Evaluation and Management of Pancreatic Cystic Lesions

by V. Patwardhan, J. Levey, J. Zivny, R. Jaffar, B. Banner, S. Shankar, W. Wassef

Pancreatic cystic lesions are now being encountered more frequently in clinical practice because of widely available high quality imaging. These lesions have varying malignant potential and include benign pseudocysts and serous cystadenomas (32%–29%), pre-malignant mucinous cystadenomas (10%–45%) and intraductal papillary mucinous neoplasms (21%–33%), and malignant mucinous cystadenocarcinomas (<1%). The benign lesions can be followed conservatively while pre-malignant and malignant lesions require surgical resection. Although surgery is the only definitive way to diagnose these lesions, endoscopic ultrasound with fine-needle aspiration for cytology and cyst fluid analysis is currently the best non-surgical approach available to aid in the diagnosis of these lesions. There is currently no consensus guideline for the management of pancreatic cystic lesions. In this article we attempt to summarize the literature on pancreatic cysts and review the latest methodology for evaluation and management.

INTRODUCTION

Pancreatic cysts are now being encountered by primary and specialty care physicians with ever increasing frequency due to the widespread use of high quality cross-sectional imaging (1,2). The majority of these cystic lesions are incidental asymptomatic findings, and therefore can present both diagnostic and therapeutic dilemmas.

The differential diagnosis of cystic pancreatic lesions includes both inflammatory lesions, such as pseudocysts and abscesses that follow pancreatitis, as well as neoplastic lesions. Cystic neoplasms of the pancreas are composed of a variety of neoplasms with a wide range of malignant potential. They account for approximately 10%–15% of cystic lesions of the pancreas and less than 1% of all pancreatic neoplasms (3–6). These neoplasms include serous cystadenomas (32%–

V. Patwardhan, J.Levey, J. Zivny, W. Wassef, Division of Gastroenterology; R. Jaffar, B. Banner, Department of Pathology; S. Shankar, Department of Radiology, University of Massachusetts Medical School, Worcester, MA.

29%), mucinous cystadenomas (10%–45%), intraductal papillary mucinous neoplasms (IPMNs) (21%–33%), and mucinous cystadenocarcinomas (<1%) (7,8).

Since pancreatic cystic neoplasms represent a spectrum of benign, pre-malignant, and malignant tumors, differentiating among the various lesions is clinically important. This article represents a review of the literature on this topic and attempts to summarize the latest consensus on diagnosis and management.

EPIDEMIOLOGY

Pancreatic cysts are found with increasing frequency in older patients. A study utilizing abdominal ultrasound revealed pancreatic cysts in 0.21% of 130,951 younger adults while a review of MRI images revealed 15%–20% of 1,444 patients had at least 1 pancreatic cyst, with older patients having a greater percentage than younger patients (9,10). Additionally, most pancreatic cystic lesions are incidental findings. By using CT, Spinelli, et al (11) estimated that 1.2% of patients at a major medical center had a pancreatic cyst lesion, and in an autopsy study, pancreatic cysts were found in nearly

25% of patients who underwent a detailed autopsy of the pancreas. Of these lesions, 16% had abnormal epithelium, with carcinoma in situ found in 3.4% (12).

CLASSIFICATION OF PANCREATIC CYSTIC LESIONS

Cystic neoplasms of the pancreas are traditionally organized by their epithelial lining since this feature determines malignant potential as well as management (4).
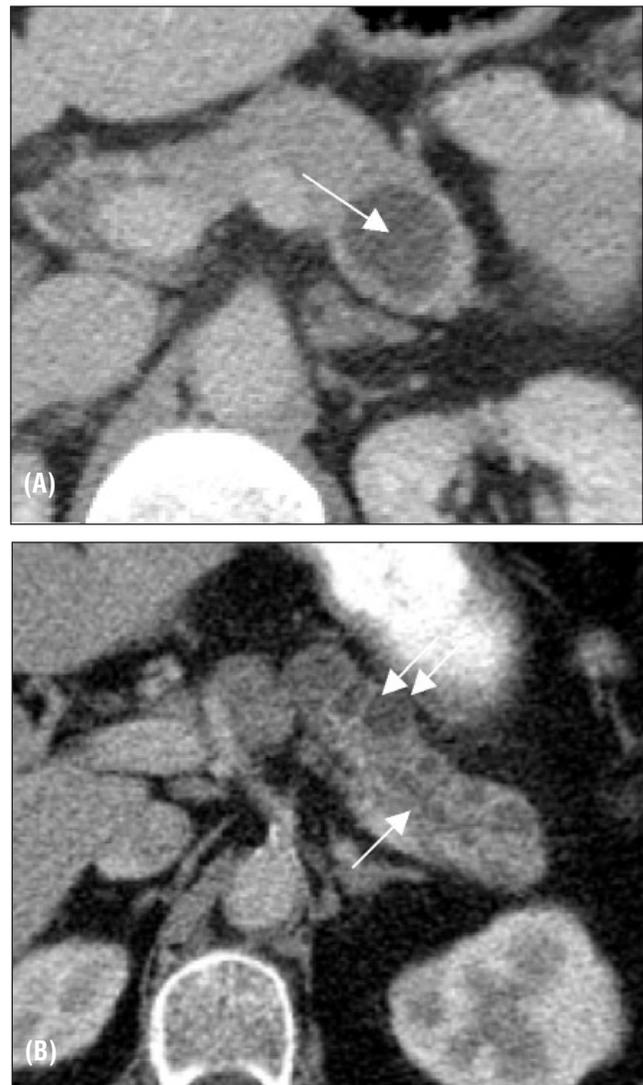
Serous Cystadenoma

Serous cystadenomas are seen predominantly in women and are asymptomatic in a third of cases (3). They represent approximately 30% of pancreatic cystic neoplasms and occur at an average age of 62 years (13). They are microcystic and composed of multiple small, thin-walled cysts with a honey-comb appearance on cross section (14). The cysts are lined by lined by a simple, glycogen-rich cuboidal epithelium and often have a fibrotic or calcified central scar (15). An example is seen in Figure 2. Typically, serous cystadenomas have numerous (>6) small (<2 cm), well defined cystic loculations, with characteristic CT findings such as central calcifications, enhancement around microcysts after injection, and larger cysts on the periphery of the mass. These CT scan signs are conclusive for diagnosis (16–20), but only occur in up to 30% of these neoplasms (21). A CT image of a serous cystadenoma is seen in Figure 1. These lesions are benign and have an extremely low potential for malignant disease (14).

Mucinous Cystadenoma

Mucinous cystadenomas represent 44%–49% of pancreatic cystic neoplasms (3). The median age at presentation is lower than that for serous cystadenoma and 90% of cases are detected in women (5,22). They are lined by mucus-producing columnar epithelium which often contains a unique, highly cellular ovarian stroma (15). The presence of mucin is most characteristic of mucinous cystadenomas, and is seen in 35% or more of diagnostic specimens (6,23). They are composed of large compartments and are typically macrocystic with thin septa within them and may have an eccentric solid

component (24). They exhibit variable malignant potential (25), which is underscored by findings described by Wilentz, et al (26) who in a series of 61 patients with mucinous cystic neoplasms, classified 44% as adenomatous, 8% as borderline, and 15% as carcinoma in situ. Mucinous cystadenomas do have the potential to become malignant mucinous cystadenocar-

Figure 1. (A) CT scan of a serous cystadenoma in the tail of the pancreas with thinly septated microcysts (arrow pointing to a faintly visible septation). **(B)** CT scan of an IPMN with multiple cystic lesions (double arrow pointing to one of many cysts anterior to the pancreatic duct) throughout the pancreas and a dilated pancreatic duct (single arrow).
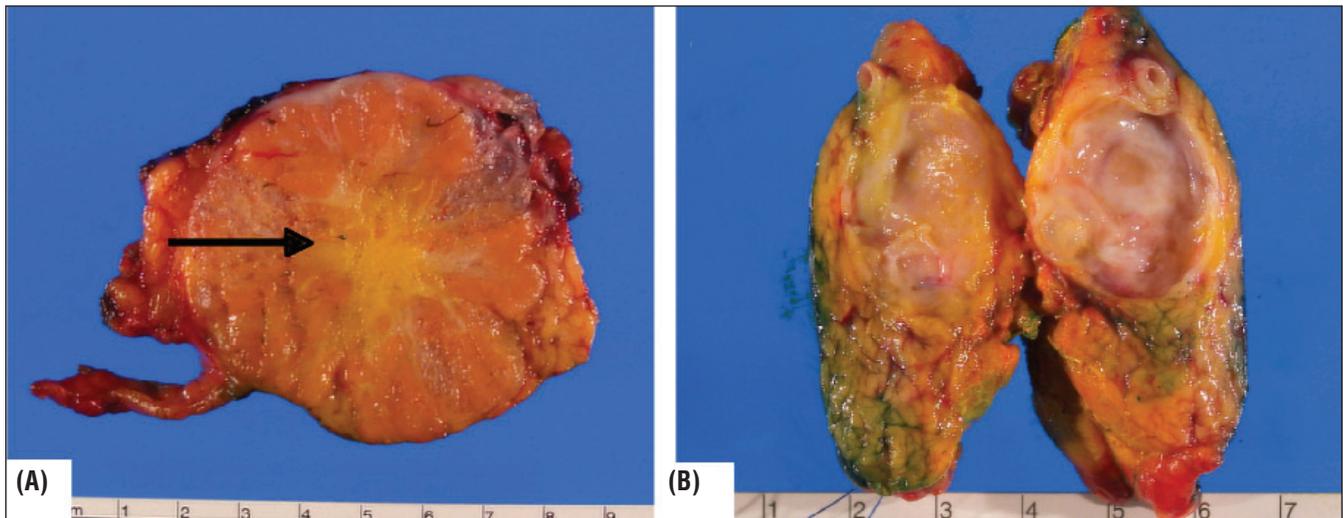
Figure 2. (A) Gross photograph of serous cystadenoma. The cut surface appears solid grossly, but is in fact composed of multiple microcysts. There is is a central scar (arrow), which is typical of this tumor. **(B)** Gross photograph of mucinous cystadenoma showing a single cavity with a thin wall.

cinomas, but technically are benign lesions. Examples of typical gross and microscopic appearances of mucinous cystadenomas are seen in Figures 2 and 4.

## INTRADUCTAL PAPILLARY MUCINOUS NEOPLASIA

Unlike serous and mucinous cystadenomas, IPMNs are found predominantly in men in their 6th and 7th decades (27,28). They account for 0.5% of all pancreatic neoplasms found at autopsy; 7.5% of clinically diagnosed pancreatic neoplasms, and 16.3% of surgically resected pancreatic neoplasms (29). They are very similar to mucinous cystic neoplasms in that they both contain columnar mucin-producing epithelium. However, IPMNs have a papillary epithelium that arises from ductal epithelium and lack the ovarian-type stroma of mucinous cystic neoplasms (23). They also differ from mucinous cystadenomas in that mucinous cystic neoplasms characteristically lack a communication with the pancreatic ductal system, whereas a communication with the pancreatic ductal system is a key feature of IPMNs (25). Examples of a CT image, cytology specimen from fine needle aspiration (FNA), and microscopic appearance of a benign IMPN are seen in Figures 1, 3, and 4.

Similar to other mucinous neoplasms, IPMNs are pre-malignant lesions that have been found to harbor occult malignancy. According to Kloppel, et al (30),

carcinoma in situ is found in 5%–27% of IPMNs and invasive carcinoma in 15%–40%. In all, 20%–50% of patients with IPMN have an invasive neoplasm at the time of surgery, with central main pancreatic duct IPMNs having higher rates of malignancy than peripheral side-branch IPMN lesions (28,31,32,33). This propensity for dysplastic change guides the management of these lesions.

MUCINOUS CYSTADENOCARCINOMA

As previously stated, there is significant data to suggest that mucinous cystadenocarcinoma arises from mucinous cystadenoma and IPMNs. However, there is less of a female predominance with cystadenocarcinoma than with mucinous cystadenoma even though IPMN is seen more frequently in males (34). Malignant degeneration within mucinous cystadenoma is relatively common and has been described even after 17 years of follow-up (3,22). Additionally, although more commonly associated with older patients, pancreatic mucinous cystadenocarcinoma has also been reported to arise in young women during pregnancy and post-partum, often with rapid cyst enlargement occurring during pregnancy (35). Typical mucinous cystadenocarcinoma is a thick walled macrocyst with a solid, often intramural, component and a peripheral
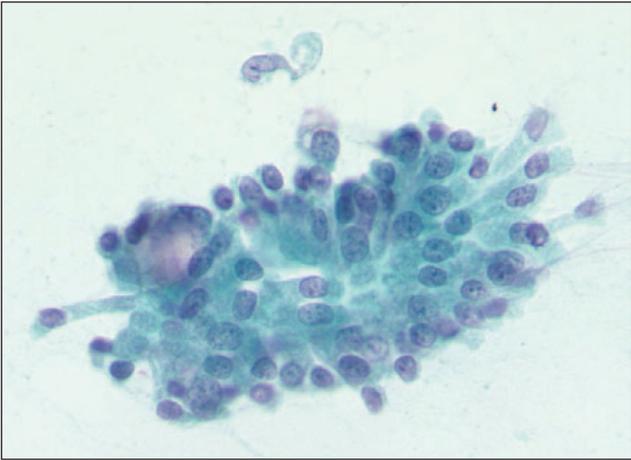
Figure 3. Cytology of IPMN from EUS-guided FNA. Cytology shows a cluster of tall columnar mucin producing epithelial cells in slight disarray. The even distribution of chromatin within the nuclei is consistent with a benign neoplasm. (Papanicolau stain ×600)

rim of calcifications (5,19,20). When malignancy arises from an IPMN lesion the foci of early malignancy may be evident by the presence of mural nodules and diffuse dilatation of the pancreatic duct on imaging (36,37). An example of the microscopic appearance of a mucinous cystadenocarcinoma arising from an IPMN is seen in Figure 4.

There are no well described risk factors of mucinous cystadenocarcinoma other than having mucinous cystadenoma or IPMN. However, studies have shown that male sex, abdominal pain, weight loss, and jaundice are associated with mucinous cystadenocarcinoma (38,39). These signs and symptoms are not specific, however.

INFLAMMATORY PANCREATIC CYSTIC LESIONS

Inflammatory pancreatic cystic lesions include pseudocysts, abscesses, and pancreatic necrosis and arise from complications of pancreatitis, pancreatic trauma, and may follow pancreatic surgery (40). Pseudocysts are composed of walled off collections of pancreatic secretions and have no epithelial lining in the wall. Chronic pseudocysts characteristically have a thick wall that is adherent to the stomach or the duodenum (41). These lesions are benign and pose no risk of malignancy. However, they can often be confused with pancreatic cystic neoplasms and vice versa due to similar clinical presentations and appearance on imaging (23,42). A photomicrograph of the wall of a pseudocyst is seen in Figure 4.

CLINICAL PRESENTATION

Most patients with pancreatic cystic lesions are asymptomatic. When patients do present with symptoms related to their pancreatic cystic lesions, they may present with recurrent pancreatitis, chronic abdominal pain, or jaundice (4). The most common symptom is abdominal discomfort or low-grade abdominal pain (5,13) These symptoms may stem from mass effect with compression of the pancreatic duct by the cysts causing mild or chronic pancreatitis. However, the finding of pancreatitis is not specific as both inflammatory pseudocysts and cystic neoplasms, both benign and malignant, can be associated with pancreatitis. Additionally, while pseudocysts are a well-known sequela of pancreatitis, cystic neoplasms can themselves be the cause of pancreatitis, and therefore are often confused with pseudocysts.

The clinical presentation is identical for both benign mucinous and serous cystadenomas, although recurrent pancreatitis is more frequent in mucinous cystadenoma (34). Patients with an advanced cystic neoplasm present with symptoms similar to those of pancreatic ductal carcinoma, including pain, weight loss, and jaundice (43). Malignancy of IPMNs has also been associated with new onset diabetes, jaundice, elevated glucose, and elevated alkaline phosphatase while chronic pancreatitis has not been shown to be a predictor of malignancy (39). Grieshop, et al (44) found that almost all patients with malignant mucinous cystadenocarcinoma were symptomatic. However, it is well documented that the absence of symptoms does not exclude the diagnosis of malignancy in patients with pancreatic cystic lesions.

DIAGNOSTIC WORK UP AND DIFFERENTIAL DIAGNOSIS

The initial diagnosis of a pancreatic cyst is usually made by abdominal CT or MRI, often incidentally or in the workup of abdominal pain. Although pancreatic
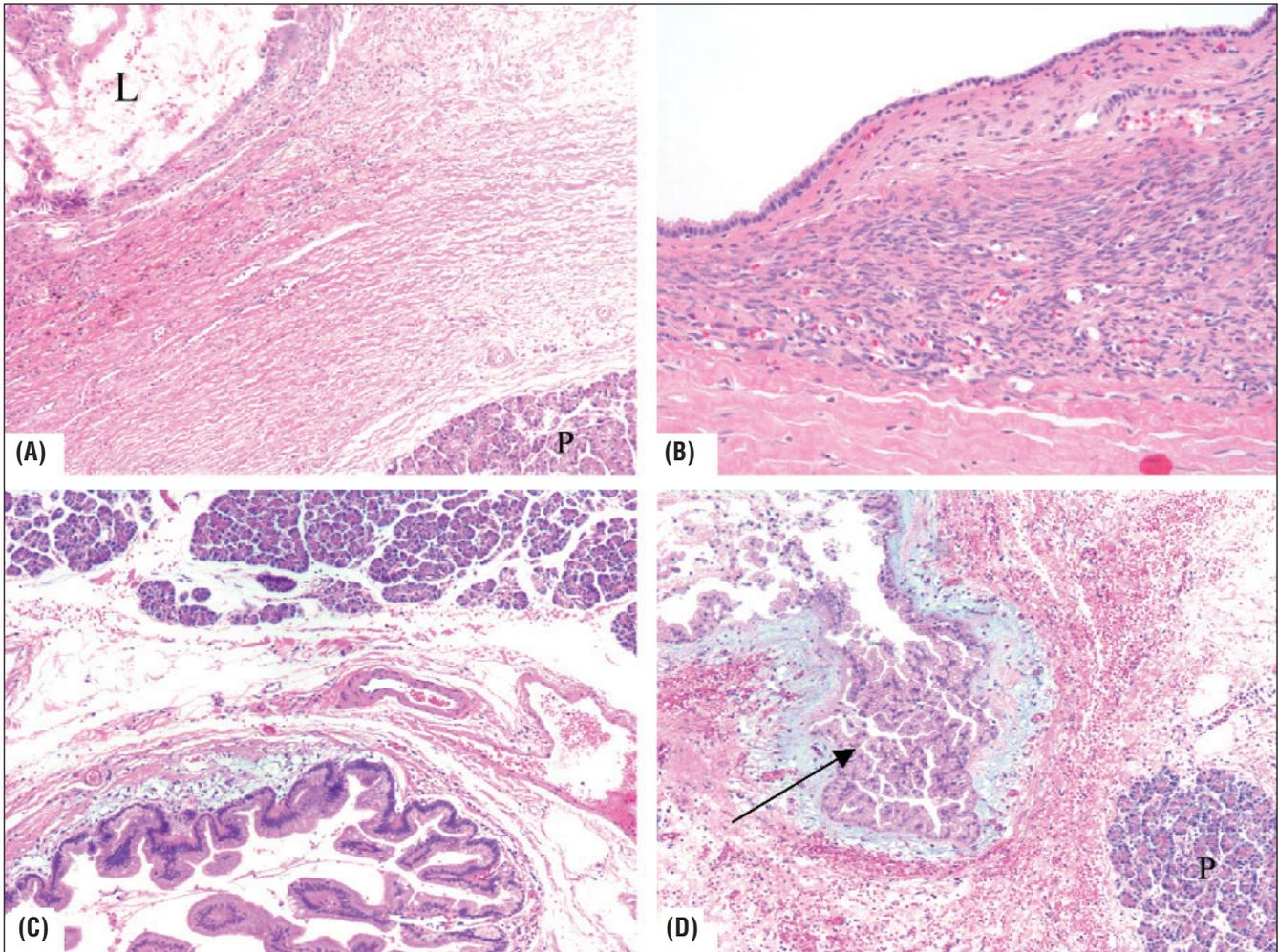
Figure 4. (A) Histological features of various pancreatic cystic lesions. A. Section of a pseudocyst across the cyst wall from the lumen (L) to the pancreas (P). Pseudocyst wall is composed of fibrous tissue. No epithelium is present. (Hematoxylin and eosin ×100). **(B)** Mucinous cystadenoma. Cyst wall lined by single layer of tall columnar cells. Highly cellular stroma resembles ovarian stroma. (Hematoxylin and eosin ×100) **(C)** Benign IPMN with papillary fronds composed of mucin-producing epithelial cells (intestinal-type). (H & E ×100). **(D)** Malignant IPMN showing complex arborizing papillary fronds (arrow) with atypical mucin producing epithelial cells and some residual pancreas (P). (H & E ×100).

neoplasms are recognized more frequently, differentiating benign from malignant pancreatic cystic lesions based on CT and MRI remains difficult (45–47). A study by Procacci, et al (48) found that CT allowed for correct characterization of only 60% of pancreatic lesions, and Curry, et al (47) found that for a single cohort of lesions, diagnosis of serous cystadenoma varied between 23% and 41%. CT and MRI can, however, still help to better characterize pancreatic cystic lesions. CT has the benefit of visualizing calcification of the cyst wall, septa, mural nodules, and findings suggestive of pancreatitis while MRI allows for better characterization of cyst morphology and may show a communication between the cyst and the pancreatic duct, which can aid diagnosis (47,49,50). Additionally, while CT is poor at differentiating between pseudocysts and mucinous cystadenomas, it may be diagnostic for serous cystadenomas (48).
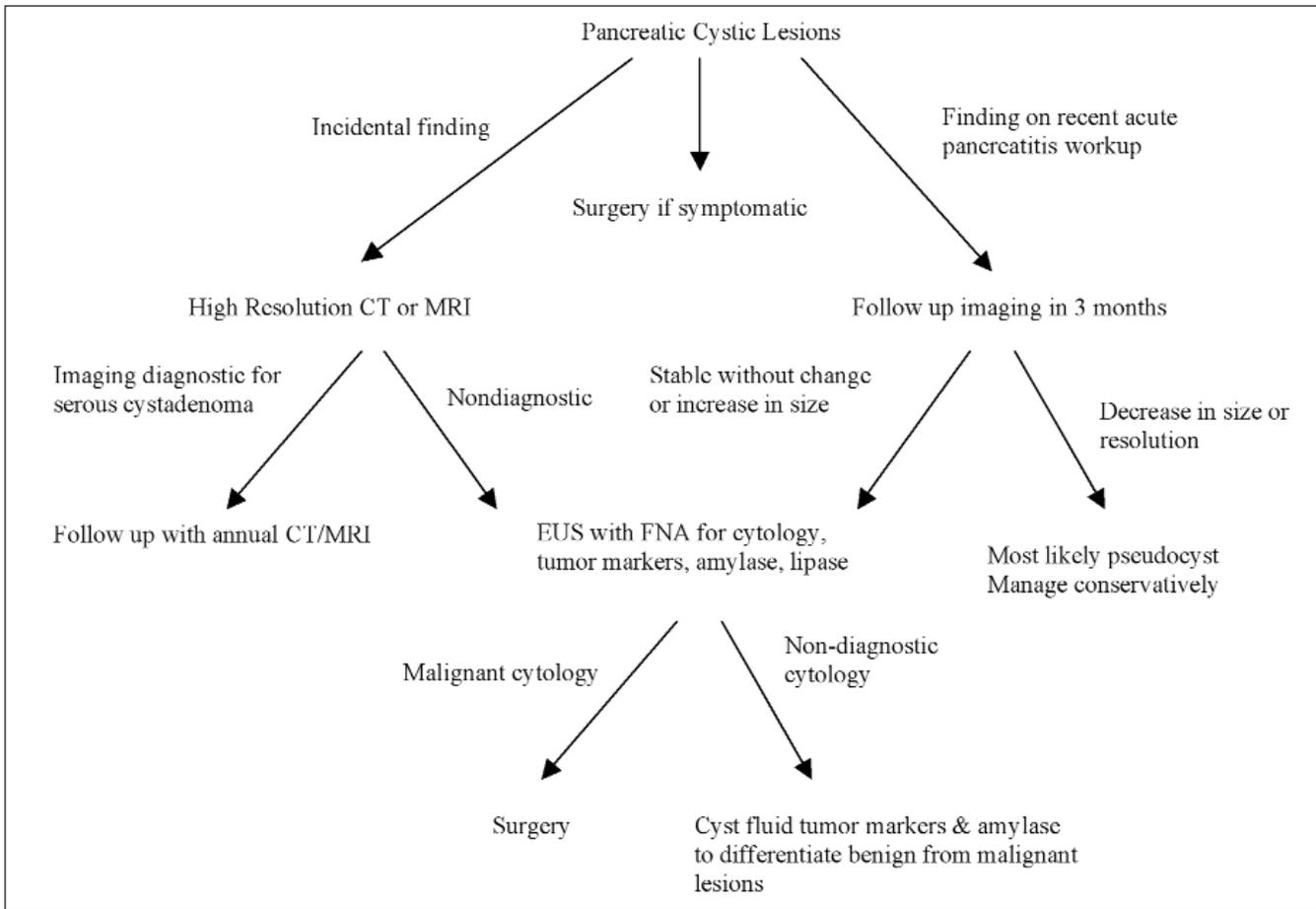
Figure 5. Algorithm for the Management of Pancreatic Cystic Lesions

When the diagnosis cannot reliably be made with CT or MRI, endoscopic ultrasound (EUS) can provide images of higher resolution and also permit sampling of cyst fluid, mass lesions, and lymph nodes. EUS-guided FNA of pancreatic lesions can yield fluid for cytological, chemical, and tumor marker analysis. For these reasons, EUS with FNA has now become the modality of choice to further characterize cystic lesions of the pancreas (51,52).

However, the data on both EUS and EUS-guided FNA in aiding in the diagnosis and management of pancreatic cystic lesions is varied. For instance, Sedlack, et al (19) found EUS alone to be sensitive and accurate (91% and 82% respectively) in identifying malignant/potentially malignant pancreatic cystic lesions, while others have found that EUS accuracy varied from as low as 40% to as high as 93% (53).

Additionally, even though the aspiration of malignant or dysplastic cells from a pancreatic cystic lesions can give a definitive diagnosis, FNA cytology has been described to have large variations in sensitivity (42). In a recent report by the American Society for Gastrointestinal Endoscopy, cytology was noted to have a reported sensitivity between 25%–88% for malignancy within a cystic neoplasm and an overall accuracy for diagnosing various cystic lesions of 54%–97% (40). In a pooled analysis by van der Waaij, et al (42), diagnostic cytology was found in only 48% of malignant cysts, 45% of mucinous cysts, and 38% of serous cysts.

Similarly, although the aspirate from a pseudocyst characteristically only yields inflammatory cells, mucinous cystadenomas that yield only inflammatory aspirate can be misdiagnosed as pseudocysts (54). This

Table 1.
Characteristics of Common Pancreatic Cystic Lesions

	Inflammatory Lesions	Neoplasms			
	Pseudocysts	Serous Cystadenoma	Mucinous Cystadenoma	IPMN	Mucinous Cystadenocarcinoma
Gender	Male	Female	Female	Male	Male
Age (decade)	Variable	7th	5th-6th	6th–7th	6th–7th
% of cystic neoplasms	75–80% of all cystic lesions	32–39	10–45	21–33	<1
Epithelial lining	None	Glycogen-rich cuboidal epithelium without mucin	Columnar mucin-producing	Papillary mucin-producing	Dysplastic mucin-producing
Malignant potential	None	Very low; very few reports of serous cystadenocarcinoma	High	Moderate	—
Cytology	Neutrophils and macrophages	PAS-staining cuboidal epithelium	Mucinous columnar cells with variable atypia; positive mucin stain	Mucinous columnar cells with variable atypia; positive mucin stain	Malignant mucinous columnar cells with varying degrees of atypia seen within the same cystic lesion
Prognosis	Excellent	Resection curative	Excellent if resection before invasive carcinoma	Excellent if resection before invasive carcinoma	Poor, but better than ductal adenocarcinoma

rate has been cited between 9%–37% including a study by Le Borgne, et al (34) where 16% of malignant mucinous cystadenocarcinomas were misdiagnosed as pseudocysts based on EUS-FNA (2,5).

Since diagnosis of pancreatic cystic lesions using CT, MRI, EUS, and fine needle aspiration for cytology has been shown to have variable and somewhat suboptimal accuracy, many are adding cyst fluid analysis of tumor markers to FNA. Tumor markers that have been studied include CEA, CA19-9, CA125, CA72-4, and CA15-3 with CEA showing the most promise. It has been shown that malignant cystic tumors tend to have the highest CEA levels in their cyst fluid when compared to benign cystic neoplasms, but there are no published cutoff values that provide sufficient accuracy for clinical use (6,23,42). For instance, Brugge, et al (23) determined that a CEA >192 helped to differentiate benign serous cystadenomas and pseudocysts from malignant and potentially malignant mucinous cystic neoplasms while van der Waaij, et al (42) found a value of >800 to be the best predictor, with 80% accuracy. At

our center, CEA >1,300 was found to predict malignancy with the best accuracy (unpublished data).

Elevated serum CA19-9 levels have been shown to correlate with pancreatic adenocarcinoma and with recurrence after surgical resection (55). This has prompted investigation into cyst fluid CA19-9 to help diagnose pancreatic cystic lesions (Table 2) (56). Studies have shown that cyst fluid CA19-9 does indeed correlate with risk of malignancy (6,56), but there is not yet enough data for these markers to aid in the differential diagnosis of pancreatic cystic lesions.

ERCP can also aid in the diagnosis of pancreatic cystic neoplasms. However, most ERCP findings are fairly nonspecific when associated with pancreatic cystic neoplasms. ERCP may help to visualize a diffusely dilated pancreatic duct, but this finding alone does not differentiate between potentially malignant IPMT and chronic pancreatitis (41). It has also been shown that ERCP is not helpful in distinguishing cystic tumors from pseudocysts (57,58). ERCP can, however, confirm the diagnosis of IPMN when mucus is

Table 2.
Tumor Markers in the Analysis of Pancreatic Cyst Fluid

	Pseudocysts	*Serous Cystadenoma*	*Mucinous Cystadenoma*	*IPMN*	*Mucinous Cystadenocarcinoma*
CEA	Low but variable	Low	High	High	High but variable
CA 19-9	High, but variable	Variable	Variable	Variable	Variable
CA 72-4	Low, but variable	Low	High	High	High
CA 15-3	Low	Low	High	Low, but variable	High
Amylase	High	Low, but variable	Low, but variable	High	Low, but variable
Cytology	Neutrophils and macrophages	PAS-staining cuboidal epithelium with glycogen	Mucinous columnar cells with variable atypia; positive mucin stain	Mucinous columnar cells with variable atypia; positive mucin stain	Malignant mucinous columnar cells with varying degrees of atypia seen within the same cystic lesion

* Relative values

seen extruding from a widely patent ampulla. This finding is considered pathognomonic for IPMN, and likely represents the most beneficial use of ERCP when evaluating pancreatic cystic lesions (4,59).

RISKS OF EUS-FNA

As most patients with pancreatic cysts will undergo an EUS-guided FNA, it is important to know the potential complications. Complications of EUS-FNA are rare, but include pancreatitis (0.5%–4%) (60), hemorrhage within the cyst (<1%) (6,23), retroperitoneal bleeding (<0.01%) (61), and infection (<1%) (6,60). No patient or cyst characteristics have been shown to predict which patients are at risks for complications following EUS-FNA (61,62). Pancreatitis, the most common complication, is thought to result from the passage of the needle through healthy pancreatic tissue and from inflammation as a result of intracystic hemorrhage (52,63). To prevent pancreatic infection many centers use preoperative antibiotics or fluoroquinolones for two-to-five days following the procedure. However, it is still unclear whether administration of preoperative antibiotics or post-puncture antibiotics significantly reduce the risk of post FNA infection (60).

PROGNOSIS AND MANAGEMENT

The management of pancreatic cystic lesions depends on their type. Asymptomatic benign lesions such as pseudocysts and serous cystadenomas are best managed conservatively while symptomatic lesions and cysts with malignant potential such as mucinous cystadenomas, IPMNs, and cystadenocarcinomas require surgical resection (14,34,55). The importance of surgery for mucinous lesions is underscored not only by their propensity for becoming malignant, but also because of their increased survival post-resection when compared with ductal adenocarcinomas of the pancreas. Siech, et al (64) noted that resected malignant cystic neoplasms had a better prognosis than solid adenocarcinomas, with five-year survival rates of 32%–64% depending on the extent of malignancy compared to less than 5% for ductal adenocarcinoma (26,34,65,66). Furthermore, if pre-malignant mucinous lesions are operated upon before transmural invasion of malignant cells, the survival is nearly 100% (25,67). Prognosis is good after resection even for borderline mucinous cystic tumors and for IPMNs containing carcinoma, for which the five-year survival rate is >40% (3,27,33,34).

The decision whether to proceed with surgery, however, must also take into account the patient's age, the degree of surgical risk for the patient, and the location and size of the lesion (4). Lesions in the head of the pancreas require the Whipple procedure for surgical resection and distal lesions require distal pancreatectomy even if splenectomy can be avoided. Both these operations are associated with morbidity even in specialized centers where the death rate for such surgeries is less than 2%

(68). For these reasons, in asymptomatic patients, patients with increased surgical risk, and patients with an uncertain diagnosis it is especially important to distinguish premalignant and malignant tumors (mucinous cystadenoma, IPMN, and cystadenocarcinoma) from benign pseudocysts and serous cystadenomas before deciding on whether to proceed with surgical resection (42). It is for situations such as these that referral to a gastroenterologist for EUS-FNA is most valuable.

A number of diagnostic approaches have been proposed in the literature. Brugge (69) and van der Waaij, et al (42) have proposed approaches in which cyst fluid CEA is used to determine malignancy when diagnostic cytology is nondiagnostic and after initial imaging has been performed. Neither of these algorithms however, have yet been tested.

We propose that the initial management of an incidentally discovered cyst should be to better clarify patient symptoms and look for signs of pancreatitis and obstruction. While identifying the presence of pancreatitis does not help with the differential diagnosis, it can help clarify symptoms and therefore, guide management. Similarly, findings of biliary obstruction without obvious jaundice will prompt more aggressive management.

Following the finding of a pancreatic cystic lesion, we recommend EUS-guided FNA for all patients lacking pathognomonic CT signs of serous cystadenoma. However, in patients with advanced age, very high surgical risk, or for whom diagnosis will not impact care, our opinion is that EUS-FNA can be deferred. On the other hand, given the low-risks of serious complications associated with EUS-FNA, an EUS-FNA is very appropriate in older patients and those with increased surgical risk to better differentiate a cystic lesion and provide the patient with better information to make a more informed decision.

In patients with a cystic lesion in the context of recent acute pancreatitis and high likelihood of pseudocyst formation, we recommend conservative management with follow-up imaging in three-to-six months. However, given that pseudocysts are often confused with cystic neoplasms in the context of pancreatitis, an EUS-guided FNA is recommended if resolution of the cystic lesion is not seen on follow-up. Similarly, cystic lesions with signs of secondary infec-

tion can be drained endoscopically using EUS guidance or percutaneously (49).

If EUS-guided FNA to assess cyst morphology, cytology, and tumor markers such as CEA suggests malignancy or mucinous neoplasm, the patient should be referred to a surgeon for resection, with surgical risks and patient age to be taken into account. If EUS-FNA of an asymptomatic lesion does not show signs of malignancy or mucinous neoplasm, we recommend that the patient be managed conservatively with follow-up imaging and EUS-guided FNA every six-months to one-year. Symptomatic lesions should be referred to a surgeon for resection.

In all cases, we agree with Brugge, et al (4) who advocated that any conservative management strategy include at least yearly imaging with CT or EUS-FNA and that high resolution CT or MRI be performed as part of planning in all cases.

SUMMARY

Even though physicians are encountering pancreatic cystic lesions with increasing frequency, there is currently no consensus guideline for the diagnostic workup and management of pancreatic cysts. These lesions comprise neoplastic processes ranging from benign to malignant, with benign mucinous lesions having the propensity to evolve into malignant lesions over time. There is currently no definitive way to diagnose these lesions other than surgery, which carries with it a morbidity that is not insignificant, especially for older patients in which pancreatic cystic lesions are more prevalent.

Nevertheless, EUS-guided FNA with cytological and tumor marker analysis appears to be the best method currently for assessing the malignant risks associated with pancreatic cystic neoplasms. EUS-guided FNA can help to better determine the malignant potential of a pancreatic cyst, but the ultimate decision of whether to manage aggressively or conservatively involves a discussion between the patient and multiple providers, including the gastroenterologist, surgeon, and primary care physician. The optimal management of a lesion will likely need to be determined on a case-by-case basis as cystic lesions are found most often in asymptomatic, medically complex older patients.

Questions that remain unanswered center on the best method of surveillance once a cystic lesion has been identified and at what point a cystic lesion requires surgery. Currently, recommended surveillance involves imaging studies and EUS-FNA. The role of cyst fluid analysis for tumor markers and genetic profiles in predicting the malignant potential of pancreatic cystic lesions is currently being studied. Further study into these areas may help in aiding the diagnosis of pancreatic cystic lesions, and therefore improve management strategies. ■

References

1. Irie H, Honda K, Kuroiwa T, et al. Measurement of the apparent diffusion coefficient in intraductal mucin-producing tumor of the pancreas by diffusion-weighted echo-planar MR imaging. *Abdom Imaging,* 2002;27:82-87.
2. Delcore R, Thomas JH, Forster J, et al. Characteristics of cystic neoplasms of the pancreas and results of aggressive surgical treatment. *Am J Surg,* 1992;164:437-442.
3. Fernandez-Del Castillo C, Warshaw AL. Cystic tumors of the pancreas. *Surg Clin North Am*, 1995;75:1001-1016.
4. Brugge WR, Lauwers GY, Sahani D, et al. Cystic neoplasms of the pancreas. *NEJM*, 2004;351:1218-1226.
5. Warshaw AL, Compton CC, Lewandrowski K, Cardenosa G, Mueller PR. Cystic tumors of the pancreas. New clinical, radiologic, and pathologic observations in 67 patients. *Ann Surg,* 1990;212:432-443
6. Frossard JL, Amouyal P, Amouyal G, et al. Performance of enosonography-guided fine needle aspiration and biopsy in the diagnosis of pancreatic cystic lesions. *Am J Gastroenterol,* 2003;98:1516-1524.
7. Fernandez-Del Castillo C, Targarona J, Thayer SP, et al. Incidental pancreatic cysts: clinicopathologic characteristics and comparison with symptomatic patients. *Arch Surg,* 2003;138:427-434.
8. Adsay NV, Klimstra DS, Compton CC. Cystic lesions of the pancreas: Introduction. *Semin Diagn Pathol,* 2000;17:1-6.
9. Ikeda M, Sato T, Morozumi A, et al. Morphologic changes in the pancreas detected by screening ultrasonography in a mass survey, with special reference to main duct dilatation, cyst formation, and calcification. *Pancreas,* 1994;9:508-512.
10. Zhang XM, Mitchell DG, Dohke M, et al. Pancreatic cysts: depiction on single-shot fast spin-Echo MR images. *Radiology*, 2002;223:547-553.
11. Spinelli KS, Fromwiller TE, Daniel RA, et al. Cystic pancreatic neoplasms: observe or operate? *Ann Surg,* 2004;239:651-657.
12. Kimura W, Nagai H, Kuroda A, et al. Analysis of small cystic lesions of the pancreas. *Int J Pancreatol,* 1995;18:197-206.
13. Sarr MG, Kendrick ML, Nagorney DM, et al. Cystic neoplasms of the pancreas; benign to malignant epithelial neoplasms. *Surg Clin North Am,* 2001;81:497-509.
14. Pyke CM, van Heerden JA, Colby TV, et al. The spectrum of serous cystadenoma of the pancreas: clinical, pathologic, and surgical aspects. *Ann Surg,* 1992;215:132-139.
15. Brugge WR. Cystic Pancreatic Lesions: Can we diagnose them accurately what to look for? FNA marker molecular analysis resection, surveillance, or endoscopic treatment? *Endoscopy*, 2006; 38(S1): S40-S47.
16. Johnson CD, Stephens DH, Charboneau JW, et al. Cystic pancreatic tumors: CT and sonographic assessment. *Am J Roentgenol,* 1988;151:1133-1138.
17. MacCarty RL. Cyst fluid analysis and imaging of pancreatic cystic lesions. *Am J Roentgenol,* 1995;164:820-821.
18. LeBorgne J. Cystic tumours of the pancreas. *Br J Surg,* 1998;85:577-579.
19. Sedlack R, Affi A, Norton I, et al. Utility of EUS in the evaluation of cystic pancreatic lesions. *Gastrointest Endosc,* 2002;56:543-547.
20. Song MH, Lee SK, Kim MH, et al. EUS in the evaluation of pancreatic cystic lesions. *Gastrointest Endosc,* 2003;57:891-896.
21. Gourgiotis S, Germanos S, Ridolfini MP. Presentation and management of pancreatic cystic neoplasms. *J Clin Gastroenterol,* 2007;41:599-608.
22. Compagno J, Oertel JE. Mucinous cystic neoplasms of the pancreas with overt and latent malignancy (cystadenocarcinoma and cystadenoma). A clinicopathologic study of 41 cases. *Am J Clin Pathol,* 1978;69:573-580.
23. 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: 1330-1336.
24. Sakorafas GH, Sarr MG. Cystic neoplasms of the pancreas; what a clinician should know. *Can Treat Rev,* 2005;31:507-535.
25. Zamboni G, Scarpa A, Bogina G, et al. Mucinous cystic tumors of the pancreas: clinicopathological features, prognosis, and relationship to other mucinous cystic tumors. *Am J Surg Pathol,* 1999;23:410-422.
26. Wilentz RE, Albores-Saavedra J, Zahurak M, et al. Pathologic examination accurately predicts prognosis in mucinous cystic neoplasms of the pancreas. *Am J Surg Pathol,* 1999;23:1320-1327.
27. Chari ST, Yadav D, Smyrk TC, et al. Study recurrence after surgical resection of intraductal papillary mucinous neoplasms of the pancreas. *Gastroenterology*, 2002;123: 1500-1507.
28. Salvia R, Fernandez-Del Castillo C, Bassi C, et al. Main-duct intraductal papillary mucinous neoplasms of the pancreas: clinical predictors of malignancy & long-term survival following resection. *Ann Surg,* 2004;239:678-687.
29. Furuta K, Watanabe H, Ikeda S. Difference between solid and duct-ectatic types of pancreatic ductal carcinomas. *Cancer*, 1992;69:1327-1333.
30. Kloppel G. Clinicopathologic view of intraductal papillary-mucinous tumor of the pancreas. *Hepatogastroenterology*, 1998;45:1981-1985.
31. Cellier C, Cuillerier E, Palazzo L, et al. Intraductal papillary and mucinous tumors of the pancreas: accuracy of preoperative computed tomography, endoscopic retrograde pancreatography and endoscopic ultrasonography, and long term outcome in a large surgical series. *Gastrointest Endosc,* 1998;47:42-49.
32. Loftus EV, Olivares-Pakzad BA, Batts KP, et al. Intraductal papillary-mucinous tumors of the pancreas: clinicopathologic features, outcomes, and nomenclature. *Gastroenterology,* 1996;110:1909-1918.
33. Sohn TA, Yeo CJ, Cameron JL, et al. Intraductal papillary mucinous neoplasms of the pancreas: an updated experience. *Ann Surg,* 2004;239:788-797.
34. Le Borgne J, de Calan L, Partensky C, et al. Cystadenomas and cystadenocarcinomas of the pancreas. A multi-institutional retrospective study of 398 cases. *Ann Surg,* 1999; 230:152-161.
35. Herring AA, Graubard MB, Gan SI, et al. Mucinous cystadenocarcinoma of the pancreas during prengnancy. *Pancreas*, 2007;34:470-473.
36. Tanaka M. Intraductal papillary mucinous neoplasm of the pancreas: diagnosis and treatment. *Pancreas,* 2004;28:282-288.
37. Irie H, Honda H, Aibe H, et al. MR cholangiopancreatographic differentiation of benign and malignant intraductal mucin-producing tumors of the pancreas. *Am J Roentgenol,* 2000;174:1403-1408.

38. Javle M, Shah P, Yu J, et al. Cystic pancreatic tumors (CPT): Predictors of malignant behavior. *J Surg Onc,* 2007;95:221-228.

39. Wiesenauer CA, Schmidt CM, Cummings OW, et al. Preoperative predictors of malignancy in pancreatic intraductal papillary mucinous neoplasms. *Arch Surg,* 2003; 138:610-618.

40. Jacobson BC, Baron TH, Adler DG, et al. ASGE guideline: The role of endoscopy in the diagnosis and the management of cystic lesions and inflammatory fluid collections of the pancreas. *Gastrointest Endosc,* 2005;61:363-370.

41. Brugge WR. The role of EUS in the diagnosis of cystic lesions of the pancreas. *Gastrointest Endosc,* 2000;52(Suppl 6):S18-S22.

42. van der Waaij LA, van Dullemen HM, Porte RJ. Cyst fluid analysis in the differential diagnosis of pancreatic cystic lesions: a pooled analysis. *Gastrointest Endosc,* 2005;62: 383-389.

43. Kerlin DL, Frey CF, Bodai BI, et al. Cystic neoplasms of the pancreas. *Surg Gynecol Obstet,* 1987;165:475-478.

44. Grieshop NA, Wiebke EA, Kratzer SS, et al. Cystic neoplasms of the pancreas. *Ann Surg,* 1994;60:509-515.

45. Wolfman NT, Ramquist NA, Karstaedt N, et al. Cystic neoplasms of the pancreas: CT and sonography. *Am J Roentgenol,* 1982;438:37-41.

46. Friedman AC, Lichtenstein JE, Dachman AH. Cystic neoplasms of the pancreas. Radilogcal-pathological correlation. *Radiology,* 1983;149:45-50.

47. Curry CA, Eng J, Horton KM, et al. CT of primary cystic pancreatic neoplasms: can CT be used for patient triage and treatment? *Am J Roentgenol,* 2000;175:99-103.

48. Procacci C, Biasiutti C, Carbognin G, et al. Characterization of cystic tumors of the pancreas: CT accuracy. *J Comput Assist Tomogr,* 1999;23:906-912.

49. Minami M, Itai Y, Ohtomo K, et al. Cystic neoplasms of the pancreas: comparison of MR imaging with CT. *Radiology,* 1989;171:53-56.

50. Koito K, Namieno T, Ichimura T, et al. Mucin-producing pancreatic tumors: comparison of MR cholangiopancreatography with endoscopic retrograde cholangiopancreatography. *Radiology,* 1998;208:231-237.

51. Wiersema MJ, Vilmann P, Giovannini M, et al. Endosonography-guided fine needle aspiration biopsy: diagnostic accuracy and complication assessment. *Gastroenteroogyl,* 1997;112:1087-1095.

52. Gress FG, Hawes RH, Savides TJ, et al. Endoscopic ultrasound-guided fine-needle aspiration biopsy using linear array and radial scanning endosonography. *Gastrointest Endosc,* 1997;45:243-250.

53. Ahmad NA, Kochman ML, Brensinger C, et al. Interobserver agreement among endosonographers for the diagnosis of neoplastic versus non-neoplastic pancreatic cystic lesions. *Gastrointest Endosc,* 2003;58:59-64.

54. Nguyen GK, Suen KC, Villanueva RR. Needle aspiration cytology of pancreatic cystic lesions. *Diagn Cytopathol,* 1997;17:177-182.

55. Glenn J, Steinberg WM, Kurtzman SH, et al. Evaluation of the utility of a radioiummune assay for serum CA 19-9 levels in patients before and after treatment of carcinoma of the pancreas. *J Clin Oncol,* 1988;6:462-468.

56. Sperti C, Pasquali C, Guolo P, et al. Serum Tumor Markers and Cyst Fluid Analysis are Useful for the Diagnosis of Pancreatic Cystic Tumors. *Cancer,* 1996;78:237-243.

57. Lumsden A, Bradley EL. Pseudocyst or cystic neoplasm? Differential diagnosis and initial management of cystic pancreatic lesions. *Hepatogastroenterology,* 1989;36: 462-466.

58. Sachs JR, Deren JJ, Sohn M. Mucinous cystadenoma: Pitfalls of differential diagnosis. *Am J Gastroenterol,* 1989;84:811-816.

59. 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;39:457-464.

60. O'Toole D, Palazzo L, Arotcarena R, et al. Assessment of complications of endoscopic ultrasound-guided fine needle aspiration. *Gastrointest Endosc,* 2001;53:470-474.

61. Lee LS, Saltzman JR, Bounds BC, et al. EUS-guided fine needle aspiration of pancreatic cysts: a retrospective analysis of complications and their predictors. *Clin Gastroenterol Hepatol,* 2005;3:231-236.

62. Varadarajulu S, Eloubeidi MA. Frequency and significance of acute intracystic hemorrhage during EUS-FNA of cystic lesions of the pancreas. *Gastrointest Endosc,* 2004,60:631-635.

63. Binmoeller KF, Brand B, Thul R, et al. EUS-guided, fine-needle aspiration using a new mechanical scanning puncture echoendoscope. *Gastrointest Endosc,* 1998;47:335-340.

64. Siech M, Tripp K, Schmidt-Rohlfing B, et al. Cystic tumours of the pancreas: diagnostic accuracy, pathologic observations and surgical consequences. *Langenbecks Arch Surg,* 1998;383:56-61.

65. Suzuki Y, Atomi Y, Sugiyama M, et al. Cystic neoplasm of the pancreas: a Japanese multi-institutional study of intraductal papillary mucinous tumor and mucinous cystic tumor. *Pancreas,* 2004;28:241-246.

66. Pingpank JF, Hoffman JP, Ross EA, et al. Effect of preoperative chemoradiotherapy on surgical margin status of resected adenocarcinoma of the head of the pancreas. *J Gastroint Surg,* 2001;5:121-130.

67. Thompson LD, Becker RC, Przygodzki RM, et al. Mucinous cystic neoplasm (mucinous cystadenocarcinoma of low grade malignant potential) of the pancreas: a clinicopathologic study of 130 cases. *Am J Surg Pathol,* 1999;23:1-16.

68. Balcom JH IV, Rattner DW, Warshaw AL, et al. Ten-year experience with 733 pancreatic resections: changing indications, older patients, and decreasing length of hospitalization. *Arch Surg,* 2001;136:391-398.

69. Brugge WR. Should all pancreatic cystic lesions be resected? Cyst-fluid analysis in the differential diagnosis of pancreatic cystic lesions: a meta-analysis. *Gastrointest Endosc,* 2005;62: 390-391.