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ROUND TABLE

Defining the Diagnostic Algorithm in Pancreatic Cancer

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Summary

Most patients with pancreatic cancer present with a mass on radiologic studies, however, not every pancreatic mass is cancer. Since radiological studies alone are insufficient to establish the diagnosis of a pancreatic mass and patient management depends on a definitive diagnosis; confirmatory cytology or histology is usually required. As a minimally invasive procedure, EUS and EUS FNA avoid the risk of cutaneous or peritoneal contamination that may occur with CT or US-guided investigations and is less invasive than surgical interventions. As a result, EUS FNA of pancreatic masses is becoming the standard for obtaining cytological diagnosis.
This chapter presents an EUS-based diagnostic algorithm for the evaluation of pancreatic lesions and is based upon a review of the pertinent literature in the field of pancreatic endosonography that has been the most influential in helping to guide this evolving field. Realizing there is much overlap among the EUS characteristics of various pancreatic lesions, for the sake of simplicity we have structured our discussion in broad terms of solid versus cystic lesions and discuss various pancreatic lesions within this framework. The additional contributors to this round table discussion have been asked to provide a more dedicated, focused discussion of the various subcategories of pancreatic lesions in greater detail than we could hope to achieve here. We provide this final contribution to the round table as a means of bringing the discussion back to the big picture of pancreatic lesions, rather than trying to hone in on the fine details of any one subclass.

Pancreatic cancer is one of the deadliest gastrointestinal cancers with 32,000 deaths attributed to this malignancy annually in the USA. It is the fourth leading cause of cancer death in men and women. Unfortunately, most patients with pancreatic cancer present late in the course of the disease. This explains why only 20% of patients are surgical candidates and the overall prognosis dismal with a 5-year survival rate hovering around 5%. The evaluation of pancreatic lesions suspected to be malignant could be a daunting undertaking unless one approaches the task in a focused, diligent manner. Most patients with pancreatic cancer present with a mass on radiologic studies, however, not every pancreatic mass is cancer. The differential diagnosis for a pancreatic mass on radiologic imaging includes, but is not limited to, pancreatitis, pancreatic adenocarcinoma, solid pseudopapillary tumor, neuroendocrine tumors, mucinous cystic tumors and serous cystadenoma. Since radiological studies alone are insufficient to establish the diagnosis of a pancreatic mass and patient management depends on a definitive diagnosis; confirmatory cytology or histology is usually required. Histologic diagnosis generally requires surgical intervention, an invasive procedure that may not be needed for patients

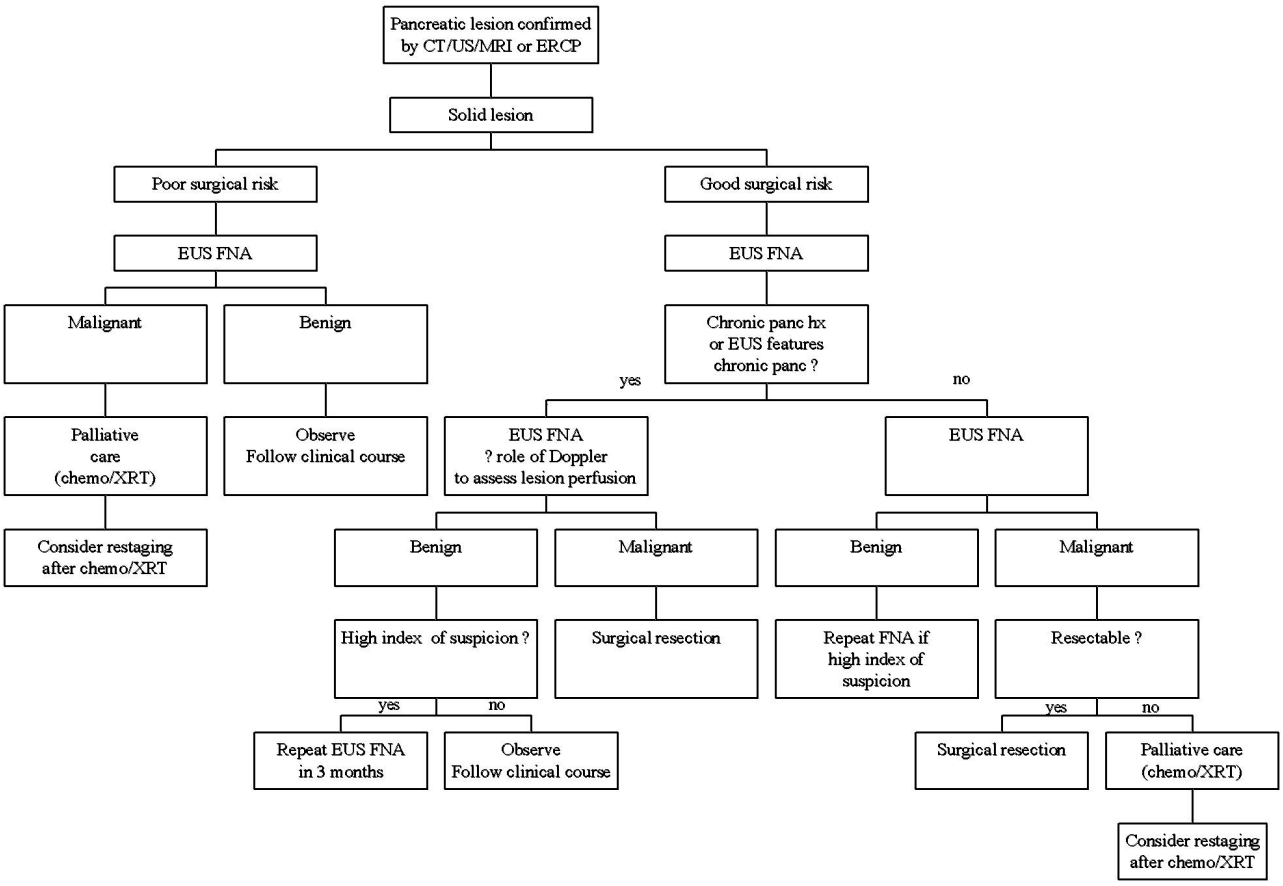

Figure 1. Algorithm for pancreatic lesions (solid lesions).

who have benign disease or who have advanced cancer.

On the other hand, a cytological diagnosis can be obtained utilizing minimally invasive methods, including a radiological- (CT or US) guided, endoscopic ultrasound-guided (EUS), or laparoscopic-guided approach. CT/US-guided fine needle aspiration (FNA) carries the risk of cutaneous or peritoneal seeding and laparoscopy needs to be performed in an operating room setting and is more invasive than CT or EUS. Since EUS is a minimally invasive procedure and EUS-guided FNA avoids the risk of cutaneous or peritoneal contamination, EUS-guided FNA of pancreatic masses is becoming the standard for obtaining cytological diagnosis.

In this chapter, we present an EUS-based diagnostic algorithm for the evaluation of pancreatic lesions (Figures 1 and 2). As we take the reader through the algorithm, we will discuss the pertinent literature in the field of pancreatic endosonography (EUS) that has been the most influential in helping to design this algorithm.

Background

Initially, pancreatic EUS was used to stage neoplasms that were diagnosed as malignant following percutaneous biopsy. Subsequently, clinical applications for EUS and EUS-guided FNA have continued to grow, since the first EUS-guided FNA of pancreatic carcinoma was reported in 1994 [1]. Pancreatic lesions usually come to the attention of gastroenterologists after transabdominal ultrasound, CT or MRI scans are performed to evaluate abdominal symptoms. Depending on the quality of the imaging modality performed and the use of contrast enhancement, the appearance of a pancreatic lesion may be quite vague. As most endosonographers will attest, the request to perform EUS for "fullness" or "focal enlargement" of the pancreas is not uncommon and, as we recently reported, even in the absence of an obvious mass by conventional cross-sectional imaging, these vague findings can be associated with malignancy in up to 9% of cases [2, 3].

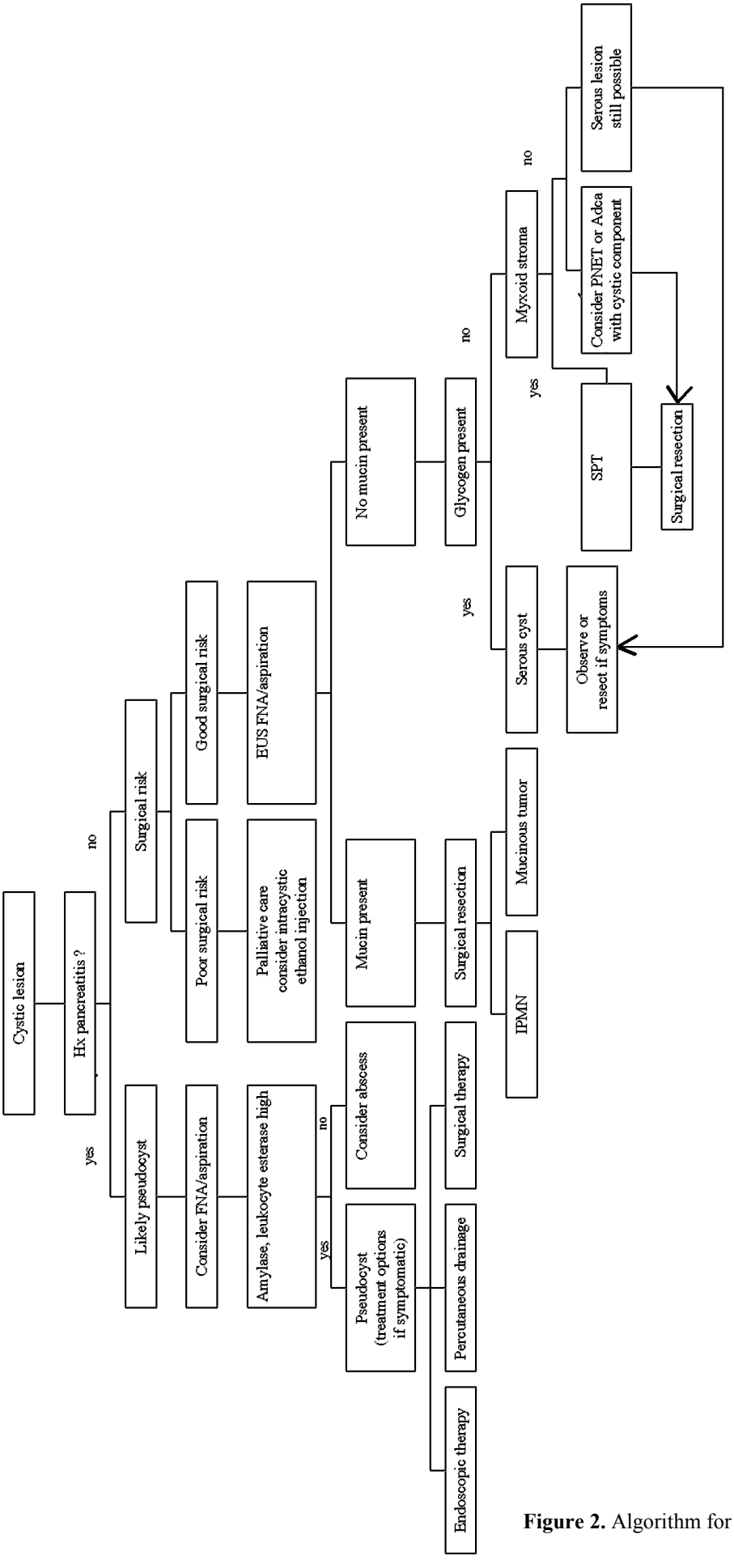

Figure 2. Algorithm for pancreatic lesions (cystic lesions).

Initial evaluation should address whether the lesion appears pancreatic or peri-pancreatic in location. For example, peri-pancreatic lymph nodes and even vascular thrombosis or hematoma can occasionally appear to be intrinsic to the pancreas on cross-sectional imaging and EUS can clarify this with certainty before proceeding on a dead-end evaluation of a presumed pancreatic lesion. Once a lesion has been confirmed as arising from the pancreas, the first branch point in the diagnostic algorithm is to define the lesion as solid or cystic.

EUS for Solid Pancreatic Lesions

EUS and Pancreatic Adenocarcinoma

Since the most common solid pancreatic tumor is adenocarcinoma, we will discuss pancreatic cancer first. One of the major advantages of EUS in the evaluation and staging of pancreatic carcinoma has been the ability to visualize features such as liver and lymph node metastasis, vascular invasion or features of locally advanced disease that had not been appreciated on conventional cross-sectional imaging. In doing so, patients found to be advanced or metastatic at the time of EUS can be spared the additional morbidity of a staging exploratory laparotomy or non-curative Whipple procedure. Pancreatic adenocarcinoma will appear most often as an irregularly shaped hypoechoic or inhomogeneous mass relative to the underlying parenchyma [4]. Small tumors (less than 2 cm) may have a more homogeneous echotexture as well as smooth borders [5, 6, 7]. In one early study, 17 of 23 small pancreatic cancers demonstrated a homogeneous echogenicity [8].

Tumors in the body and tail of the pancreas are imaged via a transgastric window, while those located in the head and uncinate processes are best seen with the echoendoscope in the duodenum. This distinction is important as it relates to the route through which the FNA needle passes when performing diagnostic sampling. The majority of pancreatic cancers will arise in the head of the pancreas. A concern surrounding radiographic-guided percutaneous FNA of pancreatic malignancy is the risk of peritoneal carcinomatosis or needle tract seeding secondary to the procedure [5]. Although there is a single case report of dissemination following EUS FNA of a lesion in the pancreatic body [6], the risk of this occurrence complicating the course for patients that have undergone EUS FNA of the pancreatic head is believed to be even lower as a result of both a significantly shorter needle path and the fact that the needle tract itself is resected at the time of pancreaticoduodenectomy [7].

When EUS is available, its use or nonuse depends on local treatment algorithms-specifically, whether neoadjuvant chemotherapy and radiation therapy is offered to attempt to downstage patients prior to surgical resection. In centers where neoadjuvant therapy is not part of treatment algorithms, the decision to use EUS and EUS FNA then rests with the surgeon caring for the patient.

In centers where surgeons make the decision to operate based on clinical presentation (with or without elevated tumor markers) and suggestive CT/MRI/MRCP or ERCP findings, pre-operative tissue is generally not obtained and EUS exists as an additional staging tool. If the decision has already been made to operate, a local or regional referral for an EUS may be viewed as an unnecessary delay in (operative) therapy rather than a tool contributing to the overall quality of the evaluation. Some surgeons still practice with the concern that any pre-operative needle biopsy (CT/US- or EUS-guided) may cause tumor dissemination along the needle tract or within the peritoneum and deliberately choose not to perform these tests when a patient has no obvious radiographic evidence of advanced disease and, therefore, a good chance at surgical cure. This is a valid concern in centers where neoadjuvant therapy for pancreatic cancer is not routine as even the smallest chance of needle tract seeding and peritoneal carcinomatosis can change the prognosis of a patient quite drastically.

In centers where treatment algorithms include standard combined neoadjuvant chemo-therapy and radiation therapy, preoperative needle biopsy is mandatory, as definitive histology must be obtained in order to justify administering these (potentially) toxic therapies. Certainly, no medical or radiation oncologist can administer therapy to a patient "suspected" of having pancreatic cancer. Diagnostic proof from either staging laparotomy, US/CT or EUS guided FNA must exist first. In centers where neoadjuvant therapy is not practiced, operative candidates may go directly to surgery for what eventually becomes either exploration or attempt at cure, depending on how accurate pre-operative staging has been.

Our recommendation that EUS and EUS FNA be considered first in the diagnostic algorithm for patients with pancreatic lesions is influenced by the fact that our local practice includes neoadjuvant therapy for patients with suspected pancreatic cancer. Since an accurate tissue diagnosis means that chemotherapy and radiation therapy can commence for these anxious, unfortunate patients; every effort is made to perform EUS with FNA as soon as possible if intraductal brushings from ERCP performed for biliary decompression are nondiagnostic.

EUS and Pancreatic Neuroendocrine Tumors

In comparison to adenocarcinoma, functioning neuroendocrine tumors of the pancreas (PNET) will usually be small, rounded, hypoechoic, homogenous lesions with distinct margins and, often, a hypoechoic perimeter [9, 10, 11, 12, 13, 14]. Nonfunctioning islet cell tumors of the pancreas, on the other hand, are usually larger, more frequently malignant, and more often apparent on conventional US and CT imaging [15, 16, 17, 18, 19, 20, 21, 22, 23]. Functioning PNETs are suspected based on clinical signs and symptoms and diagnosed following confirmatory laboratory studies. Localization for curative surgical resection in patients with nonmetastatic disease is the aspect of PNET evaluation that proves to be the most difficult and is the role for which EUS appears to be best suited. PNETs can be functional tumors causing significant symptoms and morbidity even when in the range of 2 to 3 mm in size. Small tumors may not be readily palpable at surgery in up to 20% and even with intraoperative ultrasound, up to 10% of PNETs may be missed [24]. Concern regarding the use of intraoperative ultrasound has been raised, however, due to reports of rupture of the splenic vessels resulting from mobilization of the pancreas [25, 26, 27].

Endoscopic ultrasound has had a remarkable impact on the evaluation of patients suspected of having a functioning PNET. A cost-effectiveness study of EUS for preoperative localization of PNET found that EUS decreased the need for additional invasive testing and avoided unnecessary morbidity and resource utilization [28]. A multicenter study has been reported in abstract form stating that EUS guided FNA significantly increases the accuracy of EUS for the detection of PNET [25, 29].

The largest, prospective single center study evaluating the role of EUS in diagnosing PNETs evaluated 82 patients and reported an overall sensitivity of 93% and specificity of 95% [9]. EUS was more accurate than both CT and angiography (with and without stimulation testing) in this study. Recently, due to the ability to scan at higher frequencies (20-30 MHz) and therefore detect lesions of smaller size, intraductal ultrasonography has been reported to be of additional assistance in cases where EUS is falsely negative [24]. Furthermore, contrast-enhanced EUS using a microbubble agent (Levovist) has been reported helpful in the pre-operative localization of very small tumors [30]. Additionally, we reported the practice of inking small neuroendocrine tumors via EUS FNA to help guide surgical localization for possible enucleation [25].

While EUS has been reported to be less sensitive in detecting small neuroendocrine tumors in the tail of the pancreas [31], EUS was the only modality that was able to localize and diagnose a 2 cm nonfunctioning

islet cell tumor in the tail that eluded detection by US and CT scan in one case report [17].
Finally, a report by Sugiyama *et al*. has suggested that EUS can be used to help distinguish benign nonfunctioning islet cell tumors from malignant ones [21]. They noted that four out of four benign tumors imaged as homogeneous, hypoechoic masses with a regular central echogenic area while all three malignant tumors had an irregular central echogenic area. This study must be interpreted with caution due to the small number of patients evaluated, but the results are intriguing nonetheless. Given the currently available evidence, we strongly recommend referral for EUS in patients suspected of pancreatic neuroendocrine tumor.

EUS and Chronic Pancreatitis

Focal chronic pancreatitis may have an appearance similar to that of a pancreatic mass and malignancy; however, the clinical history and the presence of EUS features characteristic of chronic pancreatitis noted elsewhere in the gland might aid in discriminating this benign entity from malignancy. Criteria for assessing the presence of chronic pancreatitis by EUS have been established [32]. While there is a good correlation with moderate to severe chronic pancreatitis when more than 5-6 of these criteria are present [32, 33], there remains a debate as to the significance in patients where only 1 to 4 criteria are present [33].
In cases where features of chronic pancreatitis are not present elsewhere in the gland, the use of contrast enhanced color- and power-Doppler EUS demonstrating markedly increased flow within the lesion may help to distinguish a "hyperperfused" inflammatory pseudotumor related to chronic pancreatitis from the "hypoperfused" parenchyma indicative of pancreatic carcinoma [34]. With 94% sensitivity and 100% specificity for differentiating between pancreatic carcinoma and focal inflammatory pseudotumor reported from this study, one might even conclude that FNA could be avoided in cases where the history and/or additional EUS features suggestive of chronic pancreatitis decrease the clinical suspicion of malignancy. Concern has recently been raised in the NEST (No Endosonographic Detection of Tumor) Study, however, where 12 out of 20 cases of pancreatic carcinoma missed by 9 experienced endosonographers had features of chronic pancreatitis [35]. These authors suggest re-imaging with EUS after 2-3 months if there remains a high clinical suspicion of malignancy, yet a negative initial EUS study.
The NEST study was an EUS database survey of high volume centers and EUS FNA was not performed in any of the patients, which comprises the study cohort. In addition, the methodology does not state whether Doppler was used to interrogate the tissue. We routinely perform EUS FNA in all of our patients with a focal mass on EUS regardless of a history of chronic pancreatitis or presence of EUS characteristics consistent with chronic pancreatitis. Realizing that chronic pancreatitis is a risk factor for pancreatic carcinoma, we believe that overlooking a focal mass as pseudotumor in a patient with a history of chronic pancreatitis is a guaranteed way to miss the diagnosis of malignancy in those few patients destined to develop a tumor. If clinical suspicion remains high, we agree with the suggestion of the NEST study to repeat EUS with FNA in 3 to 6 months to ensure stability of the lesion.

EUS and Solid-Pseudopapillary Tumor (SPT)

Solid-pseudopapillary tumors account for approximately 1% of all pancreatic cancers and 3% of pancreatic cystic lesions [36, 37]. These tumors present predominantly in young women (mean age 27, range 2-81) as nausea, vomiting, abdominal pain or vague abdominal symptoms due to compression of adjacent organs, if symptoms are present at all [36, 37]. The most common locations are the

pancreatic body and tail. SPT can be quite large; sizes have been reported up to 30 cm with a mean of 10.5 [38].
The clinical course of these tumors is variable with most demonstrating an indolent course. Surgical resection often leads to complete cure, though approximately 10-15% are malignant and can demonstrate local infiltration, recurrence or distant metastasis [38, 39]. Finally, spontaneous regression of tumors has also been described [40].
The EUS appearance of SPT is described as an heterogeneous solid or mixed solid and cystic hypoechoic lesion [36]. Cytopathological findings of branching papillae with myxoid stroma from EUS FNA are diagnostic and allow ready differentiation from other cystic or solid pancreatic tumors [36, 41].

EUS for Cystic Lesions of the Pancreas

Cystic lesions of the pancreas may be benign, pre-malignant or overtly malignant. The majority (80-90%) will be benign pseudocysts resulting from previous inflammatory disease of the pancreas, however 10 to 15% will be cystic tumors [42]. The benign cystic lesions include pseudocysts, pseudotumor, serous cystadenoma, cystic lymphangioma, hemangioma and cystic teratoma. Malignant and pre-malignant cystic lesions are comprised of mucinous cystadenoma and cystadenocarcinoma, although PNET and adenocarcinoma can also present as cystic lesions. With its high sensitivity for detecting and defining internal echoes as fluid, debris, septations and mural nodules, EUS and EUS FNA has become the premier tool for the differentiation and diagnosis of cystic pancreatic lesions. FNA of cyst contents via EUS for fluid viscosity, tumor markers, cytology and serum amylase has also contributed to the diagnostic potential of this modality.
The primary role of EUS in evaluating cystic lesions is to determine whether features are present that can help differentiate benign cysts from malignant types, as the former can be conservatively managed with drainage or serial observation while the latter should be referred for surgical resection. An early study of 52 solitary cystic lesions of the pancreas sought to determine whether a correlation could be made between certain EUS patterns and the final pathologic finding from surgical resection [43]. Six patterns were observed - thick wall type, tumor protruding type, thick septal type, micro cystic type, thin septal type and simple type - with all neoplastic cysts belonging to the first 4 patterns and all non-neoplastic cysts belonging to the latter two [43]. This classification schema appeared to be quite useful with 2 independent, blinded observers demonstrating diagnostic accuracy rates of 92% and 96% [43].
Accuracy rates varied with tumor size, though even when tumors were less than 2 cm the EUS accuracy rate of 82-91% was superior to that which is seen with CT, US and MRI [43]. The accuracy rate increased to 94-97% for tumors between 2-4 cm and reached 100% for tumors between 4-6 cm, though with tumors larger than 6 cm EUS was less accurate due to its inability to reliably access the peripheral architecture of these larger tumors [43]. Therefore, conventional imaging modalities such as US, CT and MRI are generally superior to EUS in this setting.
Although imaging with EUS is useful to distinguish neoplastic from non-neoplastic cysts, tissue diagnosis will undoubtedly still be required for definite diagnosis of neoplastic or equivocal cysts. In cases where patient or physician factors are not in favor of a surgical resection for diagnosis, EUS-guided FNA, when available, has become the preferred method to sample a cystic lesion. EUS-guided FNA reduces the risk of intraperitoneal contamination with cyst contents, needle tract seeding and provides additional information about the internal cyst structure that may not be apparent with conventional cross-sectional imaging [44, 45, 46].
In contrast to solid lesions where the sensitivity and specificity of EUS FNA ranges from 86-92% and 94-100% [45, 47], the sensitivity and specificity of cytology and mucin stains from mucinous tumors have

been reported at 75% and 80% respectively [48]. The explanation for these lower values may lie in the fact that up to 40% of the cyst wall can be denuded from the epithelium [46, 47, 48, 49]. The diagnostic yield from FNA of cystic lesions can be improved by performing both cyst aspiration for fluid analysis as well as FNA of the cyst wall with on site cytopathology interpretation to ensure an adequate specimen has been obtained. Complication rates also differ among solid and cystic lesions. Concern regarding a rate of infection of up to 10% associated with FNA has led to the recommendation that prophylactic antibiotics be given when aspiration is anticipated. One should attempt to aspirate the entire cyst contents, if possible, with the first pass of the needle to minimize leakage. Furthermore, if the results of an FNA will not change management, FNA and aspiration of cyst contents should be avoided to minimize risk of both leak and infectious complications [46].

Despite the possible risks associated with EUS FNA of cystic lesions, it appears that FNA will usually be required for a definitive assessment, as EUS characteristics alone have yet been shown to be sufficient to make a final determination of neoplastic from non-neoplastic. A retrospective comparative review of EUS examinations with surgical and pathologic results was performed by two experienced endosonographers on 48 patients that had undergone prior non-diagnostic cross-sectional imaging. They found that EUS characteristics alone were unable to reliably differentiate benign from cystic lesions [50].

Similar results were found when a group of eight experienced endosonographers were asked to review a study videotape of 31 histopathologically proven EUS examinations of cystic lesions [51]. In this study, the participants were asked to determine whether the lesion was neoplastic or non-neoplastic and to provide a specific diagnosis of each lesion. While there was an overall accuracy of 71% for these experienced reviewers (range 40-93%), the final conclusion was that there was little more than chance inter-observer agreement for the diagnosis of neoplastic versus non-neoplastic lesions (kappa=0.24), specific diagnosis and EUS features of cystic lesions [51]. Agreement, as judged by the kappa statistic, varied from slight (assessment of cyst margins and abnormal parenchyma), to fair (assessment of pancreatic duct, debris and septations), to moderate (assessment of solid cyst components) respectively [51]. While the study was limited by the fact that the reviewers were not given any clinical history, the videotape quality was not addressed, and the videotape may not have completely reproduced the diagnostic findings as seen in real-time, it did suggest that a lack of uniform nomenclature contributed to the mediocre agreement among some of the nation's best endosonographers. However, it should be noted that conventional imaging with CT and US has been reported to misdiagnose up to 40% of mucinous and 33% of serous cystadenoma as pseudocysts with resultant errors in treatment [52, 53, 54].

Studies such as these have called attention to the fact that the continued growth of endosonography depends on further well-designed multicenter studies to help develop a consensus on nomenclature and descriptors that can then be used to better categorize findings and hence improve diagnostic accuracy.

Benign Cystic Lesions

Pseudocyst and Simple Cyst

The most common benign cystic lesion of the pancreas is the pseudocyst. Since pseudocysts arise from inflammatory destruction of the pancreas, the EUS findings associated with a pseudocyst may vary depending upon the time at which the pancreas is imaged along the course of pancreatitis. Pseudocysts may present as simple cysts or may have internal septations, echogenic debris and even mural nodules [42]. While it can sometimes be difficult to distinguish a pseudocyst from a cystic neoplasm, the presence of parenchymal changes (calcification, atrophy or change in echotexture) was found to be strongly suggestive of a pseudocyst [42]. Combining

this with the absence of septa and/or the absence of mural nodules led to an accuracy, sensitivity and specificity of 88%, 94% and 85% respectively, for the diagnosis of pseudocyst [42]. Furthermore, the analysis of pseudocyst fluid should also allow differentiation from neoplastic cysts. For example, pseudocyst fluid will have a predominance of inflammatory cells and histiocytes, low viscosity and high amylase content (greater than 5000 U/mL) [55]. Serous cystadenoma, (discussed below), may be difficult to distinguish from inflammatory pseudocyst using cyst fluid appearance since both will tend to have thin, non-viscous contents. A study by Yong *et al*. measured the tumor marker NB/70K using a commercial immunoassay and leukocyte esterase using Chemstrip SG urine test strips, demonstrating significantly higher levels of both in pseudocysts than serous cysts [56]. In comparison with pseudocysts, neoplastic lesions tend to have an elevated viscosity and carcinoembryonic antigen (CEA) level [57, 58].

Simple cysts may be either unilocular or multilocular and will appear as well demarcated, anechoic or hypoechoic lesions without evidence of pancreatic disease in the remainder of the pancreas. In the case of multilocular cysts, the septa should be thin (less than 3 mm) and the wall should be smooth and regular without evidence of focal thickening or mural nodules [43, 46, 59].

Serous Cystadenoma

The serous cystadenoma, formerly referred to as the microcystic adenoma, is a cystic lesion whose diagnosis may be strongly suspected when the characteristic "honeycomb" pattern of multiple small cysts is seen at EUS. Unfortunately, this pattern is not always present, as one study demonstrated the "honeycomb" pattern in only 20% (2 of 10) patients that were histopathologically confirmed to have serous cystadenoma; the remaining 8 patients demonstrating a macrocystic pattern (n=1), multilocular cysts (n=5) or unilocular cysts with a lobulated contour (n=2) [42]. Other tumors, even neuroendocrine tumors [60], may have the "honeycomb" pattern as well, stressing the importance of FNA for histologic diagnosis.

Clinically, serous cystadenoma are more common in women (65-78%) in their 7th decade, presenting with abdominal pain or symptoms due to mass effect [46]. In contrast to mucinous lesions (discussed below) which predominate in the body and tail, serous lesions are more commonly seen in the head and neck of the pancreas [61].

The macrocystic variant of serous cystadenoma was reported in the pathology literature in 1992 [62], but the EUS features of this variant was not described until several years later by Gouhiri *et al*. [63]. The majority of cystic lesions of the pancreas will either be found incidentally or will be imaged with CT or US as the first diagnostic imaging modality. It has been reported that calcification is more often present in serous than mucinous cystadenoma, though in neither is it considered diagnostic. The case report by Gouhiri *et al*. [63] also raises the important issue that cystic lesions may hemorrhage and the resulting intracystic clot can be confused as a solid cystic component.

Fluid aspiration demonstrating glycogen or glycogen-containing cells is diagnostic of serous cystadenoma though due to the small amount of fluid in each cystic compartment cytology from FNA is diagnostic in only 50% of cases [64, 65]. Cyst fluid analysis will reveal an amylase content that will be variable and a CEA level that should be low (less than 5 ng/mL) [55, 57, 66].

Malignant and Pre-Malignant Cysts

EUS and Mucinous Cystic Lesions

In addition to excluding the less than 1% of pancreatic adenocarcinoma that may present with a cystic component, the major role for EUS in the evaluation of cystic lesions is distinguishing mucinous from serous lesions. In contrast to serous lesions, mucinous lesions are either pre-malignant - in the case of cystadenoma - or overtly malignant when

cystadenocarcinoma is the finding. A recent large, multicenter study of 341 patients that underwent EUS and FNA of pancreatic cystic lesions found either borderline or frank malignancy in 40 of 68 patients with mucinous cystic lesions, underscoring the importance of accurately diagnosing these lesions [58].

Clinically, mucinous tumors occur predominantly in women (72-83%) in their fifth to seventh decades [49, 67], and present most commonly as abdominal pain (59%), followed by nonspecific gastrointestinal symptoms (24%) and weight loss (23%) [46]. Bleeding and jaundice are suggestive of more aggressive malignant forms of these tumors [52]. Up to 25-30% of these tumors are found incidentally on US or CT performed for other reasons [46, 52, 68].

Mucinous lesions are generally macrocystic and unilocular with a thickened, definable cyst wall [69]. The tumors, which arise from the peripheral ducts, are filled with thick, mucoid material or hemorrhagic fluid [44, 61]. While a recent review stated mucinous cystadenomas rarely have internal septations [66], other authors have reported the presence of septations [43, 69], with one study reporting internal septations in up to 90% (9 of 10) with mucinous cystic tumors [42]. The septa between locules are thick, irregular, fibrotic and occasionally calcified [46, 70]. While mural nodules have been reported in 25-50% of the patients with mucinous cystadenoma [42, 69], the presence of mural nodules and papillary protuberances suggests invasive carcinoma [71].

A study of solitary cystic pancreatic tumors by Koito *et al*. included 17 patients with mucinous tumors [43]. In this study, all mucinous tumors appeared as hypoechoic masses and were characterized by one of three patterns: 1) thick wall type (thick wall and some with multiple cysts in the tumor, 2) protruding type (mural nodule(s) with or without papillary projections in the tumor, and 3) thick septal type (internal septations greater than 3mm in width) [43]. In this study mucinous cyst adenomata were characterized by all 3 of these patterns while mucinous cyst adenocarcinoma were either thick wall or protruding types but not thick septal type. Mural nodules have been reported in 25-50% of the patients with mucinous cystadenoma [42, 69].

Cyst fluid analysis from mucinous lesions will demonstrate a high viscosity. Studies have demonstrated higher levels of CEA and CA 72-4 in mucinous cysts compared with non-mucinous cysts, however, cutoff levels have varied among studies making it difficult to arrive at a consensus value. The largest study to date found the optimal cutoff value for distinguishing mucinous from non-mucinous lesions was 192 ng/mL [58]. The sensitivity, specificity and accuracy of CEA from this study were 75%, 83.6% and 79.2%, respectively, with CEA demonstrating a significantly greater accuracy than either cytology (59%) or EUS morphology (51%; $P<0.05$) [58].

Within the mucinous cyst category exists the benign cystadenoma and malignant cystadenocarcinoma. An earlier study by Rubin *et al*. demonstrated the utility of CA 15-3 for distinguishing mucinous cystadenoma from mucinous cystadenocarcinoma [72]. Using an upper cutoff value of 30 U/mL, they were able to distinguish mucinous cystadenoma from mucinous cystadenocarcinoma with 100% sensitivity and 100% specificity ($P=0.01$) [72].

EUS and Intraductal Papillary Mucinous Neoplasia (IPMN)

Intraductal papillary mucinous neoplasia (IPMN) is considered a pre-malignant lesion and therefore carries a less grim prognosis than adenocarcinoma. Several series have shown however, that pancreatic adenocarcinoma ranging from carcinoma in situ to metastatic disease may be present in 30 to 68% of surgical resections for IPMN [73, 74]. Accordingly, it is crucial to make this distinction in order to avoid the excessive morbidity associated with a missed diagnosis or an unnecessary surgical resection.

Suspicion for IPMN should be considered in patients presenting with a markedly diffuse dilatation of the pancreatic duct seen on cross sectional imaging of the pancreas and a clinical history of recurrent pancreatitis or unexplained abdominal pain. In addition to pancreatic duct dilatation, EUS may also demonstrate a complex cystic lesion or intraductal solid lesion(s). IPMN may be suspected at the time of endoscopy in cases where mucin can be seen exuding from a gaping "fish-eye" pancreatic duct orifice. A positive mucin stain performed on fluid aspirated from the pancreatic duct can be diagnostically useful when EUS FNA is negative or equivocal.

In contrast to the mucinous and serous lesions discussed above, IPMN are more common in men, presenting in the 6^{th}-8^{th} decade (mean age of 63) as abdominal pain (75%), weight loss (42%), diabetes (37.5%), steatorrhea (37.5%), back pain (25%) and jaundice (25%) [46, 75]. IPMN should always be considered in the differential diagnosis of pancreatitis in the elderly as acute pancreatitis can be seen in 29% (range 22-45%) [46, 61, 76].

Although some characterize IPMN as a solid tumor, the accompanying ductal dilatation may be quite marked and more often leads to confusion with chronic pancreatitis and cystic lesions of the pancreas. EUS has been shown to be more accurate than ERCP or abdominal ultrasound in differentiating IPMN from cystic pancreatic lesions [77]. Clearly, the results of an EUS demonstrating an associated mass or EUS FNA cytology consistent with carcinoma will carry a very different prognosis than that for the pre-malignant variant of IPMN. A retrospective study of 51 patients with surgically confirmed IPMN who had all undergone preoperative EUS reported an accuracy of 86% for distinguishing between benign and malignant tumors [78]. The characteristics that were found to be most suggestive of malignancy in this study were main duct diameter greater than 10 mm, side branches greater than 4 mm with irregular septa and the presence of mural nodules greater than 10 mm.

Role of Cyst Fluid Analysis

As stated above, the use of EUS FNA for cytology and cyst fluid analysis has complemented and assisted in differentiating cystic lesions when cyst morphology or echo-characteristics are nondiagnostic. Numerous markers have been studied to try and help differentiate mucinous (high CA 19-9, high CEA, high CA 72-4, high tissue polypeptide antigen (TPA)) from serous (low CEA) and from inflammatory (high NB/70K, leukocyte esterase and amylase) cysts with varying degrees of success [55, 56, 57, 72, 79, 80]. Different studies have used various cutoffs to try and maximize sensitivity and specificity, but there is still no uniform consensus or "recipe" of markers that can be considered diagnostic. We view the use of cyst fluid markers as useful guides that should be used in the context of clinical history, EUS morphology and cytology results to help with the diagnosis of pancreatic cystic lesions.

Conclusions

The role of EUS and EUS-guided FNA in the diagnosis and management of pancreatic lesions continues to evolve. Prospective multi-center trials are needed to clarify and improve upon the diagnostic EUS criteria in use today for evaluating these lesions. Although the algorithm we have discussed in this chapter represents the current consensus in the literature, we are hopeful that future studies will improve upon this clinical management schematic in positive ways so as to improve patient outcomes.

Keywords Biopsy, Fine-Needle; Endosonography; Pancreatic Cyst; Pancreatic Diseases; Pancreatic Neoplasms; Pancreatic Pseudocyst

Abbreviations CEA carcinoembryonic antigen; IPMN: intraductal papillary mucinous neoplasia: NEST study: No Endosonographic Detection of Tumor study;

PNET: pancreatic neuroendocrine tumors; SPT: solid-pseudopapillary tumor; TPA: tissue polypeptide antigen

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