Endoscopic Ultrasound in the Diagnosis and Staging of Pancreatic Cancer

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Patients with signs and symptoms suggestive of a pancreatic neoplasm typically undergo initial imaging with transabdominal ultrasound or computed tomography. This evaluation often reveals the presence of a pancreatic mass or fullness.

Endoscopic ultrasound was developed in the early 1980s to overcome the limitations of transabdominal ultrasound in imaging the gastrointestinal wall and retroperitoneum.[1] The ultrasound transducer (positioned at the endoscope tip) is applied directly against the duodenal or gastric wall. This enhances the image quality by minimizing intervening adipose tissue and air that must be traversed by the ultrasound. The proximity of the transducer to the target tissue allows the use of higher frequency ultrasound and leads to greater image resolution. Accordingly, the use of endoscopic ultrasound has become routine for diagnosing and staging pancreatic and other gastrointestinal tumors.[2-4]

Dedicated Instruments

Two types of dedicated instruments are available with which to perform endoscopic ultrasound—each has different properties that offer unique advantages and disadvantages. For both instruments, acoustic coupling is achieved by filling either the intestinal lumen or a balloon attached to the tip of the endoscope with water. An oblique forward-viewing fiber or video optic system is used to help direct instrument passage.

The most commonly used instrument is the radial echoendoscope, which has a mechanically rotating transducer that provides a 360-degree transverse image. This image is in a plane perpendicular to the longitudinal axis of the endoscope. The complete scanning arc and the radial orientation of the image simplify structure recognition. Operating from 7.5 to 20 MHz, the transducer can be easily switched from one frequency to another during the endoscopic ultrasound examination, thus modifying the depth of penetration and image resolution.

A linear echoendoscope, equipped with an electronic array transducer that produces a sagittal image parallel to the longitudinal axis of the endoscope, is also available. Operating at 5 and 7.5 MHz, this instrument allows continuous real-time imaging and guidance of a 19- or 22-gauge needle as it is passed from the endoscope into a lesion. This feature allows one to perform fine-needle aspiration (FNA) of peri-intestinal tumors, lymph nodes, and fluid collections. In a similar fashion, therapeutic interventions such as celiac plexus neurolysis and pseudocyst draining may be achieved. Doppler and color Doppler are available and are used to identify vascular structures.

Detection of Pancreatic Tumors

Extensive data indicate that endoscopic ultrasound is a highly sensitive method for identifying pancreatic neoplasms, with detection rates greater than 90% (Table 1).[2,5-12] In most studies, endoscopic ultrasound has proven superior to transabdominal ultrasound, computed tomography (CT), endoscopic retrograde cholangiopancreatography (ERCP), and angiography in the detection of pancreatic tumors.[2,6,12-14] In a study by Rosch and colleagues, endoscopic ultrasound demonstrated greater sensitivity (99%) and specificity (100%) than abdominal ultrasound (sensitivity: 67%, specificity: 40%) and CT scan (sensitivity: 77%, specificity: 53%) for detecting pancreatic tumors.[2] Recent studies comparing endoscopic ultrasound with helical CT, magnetic resonance imaging (MRI), and positron-emission tomography have found endoscopic ultrasound to have a greater sensitivity for identifying pancreatic neoplasms.[5,7,11,15] In another study of 34 patients with elevated levels of CA 19-9 and a normal pancreas according to transabdominal ultrasound and CT scan, endoscopic ultrasound was 94% accurate in detecting a pancreatic or biliary neoplasm, with a positive and negative predictive
value of 92% and 100%, respectively.[16]
The advantage of endoscopic ultrasound is even greater for recognizing tumors that are less than 2 to 3 cm in diameter.[2,7,12,17,18] For pancreatic tumors less than 2 cm, Yasuda and colleagues found that endoscopic ultrasound had a detection rate of 100% (ERCP: 57%, transabdominal ultrasound: 29%, CT: 29%, and angiography: 14%).[12] In another study by Rosch and associates, the diagnostic sensitivity of endoscopic ultrasound for detecting tumors smaller than 3 cm was 100%, compared with 57% for transabdominal ultrasound and 68% for CT.[19]

Neuroendocrine Pancreatic Tumors

Endocrine tumors of the pancreas are rare, with a prevalence of less than 1 per 100,000 persons.[20] Insulinoma, gastrinoma, and nonfunctioning tumor are most common, while glucagonoma, somatostatinoma, and vipoma are less often reported (Figure 1). Resection offers the only chance for cure and should be undertaken whenever possible due to the malignant potential of these tumors.

Preoperative determination of the tumor’s location and extent is necessary to enable the surgeon to plan the optimal surgical approach. Preoperative localization is also important because it is difficult to locate these tumors during surgery in up to 20% of insulinomas and as many as 50% of gastrinomas.[20] Efforts at tumor localization should be reserved for patients in whom biochemical studies support the clinical diagnosis of a pancreatic neuroendocrine tumor and not as part of a screening examination.[21]

The approach to tumor localization is similar for all tumor types. Various imaging modalities are available for preoperative identification of pancreatic endocrine tumors. They include transabdominal ultrasound, CT, selective abdominal angiography, selective venous sampling, radiolabeled somatostatin analog (octreotide)-receptor scintigraphy (SRS), intraoperative ultrasound, and, most recently, endoscopic ultrasound.

Insulinomas

Endoscopic ultrasound is increasingly being used in the diagnostic evaluation of endocrine tumors of the pancreas because of its ability to identify small lesions (Figure 2). Studies report a localization rate of approximately 77% to 93% for insulinomas.[4,20,22-27] In these same studies, CT was able to locate the tumor in 0% to 20% of patients, and SRS in only 12% to 14%. Insulinomas have a low density of somatostatin receptors and as a result often go undetected by SRS. The high detection rate of endoscopic ultrasound for insulinomas is likely explained by the fact that 99% of insulinomas are confined to the pancreas.[25,28,29]

Gastrinomas

About 75% to 100% of pancreatic gastrinomas are localized by endoscopic ultrasound,[4,20,22,25,26,30] but only 0% to 67% of duodenal gastrinomas can be identified.[20,22,26] Endoscopic ultrasound 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.[20,22,26,31] This is important, since as many as 30% to 45% of gastrinomas (single or multiple lesions) are located in parapancreatic locations, most notably the duodenal wall or lymph nodes.[28] Duodenal wall gastrinomas are commonly missed by endoscopic ultrasound, despite special attention to this area, unless previously identified endoscopically.[25] Therefore, the endoscopic ultrasound examination should always be accompanied by a careful forward- and side-viewing examination of the duodenal wall.

General Observations

Endoscopic ultrasound FNA increases the accuracy for detection of pancreatic endocrine tumors. Accuracy rates of 75% to 80% have been reported.[21,30,32] In addition, endoscopic ultrasound may also identify multifocal tumors not seen by other imaging modalities.[32] In a multicenter trial involving 37 patients with a suspected neuroendocrine pancreatic tumor undetected by transabdominal ultrasound and CT, the sensitivity and specificity of endoscopic ultrasound for tumor localization was 82% and 95%, respectively.[2] 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 these tumors were identified by angiography. All patients underwent surgical resection, with 36 of 37 patients considered cured based on clinical and laboratory parameters. The endoscopic ultrasound appearance of neuroendocrine pancreatic tumors is similar, regardless of the type of tumor. They typically appear as round, well-delineated, homogenous, echo-poor lesions, with a surrounding hyperechoic rim. Their appearance can vary with reports of cystic or calcified tumors, echo-rich lesions, an echo-poor border, or echotexture similar to the surrounding pancreatic
parenchyma.[2,36,37] The endoscopic ultrasound technique for localizing these tumors is identical to that of adenocarcinomas, except that a more thorough examination may be needed to find these small lesions.

The parapancreatic region should also be carefully examined not only to search for malignant lymph nodes but to look for primary tumors as well.[17,38] Parapancratic tumors are more difficult to locate than intrapancratic tumors; they may be attached by a pedicle or completely separate from the pancreas.[25,35] As with other tumors, infiltration into adjacent organs and vessels should be evaluated. Endoscopic ultrasound FNA helps differentiate benign parapancratic lymph nodes from a primary neuroendocrine pancreatic tumor, a distinction that may be especially difficult to make for insulinomas.[4,23-25,32,39-41]

**Cost-Effectiveness**

The cost-effectiveness of endoscopic ultrasound for the preoperative localization of pancreatic endocrine tumors was recently demonstrated by Bansal and colleagues in a case-control study. They compared the costs of performing tumor localization with and without endoscopic ultrasound as part of the protocol, and found that the use of endoscopic ultrasound significantly reduced the costs of preoperative staging ($2,620 vs $4,846). The savings occurred because of both a decrease in the number of angiograms and venous sampling procedures performed and a reduction in surgical and anesthesia times. The cost per tumor located was $3,144 when endoscopic ultrasound was used vs $5,628 when it was not.

**Recommendations**

Endoscopic ultrasound is an accurate technique for detecting functioning neuroendocrine pancreatic tumors. We suggest performing an endoscopic ultrasound in all patients in whom surgery is planned; some practitioners favor its use only when noninvasive studies detect no metastases and no primary tumor is seen. We favor this approach even when a lesion has already been identified in order to detect unsuspected multifocal or metastatic disease. The additional information obtained by endoscopic ultrasound FNA allows cytologic confirmation of the diagnosis with reduced false-positive imaging results. It also allows the surgeon to plan the optimal strategy (ie, tumor enucleation vs pancreatic resection). More studies are needed, however, to determine the role and utility of endoscopic ultrasound FNA when noninvasive studies have already localized a tumor.

**Cystic Pancreatic Tumors**

Cystic neoplasms of the pancreas are rare, accounting for less than 1% of all pancreatic tumors. That said, they are being recognized in greater numbers as the use of high-resolution abdominal imaging increases. These lesions may represent an inflammatory mass, benign lesion, or malignancy.[37] The most common cystic pancreatic tumors are serous cystadenomas, mucinous cystadenomas, mucinous cystadenocarcinomas, and intraductal papillary mucinous tumors. With rare exception, serous cystadenomas are benign and can generally be managed with observation alone.[42] The other lesions are premalignant or malignant and, in good surgical candidates, are generally indications for resection.[42-44] Detection is important even after malignant transformation because these tumors have a better prognosis than ductal adenocarcinoma.

It is often difficult to distinguish the various types of cystic pancreatic tumors, as well as to distinguish a benign from malignant tumor. Conventional imaging studies, such as transabdominal ultrasound, CT, and MRI, often inadequately characterize and differentiate these types of tumors.[45,46] The diagnostic yield of transabdominal ultrasound or CT can be improved by analyzing aspirated cystic fluid (Table 2). The fluid viscosity and amylase levels, along with tumor marker (CA 19-9, CA 15-3, CA 72-4, and carcinoembryonic antigen [CEA]) concentrations, may be used to increase the diagnostic yield of cystic fluid cytology.

The fluid viscosity tends to be high in mucinous tumors and intraductal papillary mucinous tumors, and low in serous cystadenomas and pseudocysts. The amylase level is typically low in mucinous tumors unless they communicate with the pancreatic duct and serous cystadenomas. An elevated amylase is seen in the majority of pseudocysts that communicate with the pancreatic duct and intraductal papillary mucinous tumors.[47] The CA 19-9 level may be increased as a result of inflammatory processes or malignancy, and, therefore, it is not useful for differentiating cystic tumors.[47] Concentrations of CA 15-3, CA 72-4, and CEA in fluid aspirated from mucinous tumors are usually higher than when measured from serous cystadenomas and pseudocysts.[48] Elevated CEA levels have been reported, however, in patients with an infected pseudocyst.[47]

Endosonography is useful for identifying and characterizing cystic pancreatic tumors, especially for lesions less than 2 to 3 cm in diameter that are difficult to identify by conventional imaging. Cystic
pancreatic tumors are typically hypoechoic and easily discerned from the hyperechoic normal pancreatic parenchyma. Endoscopic ultrasound tumor characteristics may be used to help predict the likelihood of a cystic neoplasm.[37] The spectrum ranges from a simple well-defined lesion, which is unilocular or has only thin septations, to a complex cyst, which has a thick irregular wall, thick septations, and solid tissue protruding into the cyst.[37] The information obtained from these examinations is useful in guiding management decisions.

**Serous Cystadenomas**

Serous cystadenomas appear as focal, well-demarcated, multiloculated masses containing numerous small microcysts interspersed within a dense fibrous honeycomb (Figure 3). Usually less than 1 cm in diameter, individual cysts are separated by thin-walled septations. However, a minority of these tumors may be macrocystic and contain a central area of fibrosis or calcification.[11,49] Cytologic analysis is diagnostic in only 50% of aspirates.[50] The presence of glycogen-staining cells establishes the diagnosis.

**Mucinous Cystadenomas/Cystadenocarcinomas**

Mucinous cystadenomas are typically macrocystic (2 cm or more); a microcystic appearance is less commonly reported (Figure 4).[51] A thin wall lined with mucinous columnar epithelium that forms papillary projections which may contain foci of dysplastic cells or invasive carcinoma surrounds these lesions. While the lesions are usually unilocular, they may be divided into multiple fluid-filled cavities separated by thin septations. One must search for the evidence of a thick irregular wall or adjacent mass that may suggest malignancy.[51] Mucin may be seen floating within the cyst as well. Although infrequently seen, peripheral calcification is usually pathognomonic.

Fluid obtained during endoscopic ultrasound FNA should be examined for the presence of both columnar epithelial cells and mucin, which strongly suggests the presence of mucinous tumor.[52] Malignant epithelial cells may also be identified, especially in the presence of an intracystic mass component.[53]

**Intraductal Papillary Mucinous Tumors**

Intraductal papillary mucinous tumors are also referred to as mucin-hypersecreting neoplasm, mucin-producing tumor, intraductal carcinoma, intraductal mucin-producing tumor, ductectatic mucinous cystadenoma/cystadenocarcinoma, and mucinous ductal ectasia. The variable clinical presentation and appearance of intraductal papillary mucinous tumors may lead to confusion regarding the diagnosis.

Initial endoscopic inspection of the papilla may reveal the presence of a wide patent (gaping or fish-mouth) papilla extruding mucus.[54] These lesions are usually characterized by the presence of a diffusely dilated pancreatic duct, but they may have a focal distribution as well. A cystic mass, solid mass, or focal ductal wall lesion may also be identified.[51,55-57] The cystic component may simulate serous or mucinous cystadenomas.

While these tumors may mimic chronic pancreatitis, the findings of a normal pancreatic parenchyma and viscous mucus emanating from the papilla support the diagnosis of intraductal papillary mucinous tumor. Chronic pancreatitis may develop in patients with these tumors, however, because of pancreatic duct obstruction from intraductal tumor growth or inspissated mucus. Cytologic analysis of aspirated duct or cyst fluid demonstrates findings similar to mucinous cystadenomas that include the presence of benign or malignant columnar epithelial cells, often associated with large amounts of mucin. The presence of a malignancy should always be considered, and it may be suggested by findings of a focal hypoechoic mass, mural nodules, or a large unilocular cystic component.[58] The lesions should be aspirated to document that the malignancy is present.

**Endosonography in Cystic Pancreatic Tumors**

- **Cytologic Confirmation** To assess the ability of endoscopic ultrasound to discriminate cystic pancreatic tumors, Kojio and colleagues prospectively analyzed 52 patients who underwent endoscopic ultrasound followed by surgical resection.[37] The lesions included nonneoplastic cysts (n = 15), intraductal papillary mucinous tumors (n = 10), mucinous cystadenomas (n = 10), mucinous cystadenocarcinomas (n = 7), serous cystadenomas (n = 5), and solid and papillary epithelial neoplasias (n = 5). They found that endoscopic ultrasound correctly categorized 94% of the tumors.

Others have found that the endoscopic ultrasound morphology is more limited in predicting the tumor type. Mallery and associates showed that endoscopic ultrasound morphology has limited accuracy, while endoscopic ultrasound-guided cystic fluid analysis improves the ability to determine the nature of these lesions.[59] In their study, the sensitivity of cytology was 57% for malignant lesions; the specificity, however, was 100%. The addition of tumor marker analysis and mucin staining increased the accuracy of identifying mucinous tumors and detecting malignant lesions. A
positive cytology or an elevated tumor marker level had an accuracy of 86% for diagnosing a cystic neoplasm.
Infection is rarely associated with endoscopic ultrasound FNA of cystic pancreatic tumors. With this more recent practice, infection is now uncommon. Most studies have described no complications,[59,60] whereas a multicenter evaluation reported an infection rate of 14% when aspirating cystic lesions.[61] None of the patients in this study received prophylactic antibiotics. The detailed imaging possible with endoscopic ultrasound permits aspiration of solid components of the cyst, including the septation or cyst wall, and may improve the diagnostic yield. Occasionally, one may identify an adjacent mass that can also be aspirated for cytologic analysis.

Follow-up

The ability of endoscopic ultrasound to obtain high-quality images of the pancreas and to guide FNA of cyst contents helps determine the nature of cystic pancreatic masses. Those patients with cystic pancreatic tumors of uncertain malignant potential should be referred for endoscopic ultrasound and undergo cyst aspiration. Although the sensitivity of endoscopic ultrasound and endoscopic ultrasound FNA for detecting malignancy may be limited, such findings will alter therapy for patients who otherwise may not proceed to surgery, instead being followed with periodic imaging. As with solid pancreatic masses, a negative or benign finding does not necessarily exclude a malignancy, and surveillance follow-up imaging is recommended when surgery is not performed.

Pancreatic Adenocarcinoma

The incidence of pancreatic adenocarcinoma is increasing, and more than 28,000 new cases were diagnosed in the United States last year.[62] It is the fourth leading cause of cancer-related mortality and is the second most common cause of cancer deaths for all gastrointestinal-related carcinomas.[62] Most patients with pancreatic cancer present late in the course of the illness and have either locally extensive or metastatic disease.[63] The late presentation, aggressive nature, and lack of effective therapies all result in a poor prognosis. Only 10% to 20% of patients are considered candidates for curative resection at the time of diagnosis.[64] Accurate staging of the pancreatic adenocarcinoma is important to identify the subset of patients who have potentially resectable localized cancers. Unfortunately, at the time of diagnosis, only a small number of patients are considered candidates for curative resection. While early detection is crucial to improving prognosis, the determination of resectability is also important, to help avoid unnecessary surgical intervention.

TNM Staging

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). Endoscopic ultrasound can evaluate all necessary structures to allow locoregional staging of pancreatic adenocarcinomas and, at times, can detect hepatic metastases (Figure 5). Gress and colleagues evaluated the use of endoscopic ultrasound to stage 99 patients with pancreatic cancer. In the 59 patients undergoing surgical resection, the accuracy of endoscopic ultrasound for T stage, N stage, and vascular invasion was 87%, 80%, and 95%, respectively.[65] Similarly, Tio and associates demonstrated that the overall accuracy of endoscopic ultrasound for T and N staging is about 84%.[66] Although distant metastasis must be evaluated by other means (ie, CT or laparoscopy), local resectability is accurately predicted by endoscopic ultrasound in 75% to 90% of patients.[5,6,67] Its overall accuracy for predicting lymph node invasion (N stage) is lower than for primary tumor staging (T stage). In three studies,[7,68,69] the accuracy of endoscopic ultrasound for pancreatic T staging was 82% to 91%, and for N staging, 64% to 73% (Table 4).[7,15,69] Early endoscopic ultrasound reports demonstrated superior accuracy (85% to 100%) for preoperative staging of pancreatic cancer compared with dynamic CT (64% to 66%) and transcutaneous ultrasound (61% to 64%)[3,12,70]. Gress reported 81 pancreatic adenocarcinoma patients who were preoperatively evaluated by both dynamic CT and endoscopic ultrasound.[15] The results achieved with endoscopic ultrasound were superior to dynamic CT for T staging (85% vs 30%, P < .0001) and N staging (72% vs 55%, P < .0001), as well as for vascular invasion (93% for endoscopic ultrasound vs 60% for CT, P < .0001).

Endoscopic Ultrasound vs Helical CT

The use of rapid scanning helical CT permits many scans to be obtained through the abdomen during different phases of contrast enhancement. This technology allows imaging timed to when arterial
and pancreatic parenchymal features are optimally visible and then later to when hepatic metastases may be better detected. Leggmann and colleagues compared this technique with endoscopic ultrasound in 30 patients with suspected pancreatic carcinoma.[5] The diagnostic sensitivity was statistically similar for both (100% for endoscopic ultrasound and 92% for CT), with an overall staging accuracy of 93% for both techniques. Both tests predicted resectability with 90% accuracy. Endoscopic ultrasound was more sensitive than CT for detecting hepatic artery encasement, but less sensitive for demonstrating superior mesenteric artery invasion.

Midwinter and associates reported their experience in 48 patients in whom a helical CT and endoscopic ultrasound were performed to evaluate a clinically suspected pancreatic mass.[71] Endoscopic ultrasound was more sensitive at tumor detection, compared with helical CT (97% vs 76%). Both studies assessed portal vein, superior mesenteric vein, and lymph node involvement comparably. However, endoscopic ultrasound evaluated superior mesenteric artery invasion less accurately, as found by Leggmann.[5]

CT vs MRI
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.[72] The introduction of faster helical CT scanners and higher Telsa strength MRI units with various imaging sequences and contrast agents have led to even better performance of both techniques. A recent study found the accuracy of dual-phase CT and MRI for determining resectability to be 81% and 96%, respectively.[73] Additional 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.[74]

Diagnostic Accuracy of Endoscopic Ultrasound
Endoscopic ultrasound appears to be the most accurate method for assessing portal venous tumor infiltration,[2,3,10,70,75] and can correctly identify tumor infiltration of the portal venous system in approximately 90% of patients,[2,3] making it superior to transabdominal ultrasound, CT, and angiography.[10,70] Various studies have used different endoscopic ultrasound criteria for establishing the presence of vascular invasion,[21,69,71,76-78] including the proximity of the mass to the vessel, an irregular venous wall contour with loss of the bright vessel-tumor interface, a tumor extension directly into the vessel lumen, and the presence of regional collateral vessels. Endoscopic ultrasound should be considered not only when CT cannot identify a mass in patients, but also when CT demonstrates equivocal information regarding locally advanced disease (eg, vascular invasion). Endoscopic ultrasound may be the most accurate way to assess portal vein and splenic vein infiltration (Figure 6), but results are less impressive for evaluating superior mesenteric vein and arterial (ie, superior mesenteric and celiac) involvement.[3,76,77] From a practical standpoint, the limitations of endoscopic ultrasound in evaluating the superior mesenteric vein should have minimal effect on the management of patients with pancreatic neoplasia. If infiltration of the portal vein is noted, then the patient would be unresectable regardless of the status of the superior mesenteric vein or arterial structures. Also, isolated invasion of the superior mesenteric vein seldom occurs.[76] Errors in image interpretation may explain some of the shortcomings of endoscopic ultrasound. Several normal structures may be misinterpreted as a pancreatic mass, such as the normal ventral anlage, caudate lobe, lymph nodes, collateral vessels, or jejunal loops.[79] Oblique scanning increases the chance of incorrectly determining the dimensions and location of a tumor and its anatomic relation to surrounding structures. It can also be difficult to distinguish vascular compression from tumor infiltration. Finally, there are sonographic features of pancreatic masses and normal tissues that may diminish the capacity to differentiate benign from malignant tumors[2,6,70,80]; these include the presence of chronic pancreatitis, focal pancreatitis, inflammation, or the presence of similar echogenicity for the tumor or surrounding normal pancreatic parenchyma. These limitations account for many of the errors in understaging or overstaging of pancreatic carcinomas. The use of endoscopic ultrasound FNA improves the diagnostic accuracy.[81-85]

Endoscopic Ultrasound-Guided FNA
The traditional approach for establishing the diagnosis of pancreatic carcinoma has been transabdominal ultrasound or CT-guided biopsy. The accuracy and safety of these methods are well established and support their use for initial attempts at diagnosis.[86] However, these methods are limited by their poor sensitivity in detecting small lesions and by concerns regarding the potential for
needle tract seeding.\[87\] Since the initial report of endoscopic ultrasound FNA of a pancreatic tumor in 1992,\[88\] multiple series have established the sensitivity (~75% to 90%), specificity (~94% to 100%), and safety of this approach in providing cytologic diagnoses of pancreatic masses.\[81-83,85,89,90\] The combined results of three recent reports\[61,91,92\] involving 366 patients with pancreatic masses yield a sensitivity of 87%, specificity of 98%, and overall accuracy of 90% (Table 5).\[32,91,92\] Endoscopic ultrasound FNA may offer advantages over radiologically guided techniques. The close proximity of the endoscope to the pancreatic mass shortens the distance the needle must travel and may reduce the risk of tumor seeding. In addition, the needle tract of endoscopic ultrasound FNA is typically included within the resected specimen. Endoscopic ultrasound FNA can often be used to biopsy lesions not visualized or inaccessible by transabdominal ultrasound or CT-guided techniques. The safety of pancreatic endoscopic ultrasound FNA has been demonstrated, with complications occurring in less than 1% of patients.\[61,91-93\] Most complications are mild and self-limited; fatal complications have never been reported.

The utility of endoscopic ultrasound FNA of pancreatic masses is somewhat limited 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.\[91\] Ideally, FNA should be performed with a cytopathologist present to verify the adequacy of the sample. When performing FNA without this on-site assessment, multiple passes (> 5) should be made to improve the diagnostic yield.\[94\] The sensitivity of endoscopic ultrasound FNA has been reported to be decreased by the presence of peritumoral inflammation that may lead to aspiration of atypical or suspicious cells.\[94\] However, the finding of atypical or suspicious cells in patients with a high clinical suspicion of cancer strongly correlates with the neoplastic process.\[95,96\]

**Diagnostic Approaches**

When a pancreatic tumor is suspected and the patient has no comorbid conditions precluding surgery, the goal is to determine the potential resectability of the lesion. Currently, the most streamlined approach to management of patients with suspected pancreatic cancer would be to perform a protocol helical CT.

**Percutaneous Techniques**

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 is debated. In the setting of pancreatic adenocarcinoma, the results may not alter the patients’ management. If the use of chemotherapy and/or radiation therapy is contemplated, however, then a biopsy should be considered, since most physicians withhold their 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 and/or radiation therapy.\[97,98\]

In patients with a presumably resectable tumor based on imaging, the need for preoperative tissue diagnosis is debated and the decision depends on the current practice of the surgeon. Some practitioners would recommend against pursuing a tissue diagnosis because of the low negative predictive value of radiologically or endoscopically guided FNA. Since a negative biopsy result does not rule out malignancy, it would not influence the decision to proceed with surgery.\[2\] Additionally, procedure-related hemorrhage or pancreatitis\[although infrequent (< 1%)\] 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.

**Endoscopic Ultrasound**

Patients requiring neoadjuvant chemotherapy and/or radiation therapy will need a tissue diagnosis. In these cases, endoscopic ultrasound may be preferred over percutaneous approaches because of the theoretically reduced risk of tumor seeding and its greater sensitivity for detecting small pancreatic tumors.

For patients presenting with biopsy-proven, resectable tumors, the added benefit of endoscopic ultrasound is unknown at this point and is being actively investigated. In patients in whom CT or other imaging techniques demonstrate equivocal findings (ie, uncertainty regarding resectability or absence of a mass lesion), endoscopic ultrasound is helpful in further clarifying whether a mass lesion is present and if advanced disease can be identified. Patients found to have unresectable disease on endoscopic ultrasound should be considered for FNA at the same time, to allow tissue confirmation of the diagnosis. Patients with unresectable disease may also be considered for
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Conclusions

The use of endoscopic ultrasound has become routine for evaluating pancreatic masses. The advantage of endoscopic ultrasound over other imaging modalities is diminishing, but it continues to have a greater sensitivity in detecting pancreatic disease. By offering high-resolution imaging and guided fine-needle aspiration, endoscopic ultrasound can often determine whether a mass is inflammatory, benign, or malignant when other studies are unable to make this distinction. Once the laboratory diagnosis has been made, endoscopic ultrasound should be performed for all potentially resectable neuroendocrine pancreatic tumors because of its sensitivity for tumor localization and accuracy in assessing lymph node and vascular involvement. Endoscopic ultrasound may also detect unsuspected multifocal or metastatic disease and, therefore, influence management decisions.

Endoscopic ultrasound is an ideal method for evaluating cystic pancreatic lesions due to its accuracy in identifying and characterizing these tumors. The production of high-resolution images and use of endoscopic ultrasound FNA of cyst contents often helps to establish the nature of these lesions. Staging evaluation of patients with suspected or known pancreatic adenocarcinoma should start with a multiphase helical CT. If resectability is identified, the role of endoscopic ultrasound is uncertain. However, when CT is equivocal, endoscopic ultrasound may help assist in determining resectability, particularly when endoscopic ultrasound FNA confirms distant lymph node metastases (Figure 7). Endoscopic ultrasound FNA can be used to establish the diagnosis when other biopsy methods have failed, are not possible, or the patient is being considered for preoperative adjuvant therapy. The ability to perform celiac plexus neurolysis in nonoperable patients, or those with nonresectable disease, adds to the usefulness of endoscopic ultrasound. Endoscopic retrograde cholangiopancreatography should be reserved for palliation of jaundice and should not be used as a primary diagnostic modality for pancreatic adenocarcinoma.

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