Endoscopic Evaluation in the Workup of Pancreatic Cancer

Ajaypal Singh, MD*, Ashley L. Faulx, MD

KEYWORDS

- Pancreatic ductal adenocarcinoma (PDAC) • Endoscopic ultrasound (EUS)
- Fine-needle aspiration (FNA)
- Endoscopic retrograde cholangiopancreatography (ERCP)

KEY POINTS

- Endoscopic ultrasound (EUS) imaging is the most sensitive diagnostic modality for pancreatic cancer, especially for tumors smaller than 2 cm in size.
- EUS also allows simultaneous fine-needle aspiration for cytologic diagnosis of the malignant process.
- Endoscopic retrograde cholangiopancreatography (ERCP) brushings and biopsies have low sensitivity (but high specificity) for pancreatic cancers and should not be used primarily for diagnosis owing to high risk of complications.
- Endoscopic biliary drainage via ERCP is the first-line palliative modality for malignant biliary obstruction.
- Both computed tomography and EUS play a complementary role in staging and preoperative planning; data to indicate superiority of one over the other is lacking.

INTRODUCTION

Pancreatic cancer is a relatively rare disease and ranks 12th in terms of prevalence among cancers in the United States, but it is the fourth leading cause of cancer related deaths.[1] It is projected to become the second leading cause of cancer related mortality by 2020.[2] The overall 5-year survival for pancreatic cancer is very low at 7.2%. It is around 27% for localized disease, but 2.4% for metastatic disease. Despite multiple advances in imaging technologies, less than 10% of the cancers are diagnosed at a localized stage.[1] Much emphasis is being placed on early diagnosis of this deadly disease at a stage when curative surgical resection is possible. Owing to the low sensitivity of cross-sectional imaging to detect small tumors in the pancreas, endoscopic

Division of Gastroenterology and Hepatology, Case Western Reserve University, Wearn 247, 11100 Euclid Avenue, Cleveland, OH 44106, USA
* Corresponding author.
E-mail address: ajay749@gmail.com

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diagnosis by using endoscopic ultrasound (EUS) has become a mainstay for diagnosis of pancreatic cancer. EUS also provides additional benefit of tissue sampling for histologic diagnosis. In this article, we review the clinical presentation of pancreatic cancer and the modalities available for diagnosis with special emphasis on the use of EUS and endoscopic retrograde cholangiopancreatography (ERCP).

CLINICAL PRESENTATION

Clinical presentation in patients with pancreatic adenocarcinoma is variable and depends on the location and stage of the disease. Owing to improving resolution and more frequent use of imaging, more patients are being diagnosed with smaller tumors that are discovered incidentally on scans done for unrelated reasons. Patients with symptomatic cancer can present with obstructive jaundice, abdominal pain, weight loss, acute pancreatitis, new-onset diabetes, worsening of long-standing diabetes, or paraneoplastic symptoms usually related to coagulopathy. Pancreatic head tumors usually present early with obstructive jaundice, but the diagnosis of pancreatic body and tail cancers is often delayed because these do not produce early symptoms and are commonly recognized when symptoms are produced by a nonlocalized disease process. Physical examination findings may include muscle wasting, jaundice, lymphadenopathy, and hepatomegaly. Many patients with pancreatic cancer have a normal physical examination on initial presentation. The laboratory characteristics include elevated bilirubin and alkaline phosphatase in patients with biliary obstruction. CA 19-9 is the only available serum biomarker for pancreatic cancer, but is limited by its low sensitivity and specificity.[3] It is often used to monitor the progression or recurrence of disease after surgery and/or neoadjuvant therapy.[4] The use of CA 19-9 for diagnostic purposes is not recommended.

DIAGNOSTIC MODALITIES

The diagnosis of pancreatic cancer usually involves cross-sectional imaging and endoscopy in the appropriate clinical setting. Surgical exploration for diagnosis is rarely needed with modern imaging and endoscopy. We briefly review imaging modalities for the diagnosis of pancreatic cancer (reviewed in detail elsewhere in this issue) and then focus on the role of endoscopy for diagnosis, with particular focus on EUS.

TRANSABDOMINAL ULTRASOUND IMAGING

Transabdominal ultrasound imaging is the most commonly used study in patients with jaundice and right upper quadrant pain owing to its low cost, easy availability, and lack of any radiation exposure. It has very high sensitivity in detecting biliary dilatation and also the level of obstruction, but in addition to being user dependent it has a very low sensitivity for actual detection of pancreatic masses.[5,6] In patients with suspected pancreatic malignancy, computed tomography (CT) scanning is the most commonly used initial study and the usefulness of abdominal ultrasound imaging in these patients is very limited.

CROSS-SECTIONAL IMAGING: COMPUTED TOMOGRAPHY AND MRI

CT is the most commonly used initial imaging modality in patients with suspected pancreatic malignancy. With the advent of multidetector CT (MDCT) imaging, the sensitivity of CT for diagnosing pancreatic cancer is reported to be greater than 80%.[7] However, the sensitivity of MDCT for diagnosing small pancreatic tumors (<20 mm in size) is still relatively low (around 50%).[8,9] With availability of EUS-guided

fine-needle aspiration (FNA), CT-guided percutaneous needle biopsy is currently not used as the first line method for tissue acquisition owing to the risk of needle tract seeding (discussed in detail in EUS section).[10,11] One major advantage of CT imaging is that it provides information about localized as well as distant staging of pancreatic cancer. Data have shown that CT imaging is the best available imaging modality to assess local vascular involvement and hence resectability.[12] Pancreas protocol CT scans, which include an arterial phase (scanning at 35–50 seconds after contrast injection) to allow detection of pancreatic masses and a portal phase (60–90 seconds after contrast injection) to allow for evaluation of vasculature and surrounding structures, are very important in surgical planning.

Contrast-enhanced MRI has sensitivity and accuracy approaching that of MDCT for diagnosis and staging of pancreatic cancer, but it is more costly and less readily available than MDCT. The image quality may be affected by respiratory artifact. There are some emerging data to suggest that MRI might be able to diagnose small pancreatic cancers before CT imaging owing to detection of subtle changes in pancreatic parenchyma.[13–15]

ROLE OF ENDOSCOPY IN DIAGNOSIS OF PANCREATIC CANCER

Endoscopic Ultrasound Imaging

EUS involves passage of an endoscope with an ultrasound transducer at its tip into the gastrointestinal tract. EUS provides detailed sonographic images of the gastrointestinal tract lining and the surrounding structures. The common types of echoendoscopes available are radial (sector array) and linear (convex array), although forward viewing echoendoscopes have been developed recently. The radial array echoendoscopes provide circumferential (360°) views in a plane perpendicular to the shaft of the endoscope; hence, ultrasound images are similar in orientation to those of CT scans. The linear echoendoscopes provide images in the same plane as the long axis of the endoscope, more similar to those obtained on transabdominal ultrasound imaging. Pancreatic adenocarcinoma typically appears as an irregular, hypoechoic mass in the pancreatic parenchyma with poorly defined margins on EUS. Upstream pancreatic duct dilatation and parenchymal atrophy, if present, are also more indicative of a malignant process. Malignant lymph nodes usually are round and hypoechoic with well-defined margins, and more than 1 cm in size, where as benign lymph nodes usually are triangular or oval, hypoechoic, and have poorly defined margins (**Fig. 1**). The linear array echoendoscopes provide the additional ability to perform needle sampling of the desired lesions through the working channel (**Fig. 2**). Because of this advantage,

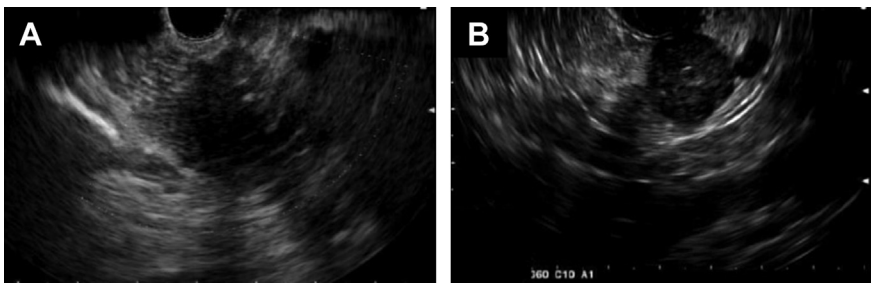

Fig. 1. Endosonographic appearance of an adenocarcinoma (*A*) and a neuroendocrine tumor (*B*) in the tail of pancreas. The adenocarcinoma has poorly defined irregular margins compared with the well-defined round contour of the neuroendocrine tumor.

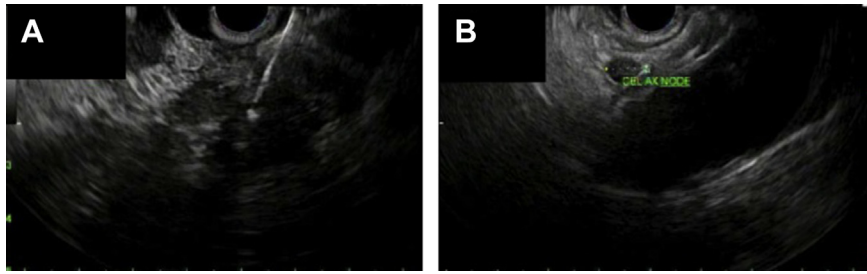

Fig. 2. Patient with newly diagnosed pancreatic head mass. (*A*) Endoscopic ultrasound imaging–guided fine-needle aspiration of the irregular, hypoechoic mass was done, cytology confirmed the diagnosis of adenocarcinoma. (*B*) A malignant appearing hypoechoic, round celiac axis lymph node with well-defined margins was also noted.

linear scopes are more commonly used for the workup of suspected pancreatic masses.

Accuracy

EUS is the most sensitive imaging modality for diagnosis of pancreatic cancer with reported sensitivity ranging from 87% to 100%.[7,16–18] Published studies have shown superiority of EUS over transabdominal ultrasound imaging, CT scanning, and MRI for diagnosis of pancreatic cancer. Although most of the data regarding superiority of EUS for pancreatic cancer diagnosis compare it with conventional CT scans, some of the published studies have shown that EUS is more sensitive than the MDCT imaging as well. Agarwal and colleagues[18] retrospectively compared EUS and pancreas protocol MDCT in 81 consecutive patients with suspected pancreatic cancer and showed that the accuracy of EUS for diagnosing pancreatic cancer was significantly higher compared with MDCT (94% vs 74%). These findings were confirmed by a prospective, observational cohort study by DeWitt and colleagues.[7] They compared EUS with MDCT in 120 patients with suspected pancreatic cancer and showed that EUS was superior to MDCT for diagnosing pancreatic masses (sensitivity 98% vs 86%; $P = .012$). In a systematic review, Dewitt and colleagues[8] reviewed 9 studies comparing CT and EUS imaging for pancreatic tumor detection and concluded that EUS was more sensitive than CT and the specificity of EUS was either superior or equivalent to that of CT imaging for diagnosis of pancreatic malignancy.

The most important predictor for survival in patients with pancreatic cancer is the stage at diagnosis and fewer than 10% of the pancreatic cancers are diagnosed at a localized stage.[1] Studies have shown that surgical resection rates and overall survival are better for smaller tumors. However, cross-sectional imaging is not very sensitive at diagnosing smaller tumors, especially those less than 2 cm in size. Published data have shown that more than 80% of pancreatic cancers were not identified on CT scan at a mean interval of 13.2 months before final diagnosis.[19] The improved sensitivity of EUS for detecting pancreatic masses is of particular significance for tumors less than 3 cm in size. One of the earlier studies comparing EUS imaging, CT scanning, and MRI for diagnosis of pancreatic cancer, showed that EUS had a sensitivity of 93% for diagnosing cancers less than 3 cm in size compared with 53% for CT and 67% for MRI.[20] More recent data are limited but also support the superiority of EUS over MDCT for detection of small pancreatic masses. In a retrospective review of 116 patients with clinical suspicion for pancreatic cancer but absence of a definite mass seen on MDCT, EUS was shown to have a sensitivity of 87% and more than 90% accuracy in diagnosing pancreatic tumors.[21]

Many patients undergo EUS to evaluate for pancreatic cancer when there is high clinical suspicion, but a definite pancreatic mass is not seen on cross-sectional imaging. It is very important in these situations for EUS to have a high negative predictive value (NPV). Studies have shown that in the setting of a normal EUS examination in patients with clinical suspicion of pancreatic malignancy, the NPV is 100% after a follow-up period of 2 years.[22,23] It should, however, be noted that this high NPV is applicable when the pancreatic parenchyma is normal, because the usefulness of EUS in the setting of parenchymal and ductal changes as seen in chronic pancreatitis is limited. The sensitivity of EUS in diagnosing pancreatic cancer in chronic pancreatitis is around 60% to 70%, but it remains superior to cross-sectional imaging.[24,25] Emerging technologies that can further improve the diagnostic capability of EUS include contrast-enhanced EUS and elastography.[26–28] Contrast-enhanced EUS is currently available in Europe but not yet in the United States.

In addition to its high sensitivity, another major advantage of EUS is the ability to perform needle sampling of the target tissue for histologic diagnosis. EUS-guided FNA of pancreatic masses was first introduced by Vilman and colleagues[29] in 1992 and is currently the first-line modality for tissue acquisition in patients with pancreatic masses. It involves the passage of a needle through the working channel of a linear-array echoendoscope to obtain samples of the pancreatic mass as well as surrounding lymph nodes, liver masses, and ascites. There are multiple commercially available needles of different sizes (19-G, 22-G, and 25-G) for sampling and multiple techniques have been studied (use of suction, number of needle passes, “fanning” technique, etc), but are beyond the scope of this article and will not be reviewed here.

The pooled sensitivity and specificity of EUS-FNA for diagnosis of pancreatic adenocarcinoma are 85% to 89% and 98% to 99%, respectively.[30,31] In addition to various technical factors, the availability of a cytopathologist on site (for rapid on site evaluation [ROSE]) has been shown to improve the diagnostic yield of EUS-FNA for diagnosis of pancreatic malignancy.[32–35] The beneficial role of ROSE for EUS-FNA of solid pancreatic masses was confirmed by a metaanalysis of 34 studies (3644 patients).[30] However, recent data from a multicenter, randomized, noninferiority trial showed that FNA of solid pancreatic masses with 7 needle passes is noninferior to ROSE but is associated with significant cost reduction.[36]

The role of EUS-FNA is clear in patients with borderline resectable or unresectable pancreatic cancer when tissue diagnosis is required for delivery of chemotherapy and/or radiation therapy. However, when a clearly resectable mass is seen in a patient with high clinical suspicion of pancreatic cancer, there is controversy regarding the need for FNA versus proceeding directly to surgery. In such circumstances, the clinician must balance the value of obtaining a definitive diagnosis and the risk associated with EUS-FNA (discussed elsewhere in this paper). In clinical practice, EUS-FNA is commonly done in patients with resectable pancreatic masses and a high clinical suspicion of cancer. Even though the sensitivity and specificity of EUS-FNA for diagnosis of pancreatic adenocarcinoma is very high, the NPV of EUS-FNA is not very high and ranges from 55% to 65%.[31] This is further decreased by the presence of parenchymal abnormalities seen in patients with chronic pancreatitis.[24,25] In patients with negative cytology but a mass seen on imaging or a high clinical suspicion for pancreatic malignancy, repeat EUS with FNA is a reasonable approach. If still negative, ERCP with brushings and/or intraductal biopsies could be considered (discussed below). EUS guided fine needle core biopsy needles are available, but are usually technically difficult to use owing to the larger needle size and stiffness of these needles. Published data have not shown superiority of fine needle core biopsy needles over the easier to use, more flexible FNA needles for diagnosis of pancreatic adenocarcinoma.[37]

Safety of endoscopic ultrasound imaging

EUS is a safe procedure with a reported overall adverse event rate of 1.1% to 3%.[38] The addition of an ultrasound transducer at the end of the endoscope leads to a rigid distal segment. The endoscopic images are also oblique-view images, making scope manipulation more difficult than with standard forward-viewing endoscopes. The reported risk of perforation with EUS is 0.06%, which is similar to that reported with standard upper endoscopy (0.03%).[38,39] A recent systematic review showed that the incidence of pain, bleeding, fever and infection after EUS-FNA of pancreatic masses were 0.38%, 0.10%, 0.08%, and 0.02%, respectively.[39] Two major possible adverse events of EUS-FNA of solid pancreatic masses include acute pancreatitis and the risk of needle tract seeding. The reported risk of acute pancreatitis after EUS-FNA of solid pancreatic masses is 0.26% to 0.85% and is much lower than what is seen after EUS-FNA of cystic neoplasms of the pancreas.[40–42] This risk can be decreased by minimizing the number of needle passes, minimizing the amount of normal appearing pancreatic parenchyma traversed with each pass, and avoiding needle insertion through the pancreatic duct unless it is absolutely needed. Needle tract seeding is a consideration with biopsy of pancreatic masses, but most of the published data are limited to case reports.[43–45] The reported incidence of needle tract seeding after EUS-FNA is much lower when compared with percutaneous CT or transabdominal ultrasound–guided sampling (2.2% vs 16.3%).[46,47] The majority of the reported cases of EUS-FNA needle tract seeding are for body and tail cancers, which were sampled through the transgastric approach. This is less of an issue for resectable pancreatic head tumors sampled transduodenally, because the site of needle puncture is included in the resection margins of a pancreatoduodenectomy. When available, EUS-FNA is the preferred method for tissue diagnosis of pancreatic masses.

Endoscopic Retrograde Cholangiopancreatography

Owing to the risk of potential adverse effects with ERCP and availability of MR cholangiopancreatography, ERCP rarely has a primary diagnostic role in the management of pancreatic masses. It is mainly used for palliation to relieve biliary obstruction. Pancreatic head tumors commonly present with obstructive jaundice owing to bile duct strictures. The fluoroscopic stricture morphology can give some clues about the etiology of the obstruction, but morphology alone is unreliable for diagnostic purposes. Long, irregular strictures with an abrupt cutoff and shelflike ends are more suggestive of a malignant process compared with smooth tapering strictures, which usually represent a benign inflammatory process, as commonly seen in patients with chronic pancreatitis (**Fig. 3**A). The presence of a double-duct sign (stricture in both bile duct and pancreatic duct with upstream dilatation) is also suggestive of a pancreatic head tumor. In these cases, tissue samples can be obtained either by cytology brushings, intraductal biopsies and cytology from removed stents. ERCP-guided brushings and biopsies have a high specificity for diagnosis of malignancy (approaching 95%), but the sensitivity is very low (23%–56% for biliary brushings and 33%–65% for fluoroscopic biopsies) leading to a low NPV of 58%.[48–51] Combining both brushings and intraductal biopsies can increase the diagnostic yield to 60% to 70%, but still is suboptimal compared with EUS.[52] There are limited published data comparing EUS-FNA with ERCP cytology for diagnosis of solid pancreatic masses, but a recent study showed the superiority of EUS-FNA compared with ERCP alone. In this retrospective analysis of 234 patients with pancreatic neoplasms, it was shown that the sensitivity, specificity, and accuracy for diagnosis of pancreatic

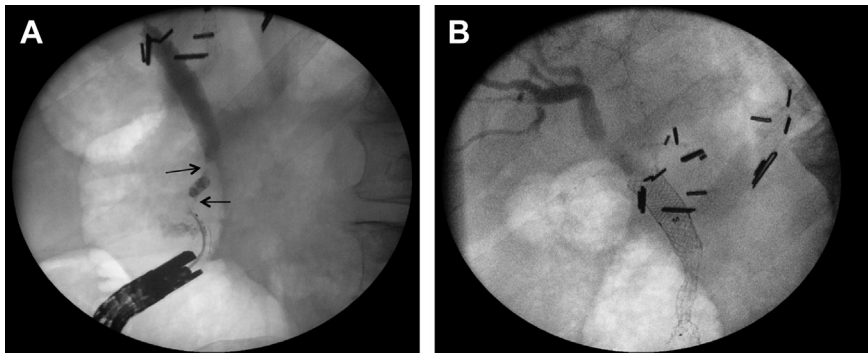

Fig. 3. Patient with metastatic pancreatic head cancer and obstructive jaundice. (*A*) Endoscopic retrograde cholangiopancreatography showed a severe, malignant distal common bile duct stricture (*arrows*). (*B*) An uncovered biliary metal stent was placed with improvement of jaundice followed by initiation of palliative therapy.

neoplasms were 98.9%, 93.3%, and 98.1%, respectively, for EUS-FNA compared with 72.1%, 60%, and 71.4%, respectively, for ERCP alone. The overall adverse events were also significant lower for EUS-FNA compared with ERCP alone (1.9% vs 6.6%).[53]

The main role of ERCP in patients with pancreatic cancer is palliative and involves relief of biliary obstruction. Transpapillary biliary drainage was first introduced in 1980 when only plastic stents were available.[54] These stents range in diameter from 7-Fr to a maximum of 11.5-Fr. These plastic stents have a short average patency of around 3 to 4 months and require scheduled stent exchange every 3 months.[55] Self-expanding uncovered metal biliary stents were developed in 1990s to overcome these issues.[56] The commonly available biliary metal stents have a diameter of 8 or 10 mm. Published data have shown that self-expanding biliary metal stents have a longer patency, have a lower incidence of occlusion and cholangitis, are associated with a shorter duration of hospital stay, and are more cost effective, especially in patients with an expected of survival more than 3 to 6 months without any difference in overall short-term mortality.[55,57–59] The average patency of metal biliary stents approaches 1 year compared with 3 to 4 months for the plastic bile duct stents.[60] The superiority and cost effectiveness of metal stents have been confirmed by metaanalyses as well.[61,62] In a recent metaanalysis comparing use of plastic versus metal stents for inoperable malignant biliary obstruction in 1133 patients (13 studies), it was shown that self-expanding metal stents were associated with lower stent dysfunction (21.6% vs 46.8%; $P<.00001$), lesser need for repeat interventions (21.6% vs 56.6%; $P<.00001$), longer stent patency (250 vs 124 days; $P<.0001$), and longer mean survival (182 vs 150 days; $P<.0001$). However, there was no difference in cost per patient, although a trend toward lower cost was seen in metal stents (€4193.98 vs €4728.65; $P<.0985$).[62]

These data suggest that self-expanding metal stents are superior to plastic stents in patients with unresectable or borderline resectable disease who need neoadjuvant therapy before reevaluation for surgery. However, the debate of metal versus plastic stents is still not resolved in patients with clinically resectable disease who are to undergo surgical resection within a short period of time. In patients with radiologic and endosonographic evidence of resectable disease and biliary obstruction, directly proceeding to surgery without endoscopic biliary drainage is

usually the preferred approach. Some investigators propose that preoperative biliary drainage can lead to improved tissue healing.[63,64] Other data suggest that preoperative biliary drainage might increase the risk of complications.[65] Biliary drainage, however, is needed for symptom relief when evaluation for surgery is ongoing, especially in patients with cholangitis or intractable pruritus. There were initial concerns that metal stents could make surgical bile duct anastomosis challenging at the time of resection, but there are no published data to support this claim. Studies have shown that as long as at least 2 cm of nonstrictured common hepatic duct proximal to the stent is available for anastomosis, the surgical outcomes are unaffected.[66,67] Efforts should be made to use the shortest metal stent possible that traverse the stricture. The proximal end of the metal stent should be placed below the line of potential surgical transection of the bile duct leaving adequate length of native, nonstrictured bile duct for anastomosis. It is our practice to place plastic stents in patients who require biliary decompression and are likely to undergo surgery in the near future or when the diagnosis of malignancy has not been confirmed. In patients with metastatic/inoperable disease or borderline resectable disease and who are to receive neoadjuvant therapy, we place self-expanding metal biliary stents (**Fig. 3**B).

Both covered and uncovered metal stents are available. The uncovered stents have a mesh design to allow embedding in the bile duct wall, but it also exposes them to risk of tumor ingrowth and eventual obstruction. The covered metal stents have the mesh covered by silicone, polyurethane, or polytetrafluoroethylene to prevent tissue ingrowth, but this puts them at increased risk of stent migration. There were initial concerns about increased risk of cholecystitis with covered stents owing to blockage of cystic duct drainage, but the data are not conclusive.[68] Although tumor ingrowth is not an issue for covered metal stents, this advantage is offset by the higher incidence of stent migration. In a randomized, nonblinded, multicenter study comparing covered versus uncovered metal stents in patients with malignant distal biliary obstruction, it was shown that there were no differences in stent patency, patient survival, or complications (including cholecystitis) in the 2 groups. Covered stents were associated with a higher migration rate whereas uncovered stents had a higher incidence of tumor ingrowth.[69] These findings have also been confirmed by other groups.[70,71] A metaanalysis involving 1078 patients with malignant biliary obstruction also showed that covered metal biliary stents had higher migration rates compared with uncovered stents without a significant difference in patency.[68] Based on these data, uncovered stents are used more commonly for malignant obstruction and covered stents are usually reserved for benign biliary obstruction.

PRETREATMENT STAGING OF PANCREATIC CANCER

Accurate staging of pancreatic adenocarcinoma is very important to determine operative resectability. The staging includes assessment of local spread and vascular involvement (T stage), nodal involvement (N stage), and metastatic involvement (M stage). The role of EUS in staging pancreatic malignancy is not as well-established; its role in diagnosis and most surgeons rely more on cross-sectional imaging than EUS for determining resectability. MDCT and EUS play a complementary role in the staging of pancreatic cancers and the data about superiority of 1 modality over the other is not conclusive. Although earlier studies showed superiority of EUS over conventional CT for local staging, vascular invasion and nodal staging, subsequent studies have shown that MDCT is either equivalent or superior to EUS for

T and N staging.[7,72–74] In a recent metaanalysis involving 12 studies comparing EUS and CT for staging of pancreatic cancer, EUS was found to have higher sensitivity for nodal staging (58% vs 24%) and vascular involvement (86% vs 58%).[75] The sensitivity for determining resectability was comparable between the 2 modalities (87% vs 90%). There are some data to suggest that CT and MRI can lead to overestimating the T stage compared with EUS and hence exclude potentially resectable tumors from going to the operating room.[74] It should be noted that EUS is user dependent and there are data to indicate that the accuracy of EUS for staging improves with operator experience.[72]

SUMMARY

Endoscopy plays an important role in the diagnosis and management of pancreatic cancer. EUS is the most sensitive modality for diagnosis of pancreatic cancers and should be the preferred modality for obtaining tissue diagnosis with FNA. Both CT and EUS play complementary roles in pancreatic cancer staging and both are comparable in terms of determining resectability. The role of ERCP in the workup of pancreatic cancer is limited to palliative biliary drainage in majority of the cases and uncovered self-expanding metal stents are preferred for biliary drainage in patients who have unresectable disease or need neoadjuvant therapy. The American Society of Gastrointestinal Endoscopy Standards of Practice Committee proposed an algorithm for patients with suspected pancreatic adenocarcinoma, which highlights the role of various diagnostic modalities (Fig. 4).[38]

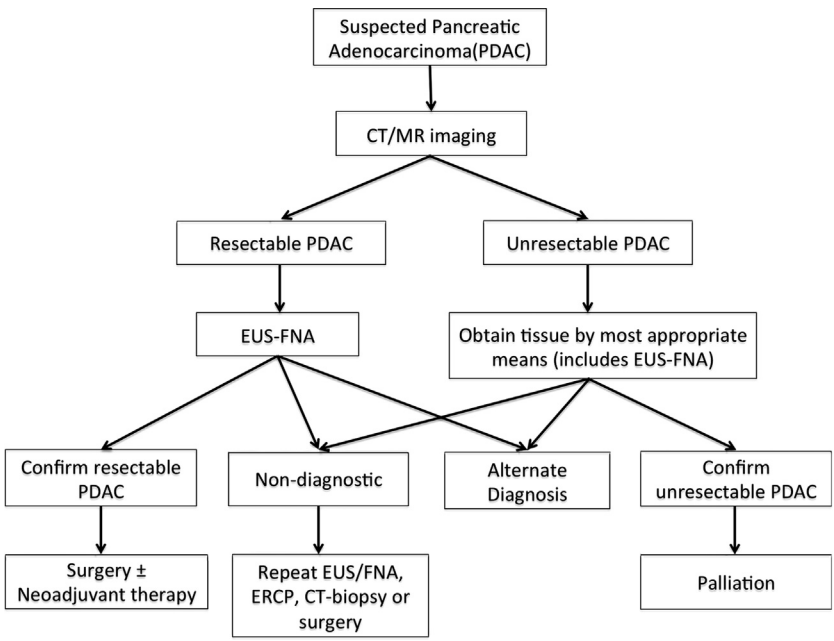

Fig. 4. Proposed algorithm for diagnosis of solid pancreatic neoplasms. CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; EUS-FNA, endoscopic ultrasound imaging–guided fine-needle aspiration. (*Adapted from* ASGE Standards of Practice Committee, Eloubeidi MA, Decker GA, et al. The role of endoscopy in the evaluation and management of patients with solid pancreatic neoplasia. Gastrointest Endosc 2016;83(1):17–28; with permission.)

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