GASTROINTESTINAL
ENDOSCOPY CLINICS
OF NORTH AMERICA

Gastrointest Endoscopy Clin N Am
15 (2005) 117–142

Pancreatic neoplasms

Michael J. Levy, MD[a,*], Maurits J. Wiersema, MD[b]

[a]*Developmental Endoscopy Unit, Division of Gastroenterology and Hepatology, Mayo Clinic, 200 First Street Southwest, Rochester, MN 55905, USA*
[b]*GI Consultants, 1900 Carew Street, Suite 1, Fort Wayne, IN 46805, USA*

Endoscopic ultrasound (EUS) is a highly sensitive imaging modality for identifying pancreatic neoplasms, with detection rates over 90% (Table 1) [1–8]. In most studies, EUS has been superior to transabdominal ultrasound (TUS), CT, endoscopic retrograde cholangiopancreatography (ERCP), and angiography in the detection of pancreatic tumors [1,3,9,10]. Rosch et al demonstrated greater sensitivity (99%) and specificity (100%) for detecting pancreatic tumors than TUS (sensitivity 67%, specificity 40%) and CT scan (sensitivity 77%, specificity 53%) [1]. Recent studies comparing EUS to dual-phase helical CT, MRI, and positron emission tomography (PET) have found EUS to have a greater sensitivity for identifying pancreatic neoplasms [2,4,8,11]. In another study of 34 patients with an elevated contrast angiography (CA) 19-9 and normal pancreas according to TUS and CT scan, EUS was 94% accurate in detecting a pancreatic or biliary neoplasm, with a positive and negative predictive value of 92% and 100% respectively [12]. The advantage of EUS is even greater for recognizing tumors less than 2 to 3 cm in diameter [1,4,9,13,14]. Yasuda et al found that EUS had a detection rate of 100%, ERCP 57%, TUS 29%, CT 29%, and angiography 14% for pancreatic tumors less than 2 cm [9]. Similarly, in a study by Rosch et al, the diagnostic sensitivity of EUS for detecting tumors smaller than 3 cm was 100%, compared with 57% for TUS and 68% for CT [15].

Neuroendocrine pancreatic tumors

Neuroendocrine pancreatic tumors (NPTs) are rare, with an incidence of less than 1 tumor per 100,000 people [16]. Gastrinoma, insulinoma, and non-

* Corresponding author.
E-mail address: levy.michael@mayo.edu (M.J. Levy).

1052-5157/05/$ – see front matter
doi:10.1016/j.giec.2004.07.014 giendo.theclinics.com

Table 1
Endoscopic ultrasound detection rates of pancreatic tumors

Author/Year/Reference	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Accuracy
Rosch, 1991 [1]	99%	100%	100%	97%	76%
Snady, 1992 [3]	85%	80%	89%	73%	83%
Yasuda, 1993 [7]	–	–	–	–	100%
Muller, 1994 [4]	94%	100%	–	–	96%
Baron, 1997 [5]	95%	88%	95%	88%	–
Legmann, 1998 [2]	100%	93%	–	–	–
Akahoshi, 1998 [6]	89%	97%	94%	93%	94%

functioning tumor are most common, with glucagonoma, somatostatinoma, and VIPoma less often reported. Preoperative determination of the location and extent is necessary to enable surgeons to plan the optimal surgical approach. Resection offers the only chance for cure and should be undertaken whenever possible because of the malignant potential of these tumors. Preoperative localization is also important because of the difficulty in identifying these tumors during surgery, which is the case in up to 20% of insulinomas, and as many as 50% of gastrinomas [16]. The approach to tumor localization is similar for all tumor types. Various imaging modalities are available for preoperative identification of NPTs. They include TUS, CT, selective abdominal angiography, selective venous sampling, radiolabeled octreotide (somatostatin–analog) receptor scintigraphy (SRS), intraoperative ultrasound, and most recently EUS.

Endoscopic ultrasound studies report a localization rate of approximately 77% to 93% for insulinomas [16–23]. In these same studies CT, was able to locate the tumor in only 0% to 20% of patients, and somatostatin receptor scintigraphy (SRS) was able to locate the tumor in only 12% to 14% of patients. Insulinomas have a low density of somatostatin receptors, and as a result they often go undetected by SRS. The high detection rate of EUS for insulinomas likely is explained by the fact that 99% of insulinomas are confined to the pancreas [21,24,25]. Approximately 75% to 100% of pancreatic gastrinomas are identified by EUS [16–18,21,22,26] versus 0% to 67% of duodenal gastrinomas [16,18,22]. EUS is comparable to SRS for detecting pancreatic gastrinomas, and both tests are clearly superior to CT. Even so, both techniques may miss a significant proportion of duodenal gastrinomas [16,18,22,27], which is important, given that 30% to 45% of gastrinomas are located in parapancreatic locations, most commonly the duodenal wall or lymph nodes [24]. Despite focused examination of the duodenal wall by EUS, gastrinomas in this location commonly are missed by EUS unless previously identified endoscopically [21]. Therefore, at the time of EUS, the authors initially perform a careful forward- and side-viewing exam of the duodenal wall.

The addition of fine needle aspiration (FNA) further increases the diagnostic accuracy for NPTs, with overall accuracy of EUS–FNA reported to be 75% to 80% [26,28], which is superior to TUS, CT, or surgical biopsies [29–31]. In addition, EUS also may identify multi-focal tumors not seen by other imaging

modalities [28,31]. In a multi-center trial involving 37 patients with a suspected NPT undetected by TUS and CT, the sensitivity and specificity of EUS for tumor localization were 82% and 95%, respectively [1]. These tumors had a mean diameter of 1.4 cm (range 0.5 to 2.5 cm) and consisted of 31 insulinomas, 7 gastrinomas, and 1 glucagonoma. In this same study, only 27% of tumors were identified by angiography. All patients underwent surgical resection, with 36 of 37 considered cured based on clinical and laboratory parameters.

The EUS appearance of NPTs is similar regardless of the type of tumor. They typically appear as round, well-delineated, homogenous, echo-poor lesions, with a surrounding hyper-echoic rim (Fig. 1). Cystic or calcified tumors, echo-rich lesions, an echo-poor border, or echo-texture, however, are similar to surrounding pancreatic parenchyma [1,32,33]. The EUS technique for localizing these tumors is identical to that for ductal adenocarcinoma, except that a more deliberate exam may be needed to find these small lesions. The parapancreatic region also should be examined carefully, not only to search for malignant lymph nodes but also to look for primary tumors [13,34]. Parapancreatic tumors may be attached by a pedicle or completely separate from the pancreas, and they are more difficult to locate than intrapancreatic tumors [21]. As with other tumors, infiltration into adjacent organs and vessels should be evaluated. EUS–FNA helps differentiate benign parapancreatic lymph nodes from a primary NPT, a distinction that can be difficult, especially for insulinomas [17,19–21,28,35–37]. EUS appearance also may predict the malignant potential of NPTs, which can be otherwise difficult to discern in the absence of extensive local invasion or distant metastasis [37,38]. The presence of a hypo-echoic lesion with anechoic regions, an irregular central echogenic area, or pancreatic duct obstruction is indicative of malignant transformation [38]. The echogenic areas correspond with hemorrhage, necrosis, or hyaline degeneration, each of which suggests a malignant tumor [38].

Once identified, it is important to accurately describe the location of tumor(s) to facilitate surgical resection. The authors recommend describing the location relative to pancreatic and peripancreatic structures. In a step further, Gress et al

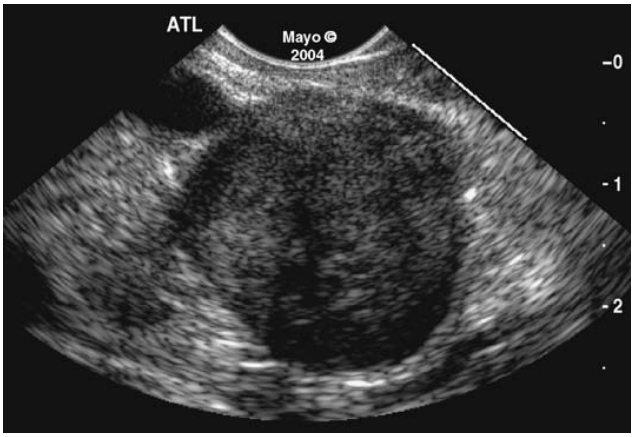

Fig. 1. Neuroendocrine pancreatic tumor. Gastrinoma identified in a patient with long-standing uncontrolled acid reflux symptoms and diarrhea.

reported their experience in one patient employing EUS-guided fine needle tattooing [39]. After identifying a 1.9 × 0.5 cm insulinoma, they injected 4 mL of sterile India ink into the lesion and continued to inject as the needle was withdrawn from the pancreas. The ink and tumor were identified readily at surgery performed the same day. This is a method that may facilitate operative localization of NPTs and in particular assist when enucleation or laparoscopic resection is planned for small tumors. For most patients, however, NPT marking is likely to be of no benefit, and the authors discourage doing so outside of a research protocol. In addition to the risks inherent to pancreatic EUS–FNA, injection of India ink may induce peritonitis, phlegmonous gastritis, and luminal and periluminal abscess formation, ulceration, and necrosis [40–43].

The cost-effectiveness of EUS for the preoperative localization of pancreatic endocrine tumors was demonstrated recently. Bansal et al compared the cost of performing tumor localization with and without EUS as part of the protocol, and found that the use of EUS significantly reduced the cost of preoperative staging ($2620 versus $4846) [32]. Savings resulted from the reduced need for angiography and venous sampling procedures and because of the reduction in surgical and anesthesia times. The cost per tumor located was $3144 when EUS was used versus $5628 when EUS was not employed.

Endoscopic ultrasound is an accurate technique for detecting NPTs. EUS is being used increasingly to search for sporadic NPTs and in patients with multiple endocrine neoplasia (type 1) because of its the ability to identify small, previously undetected tumors [44] (Fig. 2). Although some favor its use only when noninvasive studies detect no metastases and no primary tumor is seen, the authors suggest performing EUS in all patients in whom surgery is planned. They favor this approach even when a lesion already has been identified to allow detection of unsuspected multi-focal or metastatic disease and clarify the relationship of the tumor to the main pancreatic duct. The added information obtained by EUS–FNA

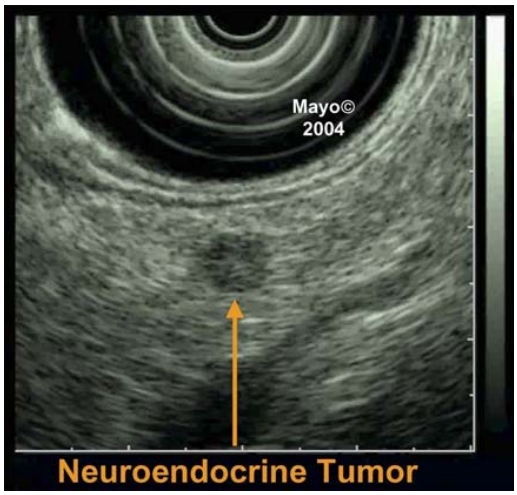

Fig. 2. Neuroendocrine pancreatic tumor. One of many small nonfunctioning neuroendocrine tumors identified by endoscopic ultrasound in a patient with multiple endocrine neoplasia (MEN) I syndrome. CT and somatostatin receptor scintigraphy failed to identify any of the lesions.

allows cytologic confirmation of the diagnosis with reduced false-positive imaging results and also allows the surgeon to plan the optimal strategy (eg, tumor enucleation versus pancreatic resection). Further study is needed, however, to determine the role, utility, and safety of EUS–FNA when noninvasive studies already have localized a tumor.

Cystic pancreatic tumors

Widespread use of high-resolution cross-sectional imaging has led to increased detection of cystic lesions of the pancreas, which may be benign, malignant, or result from an inflammatory process. Pseudocysts are most common (80% to 90%), while cystic pancreatic tumors (CPTs) account for 10% to 20% of cystic pancreatic lesions and 1% of primary pancreatic neoplasms [45,46]. The differential also includes congenital cysts, acquired cysts, and extrapancreatic cysts. In addition, solid pancreatic tumors may undergo necrosis and cystic degeneration and be mistaken for a CPT [45]. Although accounting for a minority of lesions, CPTs are an important subgroup to identify given their often distinctive presentation, diverse pathological features, and usually indolent biological behavior. CPTs are classified broadly according to their malignant potential, which impacts prognosis and therapy. Mucinous lesions (mucinous cystic neoplasms and intraductal papillary mucinous tumors) are premalignant or malignant tumors, and surgical resection generally is recommended in operative candidates [47–49]. Nonmucinous lesions include serous cystadenomas that have a very low malignant potential, and pseudocysts, which are always benign, and generally only resected when causing symptoms or complications [47–49]. Management and outcome of patients with CPTs critically depends on early tumor detection, distinction from pseudocysts, and accurate determination of tumor type. The appropriate use of clinical, imaging, laboratory, and pathology information is essential in this regard (Table 2). Detection is important even after malignancy has developed, because certain malignant CPTs have a better prognosis than ductal adenocarcinoma and a relatively high cure rate following resection.

Table 2
Analysis of aspirated cystic pancreatic tumor fluid — general characteristics

	Viscosity	Amylase	CA 19-9	CA 15-3	CA 72-4	CEA	Cytology
SCA	Low	Variable	Variable	Low	Low	Low	Glycogen
MCA	High	Variable	Variable	High	High	High	Mucinous
MCAC	High	Variable	Variable	High	High	High	Mucinous
IPMN	High	High	Variable	Variable	Variable	Variable	Mucinous
Pseudocyst	Low	High	Variable	Low	Low	Low	Histiocytes

Abbreviations: CA, carbohydrate antigen; CEA, carcinoembryonic antigen; IPMN, intraductal papillary mucinous neoplasia; MCA, mucinous cystadenoma; MCAC, mucinous cystadenocarcinoma; SCA, serous cystadenoma.

Serous cystadenoma

Serous cystadenomas (SCAs) usually appear as focal, well-demarcated lesions, containing multiple (at least six), small (less than 1 to 2 cm) fluid-filled microcysts (Fig. 3) [50–52]. Although some report that most (50% to 70%) are located in the pancreatic body or tail [53], others have found them more commonly in the head or neck region (63%) [47,54]. The individual cysts are interspersed within dense fibrous septations, producing a honeycomb appearance [55,56]. Central fibrosis or calcification may be seen, particularly in large lesions [34,57]. The resulting sunburst calcification, although pathognomonic, is present in only about 10% of patients [54,58–60]. A less common macrocystic variant contains larger (greater than 2 cm) cysts [8,51,61]. A solid variant contains numerous tiny cysts, each 1 to 2 mm, and appears as a homogenous hypoechoic mass that can be mistaken for a ductal carcinoma. Endoscopic retrograde pancreatography (ERP) infrequently demonstrates ductal distortion because of a mass effect [34], and rarely communication with the pancreatic duct [62,63]. Angiography, although seldom performed, reveals the hyper-vascular nature of most SCAs. The presence of intracystic mucin or floating debris, pancreatic duct dilatation, echogenic ductal wall thickening, and focal cyst wall nodularity or thickening are distinctly unusual and raise the possibility of a mucinous tumor [51,57,59,64–66]. Cyst fluid usually has low viscosity and tumor marker levels. Cytologic analysis is diagnostic in only 50% of aspirates [67], with the presence of bland cuboidal glycogen staining cells establishing the diagnosis [67–69]. Aspiration of SCAs may be technically challenging because of the small size of individual microcysts that limits the volume of fluid aspirated, thereby diminishing the diagnostic accuracy. The vascularity of SCAs may cause bleeding during FNA and impair cyst fluid analysis.

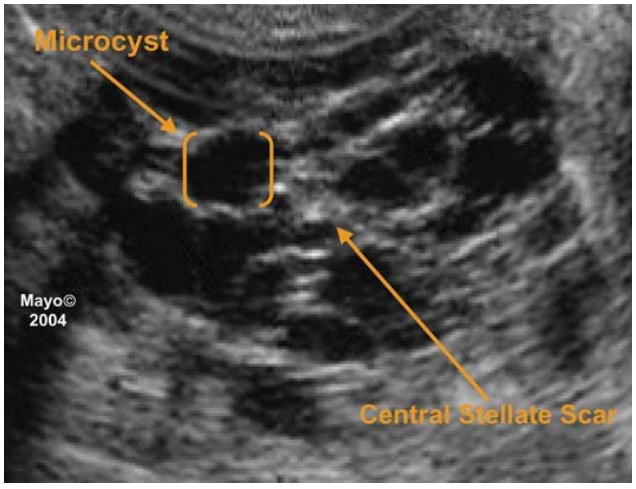

Fig. 3. Serous cystadenoma.

Mucinous cystadenoma/mucinous cystadenocarcinoma

Mucinous cystic neoplasia (MCNs) are usually (66% to 75% of the time) located in the pancreatic body or tail and contain a smooth, glistening outer surface [34,49,70–73]. They typically are comprised of several fluid-filled cavities (each greater than 1 to 2 cm) separated by thin septations (Fig. 4) [55,64]. The wall lining is thin and may contain peripheral eccentric calcifications that although pathognomonic, are only found in 15% of patients [49,57,74,75]. ERP is usually normal but may identify pancreatic duct strictures, obstruction, and displacement caused by a mass effect primarily resulting from malignant transformation [45]. Pancreatic duct communication seldom is seen, because the origin of MCNs is within the peripheral ductal system [47,62]. Although seldom obtained, angiography demonstrates the hyper-vascularity of most MCNs. These tumors may grow as large as 36 cm, with greater size correlating with malignancy [71]. Other evidence of malignancy includes cyst wall irregularity and thickening, intracystic solid regions, or an adjacent solid mass [64,72,76].

As opposed to SCAs, the larger size of the individual cystic components simplifies FNA and facilitates complete drainage. Aspiration, however, may be impaired by the presence of viscous mucous. Prolonged aspiration or use of a larger caliber needle (19 Gauge) usually allows procuring of a fluid sample. The presence of mucin or elevated tumor marker (eg, carcinoembryonic antigen [CEA]) levels strongly suggests a mucinous tumor [68,77–80]. Mucinous cuboidal or columnar epithelial cells are found in approximately 50% of cases and are diagnostic of a mucinous lesion but also may be seen with intraductal papillary mucinous neoplasia (IPMN) [78]. The results of FNA, however, can distinguish these lesions from SCAs and pseudocysts. Additionally, the interpreting pathologist must consider contamination from gastric or duodenal columnar epithelial cells. Individual tumors commonly contain a spectrum of histology ranging from regions of adenomatous change, to invasive carcinoma, with intervening denuded epithelium. The often sporadic distribution of

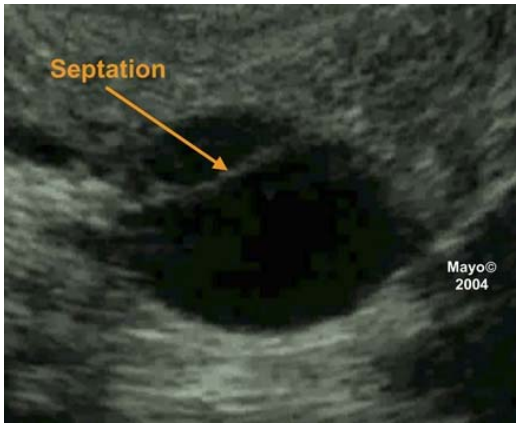

Fig. 4. Mucinous cystadenoma.

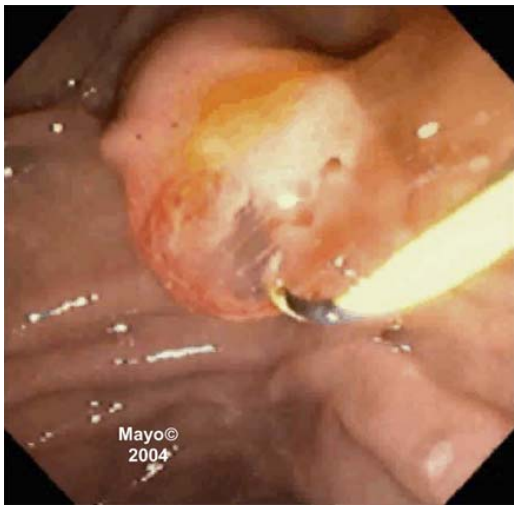

Fig. 5. Intraductal papillary mucinous neoplasia. Endoscopic visualization widely patent (gaping or fish mouth) papilla extruding mucous.

dysplastic findings prohibits high diagnostic accuracy by biopsy alone [34,73]. The sensitivity of FNA for diagnosing mucinous cystadenocarcinoma (MCAC) is 67%, in large part because of the focal distribution of malignancy [69,81]. Surgical resection may be necessary to distinguish the specific type of CPT and to establish the presence of malignancy [71].

Intraductal papillary mucinous neoplasia

Endoscopic inspection of the papilla may reveal a widely patent (gaping or fish-mouth) papilla extruding mucous (Fig. 5) [82]. IPMN can be divided into predominantly main duct or side branch disease, with EUS demonstrating a diffusely dilated main duct or one or several dilated side branches (Figs. 6, 7)

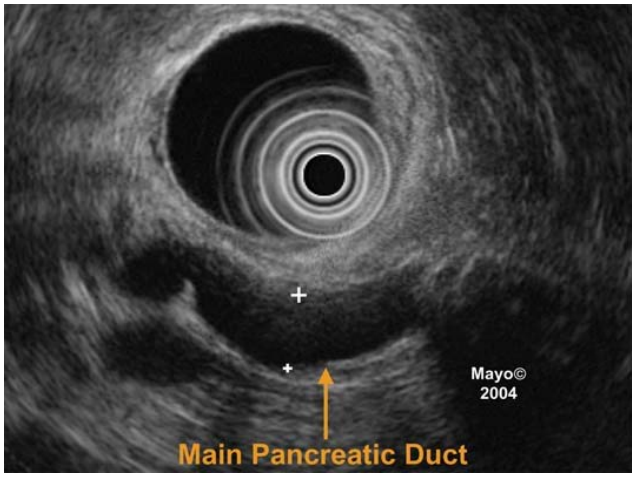

Fig. 6. Intraductal papillary mucinous neoplasia. Dilated main pancreatic duct in a patient with main duct disease.

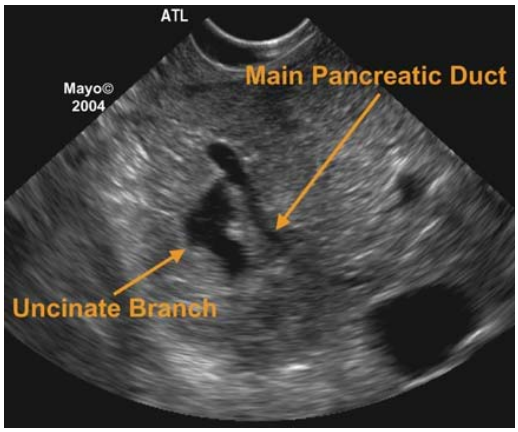

Fig. 7. Intraductal papillary mucinous neoplasia (IPMN). Dilated uncinate branch in a patient with side branch IPMN.

[51,64,83]. Although communication with the pancreatic duct is a feature of side branch IPMN and helps exclude MCN, the absence of communication does not exclude IPMN, because mucous can block the flow of contrast into the abnormal side branch. This often can be overcome by relatively forceful contrast injection, but risks inducing pancreatitis. Mucous or a mural tumor nodule (papillary projection) may cause filling defects. Patients rarely present with a predominantly solid mass that may be mistaken for a primary ductal carcinoma. Conversely, patients also may present with a cystic mass that may be misdiagnosed as a SCA or MCN (Fig. 8) [84,85]. Although IPMN can be mistaken for chronic pancreatitis, the finding of normal pancreatic parenchyma and mucous emanating from the papilla suggests IPMN. The latter finding is present in only 25% to 50% of patients with IPMN. Distinction from chronic pancreatitis may be difficult, as parenchymal changes can develop in IPMN as a result of ductal obstruction from intraductal tumor growth or inspissated mucous. Cytologic analysis of aspirated

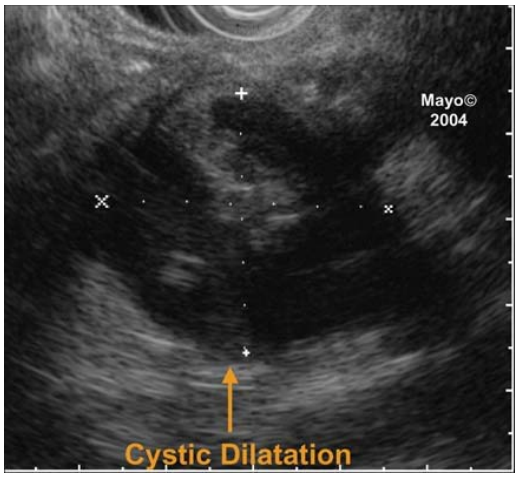

Fig. 8. Intraductal papillary mucinous neoplasia. Patient presenting with a predominant cystic component.

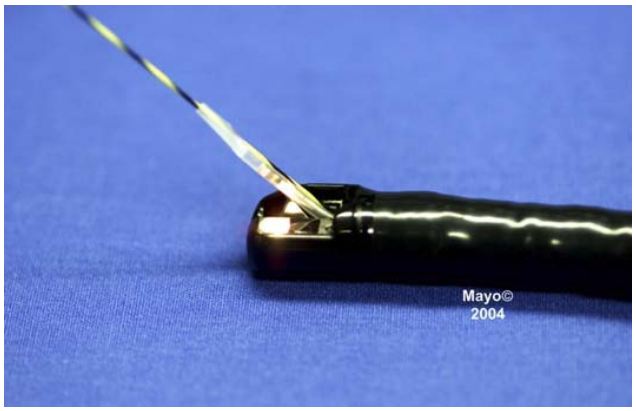

Fig. 9. Intraductal ultrasound catheter exiting a standard side viewing duodenoscope.

duct or cyst fluid demonstrates findings similar to mucinous cystadenomas, including the presence of columnar epithelial cells. Malignancy may be suggested by the finding of a focal hypoechoic mass, mural nodules, or a large unilocular cystic component [86]. Invasive carcinoma is suggested by: rupture of the main pancreatic duct wall with intrapancreatic spread of tumor, tumor invasion of the duodenum or common bile duct, malignant-appearing lymphadenopathy, and extrapancreatic spread or vascular invasion [87]. Intraductal ultrasound (IDUS) (Fig. 9) and pancreatoscopy are newer techniques that assist in the evaluation [88,89]. IDUS catheters are small-caliber (approximately 2 mm) miniprobes that are passed through standard duodenoscopes into the pancreatic duct [87,89]. These probes operate at higher frequencies (12 to 30 MHz) than standard EUS, which improves image resolution (0.07 to 0.18 mm), but limits the depth of image penetration [90]. IDUS and pancreatography can distinguish main duct from side branch IPMN, identify papillary projections (Fig. 10) to assess the risk of malignancy, and determine the longitudinal extent of tumor spread and parenchymal invasion [89].

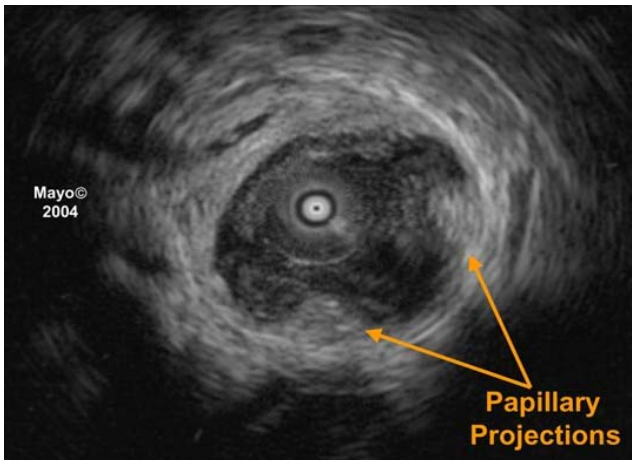

Fig. 10. Papillary projections seen during pancreatoscopy in a patient with intraductal papillary mucinous neoplasia.

Endoscopic ultrasound for cystic pancreatic tumors

The authors perform EUS in all patients with a suspected CPT to help exclude a pseudocyst, determine the specific type of CPT, and assess the risk for malignancy [33,64–66,91–93]. Doing so requires evaluation of the cyst wall (thickness, focal irregularity, mass, or papillary projections) and intracystic structures (septations, echo-dense mucous, debris). EUS examination of the pancreatic ductal anatomy, parenchyma, or the finding of previously undetected cystic or solid mass lesions can provide additional diagnostic information. The authors perform EUS even when resection is planned to assess for malignancy and locoregional or distant disease that would preclude surgical intervention. EUS features that correlate with malignancy include the presence of focal cyst wall thickening or irregularity, septal thickening, an adjacent solid mass, and the presence of collateral vessels. As with other imaging modalities, EUS alone cannot distinguish the tumor type accurately or identify malignancy, particularly when only few criteria are assessed [93–96]. In a study that solely considered the presence of an associated mass component as a sign of malignancy, the sensitivity and accuracy of EUS were only 65% and 75% for identifying premalignant or malignant cysts [96]. Others have shown equally poor results, with a sensitivity and specificity of 52% and 58%, respectively, when such a narrow spectrum of features was assessed [93]. In a prospective study involving 52 patients undergoing resection with tissue confirmation, however, EUS accurately categorized 92% of tumors [33]. Similarly, another group found that the presence or absence of at least two of three features (pancreatic parenchymal changes, septa, and mural nodules) offered a sensitivity and specificity of 94% and 85%, respectively. The limited depth of imaging with EUS reduces the diagnostic accuracy of large cystic lesions (greater than 6 cm) [33]. TUS, CT, and MRI may be particularly useful in this subgroup of patients with larger lesions.

Cytology and cystic fluid analysis

Although a recent study reported sensitivity of cytology greater than 95% [97], most centers describe a sensitivity ranging from 27% to 64% [93,94,98]. In contrast, the specificity of cytology approaches 100% in all studies [93,94,97,98]. Although aspirated fluid from CPTs may contain denuded epithelium even in the presence of malignancy, biopsies are often falsely negative as a result of sampling error. When cytology is negative, complete surgical resection is required to exclude or establish presence of malignancy [71]. Addition of cyst fluid marker levels, amylase, and mucin stain to cytology alone can increase the diagnostic accuracy to 80% to 90% [94,99].

Assessment of cyst fluid for tumor markers (CEA, CA 19-9, CA 15-3, and CA 72-4) may improve diagnostic accuracy. The CEA level appears to be the most useful to discriminate nonmucinous (benign) from mucinous (premalignant or malignant) lesions. Studies vary as to the threshold value that offers ideal

sensitivity and specificity for discriminating lesions. Lower values of CEA are thought to arise in pseudocysts and SCAs, while higher values are more common with mucinous tumors that can behave more aggressively with malignant transformation. A CEA level below 5 ng/mL offers a sensitivity of 57% to 100% and specificity of 77% to 86% [67,97,100]. Others, using a cut-off of greater than 50 ng/mL, found sensitivity for CEA to be 90% for identifying premalignant or malignant lesions [96], versus a sensitivity and specificity of only 28% and 25%, respectively in a more recent study [93]. In one report, a CEA value greater than 400 ng/mL provided 100% specificity in distinguishing MCNs from pseudocysts [101], compared with another study with a sensitivity and specificity of only 13% and 75%, respectively [97]. Although the CEA level from pseudocyst fluid tends to be very low, elevated levels are common in infected pseudocysts [47,92,102].

Limited data suggest that the CA 15-3 level is useful in differentiating benign from malignant pancreatic mucinous cysts with an upper cutoff value of 30 U/mL reported to distinguish MCAs from MCACs with 100% sensitivity and 100% specificity [103]. In another report, CA 72-4 was more useful than CEA or CA 15-3 for distinguishing MCNs, demonstrating a sensitivity and specificity of 87.5% and 94%, respectively [104]. Similarly, a CA 72-4 level greater 40 U/mL has demonstrated 63% sensitivity and 98% specificity for distinguishing MCNs from SCAs and pseudocysts [101]. A CA 19-9 cut-off level between 50,000 and 90,000 U/mL may distinguish malignant cysts [97,100]. CA 19-9 levels greater than 50,000 U/mL provide a sensitivity of 15% to 75% and a specificity of 81% to 90% for distinguishing mucinous from nonmucinous lesions [97,100]. The CA 19-9 level, however, commonly rises secondary to inflammatory conditions and when biliary obstruction is present, thereby limiting the diagnostic utility [47, 92,102].

The amylase concentration helps narrow the differential, because high levels typically are found only in fluid from cysts that communicates with the pancreatic duct (pseudocysts and IPMN) [102]. An amylase level greater than 5000 U/L provides a sensitivity and specificity of 61% and 58%, respectively, for differentiating pseudocysts from other CPTs [97].

Although EUS–FNA appears safe, the utility of morphologic assessment and cyst fluid analysis remains uncertain. Although the sensitivity of EUS–FNA for identifying malignancy may be limited, this finding alters therapy for patients in whom surgery is not intended but rather surveillance and periodic imaging are planned. Negative or benign findings do not necessarily exclude malignancy, and in these patients, surveillance imaging is suggested. The role of tumor markers is controversial, as is the threshold value that discriminates the lesion type with greatest accuracy. Another limitation is the tendency for sampling error when processing fluid from multi-locular cysts, whose fluid composition can vary within the lesion [79]. Of all tumor markers, the CEA level appears to have the most diagnostic value. The authors consider use of tumor markers to be largely investigational, however, and caution the role they should play on influencing care. The combination of cyst fluid marker analysis and cytologic examination may prove to be the most accurate diagnostic approach. When limited fluid is

available for analysis, the authors request serial evaluation for cytology with mucin stain, CEA, and amylase. In the authors' practice, determination of other tumor marker levels and biochemical studies are requested only for investigational purposes.

Performing FNA largely depends on a physician's approach to the management of CPTs. FNA ideally is reserved for situations when the results are expected to influence patient care, as for patients in whom the need for surgical intervention is debated because of diagnostic uncertainty, advanced age, or marginal health status. In general, the authors do not recommend FNA for classically benign-appearing lesions for which no intervention is intended or for resectable malignant appearing lesions for which surgery already is planned. Although a negative result does not exclude malignant or potentially malignant disease, it may support the decision for surveillance and periodic imaging. The finding of malignant cytology, a positive mucin stain, or elevated cyst fluid CEA, however, may support resection.

Pancreatic adenocarcinoma

The incidence of pancreatic adenocarcinoma is increasing, with an estimated 28,000 new cases in the United States this year [105]. Although it is the 10th most common malignancy, it is the fourth leading cause of cancer-related mortality and the second most common cause of cancer deaths for all GI-related carcinomas [106]. Most patients with pancreatic cancer present late in their course and have either locally extensive or metastatic disease with a median survival of only 4 to 6 months [107,108]. At the time of diagnosis, only 10% to 20% of patients are candidates for curative resection [109,110]. The late presentation, aggressive nature, and lack of effective therapies all contribute to the poor prognosis. Accurate staging of pancreatic adenocarcinoma is important to identify the subset of patients who have potentially resectable localized cancers. Although early detection is crucial to improve prognosis, the determination of resectability is important to help avoid unnecessary surgical intervention.

Staging as defined by the TNM classification (Table 3) depends on characteristics of the primary tumor, namely tumor size and infiltration into major vessels, (T stage), regional lymph node involvement (N stage), and the presence or absence of distant metastasis (M stage). EUS can evaluate all necessary structures to allow locoregional staging of pancreatic adenocarcinomas and at times also detects hepatic metastases. Gress et al evaluated the use of EUS to stage 151 patients with pancreatic cancer. In the 81 patients undergoing surgical resection, the accuracy of EUS for T stage, N stage, and vascular invasion was 85%, 72%, and 93%, respectively [11]. Similarly, Tio et al demonstrated the overall accuracy of EUS for T and N staging at 84% [111]. Although distant metastasis must be evaluated by other means, such as CT or laparoscopy, local resectability is predicted accurately in 75% to 90% of patients by EUS [2,3,112]. The overall accuracy of EUS for predicting lymph node invasion (N stage) is

Table 3
American Joint Committee on Cancer staging of pancreatic adenocarcinoma

Primary tumor (T):	
T1	Tumor limited to pancreas, size < 2 cm in greatest dimension
T2	Tumor limited to pancreas, size > 2 cm in greatest dimension
T3	Tumor infiltration into duodenum, bile duct, papilla, peripancreatic tissue (retroperitoneal and mesenteric fat, mesocolon, greater/lesser sac, and peritoneum) or major venous structures (portal vein, superior mesenteric vein)
T4	Tumor infiltration (extension) into stomach, spleen, colon, or major arterial structures (superior mesenteric artery, celiac trunk, hepatic artery, but not splenic vessels)
Regional lymph nodes (N):	
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis (pN1a = single regional node, pN1b = multiple regional nodes)
Distant metastases (M):	
M0	No distant metastasis
M1	Distant metastasis

Stage grouping:

Stage	T	N	M
I	1	0	0
	2	0	0
II	3	0	0
III	1	1	0
	2	1	0
	3	1	0
IVA	4	Any	0
IVB	Any	Any	1

lower than for primary tumor staging (T stage). In three studies [4,113,114], the accuracy of EUS for T stage was 82% to 91%, and for N stage, accuracy was 64% to 73%.

Early EUS reports demonstrated superior accuracy for preoperative staging of pancreatic cancer (85% to 100%) compared with dynamic CT (64% to 66%) and TUS (61% to 64%) [9,115,116]. Gress et al [11] reported on 81 patients with pancreatic adenocarcinoma who were evaluated preoperatively by dynamic CT and EUS. The results achieved with EUS were superior to dynamic CT for T staging (85% versus 30%, $P < 0.0001$) and N staging (72% versus 55%, $P < 0.0001$), and for vascular invasion (93% for EUS and 60% for CT, $P < 0.0001$).

The use of rapid-scanning helical CT permits multiple scans to be obtained through the abdomen during different phases of contrast enhancement. This technology allows timing of imaging when arterial and pancreatic parenchymal features are optimally visible and then later when hepatic metastases may be detected better. Leggmann et al compared this technique with EUS in 30 patients with suspected pancreatic carcinoma [2]. The diagnostic sensitivity was similar for both (100% for EUS and 92% for CT), with an overall staging accuracy of

93% for both techniques. EUS and CT both predicted resectability with 90% accuracy. EUS was more sensitive than CT for detecting hepatic artery encasement, but less sensitive for demonstrating superior mesenteric artery invasion. Midwinter et al [117] reported their experience in 48 patients in whom a helical CT and EUS were performed to evaluate a clinically suspected pancreatic mass. EUS was more sensitive at tumor detection compared with helical CT (97% versus 76%). Both studies assessed portal vein, superior mesenteric vein, and lymph node involvement. As found by Leggman et al, however, EUS was less accurate for assessing superior mesenteric artery invasion [2]. The role of MRI in the evaluation of patients with pancreatic adenocarcinoma is evolving. In a multicenter study, dynamic thin-section CT and MRI had identical accuracy (70% for both) in predicting resectability of pancreatic adenocarcinoma [118]. The introduction of faster helical CT scanners and higher Tesla strength MRI units with various imaging sequences and contrast agents now provides even better performance. A recent study found the accuracy of helical CT and MRI for determining resectability to be 81% and 96%, respectively [119]. Further comparative studies are needed to confirm these results. Unfortunately, CT and MRI continue to be limited by poor detection of peritoneal and small liver metastases [120].

Endoscopic ultrasound appears to be the most accurate method for assessing portal venous tumor infiltration [1,7,115,116,121]. EUS can identify tumor infiltration of the portal venous system correctly in approximately 90% of patients [1,115], and it is superior to TUS, CT, and angiography [7,116]. Various studies have used different EUS criteria for establishing the presence of vascular invasion [114,117,122,123]. They include proximity of the mass to the vessel, an irregular venous wall contour with loss of the bright vessel-tumor interface, direct tumor extension into the vessel lumen, and the presence of regional collateral vessels. As a result, EUS should be considered not only in those patients in whom a mass cannot been identified by CT, but also when CT demonstrates equivocal information regarding locally advanced disease (eg, vascular invasion).

Although EUS may be the most accurate way to assess portal vein and splenic vein infiltration, results are less impressive for evaluating superior mesenteric vein (SMV) and arterial involvement (eg, superior mesenteric artery and celiac artery) [115,122,123]. From a practical standpoint, isolated SMV invasion seldom occurs [122]. Therefore, the limitations of EUS in evaluating the SMV should have minimal impact on managing patients with pancreatic neoplasia.

Errors in image interpretation may explain some of the shortcomings of EUS. Several normal structures, including the normal ventral anlage, caudate lobe, lymph nodes, collateral vessels, or jejunal loops, may be misinterpreted as a pancreatic mass [124]. Oblique scanning increases the likelihood of incorrectly determining the dimensions and location of a tumor and its anatomic relation to surrounding structures. Distinguishing vascular compression from tumor infiltration can be difficult. Finally, sonographic features of pancreatic masses, chronic pancreatitis, focal pancreatitis, and inflammation may overlap [1,3,116,125]. In this setting, EUS–FNA can improve diagnostic accuracy [18,126–128]. Col-

lectively, these limitations account for many of the errors in tumor identification and staging.

Endoscopic ultrasound fine needle aspiration of pancreatic adenocarcinoma

The traditional approach for establishing the diagnosis of pancreatic adenocarcinoma has been TUS- or CT-guided biopsy. The accuracy and safety of these methods is established [129] and support their use for initial attempts at diagnosis. T these methods are limited, however, by their poor sensitivity in detecting small lesions (Figs. 11, 12) and because of concerns regarding the potential for needle tract seeding [130–132]. Since the initial report of EUS–FNA of a pancreatic tumor in 1992 [133], multiple series have established the sensitivity (approximately 75% to 90%), specificity (approximately 94% to 100%), and safety of this approach in providing a cytologic diagnosis of pancreatic masses [18,126–128,134,135]. The combined results of four more recent reports [136–138], involving 366 patients with pancreatic masses, yields a sensitivity of 89%, specificity of 99%, and overall accuracy of 90% (Table 4). One study recently determined that significant improvements in EUS–FNA accuracy for diagnosing pancreatic mass lesions could be achieved with a short-term hands-on training by an expert endoscopist [139]. Three endosonographers with substantial experience with diagnostic EUS and limited experience with EUS–FNA provided a diagnostic accuracy of only 33% at study onset. Following a period of closely supervised mentoring, the accuracy increased to 91%. By multivariate analysis, improvements in diagnostic accuracy correlated with the formal training and were not influenced by tumor size, location, or number of needle passes.

Endoscopic ultrasound fine needle aspiration may offer several advantages over other radiologically guided techniques. The close proximity of the endo-

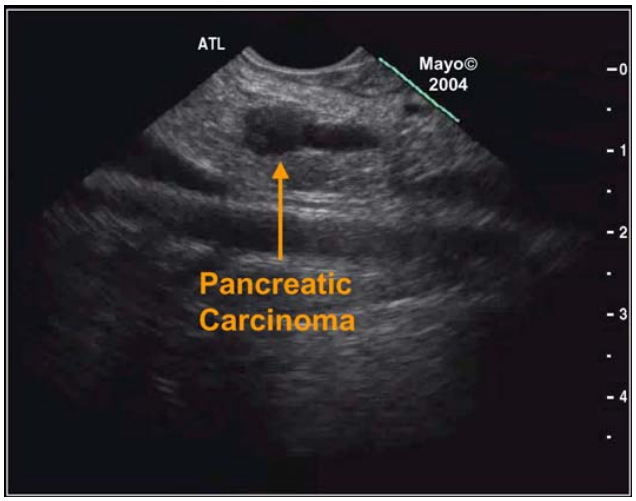

Fig. 11. Pancreas adenocarcinoma. Small (6 × 4 mm) resectable T1 tumor.

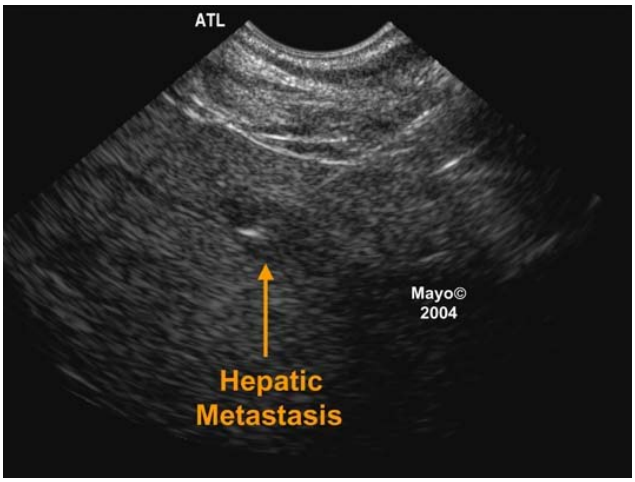

Fig. 12. Hepatic metastasis and fine needle aspiration. Small hepatic metastasis in a patient with pancreatic adenocarcinoma.

scope to the pancreatic mass shortens the distance that the needle must travel and may reduce the risk of tumor seeding. Also, the needle tract for EUS–FNA typically is included within the resected specimen. In addition, EUS–FNA often can be used to biopsy lesions not visualized or inaccessible by TUS- or CT-guided techniques. The safety of pancreatic EUS–FNA has been demonstrated, with complications occurring in less than 1% of patients [136–138]. Most complications are mild and self-limited. Fatal complications have not been reported.

The utility of EUS–FNA of pancreatic masses is limited somewhat by the low negative predictive value. As a result, even in the presence of a negative biopsy, the existence of a pancreatic malignancy cannot be ruled out [137]. FNA ideally should be performed with a cytopathologist present to verify the adequacy of the sample. When performing FNA without this onsite assessment, multiple passes (more than five) should be made to improve the diagnostic yield [140]. The presence of peri-tumoral inflammation may lead to aspiration of atypical or suspicious cells and has been reported to reduce the sensitivity of EUS–FNA [140]. The finding of atypical or suspicious cells in a patient with a high clinical suspicion of cancer, however, strongly correlates with a neoplastic process [141].

Table 4
Accuracy of endoscopic ultrasound fine needle aspiration for pancreatic mass lesions

Author/ Year / Reference	Number of patients	Sensitivity	Specificity	Accuracy
Wiersema, 1997 [136]	124	86%	94%	88%
Suits, 1999 [137]	98	96%	100%	96%
Williams, 1999 [138]	144	82%	100%	85
Raut, 2003 [145]	216	91%	100%	92%
Total	582	89%	99%	90%

Diagnostic approach

When the suspicion for a pancreatic neoplasm exists, and the patient has no comorbid conditions precluding surgery, the goal is determining the potential resectability of the lesion. The most streamlined approach for patients with suspected pancreatic neoplasms would be to perform a pancreatic protocol dual-phase helical CT. In patients with unresectable disease, percutaneous techniques can be used to establish a tissue diagnosis. The need for a tissue diagnosis in patients with an unresectable pancreatic mass remains debatable. In the setting of pancreatic adenocarcinoma, the results may not alter patient management. If the use of chemotherapy or radiation therapy is contemplated, however, then a biopsy should be considered, as most physicians withhold administration until a tissue diagnosis is made. Also, it may be important to perform a biopsy to avoid missing the diagnosis of pancreatic lymphoma or small cell carcinoma, both of which often benefit from chemotherapy or radiation therapy [142,143].

In those patients with a presumably resectable tumor based on imaging, the need for preoperative tissue diagnosis remains debatable, and the decision depends on the current practice of the surgeon. Some would suggest against pursuing a tissue diagnosis because of the low negative predictive value of radiologically or endoscopically guided FNA. As a result, a negative biopsy result does not rule out malignancy and therefore would not influence the decision to proceed with surgery [1]. Additionally, although infrequent (less than 1%), procedure-related hemorrhage or pancreatitis can make pancreatic tumor resection more difficult. For this reason, many surgeons prefer to avoid biopsying a pancreatic mass if it appears to be resectable. Patients requiring neoadjuvant chemotherapy or radiation therapy, however, will need a tissue diagnosis. In this case, EUS may be preferred over percutaneous approaches because of the theoretically reduced risk of tumor seeding and the greater sensitivity of EUS for detecting small pancreatic tumors. For patients presenting with biopsy-proven, resectable tumors, the added benefit of EUS is unknown and is being investigated. In those patients in whom CT is equivocal regarding resectability or absence of a mass lesion, EUS is helpful in further clarifying whether a mass lesion is present, and if so, if advanced disease can be identified. Patients found to have unresectable disease on EUS should be considered for FNA at the same setting to allow tissue confirmation of the diagnosis. Patients with unresectable disease also may be considered for endosonography-guided celiac plexus neurolysis, which can be performed during the same exam [144].

Summary

Endoscopic ultrasound is used routinely to evaluate pancreatic masses. The advantage of EUS over other imaging modalities is diminishing, but it continues to have a greater sensitivity in detecting pancreatic disease. By offering high-

resolution imaging with the ability to perform needle aspiration, EUS often can determine whether a mass is inflammatory, benign, or malignant when other studies are unable to make this distinction.

Endoscopic ultrasound should be performed for all potentially resectable pancreatic neuroendocrine tumors once the laboratory diagnosis has been made because of the high accuracy for tumor localization and lymph node and vascular involvement. EUS also may detect unsuspected multi-focal or metastatic disease, and it therefore influences management decisions. EUS is an ideal method for evaluating cystic pancreatic lesions because of its accuracy in identifying and characterizing these tumors. Enhanced resolution with EUS and FNA of cyst contents often helps to establish the nature of these lesions.

Staging evaluation of patients with suspected or known pancreas adenocarcinoma should start with a dual-phase helical CT. If resectability is identified, the role of EUS is uncertain. When CT is equivocal, however, EUS may assist in determining resectability, particularly when EUS–FNA confirms distant lymph node metastases. EUS–FNA can be used to establish the diagnosis when other biopsy methods have failed or are not possible, or the patient is being considered for preoperative adjuvant therapy. The ability to perform celiac plexus neurolysis for pain control in nonoperable patients or those with unresectable disease adds to the usefulness of EUS. ERCP should be reserved for palliation of jaundice and not used as a primary diagnostic modality for pancreas adenocarcinoma.

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