

## Interdisciplinary Management of an Intraductal Papillary Mucinous Neoplasm of the Pancreas

Rajesh M. Nair, MD, James S. Barthel, MD, Barbara A. Centeno, MD,  
Junsung Choi, MD, Jason B. Klapman, MD, and Mokenge P. Malafa, MD

**Background:** Intraductal papillary mucinous neoplasm (IPMN) of the pancreas is less common than classic invasive ductal adenocarcinoma of the pancreas but is being diagnosed with greater frequency since its clinicopathologic features are now clearly defined. Often multifocal in its existence along the pancreatic duct, IPMN is associated with a significant risk for recurrence and warrants vigilant surveillance, even after a margin-negative resection.

**Methods:** The authors present a case highlighting important features in the diagnosis, workup, and management of IPMN. They also review existing literature highlighting epidemiology, findings of molecular studies, and current treatment recommendations.

**Results:** Physicians and patients must carefully weigh the risks and benefits associated with treatment options. Limited resection in a patient with a high likelihood of multifocal disease preserves pancreatic parenchyma and reduces the risk of developing pancreatic endocrine and exocrine insufficiency. Though the risk of developing invasive cancer in the remnant is small, the prognosis is worse if it does develop. Conversely, total pancreatectomy eliminates the risk of future malignancy but involves life-long insulin and exogenous pancreatic enzyme dependence and significant associated morbidity.

**Conclusions:** Decision making for effective treatment of IPMN is complex and requires attention to detail by an interdisciplinary team with experience in the diagnosis and management of these tumors. Treatment must be individualized based on patient life expectancy in terms of remaining years and overall quality. Molecular profiling of these lesions may allow for more precise tailoring of treatment in the future.

### Case Presentation

**Dr Malafa:** A 67-year-old white woman with a history of hyperlipidemia was taking pravastatin in an effort to improve this condition. She developed a mild elevation of her transaminases aspartate aminotransferase and alanine aminotransferase. An abdominal ultrasound revealed fatty infiltration of the liver and mild dilatation of the common bile duct to 9 mm and of the pancreat-

ic duct to 5 mm. This study was followed by a computed tomography (CT) scan of the abdomen that confirmed the presence of biliary and pancreatic ductal dilatation and also showed a 2.3-cm cystic mass in the body of the pancreas. At this point, the differential diagnosis was broad (Table 1). She then underwent endoscopic retrograde cholangiopancreatography (ERCP). Dr Klapman, please review the findings.

**Dr Klapman:** Cystic, bulbous dilatation of the main pancreatic duct and its side branches was seen on completion of the pancreatogram (Fig 1). However, filling the pancreatic ductal system with contrast was difficult secondary to resistance. No discrete strictures were seen, but the duct had an irregular appearance and was filled with linear filling defects. Brushings of the duct were performed, but cytology was unrevealing.

**Dr Malafa:** The patient remained symptom-free and was referred to our institute for further evaluation. Her past medical history was significant for hyperlipidemia,

---

From the Gastrointestinal Tumor Program (RMN, JSB, BAC, JC, JBK, MPM) and the Departments of Surgery (RMN, MPM), Gastroenterology (JSB, JBK), Pathology (BAC), and Radiology (JC) at the H. Lee Moffitt Cancer Center & Research Institute, Tampa, Florida. Submitted February 28, 2008; accepted June 5, 2008.

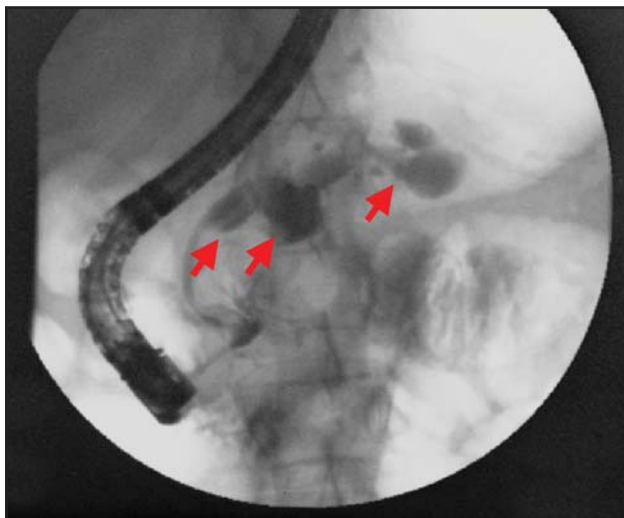
Address correspondence to Mokenge P. Malafa, MD, Gastrointestinal Tumor Program, Moffitt Cancer Center 12902 Magnolia Drive, SRB-3, Tampa, FL 33612. E-mail: mokenge.malafa@moffitt.org

**Abbreviations used in this paper:** IPMN = intraductal papillary mucinous neoplasm, ERCP = endoscopic retrograde cholangiopancreatography, EUS = endoscopic ultrasound, PanIN = pancreatic intraepithelial neoplasia, FNA = fine-needle aspiration.

hypertension, and osteoarthritis. She had previously undergone total abdominal hysterectomy for benign disease and had no history of cholecystectomy or cholelithiasis. She had a 25-pack-year history of smoking but had quit 25 years prior to evaluation. She consumed two to three alcoholic beverages daily and had done so for many years. Family history was significant for coronary artery disease in her father and leukemia in a brother. Physical examination was unremarkable. Repeat serum liver function studies including transaminases were all within normal reference ranges for the hospital laboratory. It was recommended that the patient undergo endoscopic ultrasound (EUS) of the pancreatic mass for visual assessment and potential biopsy.

**Table 1. — Classification of Cystic Masses of the Pancreas**

<b>Inflammatory</b>
<ul style="list-style-type: none"> <li>• Pseudocysts</li> <li>• Retention cysts secondary to chronic pancreatitis</li> </ul>
<b>Congenital/Hereditary</b>
<ul style="list-style-type: none"> <li>• Simple or solitary true cysts</li> <li>• Polycystic diseases</li> </ul>
<b>Infectious</b>
<b>Neoplastic</b>
<ul style="list-style-type: none"> <li>• Inherently cystic <ul style="list-style-type: none"> <li>• Serous cystadenoma</li> <li>• Mucinous cystic neoplasms</li> </ul> </li> <li>• Solid neoplasms with cystic degeneration <ul style="list-style-type: none"> <li>• Solid pseudo-papillary tumor</li> <li>• Cystic pancreatic endocrine tumor</li> </ul> </li> <li>• Intraductal neoplasms <ul style="list-style-type: none"> <li>• Intraductal papillary mucinous neoplasms</li> </ul> </li> </ul>
<b>Miscellaneous</b>
<ul style="list-style-type: none"> <li>• Lymphoepithelial cyst of the pancreas</li> </ul>

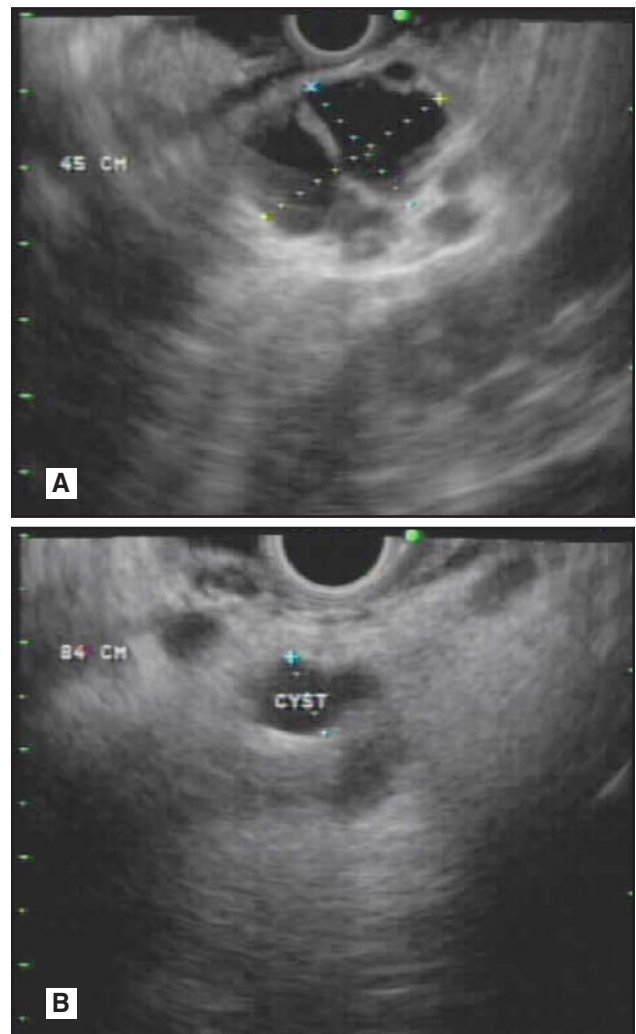


**Fig 1. —** Areas of cystic dilatation (arrows) of the pancreatic ductal system seen at ERCP.

**Dr Klapman:** A multiloculated 2.7 × 2.0-cm cystic mass was present at the junction of the body and tail of the pancreas, communicating directly with a dilated (5.9 mm) main pancreatic duct. A 7-mm cystic mass was noted in the head of the pancreas but appeared to be a simple cyst. Fine-needle aspiration (FNA) was performed of both lesions (Fig 2).

**Dr Malafa:** Dr Centeno, please describe the FNA findings.

**Dr Centeno:** We obtained 1 mL of reddish fluid from the head lesion. The specimen was interpreted as negative for malignancy with only a few epithelial cells noted other than blood. A 10-mL specimen of light pink fluid with interspersed white mucoid strands was obtained from the body lesion. Benign cyst-lining cells with minimal atypia, rare histiocytes and lymphocytes,



**Fig 2. —** EUS revealing cystic lesions in the pancreas. (A) Multi-lobulated 2.7-cm cystic mass at the junction of the body and tail of the pancreas. Communication with the main pancreatic duct, though present, is not visualized. Note the thick appearance of the septa, a characteristic frequently noted in cystic mucinous neoplasms of the pancreas. (B) A 7-mm head lesion with characteristics of a simple cyst.

and mucinous fluid were seen. I did not detect malignant cells. A mucicarmine stain was positive. These results are compatible with a neoplastic mucinous cyst (Fig 3). In addition, serum and fluid from the body lesion were submitted for measurement of carcinoembryonic antigen (CEA) tumor marker levels and amylase levels (Table 2).

**Dr Malafa:** A follow-up CT was performed. Did this demonstrate any changes?

**Dr Choi:** The CT (Fig 4) showed a 3.1 × 4.1-cm complex cystic mass abutting the splenic artery and vein at the junction of the body and tail of the pancreas. Obvious septations were present within the mass. Although the pancreatic duct was dilated throughout the gland, it was most pronounced adjacent to the mass in the body of the gland. In the tail, the ductal dilatation was associated with significant glandular atrophy. No cystic lesion was seen in the head of the gland.

Table 2. — Results of Cyst Fluid Analysis

Test (Normal Serum Range)	Serum	Cyst Fluid
Amylase (30 –110 U/L)	109 U/L	22,470 U/L
CA 19-9 (< 37 U/mL)	6 U/mL	7,240 U/mL
CEA (0 – 5 ng/mL)	0.8 ng/mL	608 ng/mL

**Dr Malafa:** The patient's case was discussed at the weekly meeting of the Institutional Multidisciplinary Gastrointestinal Tumor Board. Though no malignant cells were found on cytology, the presence of mucin in the fluid coupled with the mass's appearance on EUS and CT suggested the presence of a mucin-producing cystic neoplasm. The consensus opinion of the Tumor Board was that the patient should undergo surgical exploration for potential resection. Based on the intimate involvement of the mass with the splenic vessels, it was believed that splenic preservation would be unlikely. This was explained to the patient, who was agreeable

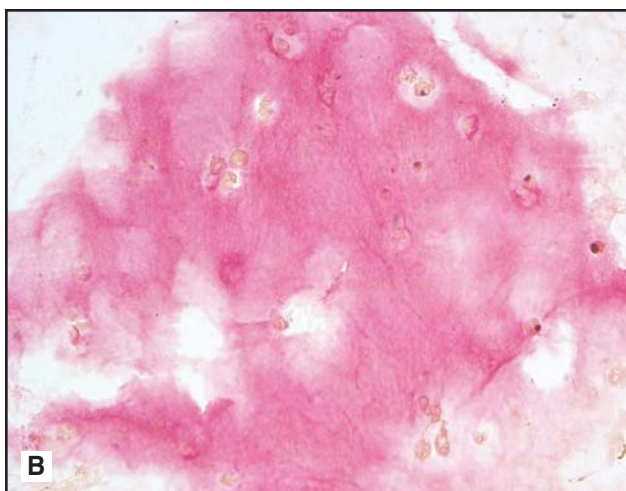
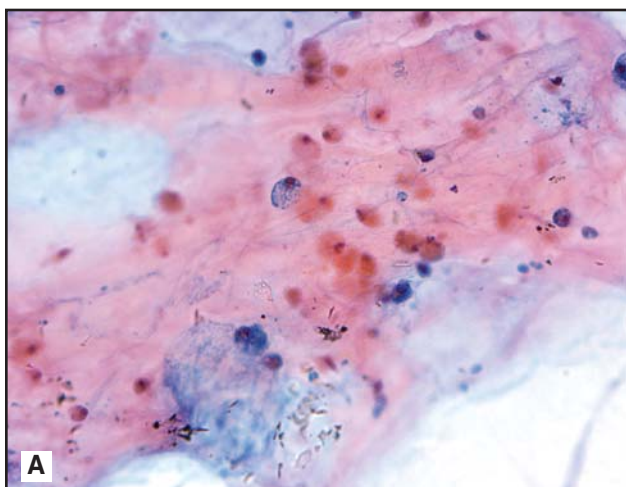


Fig 3. — FNA of cystic mass in the body of the pancreas. (A) Higher power demonstrates degenerated epithelial cells and histiocytes that are characteristically found in the mucin from the neoplastic cysts (Papanicolaou, × 40). (B) The mucicarmine stain confirms the presence of a uniform layer of thick background mucin (mucicarmine, × 40).

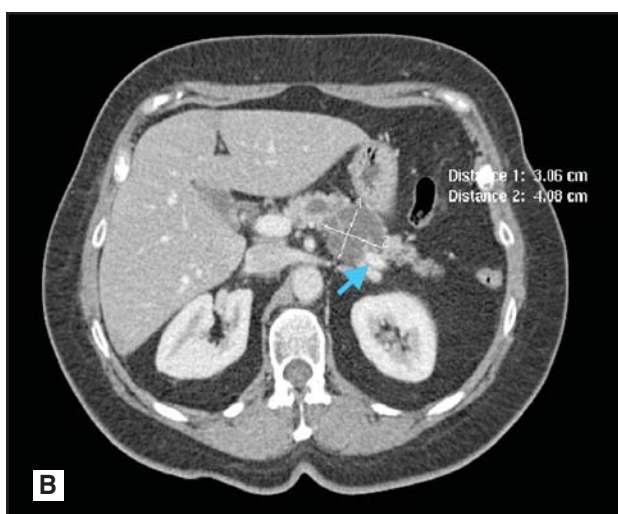
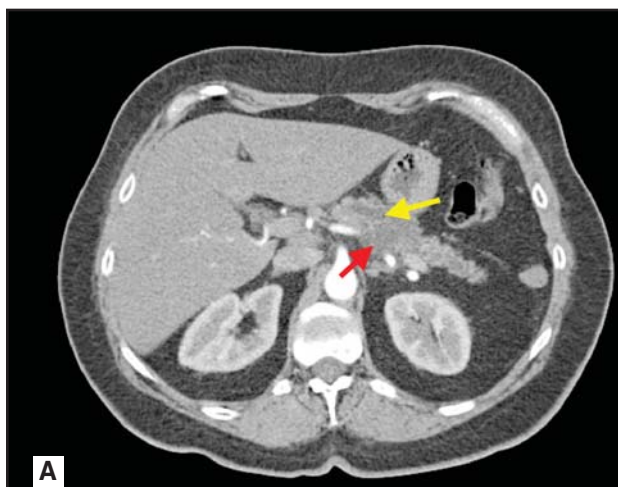


Fig 4. — Triple-phase CT. (A) Arterial phase CT demonstrates subtle septations (yellow arrow) within a cystic body mass. Note abutment of the splenic artery (red arrow). (B) Venous phase CT demonstrating relationship of the mass to the splenic vein (blue arrow).

with the treatment plan. Secondary to the high likelihood of splenectomy, the patient received preoperative vaccination against *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitidis*.

After standard surgical exploration was performed to rule out unexpected peritoneal or other metastatic disease, attention was turned fully to the pancreas. Intraoperative ultrasound of the gland was performed revealing the complex cystic mass in the body as well as ductal dilatation throughout. I found no other discrete cystic or solid masses. Based on these findings, I proceeded with distal pancreatectomy and splenectomy. Intraoperative assessment of the resection specimen was performed.

**Dr Centeno:** The presence of a cystic neoplasm was confirmed on gross examination (Fig 5). Frozen section examination of the pancreatic resection margin was negative for intraductal papillary mucinous neoplasm (IPMN) with high-grade dysplasia and also for invasive carcinoma.

**Dr Malafa:** The patient had an uneventful hospital stay and was discharged home on postoperative day 7. Dr Centeno, please describe the findings of final pathology review.

**Dr Centeno:** The patient's tumor was a main branch-type IPMN with high-grade dysplasia (Fig 5). It was the intestinal type of IPMN and was composed of multiple cysts measuring 0.8 cm to 1.5 cm in diameter. The cysts were filled with clear, mucinous material, and grossly they had smooth walls. The pancreatic duct wall was lined by a papillary excrescence and was markedly dilated up to 1.3 cm. Prominent chronic pancreatitis was present in the surrounding pancreatic tissue secondary to obstructed ducts. Evaluation of the pancreatic resection margin revealed the presence of IPMN with low-grade dysplasia but no evidence of in situ or invasive cancer. Two lymph nodes were found, but they did not contain metastatic disease.

**Dr Malafa:** The pathology findings were discussed in detail with the patient. Since her pancreatic parenchymal margin was free of in situ and invasive cancer, I told the patient that no

further surgery was immediately indicated. However, I cautioned her that close follow-up with repeat imaging would be essential secondary to the possibility of recurrent disease. She developed insulin-dependent diabetes mellitus during the course of the year but was able to keep her blood sugar under control. I requested that she return for repeat EUS after an otherwise uneventful and symptom-free year at home.

**Dr Klapman:** The study revealed an irregularly shaped, anechoic 9-mm lesion in the head of the pancreas that communicated directly with the pancreatic ductal system. About 1 mL of reddish fluid was aspirated resulting in complete collapse of the lesion.

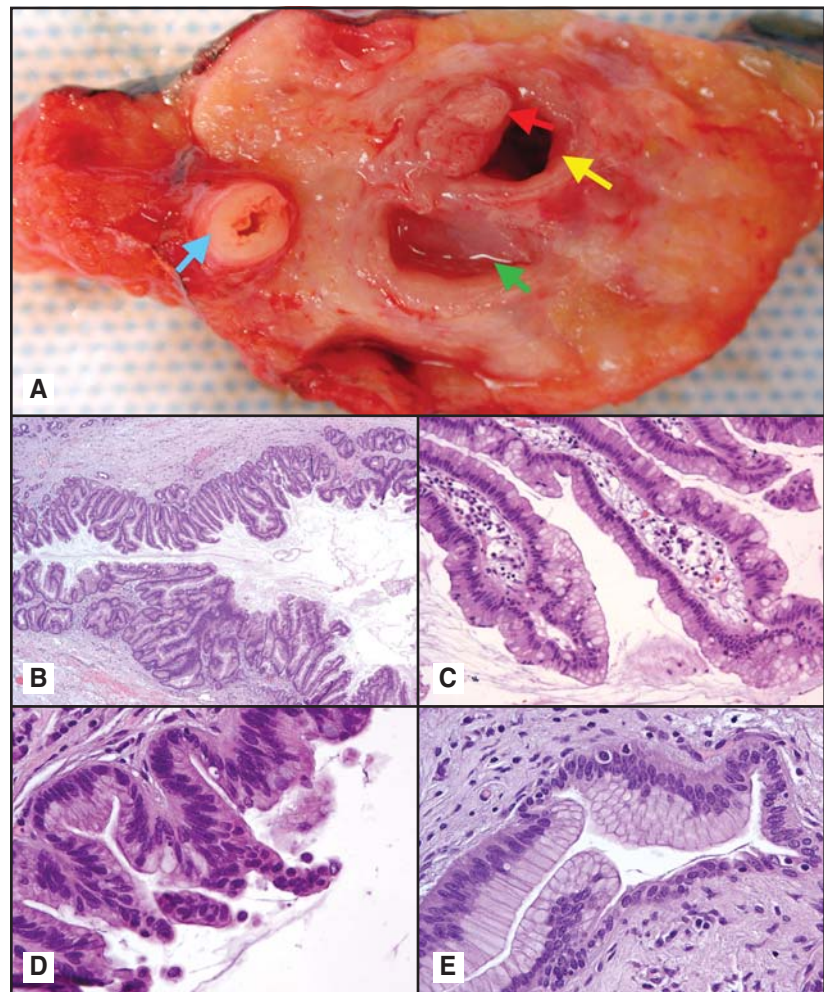


Fig 5. — Resection specimen. (A) Photograph of the resection specimen. The splenic artery is to the left (blue arrow). The top cystic-appearing structure is the main pancreatic duct (yellow arrow), which is surrounded by fibrosis. A papillary excrescence (red arrow) extrudes into the lumen. The bottom cyst is a dilated side branch (green arrow). The surrounding parenchyma has lost the yellow, lobulated appearance of normal pancreas and instead has a white, glistening, smooth-cut surface, as seen with fibrosis. (B) The main pancreatic duct is dilated. The normal lining epithelium is replaced by a papillary proliferation of mucin-containing epithelial cells (hematoxylin-eosin,  $\times 4$ ). (C) Tall, columnar cells with cytoplasmic mucin line the fibrovascular cores forming the papillae (hematoxylin-eosin,  $\times 20$ ). (D) The lining epithelium shows enlarged hyperchromatic nuclei. Small papillary tufts fall into the lumen. The nuclei of these cells are angulated. These features are typical of IPMNs with high-grade dysplasia (hematoxylin-eosin,  $\times 40$ ). (E) This duct demonstrates an abrupt transition from the normal duct lining to columnar mucinous epithelium, which occurs frequently (hematoxylin-eosin,  $\times 40$ ).

**Dr Centeno:** Cytologic analysis revealed benign pancreatic acinar cells, benign glandular cells, degenerated cells, and scant background mucin most compatible with duodenal contaminant. No malignant or neoplastic cells were detected. An aliquot of the fluid was submitted for *k-ras* mutational analysis and loss of heterozygosity (LOH) analysis using the PathFinder TG technology (RedPath Integrated Pathology Inc, Pittsburgh, Pennsylvania).

**Dr Choi:** Subsequent CT showed no evidence of a mass lesion in the residual pancreas. Ductal dilatation was again noted, although it was of a lesser degree compared with the patient's first scans.

**Dr Malafa:** Secondary to the patient's history of IPMN with in situ carcinoma, and now with a recurrent cystic lesion in the remaining gland, I was concerned about the possible presence of a new or residual pancreatic cancer. How can mutational analysis of cyst fluid assist us in decision making?

**Dr Centeno:** The assay looks at a panel of molecular parameters including DNA amount and quality, as well as *k-ras-2* oncogene point mutation and allelic imbalance (LOH) mutations of a broad panel of associated tumor suppressor genes in pancreatic neoplasia. A prospective study involving its use in 31 patients who eventually underwent surgical resection has been published.<sup>1</sup> The authors reported that molecular analysis was statistically superior to conventional diagnosis based on cytology and cyst fluid levels of CEA. They stated that *k-ras* mutation followed by allelic loss was predictive of a malignant cyst with a sensitivity of 91% and a specificity of 93% and that molecular determination of the temporal sequence of *k-ras-2* oncogene point mutation acquisition in relationship to other acquired LOH mutations was a powerful indicator of cystic disease etiology and biological aggressiveness. However, it must be stressed that these diagnostic methods remain investigational.

In this case, the assay revealed an elevated amount of good-quality DNA in the cyst fluid with a profile supporting the presence of a neoplastic mucinous cyst. To enhance the accuracy of decision making, mutational analysis of the original resection specimen was also performed to allow comparative mutational profiling. Genotyping of the resected tumor revealed a similar mutational profile, and it was believed that the cystic mass present in the pancreatic head likely represented an IPMN with the potential to harbor malignancy.

**Dr Malafa:** With these findings suggesting either a redevelopment or extension of IPMN along the pancreatic duct, I had a frank discussion with the patient. The consensus opinion of our tumor board was that

the potential benefit from completion pancreatectomy outweighed the morbidity from pancreatic endocrine and exocrine insufficiency. The challenges of potentially brittle diabetes were discussed in detail with the patient, as were the risks of repeat surgery. Despite these factors, she agreed that the resection of a potential cancer outweighed the inherent risks and is now awaiting surgery.

## Keys to Diagnostic Imaging

**Dr Malafa:** It has been postulated that one of the reasons, though certainly not the only one, that there has been such a dramatic increase in the incidence of IPMNs over the last decade is the more frequent use of high-quality abdominal CT scans. This has led to the often incidental finding of pancreatic cystic lesions in the setting of trauma, in the workup or restaging of other malignancies, or in the workup of another disease processes. These serendipitous discoveries account for 18% to 22% of cases.<sup>2</sup> While often asymptomatic, many patients complain of epigastric or diffuse abdominal pain. This may be associated with nausea and vomiting. Some patients may present with weight loss or obstructive jaundice due to obstruction of the pancreatic ductal system by the neoplasm. It is remarkable that many patients are symptomatic for at least a year, frequently even longer (up to 27 years in 1 patient), before a diagnosis is established.<sup>3,4</sup> Whether found incidentally or secondary to symptoms, the first study usually involves a CT scan. Dr Choi, please describe important features of the imaging workup in these patients.

**Dr Choi:** CT scans will typically display a lobulated, multilocular cystic mass. Secondary to often large amounts of mucin production, IPMNs may be identified radiographically by pancreatic ductal dilatation.<sup>5</sup> Sugiyama et al<sup>6</sup> described a classification system based on the location of ductal involvement. Main duct type IPMNs are characterized by isolated dilatation of the main pancreatic duct only (> 2 mm). Branch duct IPMNs have cystic lesions corresponding to dilated branch ducts only, while the third group, the combined type, includes both features. CT may be able to demonstrate communication between dilated branch ducts and the main pancreatic duct. Utilization of 2-D curved reformation along the course of the main pancreatic duct may enhance visualization of any potential communication.<sup>7</sup> Significant diffuse ductal dilatation is often associated with parenchymal atrophy, a manifestation of ductal obstruction and resulting organ damage and dysfunction. Lesions may or may not be associated with a solid component representing either invasive cancer or chronic pancreatitis. Calcifications may be seen within these solid areas or may occur in areas of surrounding pancreatitis. Intraluminal filling defects may be noted,

and their spatial relationship within the duct in relation to gravity may aid in their differentiation. When seen along the wall of the duct in the non-gravity-dependent portion, these usually represent classic papillary growths or mural nodules. They may display discrete areas of enhancement.<sup>5</sup> Thick aggregates of mucin tend to group in the dependent portions of the cystic areas. Bulging of the papilla may also be noted by CT scan. Issues of critical importance for successful CT imaging of any pancreatic mass is obtaining thin-slice intervals (2 to 3 mm) throughout the entire pancreas as well as obtaining arterial and venous phase images. Current multidetector CT (MDCT) scanners can obtain submillimeter thicknesses with high-resolution 2-D coronal and sagittal reconstructions as well as 3-D vascular reconstructions providing improved lesion localization and depiction of vascular involvement.

**Dr Malafa:** This information is essential for surgeons in planning potential resections. Additional information we seek aside from vascular involvement includes the presence of surrounding organ involvement or invasion (suggestive of malignancy), lymph node enlargement, liver or other distant organ involvement, and potential peritoneal spread. What role does positron-emission tomography (PET) play in evaluating these tumors?

**Dr Choi:** 18F-deoxyglucose PET/CT (FDG-PET/CT) has been shown to be useful in the diagnosis, preoperative staging, and management of pancreatic adenocarcinomas.<sup>8</sup> It can also be used in the evaluation of treatment response. However, a diagnosis of malignancy in cystic pancreatic lesions is more difficult. Sensitivity ranges from 57% to 94%, with specificity between 85% and 97%. These studies included small numbers of patients with IPMN. Further investigation is needed to better establish the accuracy of FDG-PET/CT for demonstrating malignancy in patients with IPMN.<sup>9-12</sup>

## The Role of the Endoscopist

**Dr Malafa:** This patient underwent ERCP prior to arriving at our institution. Dr Klapman, please describe the role of ERCP in the diagnostic workup.

**Dr Klapman:** ERCP is typically performed early in the diagnostic workup but is not essential to the decision-making process. It is most commonly performed in patients who present with signs or symptoms suggestive of obstructive jaundice. The endoscopic portion of the procedure may demonstrate mucin extruding through a bulging papilla, which is considered a pathognomonic finding and seen in up to 55% of patients.<sup>13</sup> The pancreatogram may display pancreatic ductal dilatation. This may include the main duct or

may manifest as simultaneous opacification of grapelike cystic lesions, a reflection of focal cystic dilatation of branch ducts.<sup>7</sup> Mucin plugs may manifest as filling defects within the ducts. Ductal brushings may be performed, and associated biliary obstructions can be stented. While the ability to obtain material for pathologic analysis and the potential for therapeutic biliary stenting are beneficial, some disadvantages do exist. Secondary to the often ultra-thick mucin, opacification of tumors and ducts can be problematic. The biggest concern is the possibility of inducing acute pancreatitis, which occurs in up to 5% of patients. Cumulative risk of fatal complications is 0.05%.<sup>14</sup>

**Dr Malafa:** What about magnetic resonance cholangiopancreatography?

**Dr Choi:** MRCP offers a noninvasive and more reproducible alternative to ERCP. Secondary to high-contrast resolution, MRCP can display the fine structure of cystic lesions including the presence of septa and mural nodules. Communication between the main pancreatic duct and the cystic lesion can also be seen, indicating the presence of a side-branch IPMN. Reported sensitivity of MRCP for detecting ductal dilatation associated with IPMNs is 93% to 100%.<sup>15,16</sup> Comparison of MDCT and MRCP demonstrates good correlation in the detection and characterization of IPMN with similar diagnostic accuracy.<sup>17</sup> Added benefits are the avoidance of endoscopy and the fact that contrast material is not required. However, it cannot differentiate mucin from pancreatic juice, it is unable to obtain tissue or fluid for diagnosis, and it offers poor discernment of an enlarged papilla if present.

**Dr Malafa:** Returning to the role of the endoscopist in diagnosis and treatment, Dr Klapman will describe the use of EUS.

**Dr Klapman:** EUS has become an integral part of the diagnostic workup of any pancreatic mass. EUS has rapidly become widely used because it can perform precise, real-time, ultrasound-guided FNA biopsies and it can provide detailed structural information about tumors and surrounding structures. Although an invasive procedure, EUS with FNA has a lower complication rate than ERCP, with the most serious risk, post-FNA pancreatitis, occurring in about 1% of patients.<sup>18</sup> EUS also has the ability in many cases to determine whether the cystic mass is directly involving the main pancreatic duct or is a dilated side branch of the main pancreatic duct. The internal architecture of cystic masses is also well delineated, as is the presence of mural nodules. But it is the ability to precisely aspirate pancreatic juice from the lesion itself for cytologic evaluation, measurement of tumor markers and pancreatic enzyme levels, and mole-

cular analysis that makes EUS an integral part of the diagnostic workup of these lesions. As a result, ERCP in many instances has been replaced by EUS as the initial procedure performed for evaluation of indeterminate cystic masses of the pancreas.

**Dr Centeno:** Cyst fluid aspiration with cytologic tumor marker level and enzyme level analysis is vital to help differentiate whether a cyst is nonneoplastic or neoplastic and, if neoplastic, whether it is benign or malignant. Two main distinctions exist in terms of etiology: mucinous vs nonmucinous. The category of mucinous cystic etiologies includes IPMN and mucin-producing cystic neoplasm. Nonmucinous etiologies include pseudocysts, serous cystadenomas, and cystic pancreatic endocrine tumors. Because of a lack of a single gold standard cyst fluid marker, we must rely on a combination of cytologic evaluation, measurement of tumor markers and pancreatic enzyme levels, and molecular analysis to predict a mucinous vs a nonmucinous etiology. At our institute, a cytotechnologist attends every image-guided aspirate. Typically, a drop of fluid is used to make an air-dried smear and an alcohol-fixed smear. The fluid is then triaged by the cytology lab for the various tests to be performed.

**Dr Malafa:** How do you use or interpret cyst fluid markers?

**Dr Klapman:** An elevated cyst fluid CEA level has been recognized as an indication of the presence of a mucinous neoplasm, but a cut-off value that would differentiate mucinous from nonmucinous neoplasms in all cases has not been established. Brugge et al<sup>19</sup> reported that using a cut-off value of 192 ng/mL for CEA established this marker as the most sensitive, specific, and accurate marker to differentiate between a mucinous vs nonmucinous etiology. However, this study did not establish a level that would differentiate benign from malignant neoplastic mucinous cysts, although it has been postulated that extremely high levels of CEA correlate with the presence of malignancy, whether in situ or invasive.<sup>1</sup> CA 19-9, which when elevated in serum is a marker of pancreatic-biliary malignancy, has not been shown to be accurate as a cyst fluid marker in differentiating mucinous vs nonmucinous etiologies.

**Dr Malafa:** While some progress has been made in our understanding of the significance of cyst fluid levels of various markers, their meaning in serum assays is not as clear. Review of the medical literature yields conflicting results regarding the ability of elevated serum markers such as CEA and CA 19-9 to predict malignancy. Two recent publications described an association between elevated serum CA 19-9 and malignancy. Fujino et al<sup>20</sup> retrospectively reviewed 64 cases of

resected IPMNs and their associated clinicopathologic data. Multivariate logistic regression analysis was performed on a panel of 17 parameters to assess their ability to predict malignancy. They found that a serum CA 19-9  $\geq 35$  U/mL could significantly predict malignancy with an accuracy of 62.5%, while serum CEA was not predictive. Wiesnauer et al<sup>21</sup> performed univariate and multivariate analysis of 24 serum studies and their association with malignancy. Considered a continuous variable, CA 19-9 levels did not achieve statistical significance in the logistic regression model. However, the presence of elevated serum CA 19-9 ( $> 70$  U/mL) was significantly associated with malignancy, with 3% of patients with benign IPMNs harboring an elevation compared to 37% of patients with malignant tumors. Still, the majority of published reports do not support these findings.<sup>22-27</sup> Dr Klapman, how do you interpret the level of amylase in the cyst fluid?

**Dr Klapman:** Cyst fluid amylase level is helpful when trying to differentiate a pseudocyst from a mucinous or serous cystic neoplasm. An amylase level in cyst fluid that is minimally elevated to normal virtually excludes pseudocyst as a diagnosis. When elevated, the amylase level must be used in combination with other markers to help differentiate a pseudocyst from an IPMN.

## The Role of Cytology in Decision Making

**Dr Malafa:** How accurate are we when evaluating the cytology of cyst fluid samples?

**Dr Centeno:** Overall, cytologic analysis of fluid obtained during cyst aspiration is helpful in only about 50% of cases.<sup>28</sup> This is in large part due to the scant amount of fluid or cellular material obtained with cyst aspiration, particularly with serous cystadenomas or benign neoplastic mucinous cysts. Pseudocyst remains a diagnosis of exclusion. However, with attention to cytologic features, the cytologic recognition of neoplastic mucinous cysts, including mucin-producing cystic neoplasms and IPMNs, can be enhanced. Since the patient's neoplasm is an IPMN, I will focus the discussion on this entity, but the features of mucin-producing cystic neoplasms and IPMNs are identical. The classic cytomorphological pattern of IPMN is that of mucinous, glandular epithelium set in thick background mucin. The mucin may be so viscous as to be difficult to aspirate, suggesting the diagnosis before cytologic evaluation. A definitive diagnosis of IPMN may be rendered on cytology when diagnostic epithelium is present and the findings are correlated with imaging results. If the imaging findings are not available to the pathologist, the specimen may be signed out using generic terminology such as neoplastic mucinous cyst, since the morphological features of mucin-producing

cystic neoplasms and IPMNs are identical. If only the typical background mucin is present, then the specimen may be signed out descriptively, with the comment that the findings are suggestive of a neoplastic mucinous cyst.

## Principles of Surgical Management

**Dr Malafa:** As with any pancreas tumor, IPMNs demand a methodical and careful approach to surgical resection. Collaboration with radiology and gastroenterology colleagues is essential to optimize treatment planning. A clear understanding of the tumor's proximity and relationship to neighboring structures is vital to operative success. Beyond this, consultation with the cytopathologist is critical to determine the level of preoperative suspicion that the index lesion could harbor invasive cancer. This is important in defining the extent of surgery. For example, if strong suspicion indicates that a pancreatic tail IPMN harbors invasive disease, there should be no consideration of splenic preservation during a distal pancreatectomy as attempts to do so could significantly limit the accompanying lymphadenectomy.

**Dr Choi:** Intraoperative ultrasound has become a standard part of operative evaluation due to the often multifocal nature of this disease process. It can be used to precisely define the anatomic location of the index lesion, to help identify and characterize additional lesions, and to guide intraoperative biopsies of these lesions to aid in decision making. Dr Malafa, how do you decide how much of the pancreas to resect?

**Dr Malafa:** Resection is undertaken with the goal of achieving negative microscopic margins whenever possible. This has prompted several investigators to evaluate the use of intraoperative frozen section analysis of the pancreatic margin to guide treatment decisions. Paye et al<sup>24</sup> reported their results of frozen section analysis of 39 pancreatic cut surfaces from 35 patients. Of these 39, 17 had some degree of IPMN at the frozen section pancreas margin. In all 17 of these cases, final pathology confirmed the finding. In 22 samples, frozen section was believed to be negative for IPMN at the margin. In this group, 3 patients had IPMN (no invasive cancers) at the margin on final histologic evaluation, thus yielding 85% sensitivity, 100% specificity, and 92% diagnostic accuracy for detection of IPMN by frozen section analysis of the pancreatic transection margin. With specific regard to noninvasive IPMNs, White et al<sup>29</sup> reported a 74% negative predictive value of frozen section analysis for IPMN at the pancreas resection margin in 19 patients, provided that pancreatic intraepithelial neoplasia (PanIN) lesions were not believed to constitute a positive margin. Raut et al<sup>22</sup> reported on the

**Table 3. — International Consensus Guidelines for Management of IPMNs: Indications for Resection**

- Main duct lesions
- Mixed lesions
- Symptomatic branch duct lesions
- Branch duct lesion > 3 cm\*
- Branch duct lesion containing mural nodules\*

\* The recommendation for these criteria are still a matter of debate and certain centers manage them with surgery while others prefer observation.

Data from Tanaka et al.<sup>30</sup>

results of frozen section in 29 patients treated with partial pancreatectomy. Ten of these patients had positive frozen section margins (4 of 10 patients with IPMN and invasive cancer, 6 of 19 with noninvasive IPMN). None of these patients were converted from a positive to a negative margin upon final pathologic review. Three of these “negative” margins were subsequently found to contain IPMN on final pathology or histologic re-review for the purposes of the study. In total, 8 patients were found to have noninvasive IPMN at the final pancreatic transection margin, and none of them developed recurrent disease at a median follow-up of 34 months.

**Dr Centeno:** These studies and others support the positive predictive value of frozen section analysis of the pancreatic margin. This was stressed by the International Consensus Guidelines for Management of Intraductal Papillary Mucinous Neoplasms and Mucinous Cystic Neoplasms of the Pancreas (Table 3).<sup>30</sup> However, because of the multifocal nature of the disease and a high frequency of discontinuity of the intraductal lesions, the finding of a negative margin does not guarantee that disease is not present elsewhere in the pancreatic remnant.

**Dr Choi:** Do you use pancreatoscopy to guide your resection?

**Dr Malafa:** While several authors have described the use of pancreatoscopy and intraductal ultrasound, these techniques have not had widespread acceptance secondary to limitations with image resolution and technical considerations. Nonetheless, some reports have demonstrated an improved ability to delineate the required extent of resection based on actual ductal abnormalities.<sup>13-34</sup> At this time, it is not a routine part of our practice.

## Key Pathologic Findings

**Dr Klapman:** Once the tumor has been resected, what should we take from the pathology report?

**Dr Centeno:** The classification of an IPMN has evolved over time. It is a grossly visible neoplasm characterized by the presence of mucin-producing neoplastic epithelium with a papillary growth pattern that replaces the lining epithelium of the pancreatic ductal system. The current World Health Organization (WHO) classification<sup>35</sup> and previous Armed Forces Institute of Pathology (AFIP) fascicle on tumors of the pancreas designated IPMN with in situ carcinoma as intraductal papillary carcinoma and invasive carcinoma as papillary mucinous carcinoma. Neoplasms with moderate dysplasia were considered borderline, suggesting that they had the potential to metastasize. The most benign neoplasms were called adenomas. The current international classification system for IPMNs, published in the most recent AFIP fascicle for tumors of the pancreas,<sup>36</sup> separates noninvasive and invasive components of IPMNs. The necessity for this separation is based on the fact that those IPMNs with an invasive component fare worse than noninvasive tumors.<sup>36</sup> Noninvasive IPMN is grouped into low-grade dysplasia, moderate dysplasia, or high-grade dysplasia based on the degree of dysplasia of the lining epithelium. However, it is important to note that a single tumor can harbor varying degrees of dysplasia, with the entire spectrum of disease present within the same lesion. A fascinating aspect of IPMNs is this heterogeneity of the lining epithelium, and final grading of the lesion should be based on the highest degree of dysplasia present.

IPMNs with low-grade dysplasia (adenomas in previous classification) are composed of tall columnar cells with abundant apical mucin and basally located,

uniform nuclei with minimal atypia. Nucleoli and mitoses are not prominent. The resulting papillae are architecturally simple, with the epithelium maintaining a high degree of differentiation. IPMNs with moderate dysplasia (borderline tumors in previous classification) show more nuclear stratification and a high nuclear-to-cytoplasmic ratio with a slight loss of polarity, nuclear enlargement, and nuclear pleomorphism. The papillae retain their fibrovascular cores. IPMNs with high-grade dysplasia (carcinoma in situ or intraductal papillary mucinous carcinoma in previous classification) are characterized by a cribriform growth pattern and budding of small clusters of epithelial cells into the duct lumen, atypical mitoses that may extend to the luminal surface, more significant loss of polarity, nuclear enlargement, and nuclear pleomorphism. The epithelial lining of IPMN has been further classified according to subtype: gastric foveolar, intestinal, pancreaticobiliary, and oncocytic. Gastric foveolar subtype is considered the least aggressive, intestinal type has an intermediate potential for progression, and pancreaticobiliary and oncocytic are considered the most aggressive types.<sup>36</sup>

Extension beyond the duct marks the presence of invasive cancer, referred to as IPMN with invasive carcinoma (papillary mucinous carcinoma in previous classification). Mucinous noncystic carcinomas or colloid carcinomas arise from intestinal type epithelium, and their immunohistochemical expression pattern is identical to the intestinal epithelium. Mucinous noncystic carcinoma has an excellent prognosis and is associated exclusively with IPMN as a precursor lesion.

**Table 4. — Disease Recurrence and Outcome**

Author Study Institution(s)	Year	Breakdown of Disease	Median Follow-Up (mos)	Recurrence (all types)	Death From Recurrence
Chari et al <sup>44</sup> Mayo Clinic	2002	NI: 73 I: 40	36 42	5 (7%) 26 (65%)	23/31 (74%)
Nakagohri et al <sup>42</sup> Chiba University	2002	NI: 16 “Minimally” I: 5	78	1 (6%) 2 (40%)	2/3 (67%)
D’Angelica et al <sup>40</sup> Memorial Sloan-Kettering	2004	NI: 32 I: 30	38	3 (9%) 11 (37%)	12/14 (86%)
Salvia et al <sup>43</sup> MGH/U Verona	2004	NI: 80 I: 57	31	1 (1%) 7 (12%)	5/8 (63%)
Sohn et al <sup>41</sup> Johns Hopkins	2004	NI: 84 I: 50	24	7 (8%) ≥ 21 (≥ 42%)	4/7 (57%) N/A
Wada et al <sup>47</sup> Virginia Mason	2005	NI: 75 I: 25	31 27	1.3% 46%	N/A
Raut et al <sup>22</sup> M. D. Anderson	2006	NI: 22 I: 12	30 61	0 (0%) 7 (58%)	7/7 (100%)
Takahashi et al <sup>45</sup> Osaka University	2006	NI: 17 I: 3	68	1 (6%) 1 (33%)	2/2 (100%)
Yokoyama et al <sup>46</sup> Nagoya University	2007	NI: 85 I: 15	N/A	4 (5%) 1 (7%)	0/5 (0%)

NI = noninvasive, I = IPMN-associated invasive cancers.

Tubular adenocarcinomas arise from pancreatobiliary epithelium and resemble ductal adenocarcinoma, not otherwise specified. Intraductal oncocyctic papillary neoplasms give rise to an unusual variant of invasive carcinoma, invasive oncocyctic carcinoma.

**Dr Malafa:** Please describe the difference between PanINs and IPMNs.

**Dr Centeno:** PanINs and IPMNs share an overlap in some fundamental areas, one of which is their basic composition: columnar, mucin-producing cells that can either form papillae or grow in a flat configuration. IPMNs typically involve larger ducts while PanINs usually arise in smaller ducts (< 5 mm in diameter), but either can occur in any location. The major accepted differences lay in the fact that IPMNs tend to be clinically and grossly detectable, usually forming a lesion > 1 cm in diameter, while PanINs are incidental and microscopic findings. As a result, IPMNs are usually characterized by well-formed papillae and grossly visible mucin while PanINs are not. Another important dis-

inction occurs at the molecular level. Inactivation of TP53/p53 and MADH4/SMAD4/DPC4 genes occurs much less frequently in IPMNs compared to PanINs.<sup>37-38</sup>

### The Importance of Follow-Up

**Dr Choi:** Once the tumor has been removed and the pathologist's report is finalized, what are the next steps in caring for these patients?

**Dr Malafa:** Vigilant surveillance after resection is critical as recurrence can be quite high. Whether these are true recurrences or progression of subclinical disease is uncertain. The rates of recurrence are significantly higher in patients with malignant disease, and once recurrence does occur, death from disease is usually the rule rather than the exception (Table 4).<sup>22,39-46</sup>

**Dr Choi:** How does margin status affect prognosis?

**Dr Malafa:** Another major finding from these and other studies is that the presence of noninvasive dis-

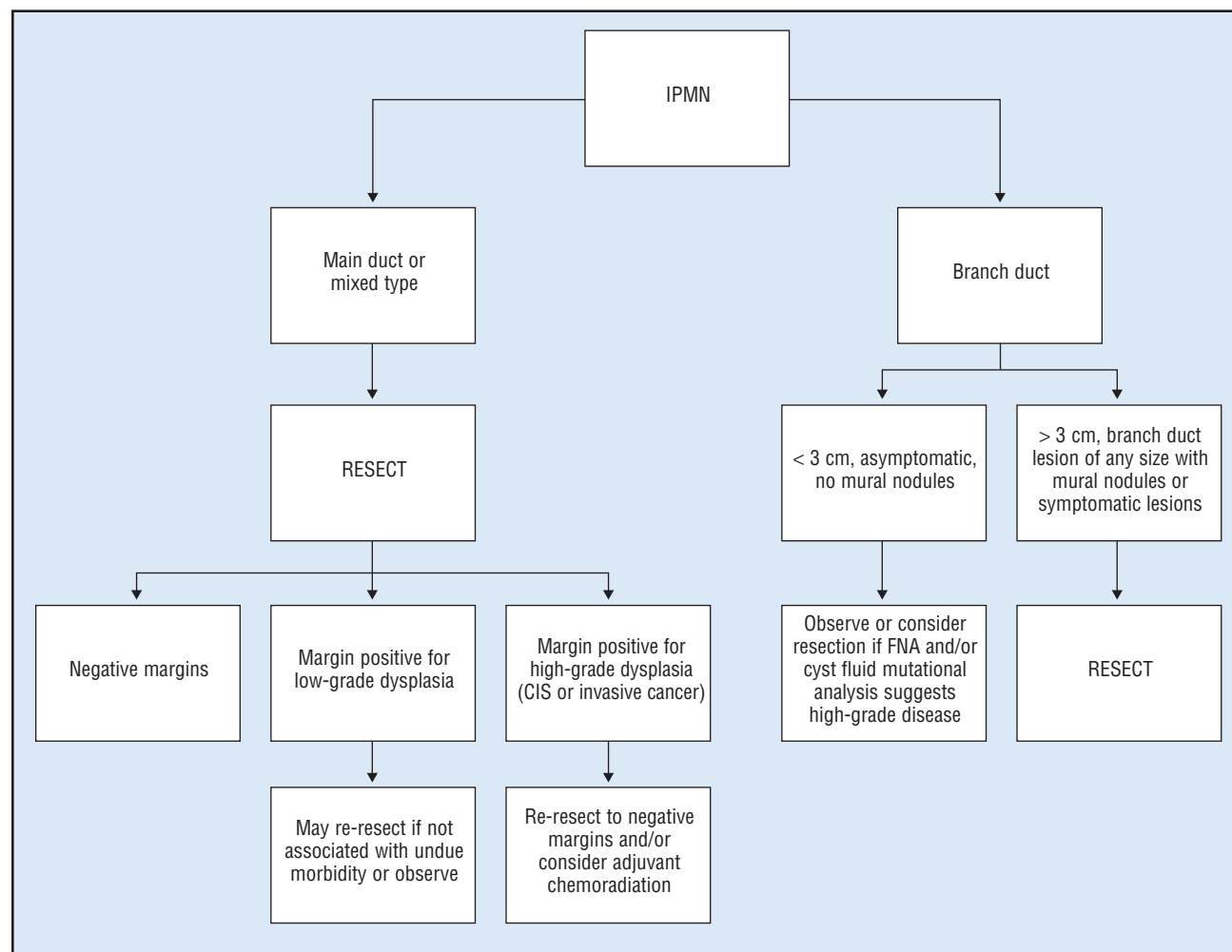


Fig 6. — Approach to treatment of intraductal papillary mucinous neoplasms at our institute.

ease (including carcinoma in situ) at the surgical resection margin does not adversely affect survival even though it may increase the rates of local recurrence.<sup>39,40</sup> In fact, Raut et al<sup>22</sup> found that there were no recurrences in patients with noninvasive IPMN at the final resection margin. Leaving residual disease, even if noninvasive, must still be tempered with caution, and the importance of close follow-up is critical. White et al<sup>29</sup> recently published a report addressing the fate of the pancreatic remnant following resection for noninvasive IPMNs. At a median follow-up of 40 months, recurrence was reported in 6 of 78 patients. Compared by margin status, 1 patient (2%) of 50 with negative resection margins recurred, while 4 (17%) of 23 patients with positive margins recurred ( $P = .02$ ). Half of these patients died of their disease.

**Dr Choi:** What follow-up strategy do you use?

**Dr Malafa:** Follow-up regimens are based on clinical experience as no strong evidence exists in the medical literature regarding the type and frequency of surveillance. The International Consensus Guidelines for Management of Intraductal Papillary Mucinous Neoplasms and Mucinous Cystic Neoplasms of the Pancreas<sup>30</sup> suggests yearly imaging and clinical examination for patients with resected benign IPMNs, with extension to a longer interval if no evidence of recurrence is present after the first few years. For malignant lesions, the panel suggests consideration of imaging every 6 months. In terms of follow-up for asymptomatic, unresected lesions, the panel recommends the following:

- yearly evaluation for lesions < 10 mm
- 6- to 12-month evaluation for lesions 10 to 20 mm
- 3- to 6-month evaluation for lesions > 20 mm

**Dr Choi:** When do you recommend resection in lesions such as these that you are following with imaging?

**Dr Malafa:** Resection should be strongly considered for interval development of symptoms, increase in lesion size, or development of intramural nodules or pancreatic ductal dilatation. The duration of follow-up is indefinite at this time as several studies report recurrences more than 5 years after resection.<sup>29,40,42,43,47</sup>

**Dr Klapman:** A final consideration for follow-up of these patients is the high rate of extra-pancreatic malignancies. Several authors have described this rate to range from 29% to 39%.<sup>48-51</sup> While these malignancies may have occurred and been treated prior to the diagnosis of IPMN, about half are found after treatment of IPMN has concluded. With the excellent prognosis associated with noninvasive IPMNs, these extra-pancreatic malignancies may be the major determinant in the

patient's subsequent survival, and regular cancer screening must be stressed.

## Conclusions

Diagnosing IPMN preoperatively can be challenging. Even with a combination of imaging studies, cyst fluid assays, and cytologic analysis, the diagnosis may be indeterminate. The major hurdles in diagnosing cystic lesions are the lack of a gold standard diagnostic test and the limited quantity of fluid obtained (especially in cysts less than 2 to 3 cm), which limits the number of studies that can be performed with the cyst fluid. A cyst fluid CEA study is the most accurate in differentiating mucinous vs nonmucinous etiologies. Noninvasive forms of IPMN carry an excellent prognosis, and while patients with IPMN invasive cancers fare worse, their prognosis appears to be better than that associated with traditional pancreatic ductal adenocarcinoma.

As clinicians, we continue to refine our treatment approach to these tumors (Fig 6), balancing aggressive resection to prevent development of invasive cancer with the understanding that we are not yet fully aware of the time course of malignant progression. It is likely that insights from the realm of molecular medicine (eg, determination of a malignant vs nonmalignant genetic signature) will help us individualize and thus improve our care by reserving our most aggressive treatments for those who will truly benefit from them.

## Disclosures

*No significant relationship exists between the authors and the companies/organizations whose products or services may be referenced in this article.*

## References

1. Khalid A, McGrath KM, Zahid M, et al. The role of pancreatic cyst fluid molecular analysis in predicting cyst pathology. *Clin Gastroenterol Hepatol.* 2005;3(10):967-973.
2. Taouli B, Vilgrain V, O'Toole D, et al. Intraductal papillary mucinous tumors of the pancreas: features with multimodality imaging. *J Comput Assist Tomogr.* 2002;26(2):223-231.
3. Kawarada Y, Yano T, Yamamoto T, et al. Intraductal mucin-producing tumors of the pancreas. *Am J Gastroenterol.* 1992;87(5):634-638.
4. Traverso LW, Peralta EA, Ryan JA Jr, et al. Intraductal neoplasms of the pancreas. *Am J Surg.* 1998;175(5):426-432.
5. Kawamoto S, Horton KM, Lawler LP, et al. Intraductal papillary mucinous neoplasm of the pancreas: can benign lesions be differentiated from malignant lesions with multidetector CT? *Radiographics.* 2005;25(6):1451-1468; discussion 1468-1470.
6. Sugiyama M, Atomi Y, Kuroda A. Two types of mucin-producing cystic tumors of the pancreas: diagnosis and treatment. *Surgery.* 1997;122(3):617-625.
7. Fukukura Y, Fujiyoshi F, Sasaki M, et al. Intraductal papillary mucinous tumors of the pancreas: thin-section helical CT findings. *AJR Am J Roentgenol.* 2000;174(2):441-447.
8. Heinrich S, Goerres GW, Schäfer M, et al. Positron emission tomography/computed tomography influences on the management of resectable pancreatic cancer and its cost-effectiveness. *Ann Surg.* 2005;242(2):235-243.
9. Mansour JC, Schwartz L, Pandit-Taskar N, et al. The utility of F-18 fluorodeoxyglucose whole body PET imaging for determining malignancy in cystic lesions of the pancreas. *J Gastrointest Surg.* 2006;10(10):1354-1360.
10. Sperti C, Bissoli S, Pasquali C, et al. 18-fluorodeoxyglucose positron emission tomography enhances computed tomography diagnosis of malignant intraductal papillary mucinous neoplasms of the pancreas. *Ann Surg.* 2007;246(6):932-937; discussion 937-939.
11. Sperti C, Pasquali C, Fiore V, et al. Clinical usefulness of 18-fluor-

- odeoxyglucose positron emission tomography in the management of patients with nonpancreatic periampullary neoplasms. *Am J Surg*. 2006;191(6):743-748.
12. Yoshioka M, Sato T, Furuuya T, et al. Positron emission tomography with 2-deoxy-2-[(18)F] fluoro-d-glucose for diagnosis of intraductal papillary mucinous tumor of the pancreas with parenchymal invasion. *J Gastroenterol*. 2003;38(12):1189-1193.
  13. Azar C, Van de Stadt J, Rickaert F, et al. Intraductal papillary mucinous tumours of the pancreas: clinical and therapeutic issues in 32 patients. *Gut*. 1996;39(3):457-464.
  14. Bilbao MK, Dotter CT, Lee TG. Complications of endoscopic retrograde cholangiopancreatography (ERCP): a study of 10,000 cases. *Gastroenterology*. 1976;70(3):314-320.
  15. Fukukura Y, Fujiyoshi F, Sasaki M, et al. HASTE MR cholangiopancreatography in the evaluation of intraductal papillary-mucinous tumors of the pancreas. *J Comput Assist Tomogr*. 1999;23(2):301-305.
  16. Koito K, Namieno T, Ichimura T, et al. Mucin-producing pancreatic tumors: comparison of MR cholangiopancreatography with endoscopic retrograde cholangiopancreatography. *Radiology*. 1998;208(1):231-237.
  17. Sahani DV, Kadavigere R, Blake M. Intraductal papillary mucinous neoplasm of pancreas: multi-detector row CT with 2D curved reformations. Correlation with MRCP. *Radiology*. 2006;238(2):560-569.
  18. Gress F, Michael H, Gelrud D, et al. EUS-guided fine-needle aspiration of the pancreas: evaluation of pancreatitis as a complication. *Gastrointest Endosc*. 2002;56(6):864-867.
  19. Brugge WR, Lewandrowski K, Lee-Lewandrowski E, et al. Diagnosis of pancreatic cystic neoplasms: a report of the cooperative pancreatic cyst study. *Gastroenterology*. 2004;126(5):1330-1336.
  20. Fujino Y, Matsumoto I, Ueda T, et al. Proposed new score predicting malignancy of intraductal papillary mucinous neoplasms of the pancreas. *Am J Surg*. 2007;194(3):304-307.
  21. Wiesenauer CA, Schmidt CM, Cummings OW, et al. Preoperative predictors of malignancy in pancreatic intraductal papillary mucinous neoplasms. *Arch Surg*. 2003;138(6):610-617; discussion 617-618.
  22. Raut CP, Cleary KR, Staerkel GA, et al. Intraductal papillary mucinous neoplasms of the pancreas: effect of invasion and pancreatic margin status on recurrence and survival. *Ann Surg Oncol*. 2006;13(4):582-594. Epub 2006 Mar 7.
  23. Yang AD, Melstrom LG, Bentrem DJ, et al. Outcomes after pancreatectomy for intraductal papillary mucinous neoplasms of the pancreas: an institutional experience. *Surgery*. 2007;142(4):529-534; discussion 534-537.
  24. Paye F, Sauvagnet A, Terris B, et al. Intraductal papillary mucinous tumors of the pancreas: pancreatic resections guided by preoperative morphological assessment and intraoperative frozen section examination. *Surgery*. 2000;127(5):536-544.
  25. Kimura W, Sasahira N, Yoshikawa T, et al. Duct-ectatic type of mucin producing tumor of the pancreas: new concept of pancreatic neoplasia. *Hepatogastroenterology*. 1996;43(9):692-709.
  26. Yamaguchi K, Ogawa Y, Chijiwa K, et al. Mucin-hypersecreting tumors of the pancreas: assessing the grade of malignancy preoperatively. *Am J Surg*. 1996;171(4):427-431.
  27. Partensky C, Berger F. Les tumeurs intracanalaires papillaires et mucineuses du pancréas. In: Le Borgne J, de Calan L, Partensky C, eds. *Les Tumeurs Kystiques du Pancréas*. Paris, France: Arnette Blackwell; 1997:90-107.
  28. Maire F, Couvelard A, Hammel P, et al. Intraductal papillary mucinous tumors of the pancreas: the preoperative value of cytologic and histopathologic diagnosis. *Gastrointest Endosc*. 2003;58(5):701-706.
  29. White R, D'Angelica M, Katabi N, et al. Fate of the remnant pancreas after resection of noninvasive intraductal papillary mucinous neoplasm. *J Am Coll Surg*. 2007;204(5):987-993; discussion 993-995. Epub 2007 Mar 27.
  30. Tanaka M, Chari S, Adsay V, et al. International consensus guidelines for management of intraductal papillary mucinous neoplasms and mucinous cystic neoplasms of the pancreas. *Pancreatol*. 2006;6(1-2):17-32.
  31. Atia GN, Brown RD, Alrashid A, et al. The role of pancreatoscopy in the preoperative evaluation of intraductal papillary mucinous tumor of the pancreas. *J Clin Gastroenterol*. 2002;35(2):175-179.
  32. Itoi T, Sofuni A, Itokawa F, et al. Initial experience of peroral pancreatoscopy combined with narrow-band imaging in the diagnosis of intraductal papillary mucinous neoplasms of the pancreas (with videos). *Gastrointest Endosc*. 2007;66(4):793-797.
  33. Venu RP, Atia G, Brown RD, et al. Intraductal papillary mucinous tumor of the pancreas: ERCP, EUS, and pancreatoscopy findings. *Gastrointest Endosc*. 2002;55(1):82.
  34. Yasuda K, Sakata M, Ueda M, et al. The use of pancreatoscopy in the diagnosis of intraductal papillary mucinous tumor lesions of the pancreas. *Clin Gastroenterol Hepatol*. 2005;3(7 suppl 1):S53-S57.
  35. Hruban RH, Takaori K, Klimstra DS, et al. An illustrated consensus on the classification of pancreatic intraepithelial neoplasia and intraductal papillary mucinous neoplasms. *Am J Surg Pathol*. 2004;28(8):977-987.
  36. Hruban RH, Pitman MB, Klimstra DS, et al. Armed Forces Institute of Pathology Atlas of Tumor Pathology: Tumors of the Pancreas. Washington DC: American Registry of Pathology; 2007.
  37. Iacobuzio-Donahue CA, Klimstra DS, Adsay NV, et al. Dpc-4 protein is expressed in virtually all human intraductal papillary mucinous neoplasms of the pancreas: comparison with conventional ductal adenocarcinomas. *Am J Pathol*. 2000;157(3):755-761.
  38. Adsay NV. Intraductal papillary mucinous neoplasms of the pancreas: pathology and molecular genetics. *J Gastrointest Surg*. 2002;6(5):656-659.
  39. D'Angelica M, Brennan MF, Suriawinata AA, et al. Intraductal papillary mucinous neoplasms of the pancreas: an analysis of clinicopathologic features and outcome. *Ann Surg*. 2004;239(3):400-408.
  40. Sohn TA, Yeo CJ, Cameron JL, et al. Intraductal papillary mucinous neoplasms of the pancreas: an updated experience. *Ann Surg*. 2004;239(6):788-797; discussion 797-799.
  41. Nakagohri T, Asano T, Kenmochi T, et al. Long-term surgical outcome of noninvasive and minimally invasive intraductal papillary mucinous adenocarcinoma of the pancreas. *World J Surg*. 2002;26(9):1166-1169. Epub 2002 Jun 6.
  42. Salvia R, Fernández-del Castillo C, Bassi C, et al. Main-duct intraductal papillary mucinous neoplasms of the pancreas: clinical predictors of malignancy and long-term survival following resection. *Ann Surg*. 2004;239(5):678-685; discussion 685-687.
  43. Chari ST, Yadav D, Smyrk TC, et al. Study of recurrence after surgical resection of intraductal papillary mucinous neoplasm of the pancreas. *Gastroenterology*. 2002;123(5):1500-1507.
  44. Takahashi H, Nakamori S, Nakahira S, et al. Surgical outcomes of noninvasive and minimally invasive intraductal papillary-mucinous neoplasms of the pancreas. *Ann Surg Oncol*. 2006;13(7):955-960. Epub 2006 May 18.
  45. Yokoyama Y, Nagino M, Oda K, et al. Clinicopathologic features of re-resected cases of intraductal papillary mucinous neoplasms (IPMNs). *Surgery*. 2007;142(2):136-142.
  46. Wada K, Takada T, Yasuda H, et al. Does "clonal progression" relate to the development of intraductal papillary mucinous tumors of the pancreas? *J Gastrointest Surg*. 2004;8(3):289-296.
  47. Salvia R, Crippa S, Falconi M, et al. Branch-duct intraductal papillary mucinous neoplasms of the pancreas: to operate or not to operate? *Gut*. 2007;56(8):1086-1090. Epub 2006 Nov 24.
  48. Sugiyama M, Atomi Y. Extrapancreatic neoplasms occur with unusual frequency in patients with intraductal papillary mucinous tumors of the pancreas. *Am J Gastroenterol*. 1999;94(2):470-473.
  49. Kamisawa T, Tu Y, Egawa N, et al. Malignancies associated with intraductal papillary mucinous neoplasm of the pancreas. *World J Gastroenterol*. 2005;11(36):5688-5690.
  50. Choi MG, Kim SW, Han SS, et al. High incidence of extrapancreatic neoplasms in patients with intraductal papillary mucinous neoplasms. *Arch Surg*. 2006;141(1):51-56; discussion 56.
  51. Eguchi H, Ishikawa O, Ohigashi H, et al. Patients with pancreatic intraductal papillary mucinous neoplasms are at high risk of colorectal cancer development. *Surgery*. 2006;139(6):749-754.