The Role of EUS in Cystic Lesions of the Pancreas

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CONTENTS

Abstract

Cystic pancreatic lesions (CPLs) are increasingly recognized in clinical practice. Although inflammatory cysts are most commonly encountered, mucinous CPLs are important to identify and follow due to the risk of progression to malignancy. Endoscopic ultrasound (EUS) is widely accepted as the test of choice for the diagnosis and follow-up of CPLs. Not only does EUS permit close high quality images of the cyst, but also allows for fine needle aspiration (FNA) of cyst fluid,

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where cytological exam is performed to determine malignancy. More recently, certain tumor markers and DNA analysis of genetic markers of cyst fluid became available and could help differentiate mucinous from nonmucinous lesions. Management of CPLs takes into account the risk of malignancy and the benefit of pancreatic resection. This decision usually depends on multiple factors, including the type of cyst, presence of clinical symptoms, suspected underlying malignancy, and patient's overall health status. Recent development of minimally invasive treatment alternatives like cyst epithelium ablation with alcohol, appear safe and effective in high risk lesions although larger long-term studies are needed to demonstrate clinical utility.

Key Words: Pancreatic cysts, Mucinous cystic neoplasms of the pancreas, IPMN, Serous cystadenomas

INTRODUCTION

Cystic pancreatic lesions (CPLs) are increasingly detected due to the widespread use of cross-sectional imaging modalities like computed tomography (CT) and magnetic resonance imaging (MRI). It is estimated that up to 1.2% of the general population have pancreatic cysts based on large scale imaging observational studies (1) and up to 24% based on autopsy studies (2). While the majority of these lesions are benign, about 10–15% can be classified as cystic neoplasms and may require further evaluation, management, and follow-up (3, 4). The differential diagnosis of cystic lesions of the pancreas remains wide. Based on surgical pathology, CPLs can be classified by the type of epithelium lining the cyst. Pseudocysts are not classified as a CPL since these are nonepithelial inflammatory fluid collections that are associated with acute or chronic pancreatitis (3). Pseudocysts constitute more than 75% of pancreatic cysts that are diagnosed and are discussed in depth in another chapter of this book. The rest of CPLs are mainly cystic neoplasms that include intraductal papillary mucinous neoplasms (IPMN), serous cystadenomas (SCA), mucinous cystadenomas (MCN), mucinous cystadenocarcinomas (MCAC), solid pseudopapillary tumors (SPT), and few other rare types (5). The ability of the different cross-sectional imaging modalities to characterize these lesions is variable but remains limited. Endoscopic ultrasound (EUS) has emerged as a real-time imaging technique that provides high resolution images and morphologic details of CPLs. The combination of fine-needle aspiration cytology with other recently available diagnostic markers has further increased its diagnostic accuracy. In this chapter, we describe the role

of EUS in the diagnosis and management of CPLs and provide an overview and management alternatives of commonly encountered CPLs in clinical practice.

EUS VERSUS OTHER IMAGING MODALITIES IN THE DIAGNOSIS OF CPLS

The large number of incidental and asymptomatic CPLs noted on routine cross-sectional imaging studies challenge clinicians to identify the type of cyst, stratify the risk of malignancy and the need for surgery. Studies describing the role of noninvasive imaging like CT and MRI in the diagnosis of CPLs have been mostly small and retrospective in design. Relying on radiologic imaging characteristics alone in CPLs has been shown to be misleading, with up to 40% of serous and mucinous lesions being misdiagnosed as pseudocysts (3, 6) (Table 1). Reported overall diagnostic accuracy for these lesions has been highly variable ranging between 20 and 83% (7–9). In one study of 50 patients, three radiologists independently and prospectively interpreted CT scans in patients with a variety of CPLs with subsequent surgical pathology confirmation (10). These authors found that only 27% of SCA were correctly diagnosed when a consensus of two out of three radiologists was used for the diagnosis. In other small, retrospective studies evaluating a mixed type of CPLs, higher diagnostic accuracy was described using CT scan, and reached 82% in one study of 18 patients (11). In the same study, endoscopic retrograde pancreatography was diagnostic in only 53%. In a large multicenter French study of 398 patients with a variety of CPLs who underwent surgical resection, preoperative radiological exams were diagnostic in only 20% of SCA, 30% of MCN, and 29% of MCAC (7). The majority of misclassified CPLs were mistaken for pseudocysts (9% of MCAs and 15% of MCACs). There are few studies using head-to-head comparison of imaging modalities, such as CT and MRI, for the diagnosis of CPLs. In one small study of patients with both serous and mucinous cystadenomas (12), MRI was found to be slightly superior to CT in diagnosing cystic neoplasms, but CT scan was superior to MRI in detecting calcification within the wall and septa seen in mucinous lesions. For IPMN, MRCP has been reportedly found to be superior to ERCP for the evaluation of the morphology of side branches and associated cysts, including communication with the main pancreatic duct, but the two modalities were similar in assessing for cyst septations or nodules (13). These results were reproduced in a recent study of 18 patients with IPMN, where MRCP was found to be superior to CT in delineating pancreatic ductal anatomy and associated changes (14).

Table 1
Characteristics of cyst fluid in the main types of CPLs

Lesion	*Location*	*Fluid color*	*Viscosity*	*Cytology*	*CEA*	*CA* 19-9	*Amylase*
Pseudocyst	Anywhere	Dark yellow to Brown	Thin	Inflammatory cells with debris, macrophages but typically no mucin	Low to minimally increased	Variable	High
Serous cystadenoma	Body/tail > head	Colorless with blood contaminant	Thin	Usually acellular. Small glycogen staining cuboidal cells may be seen in the background	Undetectable to low	Low	Low
Mucinous cystadenoma	Body/tail > head	Colorless	Thick	May be acellular with background mucin. Mucinous epithelia cells may be seen	Moderate increase	Variable	Variable
Mucinous cystadencarcinoma	Body/tail > head	Colorless	Thick	Malignant mucinous epithelia cells	Marked increase	High	Variable
Intraductal papillary mucinous neoplasm	Main duct or side branch, head > body and tail	Colorless	Thick	Acellular with background of mucin. Occasionally mucinous epithelial cells with papillary projections and variable atypia may be seen	Moderate increase	Variable	High

EUS permits close, high resolution imaging of CPLs morphology that may not be readily visualized by CT or MRI. Diagnostic accuracy of EUS imaging alone for detecting malignant or premalignant lesions is reportedly 82–96% (15–20). Earlier literature described several EUS features of pancreatic cysts associated with increased malignancy risk, including thick wall, protruding tumor, presence of nodule or mass and thick septations (15, 16). Subsequent studies, however, uncovered the shortcomings of relying on EUS alone in differentiating benign from malignant CPLs. For example, in one study, blinded expert endosonographers reviewed EUS videotapes of pathologically confirmed pancreatic cystic neoplasms and noted cyst features, type, and malignancy potential (18). The interobserver agreement was moderately good in detecting solid lesions but only fair for detecting pancreatic duct abnormalities, septations, and the diagnosis of neoplastic versus nonneoplastic lesions. Expert agreement on the diagnosis of SCAs was moderately good (κ=0.46) but only fair for the remainder of the lesions. The agreement on the presence or absence of solid component was moderately good (κ=0.43), and the overall accuracy rates for the diagnosis of neoplastic versus nonneoplastic lesions ranged from 40 to 93%. A large prospective multicenter US study found that the accuracy of EUS imaging features alone for the diagnosis of mucinous lesions was only 51% (20). Given the above limitations, EUS morphology alone is generally considered inadequate for further characterization of CPLs or predicting their malignancy potential.

EUS-FNA OF CPLS: TECHNIQUE

EUS-guided fine needle aspiration (EUS-FNA) has been shown to be an effective and safe sampling method of CPLs. Its safety has been confirmed by multiple studies and complication rates in recent literature were found to be around 1% or less (21–24).

EUS-FNA for CPLs is performed using the linear array echoendoscope under conscious sedation and appropriate cardiorespiratory monitoring (25). The ultrasound transducer on the distal tip of the echoendoscope permits needle advancement into the lesion under real-time guidance. A variety of commercially available FNA needles is available and range in size between 19 and 25 gauge. It is recommended that Doppler is used to examine the projected path of the needle to avoid puncturing intervening blood vessels, while trying to minimize the amount of normal pancreatic tissue that has to be traversed. Once the gastric or duodenal wall is punctured and the needle enters the cyst, the stylet is withdrawn and suction is applied. If possible, complete cyst aspiration

using only one biopsy is recommended. The needle is then withdrawn back into the sheath and assembly is removed. The material retrieved from the aspiration is then expressed on two glass slides: one slide is air-dried for immediate staining and on-site review while the other slide is alcohol-fixed for later pathologic exam. The presence of on-site cytopathology for rapid interpretation is recommended and has been shown to improve the diagnostic yield (26). The risk of infection from EUS-FNA of pancreatic cysts was initially reported to be as high as 14% in early studies (27). Therefore, it has become routine practice to administer IV antibiotics (such as a fluoroquinolone) prior to or immediately after EUS-FNA followed by oral antibiotics for 3–5 days to limit this risk. Recent studies have shown that this practice may limit this complication to less than 3% (24).

A recently developed cytobrush device (Echobrush®, Cook Medical Inc., Winston-Salem, NC) has been approved for use with a 19-gauge EUS-FNA needle. Suitable CPLs for cytobrush use include those that are at least 2 cm in diameter and located in the neck, body, or tail of the pancreas. These limitations mainly reflect the difficulty of using the relatively stiff 19-gauge needle to aspirate head and uncinate lesions. Once the needle is in the cyst, the stylet is withdrawn and the brush is advanced through the sheath under ultrasound guidance. The brush is moved back and forth several times to ensure adequate tangential contact with the cyst wall or any mural nodules. Patients on anticoagulation are usually excluded due to higher risk of bleeding shown in the pilot study (28). Prophylactic antibiotics are administered as described above.

EUS-GUIDED TRUCUT BIOPSIES

EUS-guided Trucut biopsy (EUS-TCB) permits the acquisition of a tissue fragment with preserved histologic architecture and has been shown to be safe for tissue sampling from a variety of solid organs (29, 30). The Quick-Core® (Cook Medical Inc., Winston-Salem, NC) is a commercially available TCB device that is a 19-gauge needle equipped with a spring-loaded cutting sheath and a tissue tray (29, 30). Initial human experience showed that EUS-TCB provides superior diagnostic accuracy for submucosal lesions, lymphoma, and autoimmune pancreatitis compared to standard EUS-FNA (31). The same studies suggested that the use of TCB in solid lesions of the pancreas may provide a diagnosis in fewer passes.

In CPLs, the TCB may offer a histological specimen from the wall cyst, supporting stroma, or any other solid components of the cyst. The use of EUS-TCB for CPLs was initially described by Levy et al. (32)

in ten patients and was found to be diagnostic in six patients, partially diagnostic in one and nondiagnostic in the remaining three. No complications were reported in this small study. The authors recommend its use only when the histologic findings are likely to change patient management. Until further randomized prospective trials become available, EUS-FNA remains the mainstay of sampling CPLs for cytology and obtaining tumor markers.

CYST FLUID EVALUATION

Cytology

Due to the inherent limitations of EUS morphology alone in accurately diagnosing CPLs, the use of FNA for cytology and fluid analysis of these lesions has been extensively evaluated. The specificity of EUS-FNA cytology for the diagnosis of CPLs is excellent and exceeds 90% in most published studies (19, 20, 33). On the other hand, the sensitivity of EUS-FNA remains widely variable with most studies reporting a sensitivity of <50% (19, 20, 33, 34). Brandein et al. reported EUS-FNA sensitivity, specificity, and an accuracy of 50%, 100%, and 89%, respectively, for the diagnosis of malignancy in 26 patients with different types of CPLs (33). In another report of 18 patients with surgical pathology correlation, Sedlack et al. (34) reported sensitivity, specificity, and an accuracy of 27%, 100%, and 55%, respectively; however, in this study FNA was only performed when there was diagnostic uncertainty. Frossard et al. (19) reported that EUS-FNA correctly identified 65 of 67 (97%) CPLs when a dedicated on-site pathologist reviewed all cytologic preparations. In a study of 48 patients from our institution, the sensitivity, specificity, and frequency of cases correctly identified by EUS-FNA cytology for the diagnosis of mucinous cystic neoplasms were 12.5%, 90.6%, and 64.6%, respectively (35). Finally, in a prospective, multicenter study, Brugge et al. (20) reported the results of EUS-FNA cytology and tumor markers in 112 patients who underwent surgery. This study reported a sensitivity and specificity of cytology of 35% and 83%, respectively. The sensitivity of EUS-FNA for the diagnosis of malignancy in mucinous lesions was only 22%. Possible reasons for this wide variation in the reported sensitivity of EUS-FNA cytology for the diagnosis of CPLs may include the variable use of on-site cytology interpretation and cytopathologist expertise, lesion sampling error, sporadic distribution of malignant epithelium in the cyst, presence of gastrointestinal contaminant, and variability of endosonographers' experience. In a recent pilot study,

CPLs cytobrushings were shown to be superior to standard cytology specimens obtained via FNA in seven out of ten patients (28). Recently updated data from a prospective blinded study comparing FNA to cytobrushings showed mucinous epithelium in 16 out of 22 patients compared to six out of 22 using FNA alone, including two cases of high grade dysplasia seen exclusively on cytobrushings (36).

Tumor Markers

Tumor markers in pancreatic cysts that have been evaluated in various studies include: carcinoembryonic antigen (CEA), CA19-9, CA 72-4, and CA 125. The most commonly evaluated marker is CEA, and this is generally found in high levels in mucinous lesions, but is lower in pseudocysts and nonmucinous tumors. An early study found that a CEA level less than 5 ng/mL provided 100% sensitivity and 86% specificity for distinguishing mucinous neoplasms from other cystic lesions (37). The same study demonstrated that a CA 19-9 level >50,000 U/mL had 75% sensitivity and 90% specificity for distinguishing mucinous from nonmucinous tumors. The same authors later reported that a cyst fluid CA 72-4 >40 U/mL had a 63% sensitivity and 98% specificity for distinguishing SCA from mucinous cystadenomas and cystadencarcinoma (38). Frossard et al. reported that a CA19-9 level exceeding 50,000 U/mL had 15% sensitivity and 81% specificity in differentiating mucinous from other cystic lesions (19). The same study demonstrated a CEA level >400 ng/mL to offer sensitivity and specificity levels of 13% and 75%, respectively, to distinguish mucinous from nonmucinous cystic lesions. Sperti et al. (39) reported multiple tumor marker levels in both serum and cyst fluid in 48 patients with pancreatic cysts. Cyst fluid CA 72-4 levels were significantly higher in mucinous cystic tumors, with 95% specificity and 80% sensitivity in detecting mucinous or malignant cysts. The results of cyst fluid CEA were less accurate than CA 72-4, with a sensitivity of 38% and a specificity of 100% in detecting benign and malignant mucinous lesions. The largest prospective study to date (20) determined that a cut-off of cyst fluid CEA of 192 ng/mL provided a sensitivity of 73% and specificity of 84% for differentiating mucinous from nonmucinous CPLs in 112 patients who underwent surgery. Cyst fluid CA 19-9 level of 2,900 offered a sensitivity of 68% and specificity of 62% for differentiating mucinous from nonmucinous tumors. No other combination of factors, including cytology, morphology, and CEA levels was found to be more accurate than CEA levels alone.

Biochemical markers such as amylase and lipase may be evaluated in these patients. Amylase is usually elevated in inflammatory cysts like

pseudocysts and IPMN due to the communication with the pancreatic duct. In a pooled analysis from 12 studies, an amylase concentration <250 U/L supported a diagnosis of SCA, MCA, or MCAC (sensitivity 44%, specificity 98%) and thus virtually excluded pseudocysts (40). In the same analysis, a CEA level <5 ng/mL suggested a SCA or pseudocyst (sensitivity 50%, specificity 95%) and a CEA >800 ng/mL strongly suggested MCN (sensitivity 48%, specificity 98%). A CA 19-9 <37 U/mL strongly suggested pseudocyst or SCA (sensitivity 19%, specificity 98%).

From the above studies, we recommend the evaluation of cyst fluid from EUS-FNA for CEA, cytology, and amylase tests whenever sufficient fluid (about 1–1.5 mL) is obtained. If less fluid is obtained, cytology should always be obtained and then CEA if enough fluid remains. Other cyst fluid tumor markers such as CA 19-9 appear to offer inferior diagnostic results compared to CEA alone and their use is not currently recommended.

Genetic Markers

In recent years, there has been increased interest in identifying specific genetic markers that are associated with higher risk of malignancy in CPLs. Modeled after the adenoma-carcinoma sequence in colon cancer, IPMNs are believed to follow a similar transformation from hyperplasia to dysplasia and carcinoma (41). K-ras gene mutation has been well studied and appears to occur early in the transformation sequence (41). As with other cancers, more than one "hit" is believed to be required for the progression of precancerous cystic tumors to malignancy. In IPMN, this is reported to be a result of tumor suppressor gene inactivation, which is represented by the loss of heterozygosity at 9p12 (p16) and 17 p13 (p53) (42). Other studies have investigated the specific genetic markers of SCA and MCN. Moore et al. (43) described allelic losses on chromosome 10q in 50% of cases and on chromosome 3p in 40% of cases. No K-ras or p53 mutations were noted in any of the 21 SCA studied. Kim et al. (44) found that one-third of MCN were associated with K-ras mutations and further variable changes in tumor suppressor genes like p16 and p53, but were not observed in any SCA.

The use of the above markers has been evaluated in clinical applications. It was found that pancreatic juice contains K-ras mutations in high frequency (60%) in patients with IPMN (45, 46). Similar to pancreatic juice, PCL fluid contains DNA shed from the epithelial lining (47). Khalid et al. (48) initially reported data from 36 PCLs with confirmed

histology showing that cyst fluid examination for K-ras mutations and microsatellite allelic loss was feasible and predictive of malignancy. In a multicenter, prospective study (49), the same author evaluated the role of DNA analysis in 124 patients undergoing EUS-FNA with malignant cytology or later confirmed surgical pathology. This study found that an elevated quantity of good quality DNA and high amplitude mutations were associated with malignant cystic neoplasms. Very high amounts of mutated DNA and mutational sequence of K-ras followed by allelic loss was very specific for malignant cysts. High amplitude and K-ras mutations were very specific for mucinous cysts. Recent data in abstract form compared the accuracy of CEA to DNA analysis in 100 patients with CPLs and found only fair agreement between those two methods. CEA alone had the highest sensitivity (82%) compared to 11% for K-ras mutation and 70% for allelic imbalance (50). The CEA and DNA analyses in this study were complementary and together identified all mucinous cysts included. A commercially available genetic test (RedPath® IP, Pittsburgh, PA) is available to identify the above genetic markers in free floating DNA which may help to provide additional information of CPLs and stratify their risk of malignancy. The role of cyst fluid DNA analysis in clinical practice, however, remains to be determined.

In the next part of the chapter, we will be discussing the common types of CPLs individually while focusing on the EUS features, cytology, and tumor markers' characteristics.

SEROUS CYSTIC NEOPLASMS

SCAs are most commonly seen in females in the seventh decade of life and are typically asymptomatic. They may be found incidentally on imaging studies performed for other reasons or may become manifested if the lesion compresses adjacent structures such as the gastrointestinal tract. Although most reports indicate a preponderance to occur in the body and tail (51), some authors report a higher incidence in the head and neck (52). The conventional endosonographic appearance of a microcystic SCA is a well-delineated lesion with multiple, small fluid filled cavities (typically less than 5 mm in size) with thin septa (Fig. 1). A central scar (usually referred to as sunburst calcification but could be only fibrosis) may be present in up to one quarter of the cases (Fig. 2) (53). The presence of any intramural nodules, cyst wall thickening, floating debris or mucin or associated pancreatic ductal dilation is unusual and could indicate an underlying mucinous lesion (16, 54).

The diagnostic yield of EUS-FNA for SCA is usually poor due to the small size of the cystic compartments and the relatively vascular intercystic

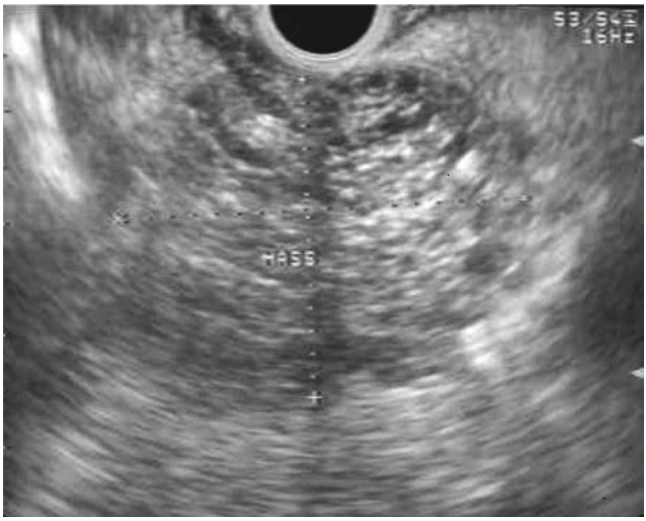

Fig. 1. Characteristic endoscopic ultrasound appearance of a microcystic serous cystadenoma in the head of the pancreas in an asymptomatic 65-year-old female patient. The lesion contains multiple small cysts separated by thin septa.

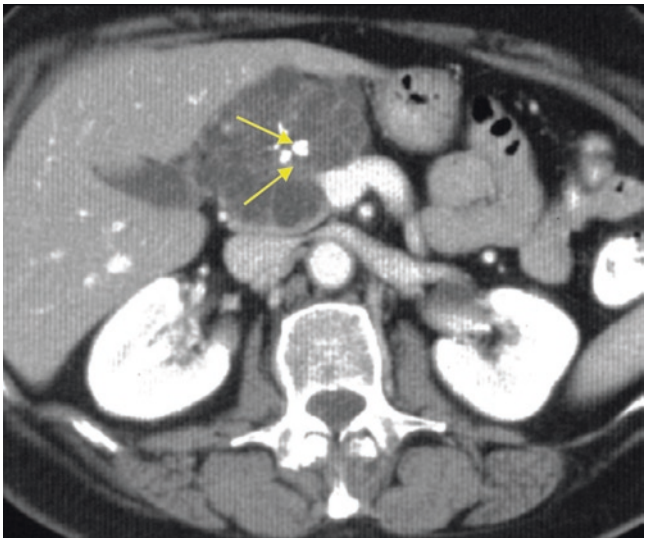

Fig. 2. CT scan of the abdomen of an incidentally detected serous cystadenoma. Central calcifications (arrows) and lobulated multicystic appearance are typical CT findings.

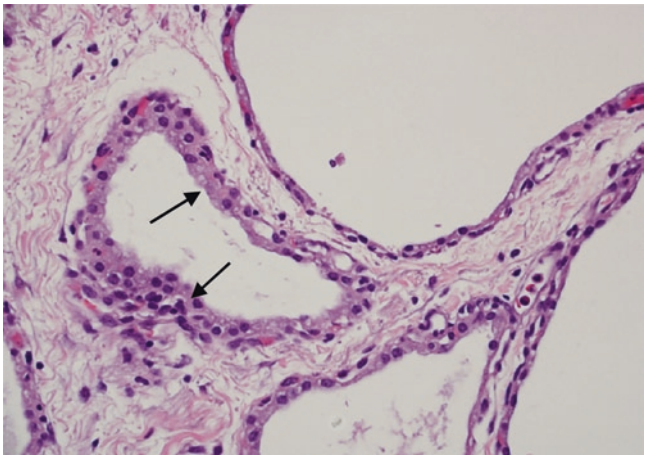

Fig. 3. Histopathology of serous cystadenoma. Cuboidal epithelial cells (arrows) are seen to line small cystic spaces. (H&E, ×400).

septa. Due to the distinctive endosonographic appearance of microcystic SCA, cyst sampling is generally not needed. If necessary, EUS-FNA of SCA should target the larger cystic compartments for fluid analysis. Fluid obtained is often thin, nonviscous and is colorless. Cellularity is usually very low, and if any, cuboidal epithelial cells have been described on aspirate that stain positive for glycogen but not mucin (Fig. 3) (55). CEA levels are usually low (less than 20 ng/mL) (56). The macrocystic variant of SCA cannot be distinguished morphologically from mucinous cystic lesions, and therefore FNA of these lesions is recommended. Generally, clinical observation alone is sufficient for SCA as these cystic lesions seldom undergo malignant transformation (57). Surgery is recommended for larger symptomatic cysts or when there is uncertainty about the diagnosis.

MUCINOUS CYSTIC NEOPLASMS

MCNs include mucinous cystadenomas and carcinomas. These tumors are usually associated with extracellular mucin production with variable degrees of atypia. Females are often more affected than males, particularly in their fifth and sixth decade (58, 59), and the lesions most commonly occur in the pancreatic body and tail. The specific histopathology hallmark of these tumors is the presence of ovarian stroma and is required to differentiate this from IPMN (60). MCNs are premalignant lesions but the risk of malignant degeneration is likely less than that

of IPMN (60). MCNs can be completely asymptomatic when incidentally noted on imaging studies, but can also be present with obstructive symptoms due to large size, or weight loss and jaundice. When jaundice is present, the suspicion of malignant transformation is raised. Main pancreatic duct communication is rarely present with MCN.

The morphology of MCN on EUS can be variable but are commonly associated with a visible wall and septations of variable thickness (Fig. 4). Peripheral calcifications can be seen in up to 15% of cases (Figs. 5 and 6) (58). The presence of thick or irregular cyst wall, intramural nodules or solid components and larger size have been associated with malignancy (16). EUS-FNA is advised for confirmation of all suspected MCN. Cytology may reveal columnar epithelial cells in up to half of the patients associated with mucin (Fig. 7) (40, 61). Mucin identified cytologically by EUS-FNA can be difficult to differentiate from gastric contaminant mucinous epithelium, therefore we recommend cyst aspiration from the duodenum whenever feasible. Cyst fluid from MCNs is typically clear but is often viscous with relatively elevated CEA levels and low amylase. The risk of malignancy in these tumors described in a recent series of 163 patients was found to be 17.5% (5.5% with carcinoma in situ and 12% with invasive cancer) (62).

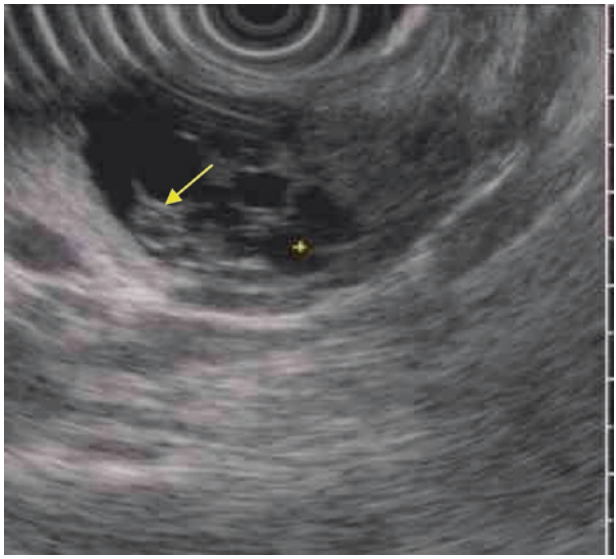

Fig. 4. EUS findings in a middle age female patient with a mucinous cystic neoplasm in the body of the pancreas. A cyst wall is present and few intracystic nodules arising from the wall (arrow) could represent a solid lesion or mucous.

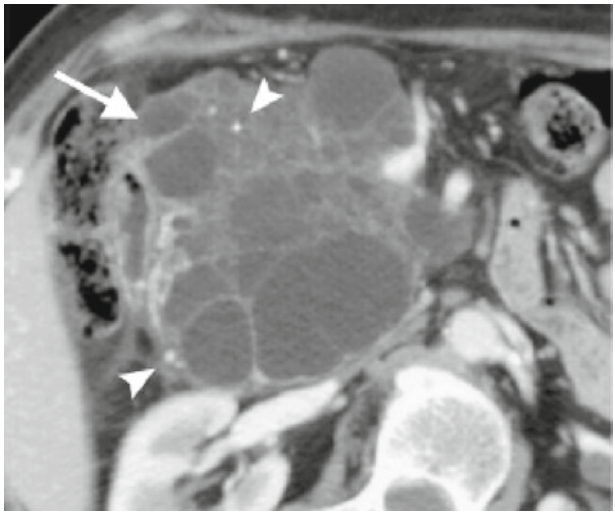

Fig. 5. CT scan findings of a patient with mucinous cystic neoplasm. Multiple cystic spaces with variable thickness septations are apparent (arrow) and generally considered a risk of malignancy. Peripheral calcifications (arrowheads) within the septa are noted in up to 15% of patients.

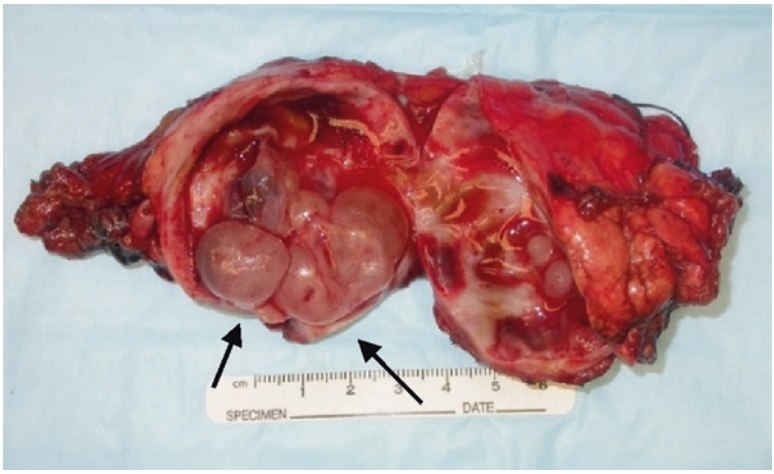

Fig. 6. Gross surgical specimen in a patient with mucinous cystic neoplasm. Multiple cystic compartments filled with mucin (arrows) are noted. No malignancy was detected in this specimen.

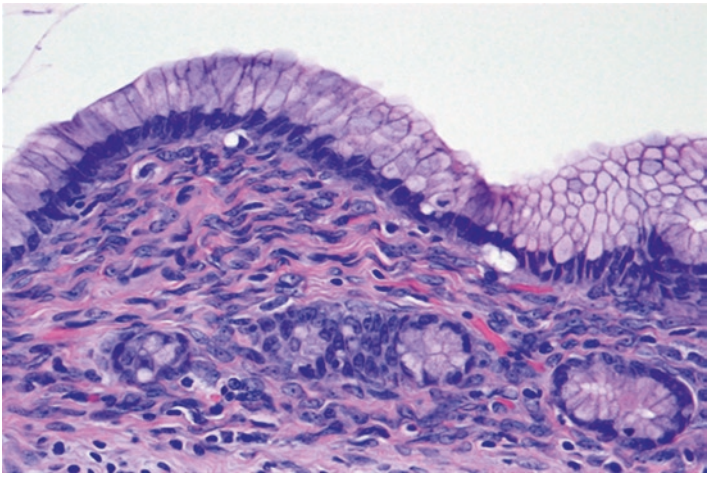

Fig. 7. Photomicrograph of a mucinous cystadenoma (H&E, ×400). Columnar mucinous epithelial cells are seen overly ovarian stroma. Ovarian stroma is the pathological hallmark of these tumors.

Therefore, surgical resection is recommended whenever feasible. The prognosis after surgery for MCN that have not undergone malignant transformation is excellent and the 5 year survival for mucinous cystadenocarcinomas postresection exceeds 60% (7, 53).

INTRADUCTAL PAPILLARY MUCINOUS NEOPLASMS

IPMN are premalignant mucinous cystic lesions that arise from the main pancreatic duct, side branch or both and are associated with ductal ectasia, intraductal papillary growth, and mucin production (63). IPMN is most prevalent in the sixth to seventh decade of life and affects males and females equally (64).

The main duct IPMN is typically easy to differentiate in EUS (Fig. 8) and ERCP (Fig. 9) due to the diffuse dilation of the pancreatic duct (Fig. 10), mural tumor growth and occasionally intraductal filling defects due to mucin production. EUS imaging of branched duct IPMN usually demonstrates visible communication of the cyst with the main pancreatic duct. However, in the absence of duct communication, branched duct IPMN may be morphologically indistinguishable from MCNs. Any visible mucin extruding from a patulous papilla supports the diagnosis and the classic "fish mouth deformity" is considered diagnostic. During EUS, any intraductal mass, mural nodule or projections

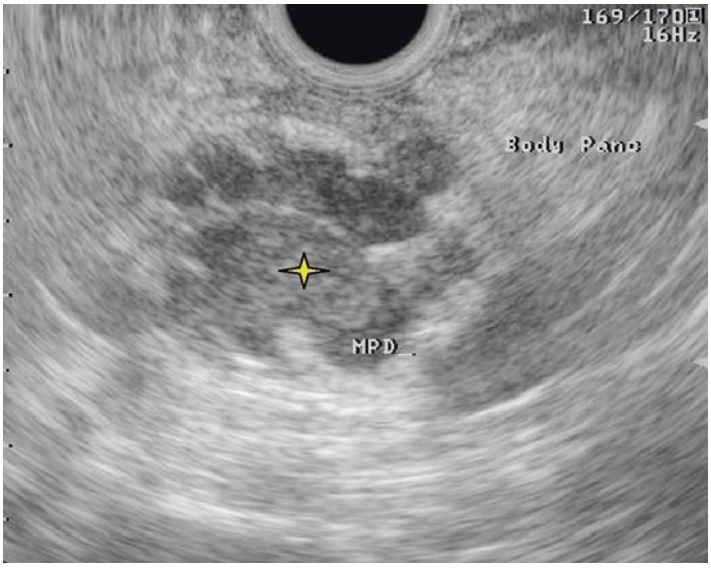

Fig. 8. Intraductal papillary mucinous neoplasm affecting the main pancreatic duct and side branches in a male patient with acute recurrent pancreatitis. EUS showed a dilated pancreatic duct within the body of the pancreas (star) with intraductal tumor growth. (MPD main pancreatic duct).

noted within the main duct or off a cyst wall should be the target of FNA. If no visible lesions are noted, the main duct or branch can be punctured for cytology and tumor markers. Cytology usually reveals thick mucin but may be thin and completely acellular (65). Occasionally, fragments of papillary mucinous epithelium can be seen on FNA (Fig. 11) or cytobrushings. Cyst fluid resembles that obtained from MCN with a relatively elevated CEA; however, amylase tends to be higher due to the ductal communication.

The risk of malignancy within IPMN is well described in the literature, although most of the earlier studies included mixed populations with both side branch and main duct IPMN. The risk of malignancy in the main duct type has been reported to range from 57% to 92% (66–70), and therefore surgery is recommended for these patients. The natural history of the side branch type remains less established. An adenoma to carcinoma sequence is believed to account for the slow growth of these tumors and the lag time observed between the detection of these lesions and the development of invasive cancer (64). Risk factors associated with invasive cancer have been described and include older age, presence of symptoms such as jaundice and weight loss, intramural nodules, and

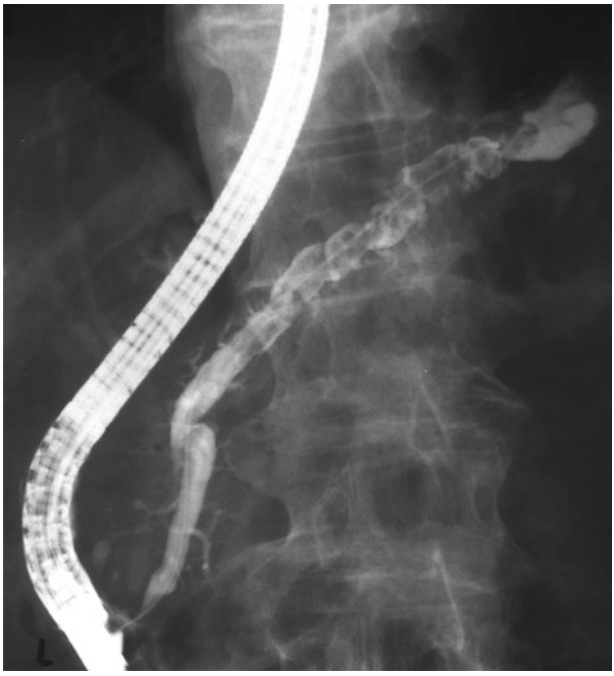

Fig. 9. ERCP appearance of a dilated main pancreatic duct in a patient with main duct IPMN. Filling defects are seen consistent with mucin.

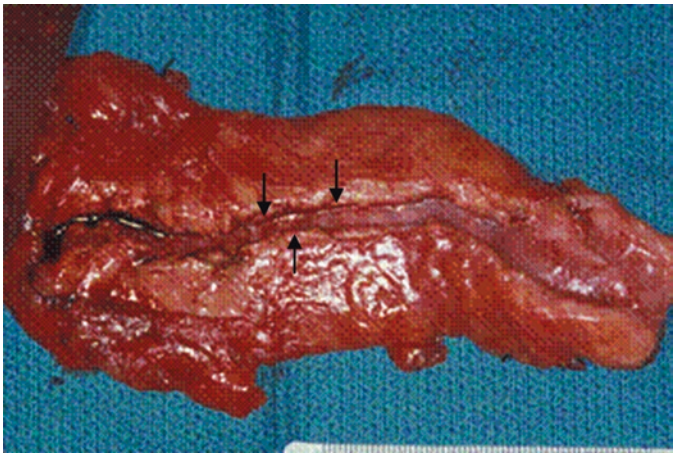

Fig. 10. Longitudinal section of a pancreas resection specimen demonstrating the diffuse dilation of the main pancreatic duct (arrows) in a patient with intraductal papillary mucinous neoplasm.

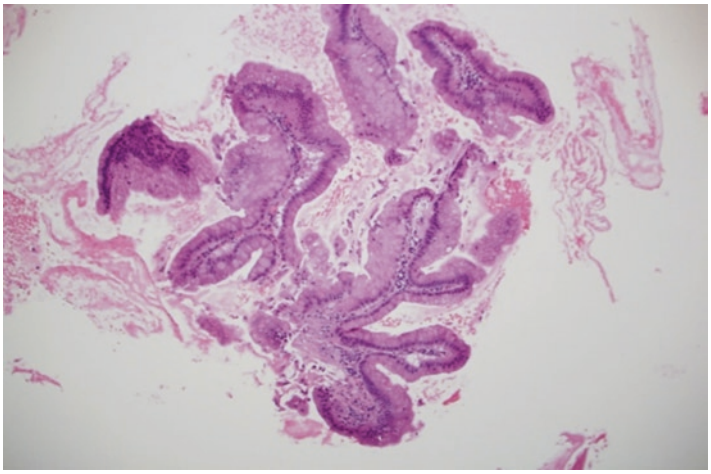

Fig. 11. Fine needle aspiration cytology smear (H&E, ×4) in a patient with a side branch intraductal papillary mucinous neoplasm. A small fragment of papillary mucinous epithelium is occasionally noted and was diagnostic in this case.

progressive dilation of the main duct. Unfortunately, a major limitation of EUS-FNA in detecting invasive malignancy preoperatively is its low sensitivity, which has been reported to be as low as 44% in two studies (40, 71). In one study by our group, Pais et al. (72) reported an EUS sensitivity as high as 75% in detecting malignancy within IPMN; however, three quarters of the patients with malignancy had an associated solid mass. This same study reported that CEA levels from IPMN could not reliably distinguish benign from invasive IPMN. Another study (73) showed that the combination of EUS and ERCP cytology samples had a 91% sensitivity for invasive IPMN carcinoma but only 40% for minimally invasive disease like carcinoma in situ/high grade dysplasia. Recently, few studies have described the role of intraductal ultrasonography (IDUS) in the diagnosis of IPMN. Hara et al. (74) reported IDUS sensitivity, specificity, and an accuracy of 68%, 89%, and 78%, respectively, for lesions protruding 4 mm or more within the duct. However, there was no statistically significant difference between carcinoma in situ and invasive carcinoma, and a differential diagnosis was not possible based on IDUS findings alone.

This inability to reliably diagnose IPMN with variable degrees of dysplasia preoperatively appears to have a higher significance in small lesions (<3 cm in size) where the general recommendations have been

to observe. In a recent study of 147 patients with only branched IPMN, the malignancy rate was 12% in patients who underwent surgical resection (75). In this same study, cyst size (>3 cm) and the presence of pancreas-related symptoms had no effect on the risk of malignancy. Two other studies have shown that the risk of malignancy in side branch lesions is 6% and 46%, respectively (67, 68) and that invasive cancer can be detected in lesions <3 cm in size (76–78).

OTHER RARE TYPES OF CPLS

Solid pseudopapillary tumors (PST) are rare neoplasms of the pancreas that affect mainly young females. Small lesions may be diagnosed incidentally while asymptomatic (Fig. 12) but could enlarge and present with symptoms due to mass effect (79–83). EUS may show a purely solid (Fig. 13) or a mixed solid and cystic mass. FNA usually shows branching papillae with myxoid stroma which is best seen on cell block slides (Fig. 14). A recent multicenter study reported that EUS-FNA with or without immunochemistry preoperatively diagnosed 75% of 28 patients (83). On immunohistochemistry, the tumor cells typically react to Vimentin and cellblock preparation is recommended when the diagnosis

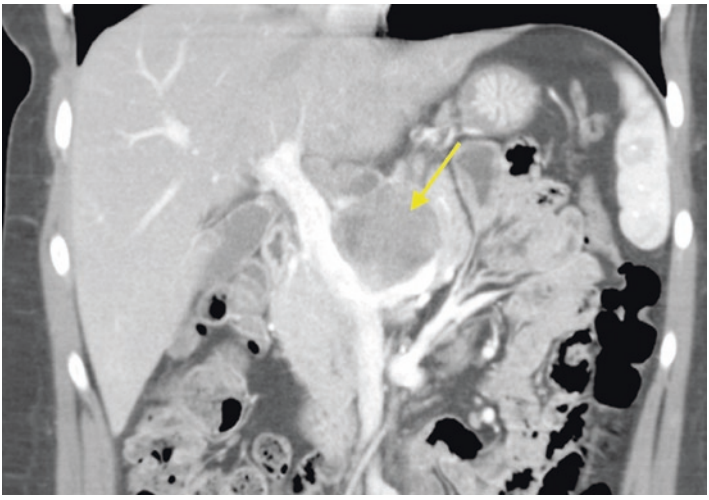

Fig. 12. CT scan of the abdomen demonstrating a solid pseudopapillary tumor in a young female patient slightly compressing the portal venous confluence under the neck and body of the pancreas.

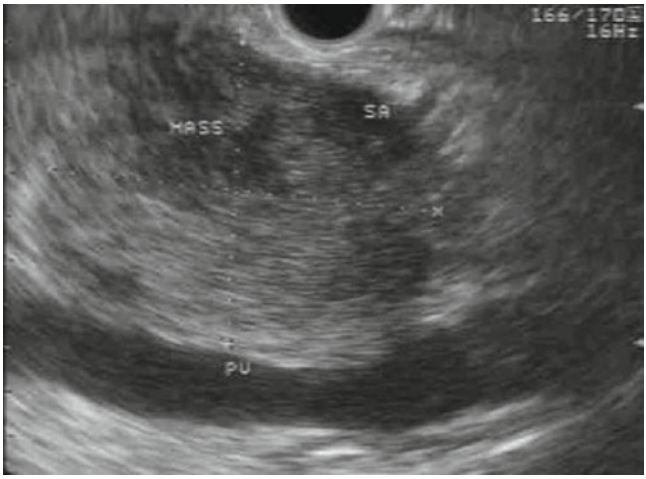

Fig. 13. EUS appearance of the solid pseudopapillary tumor in the same patient. The tumor is seen to abut the portal vein (PV) and encase the splenic artery (SA).

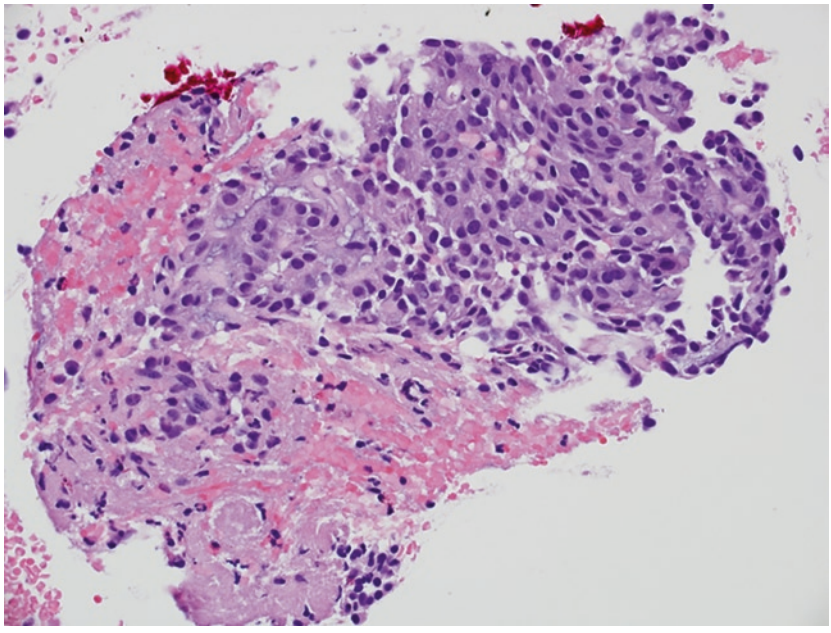

Fig. 14. Core biopsy histology of a pseudopapillary tumor. Myxoid stroma and branching papillae are seen. (H&E, ×400).

is considered. The overall prognosis after surgical resection is excellent and is generally recommended due to the risk of malignant transformation (up to 15%) and the relatively young age of the patients. Metastatic disease is rarely seen and prognosis remains good after surgical resection of metastatic lesions (84).

Approximately 10% of all pancreatic neuroendocrine tumors of the pancreas have a cystic component (85). Lesions vary in size and morphology, and therefore FNA is recommended. Cytology shows a small homogenous small cell population with round nuclei that should stain positive for chromogranin and synaptophysin. Routine cell block preparation is therefore recommended in these patients. Other rare CPLs include metastatic lesions (from renal cell carcinoma or melanoma), (86) teratomas, choriocarcinomas, teratomas, lymphoepithelial cysts (87), and lymphoceles (88).

TREATMENT OF CPLS

Expectant Management

Recent literature supports expectant observation in low risk PCLs with benign EUS features, negative FNA and, low tumor markers. In a study of 539 patients with various CPLs, the risk of progression to malignancy among those lesions <3 cm in size without a solid component was found to be 3% (89), which is similar to the mortality associated with surgical resection of the pancreas. Recently, published practice guidelines (90) take into consideration this balance between the risk of malignancy and the benefit of pancreatic resection. The proposed approach incorporates the information obtained from cross-sectional imaging, EUS, and cyst fluid analysis to differentiate mucinous (premalignant) and nonmucinous cystic lesions.

Practically, the decision to follow rather than resect a PCL is a clinical judgment and is based on consideration of the patient age, comorbidities, and an estimation of the cancer risk in the lesion. CT scan, MRI and MRCP are generally considered safe and reliable in providing follow-up data on cyst and pancreatic duct size, but are less sensitive in detecting intramural nodules, which are better evaluated by the use of EUS-FNA (89, 91). Therefore, an EUS-based algorithm is recommended for the initial evaluation and follow-up of PCLs of indeterminate behavior (92). However, in studies evaluating the outcome of conservatively managed IPMNs, for example, lack of long-term follow-up remains a major limitation, with median follow-up of 10–45 months reported (68, 75).

Surgical Management

The mainstay of treatment of malignant and premalignant PCLs remains surgical resection. Recently, reported surgical mortality rates associated with pancreatic surgery have decreased compared to earlier studies, and currently is under 3% at referral centers (93, 94). Morbidity from surgical resection, however, remains over 20% in most series. In one high-volume surgical center, the rate of complications following pancreatic cyst surgery in a group of 170 patients was 22% with a mortality rate of 0.6% (89). In the recent years, enucleation has emerged as a less invasive alternative, with reduced operative times and blood loss without increasing postoperative morbidity (95, 96). However, this approach remains limited to certain tertiary care centers and to a selective population of patients.

Alternate Nonsurgical Management and Future Developments

Alternative nonoperative therapies for CPLs have been described in the recent years. In a pilot study of 25 patients, Gan et al. (97) reported their experience using incrementally increasing concentrations of ethanol injection into CPLs. No complications were reported with this technique. Twenty three patients underwent follow-up with either surgical resection (five patients) or repeat imaging. Eight out of 23 patients had complete resolution of the cysts on radiology studies. Variable degrees of cyst epithelial ablation were reported in the five surgical cases. Subsequently, a multicenter randomized double-blinded study of 39 patients (98) with suspected mucinous or nonmucinous CPLs and pseudocysts were randomized to lavage with ethanol (23 patients) or saline (16 patients). This study found that ethanol lavage led to a statistically significant decrease in cyst surface area compared to saline lavage. Surgical pathology in three patients who underwent surgical resection following ethanol lavage demonstrated 50–100% ablation of the cyst lining. Overall 33% of patients in this series had complete cyst resolution by follow-up imaging. Two patients developed acute pancreatitis (overall 4% incidence) following ethanol lavage. The authors concluded that ethanol lavage could be a safe and effective method to ablate CPLs. Other lavage agents have been reported in renal and thyroid cystic lesions like acetic acid (99) and polydocanol (100), but no trials have been reported to date on use in CPLs.

Oh and his coworkers described the use of paclitaxel after ethanol for injecting ten patients presumed CPLs that do not communicate with the pancreatic duct (101). After a median follow-up of 6 months,

imaging showed complete resolution of cysts in six patients, partial resolution in three and no change in one. However, none of the patients underwent surgical resection to confirm the ablation. One patient was hospitalized with focal pancreatitis, and one had vague but transient abdominal pain.

CONCLUSION

CPLs are being increasingly recognized in symptomatic and asymptomatic patient populations. Diagnosis and management of such lesions should involve a multidisciplinary approach with gastroenterologists, radiologists, and surgeons. Utilization of cyst morphology by cross-sectional imaging studies or EUS alone cannot reliably differentiate benign from malignant cysts. Therefore, we recommend the routine use of EUS-FNA in the management of CPLs. Cytology, tumor markers, including CEA and DNA analysis can further characterize these lesions and increase the diagnostic accuracy of mucinous and malignant cysts. Recent advances in EUS for cyst epithelium ablation are a promising minimally invasive alternative treatment of high risk lesions.

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