiple cysts.

For patients with BD-IPMN who are good surgical candidates, resection is generally indicated if there is obstructive jaundice in a patient with an IPMN in the head of the pancreas, if there is an enhancing solid component within the IPMN, or if there is associated main pancreatic duct dilation of ≥10 mm (algorithm 2). In addition, resection is indicated if the patient has symptoms attributable to the IPMN.

For patients who do not meet these criteria for surgery, further evaluation is indicated if worrisome features are present. Worrisome features include [19,54,57]:

- IPMN size ≥30 mm
- Thickened or enhancing cyst walls on imaging
- Associated pancreatitis
- Main pancreatic duct size of 5 to 9 mm in diameter
- Presence of a non-enhancing mural nodule
- An abrupt change in the caliber of the pancreatic duct with distal pancreatic atrophy

Surgery is indicated if there is evidence of thickened walls, intraductal mucin, or mural nodules on EUS, or if cytology is suspicious or positive for malignancy. A meta-analysis of 41 studies with 5788 patients found that many of these features were associated with an increased risk of malignancy, including cyst size ≥30 mm (odds ratio [OR] 62), presence of a mural nodule (OR 9), and dilation of the main pancreatic duct (OR 7) [58].

For patients who do not meet criteria for surgery, follow-up depends on the certainty of the EUS/cytology findings and the size of the IPMN. If the EUS findings or cytology are inconclusive or if a BD-IPMN is >30 mm, we typically suggest surgery for patients who are surgical candidates and have a life expectancy ≥10 years. For all other patients, surveillance is suggested.

The optimal surveillance approach is unclear. In its guideline, the AGA suggests a magnetic resonance imaging scan in one year and then every two years for a total of five years for

patients with pancreatic cysts provided there is no change in cyst size and the cyst does not develop other worrisome characteristics (eg, a solid component or dilation of the main pancreatic duct) [13]. On the other hand, the Sendai consensus guidelines suggest variable (but more aggressive) surveillance intervals based on the size of the IPMN (ranging from CT every two to three years for cysts <1 cm to EUS every three to six months for cysts >3 cm) [54]. Our approach is similar to the AGA guideline, though it is slightly more conservative given the known malignant potential of IPMNs (eg, we do not discontinue surveillance after five years if a patient remains a good surgical candidate).

We base our approach on the size of the IPMN:

- ≥30 mm – Repeat MRCP or CT in one year. If the IPMN is stable, continue surveillance with MRCP or CT every two years provided the patient remains a good surgical candidate.
- 10 to <30 mm – Repeat MRCP or CT in one year. If the IPMN is stable, continue surveillance with MRCP or CT every two years provided the patient remains a good surgical candidate. After five years, the surveillance interval can be lengthened to every three years.
- <10 mm – Repeat MRCP or CT in one year. If the IPMN is stable, continue surveillance with MRCP or CT every two years provided the patient remains a good surgical candidate. After five years, surveillance can be discontinued.

If during surveillance there are changes in the IPMN (increase in size, development of a solid component, or development/progression of main pancreatic ductal dilation), an EUS-FNA should be performed for further evaluation. The decision to recommend surgery or continue surveillance is then based on the EUS-FNA results as described above.

Combined main-duct and branch-duct IPMN — For patients with combined MD-IPMN and BD-IPMN, each lesion is managed as it would be if it were the only lesion. For example, if a patient has a MD-IPMN in the head of the pancreas with malignant features, and a BD-IPMN in the tail of the pancreas that is 12 mm and lacks malignant features, resection would be suggested for the MD-IPMN and surveillance for the BD-IPMN.

Surveillance following surgery — Following surgery, patients are at risk for recurrence of IPMN. In patients with noninvasive IPMN, the risk of developing a subsequent recurrence in the remaining pancreas is at least 5 percent [45,48,59,60]. In such patients, yearly follow-up with MRCP or CT is reasonable, with a lengthening in the surveillance interval if no changes are detected after several years, provided there are no other IPMNs that require more frequent surveillance (as may be the case if only a dominant lesion was resected). Criteria for surgical

resection of any IPMNs that were not resected, or new IPMNs that develop during surveillance, are the same as for the initial IPMN. (See 'Branch-duct IPMN' above.)

For patients with curative resection of invasive carcinoma arising from an IPMN, studies suggest that the risk of IPMN recurrence is 25 to 50 percent [60-63] and surveillance every six months is appropriate [49]. Patients found to have a recurrence of IPMN will generally require EUS for evaluation.

Surveillance for extrapancreatic malignancies — Patients with IPMN may be at risk for extrapancreatic malignancies, particularly gastric and colon cancer. However, the magnitude of risk for extrapancreatic malignancies and the benefit of surveillance strategies remain uncertain. A reasonable approach is to perform an upper endoscopy and colonoscopy in patients with established IPMN, with subsequent surveillance guided by the initial findings and individual patient factors. (See "Intraductal papillary mucinous neoplasm of the pancreas (IPMN): Pathophysiology and clinical manifestations", section on 'Extrapancreatic malignancies' and "Colorectal cancer: Epidemiology, risk factors, and protective factors", section on 'Risk factors'.)

PROGNOSIS

Patients who do not undergo surgery — Patients with intraductal papillary mucinous neoplasm (IPMN) of the pancreas who do not have indications for surgery are still at risk for developing pancreatic cancer and require surveillance [49]. The methods used for surveillance and the frequency of surveillance depend on the type of IPMN (main duct or branch duct) and the size of the lesion. (See 'Main-duct IPMN' above and 'Branch-duct IPMN' above and "Intraductal papillary mucinous neoplasm of the pancreas (IPMN): Pathophysiology and clinical manifestations", section on 'Pancreatic malignancy'.)

In a study of 60 patients with branch-duct (BD) IPMN who did not undergo surgery, invasive carcinoma subsequently developed in five patients (8 percent) and the risk of developing cancer was approximately 1 percent/year [64]. In a second study that included 170 patients who underwent surveillance, 97 patients (57 percent) ultimately had surgery [65]. The indications for surgery were endoscopic or radiographic changes in the IPMN (55 percent), concern that the IPMN may be premalignant (eg, main-duct [MD] IPMN or BD-IPMN that met resection criteria; 29 percent), and suspicious cytology (11 percent). Invasive carcinomas were present in 18 patients (19 percent of the patients who underwent resection and 11 percent of the patients overall), 11 of which were tubular carcinomas (11 percent of those undergoing resection, 6 percent of the patients overall).

In a study that included 45 patients with IPMN who did not meet criteria for resection and who had at least one follow-up magnetic resonance cholangiopancreatography, no evolution of the IPMN was seen in 27 patients (60 percent) and morphologic changes (eg, increasing cyst diameter, appearance of mural nodules) developed in 18 patients (40 percent) [66]. In this series, no patient had malignant transformation.

Prognosis following surgery — The overall prognosis following surgery in patients with IPMN containing high-grade dysplasia (carcinoma in situ) is favorable, with up to 60 to 80 percent three-year survival, with patients with BD-IPMN faring better than those with MD-IPMN [67]. Prognosis is less favorable when an invasive component is identified:

- Only one-fifth of patients with invasive carcinoma and positive margins at the time of resection are alive at three years [48,68,69].
- Patients with lymph node metastases have worse outcomes than those with negative nodes. In a series of 104 patients with invasive carcinoma (58 percent node-negative), five-year disease-specific survival rates for those with positive and negative nodes were 29 and 80 percent, respectively [70]. In addition, patients with a lower lymph node ratio (calculated by dividing the total number of nodes harboring metastases by the total number of examined nodes) had better outcomes.

Overall, the prognosis of invasive IPMN-associated adenocarcinoma is better than that of pancreatic ductal adenocarcinoma (five-year survival 31 to 62 versus 9 to 20 percent, respectively) [71-76]. This is largely attributable to lower rates of advanced T stage, nodal metastases, high tumor grade, positive resection margins, and perineural as well as vascular invasion [75,77]. However, if any of these features is present in the resected specimen, survival outcomes are similar to those of pancreatic ductal adenocarcinoma. This was illustrated in a report from the Surveillance, Epidemiology, and End Results database, which compared outcomes of 729 patients with resected invasive IPMN-associated adenocarcinoma and 8082 patients with resected pancreatic ductal adenocarcinoma. Five-year survival rates for node-negative IPMN-associated adenocarcinoma and ductal cancer were 35 and 17 percent, respectively, whereas the corresponding values for node-positive disease were 9 and 7 percent.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Pancreatic cancer" and "Society guideline links: Pancreatic cysts".)

SUMMARY AND RECOMMENDATIONS

- Intraductal papillary mucinous neoplasm (IPMN) of the pancreas is a cystic neoplasm of the pancreas with malignant potential. It may involve the main pancreatic duct, the branch ducts, or both. Patients with IPMN involving the main duct are at increased risk of cancer compared with patients who have side-branch IPMN. (See 'Introduction' above.)

- The approach to the diagnosis of pancreatic cystic neoplasms typically starts with cross-sectional imaging (magnetic resonance imaging [MRI] with magnetic resonance cholangiopancreatography [MRCP] or computed tomography [CT]). Additional evaluation with endoscopic ultrasound (EUS) with fine-needle aspiration (FNA) may be needed to confirm a diagnosis or to assess for malignant features. (See "Pancreatic cystic neoplasms: Clinical manifestations, diagnosis, and management".)

- The evaluation of a patient with IPMN aims to determine if the patient has or is at high-risk of developing a malignancy. MRI with MRCP or a pancreatic protocol CT scan are typically the first imaging tests used to diagnose and characterize IPMN (image 1 and image 2). These studies can assess the neoplasm and its relationship to surrounding structures, may suggest lymph node involvement, and can detect metastatic disease [4-7]. (See 'Evaluation for malignancy' above.)

  Additional evaluation with EUS-FNA may not be needed if there are clear indications for surgery demonstrated on cross-sectional imaging, such as IPMN with a main pancreatic duct diameter ≥10 mm, an enhancing solid component within the cyst, or if the patient has obstructive jaundice or other symptoms attributable to the cyst. (See 'Management' above.)

  For patients without an indication for surgery, additional evaluation of the IPMN with EUS-FNA is needed if there are concerning findings on cross-sectional imaging such as (see 'Indications for additional evaluation' above):

  - IPMN size ≥30 mm
  - Thickened or enhancing cyst walls on imaging
  - Presence of a non-enhancing mural nodule
  - Associated pancreatitis
  - A dilated main pancreatic duct that is 5 to 9 mm in diameter
  - An abrupt change in the caliber of the pancreatic duct with distal pancreatic atrophy

The optimal approach to the evaluation of IPMNs ≥10 mm but <30 mm in size with no other concerning features is unclear. Our approach is to offer patients the option of undergoing additional evaluation with EUS-FNA if the patient is particularly concerned about malignancy. If additional evaluation is not performed, we follow the patient with surveillance imaging. For IPMNs that are <10 mm in size, we obtain surveillance imaging.

- Resection is typically recommended for IPMNs with high-grade dysplasia, IPMNs that have progressed to invasive carcinoma, and IPMNs with features concerning for malignancy or that are at high risk for developing malignancy. We suggest following the approach outlined in the algorithms (algorithm 2 and algorithm 1) (**Grade 2C**). However, optimal management is not clear and other groups advocate different approaches. (See 'Management' above.)

  Because of the significant morbidity and mortality associated with pancreaticoduodenectomy or distal pancreatectomy, the decision to recommend surgery should take into account factors such as the patient's age and general health, the malignant risk of the lesion, and the suspicion for malignancy. Cysts not meeting criteria for resection are typically followed with surveillance imaging.

ACKNOWLEDGMENT

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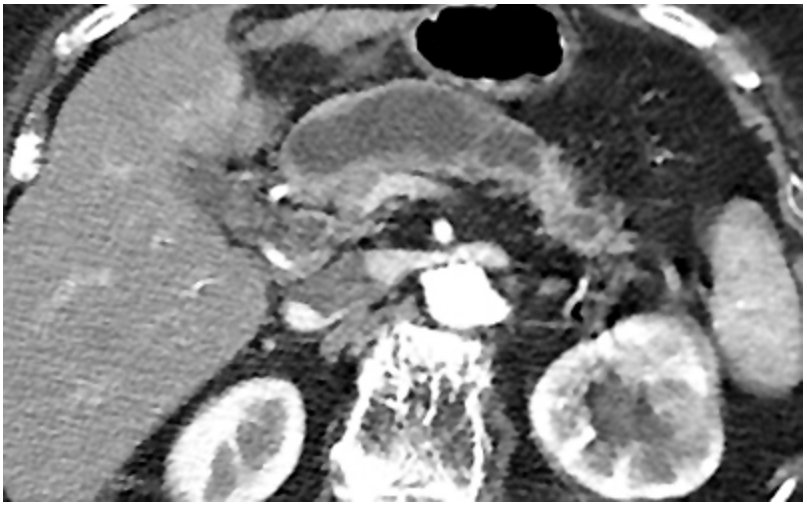
Topic 16137 Version 35.0

GRAPHICS

Computed tomography of intraductal papillary mucinous neoplasm with parenchymal atrophy



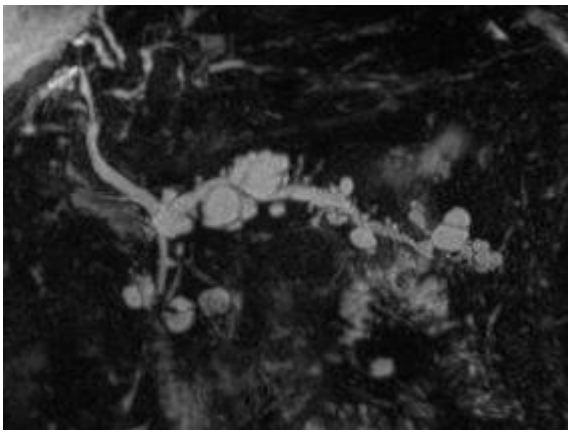
CT scan of main duct intraductal papillary mucinous neoplasm, revealing a markedly dilated pancreatic duct with parenchymal atrophy.

CT: computed tomography.

Courtesy of Kevin McGrath, MD, and Asif Khalid, MD.

Graphic 51921 Version 4.0

Mixed-type intraductal papillary mucinous neoplasm of the pancreas

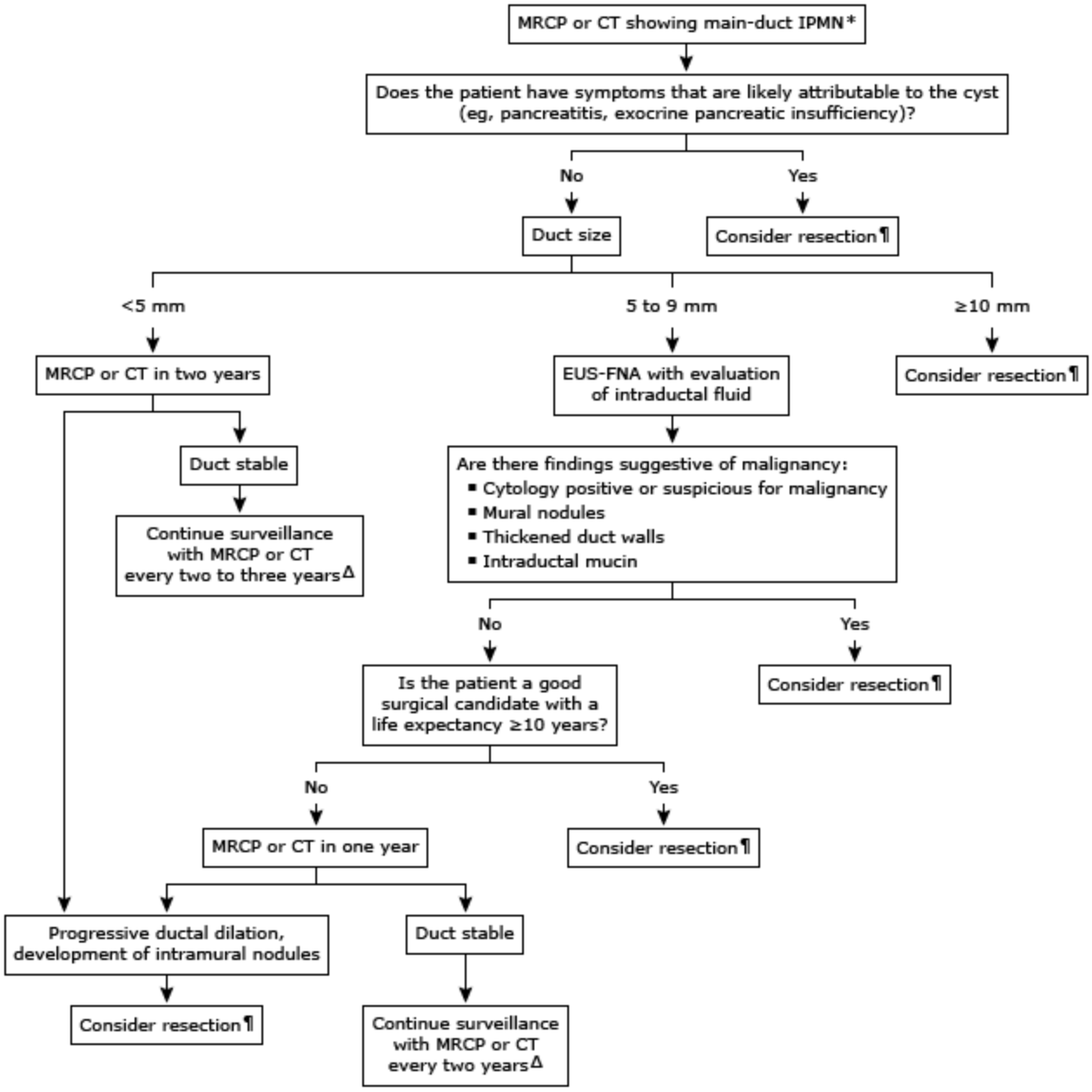


Magnetic resonance cholangiopancreatography revealing mixed-type intraductal papillary mucinous neoplasm. There are multiple dilated branch ducts and a moderately dilated main pancreatic duct in the pancreatic body region.

Courtesy of Kevin McGrath, MD.

Graphic 101892 Version 1.0

Management of main-duct IPMN



IPMN: intraductal pancreatic mucinous neoplasm; MRCP: magnetic resonance cholangiopancreatography; CT: computed tomography; EUS: endoscopic ultrasound; FNA: fine-needle aspiration.

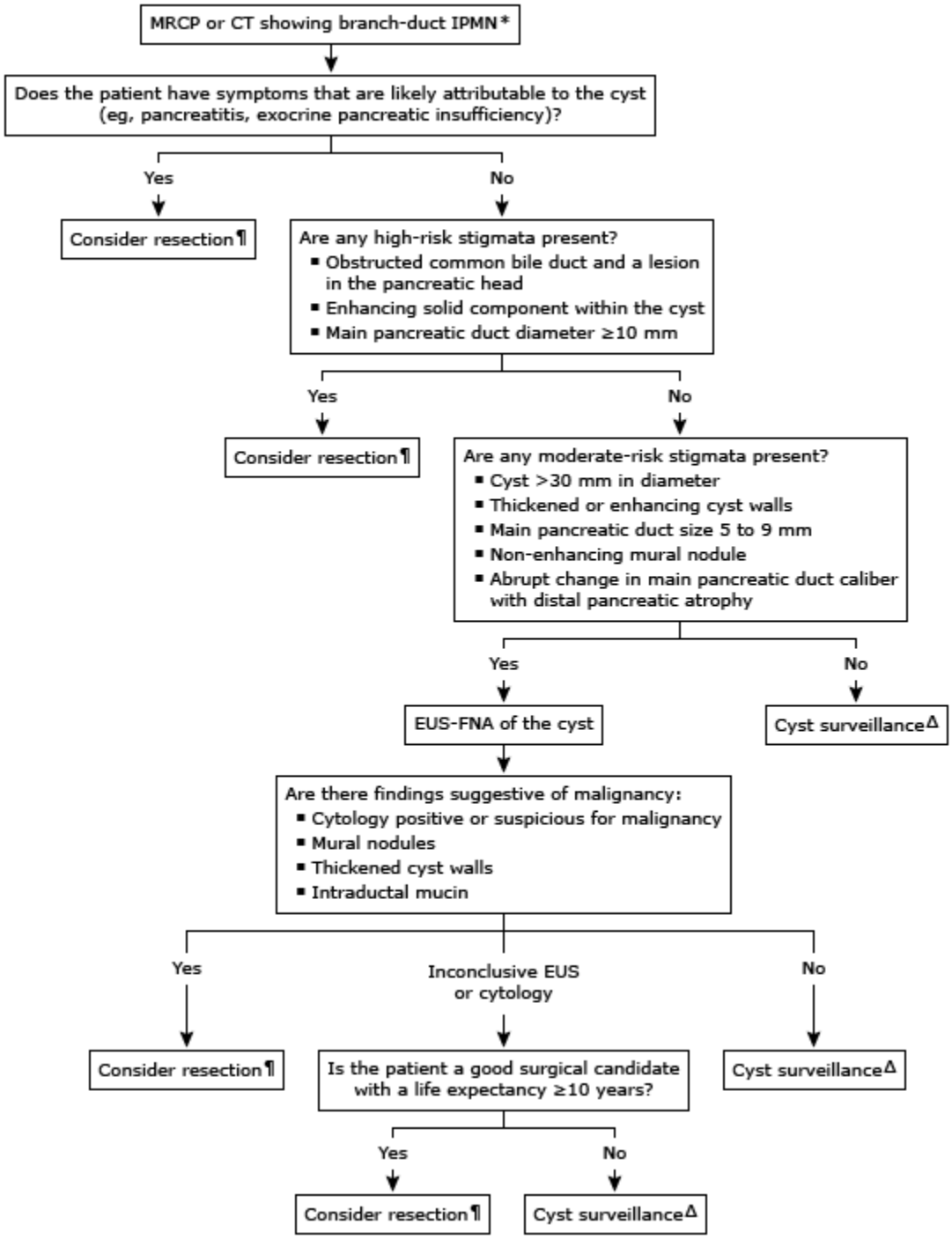
* For patients with multiple cysts, each lesion is managed as it would be if it were the only lesion. This algorithm reflects the authors' approach to management, which is generally consistent with published guidelines. Refer to UpToDate topic reviews on IPMN management for additional details.

¶ The decision to recommend surgery should take into account factors such as the patient's age and general health, the malignant risk of the specific lesion, and the suspicion for malignancy.

Δ Provided the patient remains a good surgical candidate.

Graphic 104512 Version 1.0

Management of branch-duct IPMN



IPMN: intraductal pancreatic mucinous neoplasm; MRCP: magnetic resonance cholangiopancreatography; CT: computed tomography; EUS: endoscopic ultrasound; FNA: fine-needle aspiration.

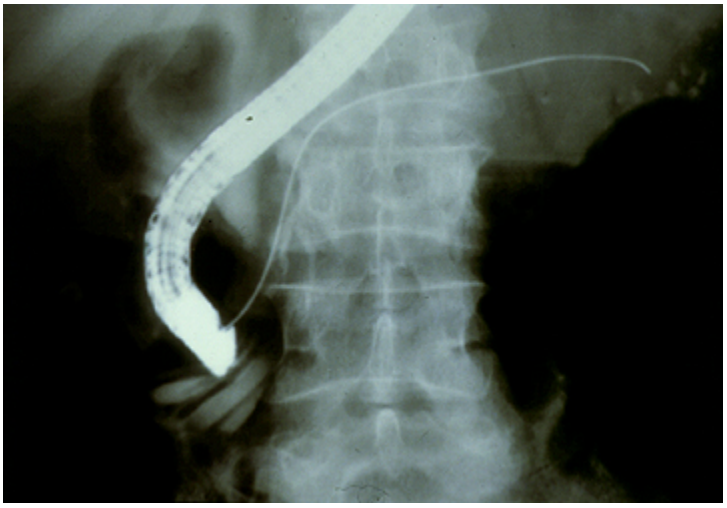
* For patients with multiple cysts, each lesion is managed as it would be if it were the only lesion. Published guidelines on the management of pancreatic cystic neoplasms are variable. This algorithm reflects the authors' approach, which is largely consistent with published guidelines. Refer to UpToDate topic reviews on IPMN management for additional details.

¶ The decision to recommend surgery should take into account factors such as the patient's age and general health, the malignant risk of the specific lesion, and the suspicion for malignancy.

Δ Surveillance recommendations will depend on the size of the cyst, whether the patient is a good surgical candidate, and whether the cyst is stable on repeat imaging. Refer to UpToDate topics on the management of IPMN for details.

Graphic 104502 Version 1.0

Pancreatoscopy

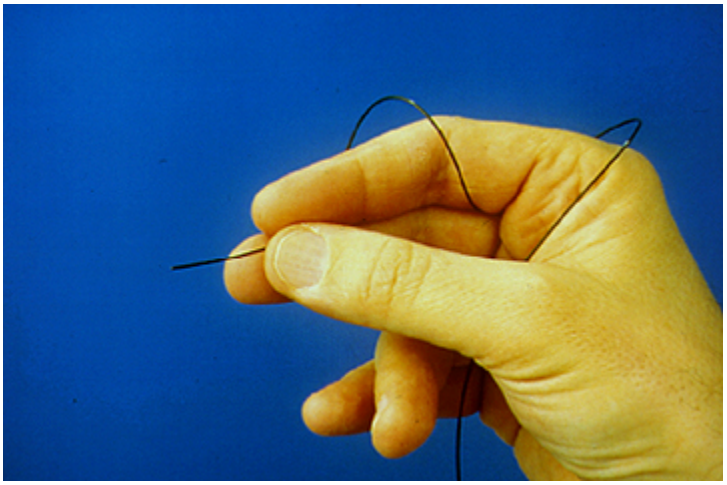


Radiologic view of an ultrathin pancreatoscope in the pancreatic duct.

Courtesy of Jurgen F Riemann, MD, PhD.

Graphic 62216 Version 2.0

Ultrathin pancreatoscope



Ultrathin pancreatoscopes with an external diameter of 5 mm have been developed.

Courtesy of Jurgen F Riemann, MD, PhD.

Graphic 81337 Version 1.0

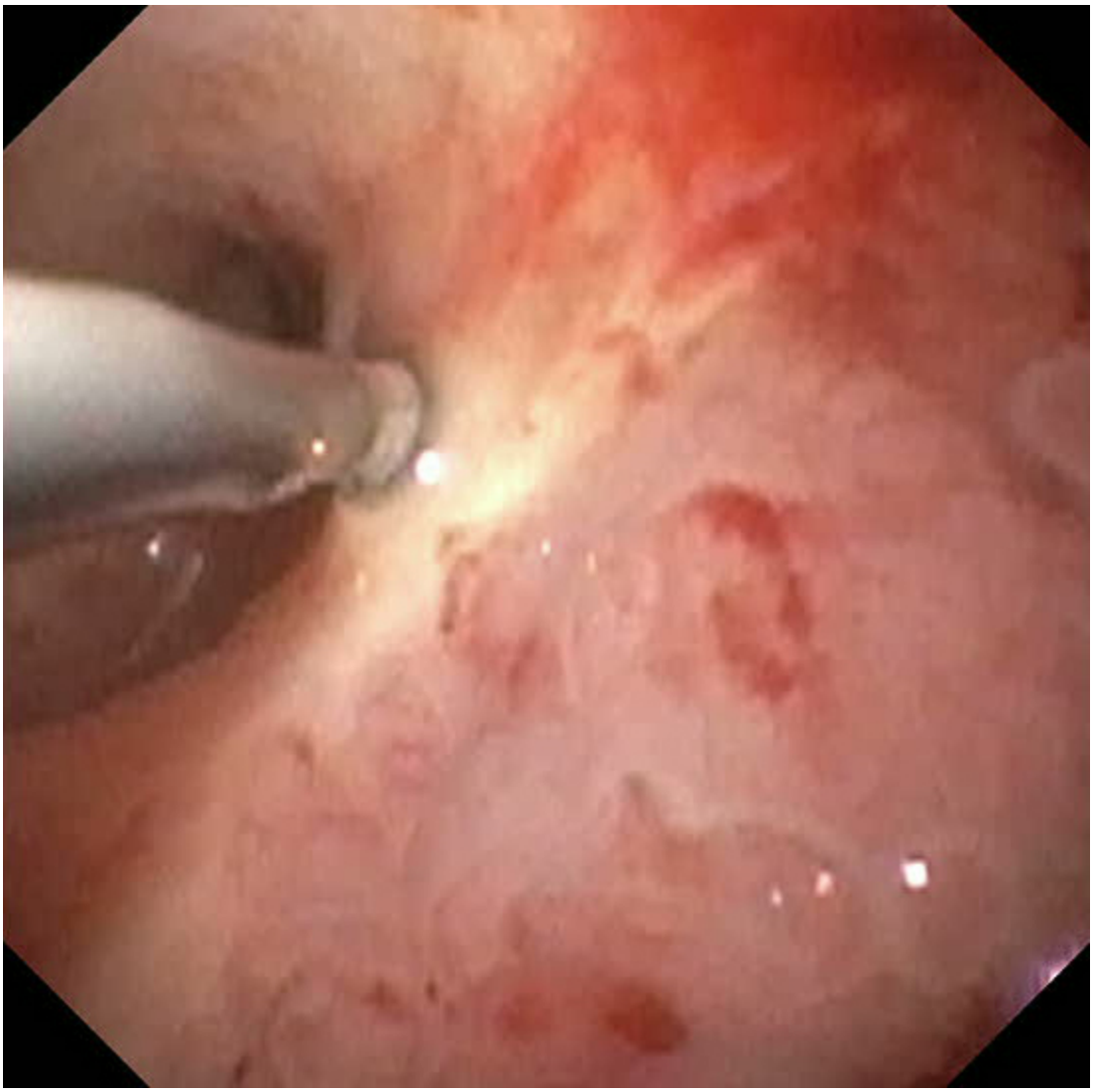
Pancreatoscopy showing a pancreatic tumor

Identification of the papillary projections by pancreatoscopy.

Courtesy of Michael J Levy, MD, Enrique Vazquez-Sequeiros, MD, and Maurits J Wiersema, MD.

Graphic 71357 Version 3.0

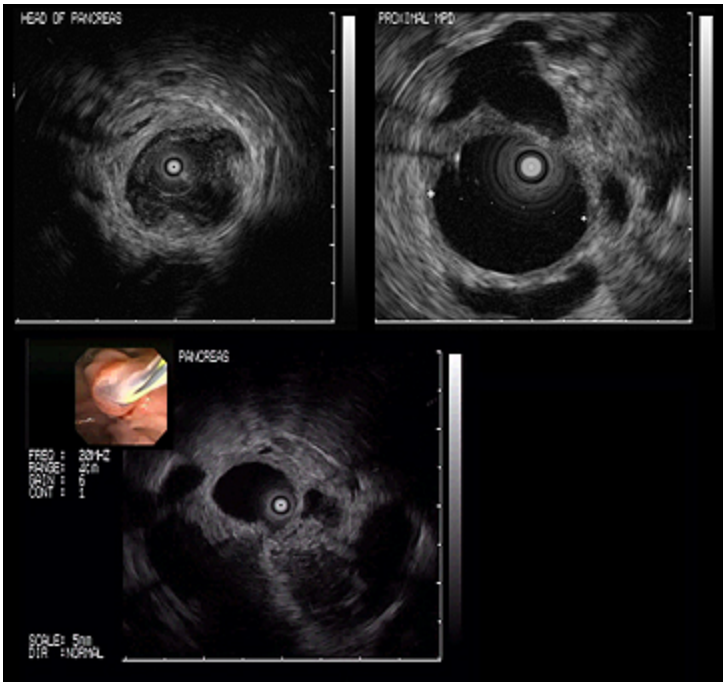
Pancreatoscopy of a main-duct intraductal papillary mucinous tumor (IPMN)



Digital pancreatoscopy of a main-duct IPMN in the pancreatic head. This lesion was not seen on magnetic resonance cholangiopancreatography or endoscopic ultrasound. A noninvasive adenocarcinoma was detected when the lesion was surgically resected.

Graphic 105589 Version 1.0

Intraductal papillary mucinous neoplasm



Intraductal ultrasound of a patient with an intraductal papillary mucinous neoplasm. The mucin and soft tissue prominence of the main pancreas duct wall were confined to the head and neck.

Courtesy of Maurits Wiersema, MD.

Graphic 79828 Version 2.0

Exocrine pancreatic cancer TNM staging AJCC UICC 8th edition

Primary tumor (T)	
T category	**T criteria**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ*. This includes high-grade pancreatic intraepithelial neoplasia (PanIn-3), intraductal papillary mucinous neoplasm with high-grade dysplasia, intraductal tubulopapillary neoplasm with high-grade dysplasia, and mucinous cystic neoplasm with high-grade dysplasia.
T1	Tumor ≤2 cm in greatest dimension
T1a	Tumor ≤0.5 cm in greatest dimension
T1b	Tumor >0.5 and <1 cm in greatest dimension
T1c	Tumor 1 to 2 cm in greatest dimension
T2	Tumor >2 and ≤4 cm in greatest dimension
T3	Tumor >4 cm in greatest dimension
T4	Tumor involves the celiac axis, superior mesenteric artery, and/or common hepatic artery, regardless of size
Regional lymph nodes (N)	
N category	**N criteria**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in one to three regional lymph nodes
N2	Metastasis in four or more regional lymph nodes
Distant metastasis (M)	
M category	**M criteria**
M0	No distant metastasis
M1	Distant metastasis

Prognostic stage groups			
When T is…	**And N is…**	**And M is…**	**Then the stage group is…**
Tis	N0	M0	0

T1	N0	M0	IA
T1	N1	M0	IIB
T1	N2	M0	III
T2	N0	M0	IB
T2	N1	M0	IIB
T2	N2	M0	III
T3	N0	M0	IIA
T3	N1	M0	IIB
T3	N2	M0	III
T4	Any N	M0	III
Any T	Any N	M1	IV

TNM: tumor, node, metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control.

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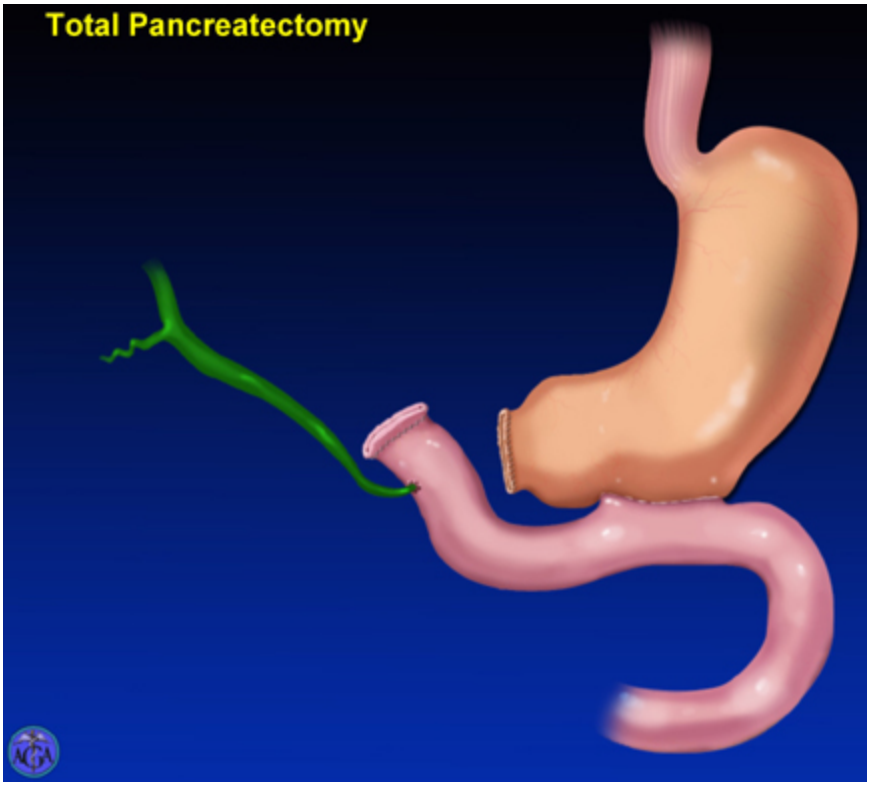
Graphic 111135 Version 9.0

Total pancreatectomy



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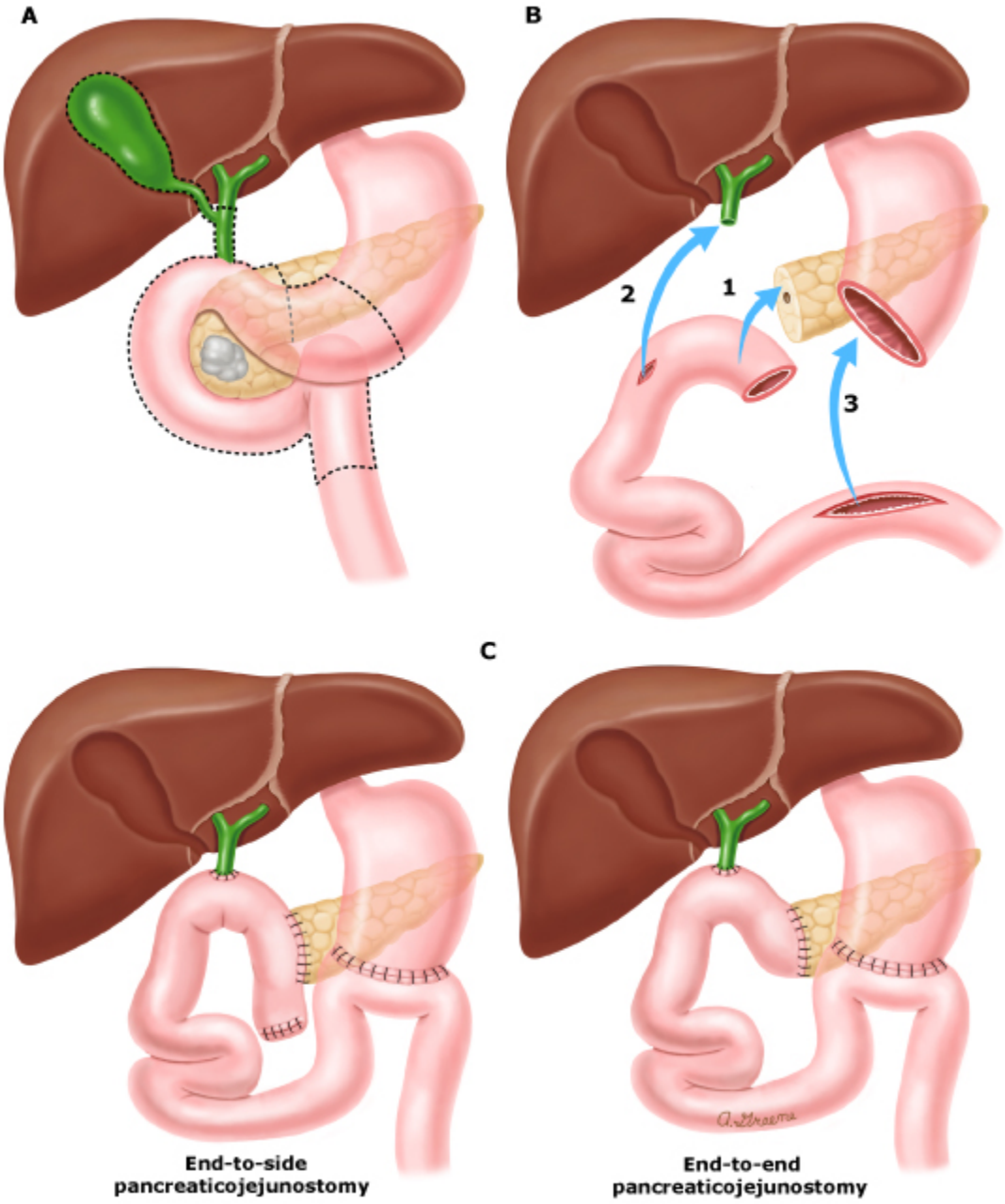
Graphic 68307 Version 4.0

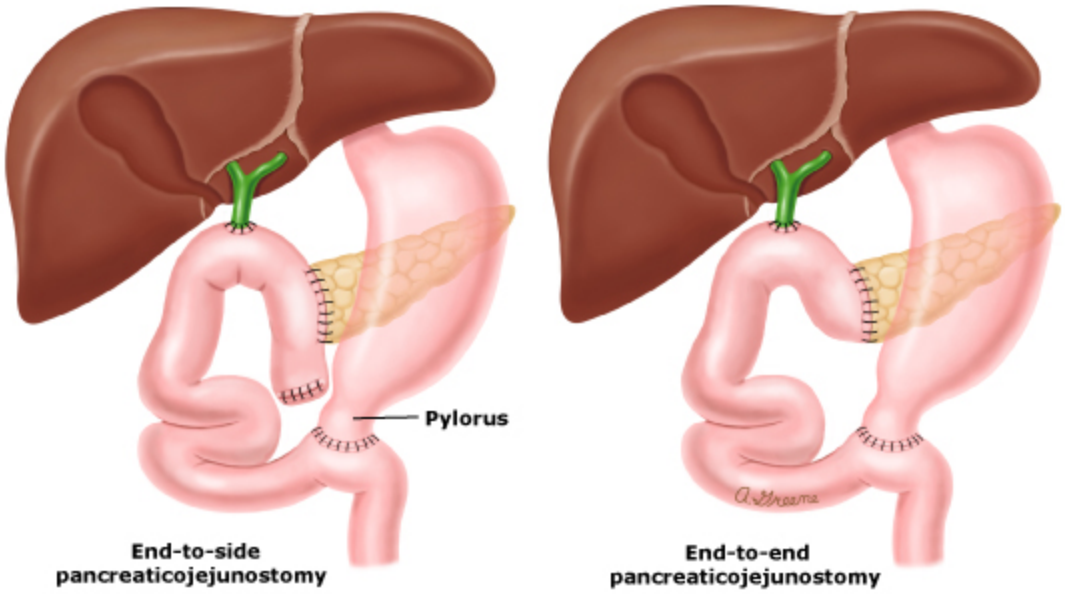
Conventional pancreaticoduodenectomy (Whipple procedure; Polya)



Polya refers to the style with which the gastrojejunostomy is constructed.

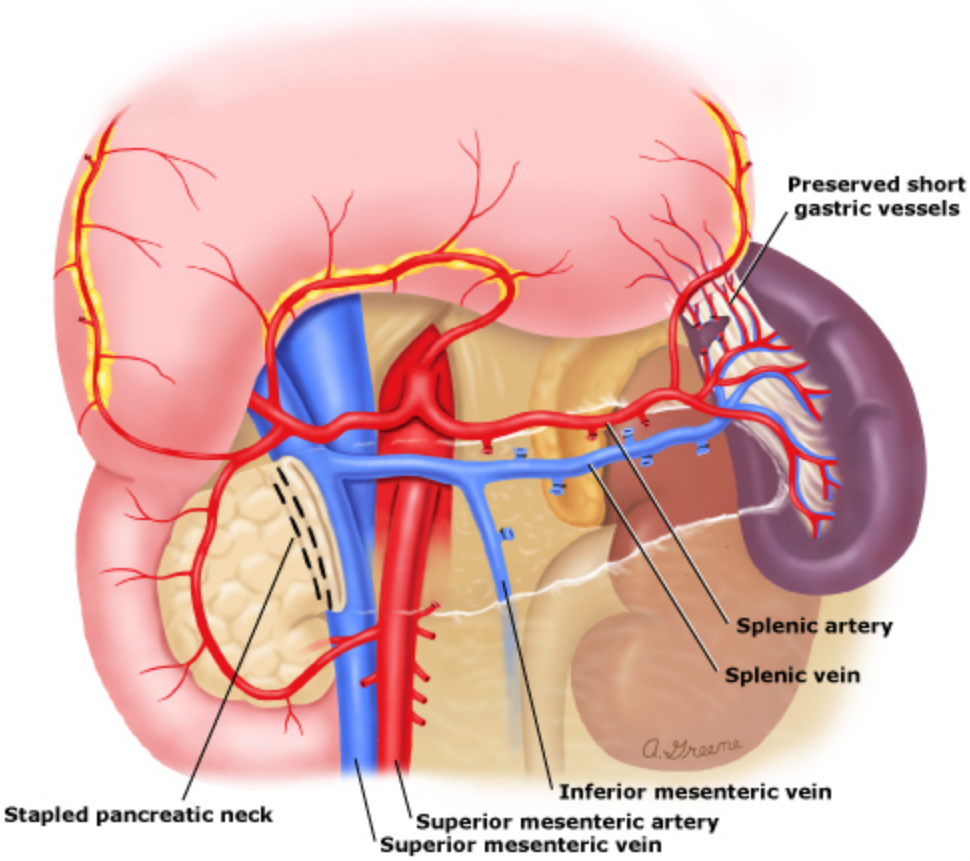
Graphic 82519 Version 3.0

Pylorus-preserving pancreaticoduodenectomy



Graphic 60689 Version 2.0

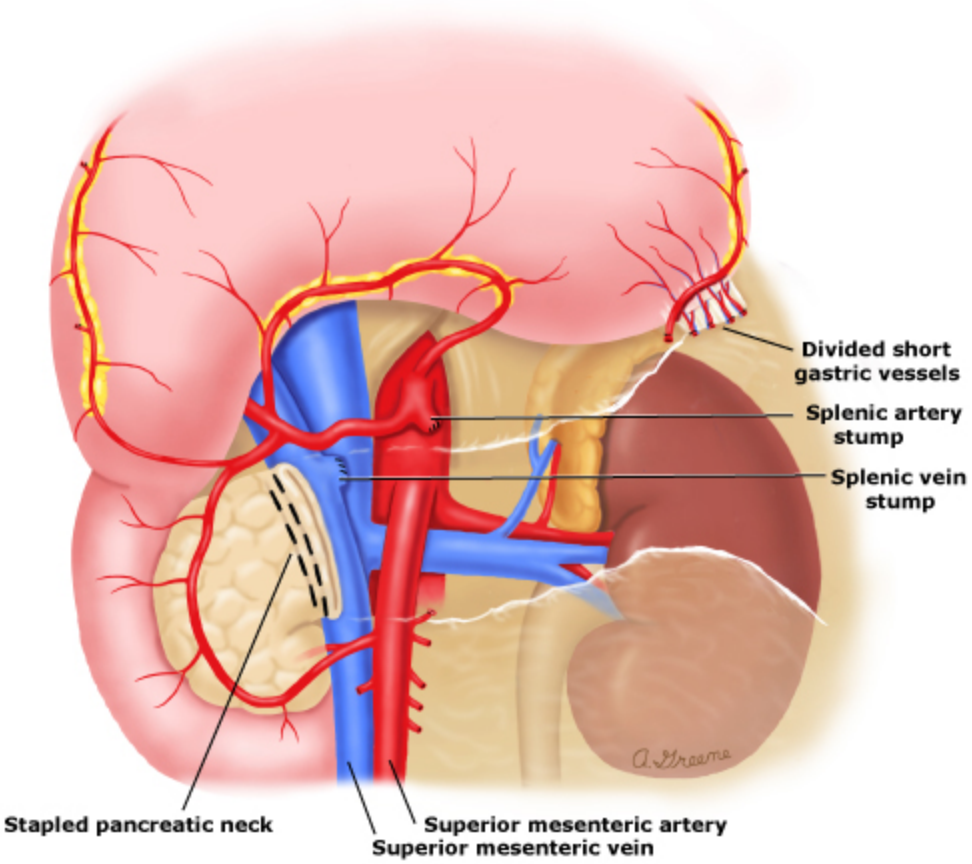
Spleen preserving distal pancreatectomy



Operative bed following distal pancreatectomy with splenic preservation.

Graphic 64624 Version 4.0

Distal pancreatectomy with splenectomy



Operative bed following distal pancreatectomy and splenectomy.

Graphic 74555 Version 4.0

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Sunil G Sheth, MD No relevant financial relationship(s) with ineligible companies to disclose. **Tara S Kent, MD, FACS** No relevant financial relationship(s) with ineligible companies to disclose. **David C Whitcomb, MD, PhD** Equity Ownership/Stock Options: Ariel Precision Medicine [Genetic testing]. Consultant/Advisory Boards: AbbVie [Pancreatic enzyme use]; Ariel Precision Medicine [Genetic testing]; BioNTech [Acute pancreatitis]; Nestle [Chronic pancreatitis]; Novartis [Chronic pancreatitis]; Organon [Pancreatic enzymes use]. All of the relevant financial relationships listed have been mitigated. **Shilpa Grover, MD, MPH, AGAF** No relevant financial relationship(s) with ineligible companies to disclose.

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