EXPERT REVIEWS

Role of endoscopic ultrasound in pancreatic cancer

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Pancreatic cancer (PC) is the fourth most common cause of cancer deaths in Western societies. It is an aggressive tumor with an overall 5-year survival rate of less than 5%. Surgical resection offers the only possibility of cure and long-term survival for patients suffering from PC; however, unfortunately, fewer than 20% of patients suffering from PC have disease that is amendable to surgical resection. Therefore, it is important to accurately diagnose and stage these patients to enable optimal treatment of their disease. The imaging modalities involved in the diagnosis and staging of PC include multidetector CT scanning, endoscopic ultrasound (EUS), endoscopic retrograde cholangiopancreaticography and MRI. The roles and relative importance of these imaging modalities have changed over the last few decades and continue to change owing to the rapid technological advances in medical imaging, but these investigations continue to be complementary. EUS was first introduced in the mid-1980s in Japan and Germany and has quickly gained acceptance. Its widespread use in the last decade has revolutionized the management of pancreatic disease as it simultaneously provides primary diagnostic and staging information, as well as enabling tissue biopsy. This article discusses the potential benefits and drawbacks of EUS in the primary diagnosis, staging and assessment of resectability, and EUS-guided fine-needle aspiration in PC. Difficult diagnostic scenarios and pitfalls are also discussed. A suggested management algorithm for patients with suspected PC is also presented.

Keywords: endoscopic ultrasound • fine-needle aspiration biopsy • management algorithm • pancreatic cancer • pancreatic surgery • pancreatology

Endoscopic ultrasound (EUS) was first introduced in the mid-1980s in Japan [1] and Germany [2] for better visualization of the pancreas. It is a combination of a small, high-frequency ultrasound transducer on the tip of a video endoscope, which allows close contact with the target organ so that high-resolution images can be obtained. The two main systems used around the world are the radial-array and the linear-array systems. The radial echoendoscope produces a 360° cross-sectional image that is perpendicular to the long axis of the scope, whereas the linear echoendoscope produces a view that is parallel to the long axis. With the introduction of the linear probe in the 1990s, the indications for EUS have expanded owing to the advantage of real-time visualization of the needle along its length, taking biopsies from the lesion of interest, making possible EUS-guided fine-needle aspiration (FNA) of fluid and tissue, as well as therapeutic procedures [3].

The widespread use of EUS in the last decade has significantly impacted on the management of pancreatic disease, as it simultaneously provides primary diagnostic, biopsy and staging information. In this article, we discuss the role of EUS in the diagnosis and management of pancreatic cancer (PC) and its relative advantages and disadvantages compared with other imaging modalities. Emerging techniques and the potential roles of EUS in pancreatic disease are also discussed.

Pancreatic cancer

Overview

Pancreatic cancer is the third most common gastrointestinal cancer and the fourth most common cause of cancer deaths in Western societies. There were an estimated 37,680 new cases and 34,290 deaths from PC in the USA in 2008, with a death–incidence ratio that approached one [4]. It is an aggressive tumor with an overall 5-year survival rate of less than 5%, one of the lowest among all types of cancer. Surgical resection remains the only possibility of a cure, with chemotherapy and radiotherapy offering only a modest survival benefit. Patients who undergo complete surgical resection for

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localized, nonmetastatic adenocarcinoma of the pancreas have a 5-year survival rate of approximately 20–25% and a median survival of 12–22 months [5]. Unfortunately, fewer than 20% of patients with PC have disease that is amendable to surgical resection at the time of presentation, as patients often present at an advanced stage with widespread metastatic or locally advanced disease [6].

The aggressive nature of the disease makes it imperative that patients with PC are diagnosed and staged accurately and in a timely manner. This enables stage-specific treatment decisions to be implemented in order to optimize not only survival but also quality of life. Therefore, there are two key issues in the diagnosis and management of suspicious pancreatic masses. The first is the accurate diagnosis, that is, the differentiation between PC and other conditions. The second is the accurate staging and assessment of resectability of the cancer once the diagnosis is established. This ensures that only patients who will benefit from surgical treatment are subjected to the morbidity and potential mortality associated with surgical resection. Both of these may be achieved with a combination of the available state-of-the-art imaging modalities.

Diagnosis, staging & assessment of resectability of PC

The imaging modalities involved in the diagnosis, staging and management of PC include computed tomography (CT), MRI, endoscopic retrograde cholangiopancreatography (ERCP), EUS and PET. The diagnosis can potentially be made by any one or a combination of these modalities. The roles and relative importance of these imaging modalities have changed over the last few decades and continue to change with rapid technological advancement in medical imaging.

Endoscopic ultrasound & endoscopic ultrasound-guided fine-needle aspiration

Diagnosis

The introduction of EUS has changed the diagnostic paradigm for PC, with many series demonstrating its superiority over CT scanning and MRI in the diagnosis and staging of the disease. However, it may not be widely available and is relatively invasive and operator dependent. It is reported to have a sensitivity of 91–100% for the diagnosis of PC, with a positive predictive value (PPV) of 92–98% and a negative predictive value (NPV) of 90–100%; however, the specificity of EUS alone is disappointing [7–12]. This has been rectified by the addition of EUS-guided FNA (EUS-FNA), which is reported to increase specificity to 94–100% [8,10,11,13,14]. Eloubeidi *et al.* prospectively evaluated a single-institution experience of 547 patients who underwent EUS-FNA [14]. The authors reported a sensitivity of 95%, a specificity of 92%, a PPV of 98% and a NPV of 80%, with an overall accuracy of 94.1% (95% CI: 92.0–94) for EUS-FNA on solid pancreatic masses. Mild, self-limiting pancreatitis occurred in less than 1% of patients. The authors concluded EUS-FNA to be safe and accurate, and to facilitate pre-operative patient counseling and avoidance of surgical biopsy in patients with inoperable disease.

Staging & assessment of resectability

Endoscopic ultrasound plays a key role in the staging and assessment of resectability of PC. Owing to the close proximity of the ultrasound probe to the pancreas, EUS is highly accurate in the assessment of the pancreas itself (T-staging) and structures adjacent to the pancreas (N-staging and local resectability); however, it performs less well in assessing distant disease (M-staging), owing to the limited distance of ultrasound penetration. A recent meta-analysis on the diagnostic accuracy of EUS for vascular invasion in PC pooled 1308 patients from 29 studies and showed a sensitivity of 73%, a specificity of 90%, a positive likelihood ratio of 9.1, a negative likelihood ratio of 0.3 and a diagnostic odds ratio of 40 when a positive study was compared with a negative one [15]. Following the meta-analysis, other studies have shown that EUS can be highly accurate in predicting R0 resections [16–18].

EUS-guided FNA

A distinct advantage of EUS is its ability to obtain tissue via FNA. EUS-FNA was first reported in 1992 [19], and it was developed to enhance the diagnostic capability of EUS by providing diagnostic material (Figure 1). As previously discussed, EUS-FNA has significantly improved the performance of EUS alone, particularly the specificity of the technique. EUS-guided biopsy is superior to percutaneous biopsy for the investigation of many intra-abdominal malignancies, as it has a lower risk of tumor seeding both along the needle tract and intraperitoneally. However, tumor seeding secondary to EUS-FNA has been reported [20]. Apart from biopsy of the primary tumor, it also has the ability to biopsy lymph nodes, liver lesions and ascitic fluid. For pancreatic head lesions, the possibility of seeding is eliminated because the needle track is included in the resection specimen [21]. EUS-FNA should only be routinely used for pancreatic head and neck lesions. For body and tail lesions, where the needle track is not resected, the risks and benefits of the procedure should be assessed on an individual basis.

There are several advantages in establishing a histological diagnosis before the final treatment plan is made. As previously noted, unusual non-neoplastic conditions and lymphoma may mimic PC but can be diagnosed if appropriate tissue can be obtained. This may alter the choice of treatment, particularly in the elderly and in patients with high risks for surgery. Suspicious second-tier lymph nodes can also be biopsied since when these are involved patients should be considered as having metastatic disease and to be incurable. Based on the tissue diagnosis, patients with borderline resectable or locally advanced tumors can be given neoadjuvant chemoradiotherapy. Tissue diagnosis must be kept within the clinical context and a negative biopsy should not preclude pancreatic resection if the clinical suspicion remains high. Most high-volume pancreatic centers worldwide accept and report benign Whipple resection rates of up to 10% for suspicious imaging [22].

EUS screening & early PC detection

One of the most challenging aspects in the managements of PC is screening and early detection. The treatment of precursor lesions has been demonstrated to improve the overall outcomes in other cancers, such as that of the colon. Unfortunately, there are no

serum biomarkers that are highly sensitive or specific for screening purposes at this time. Moreover, population-based screening for PC is not likely to be feasible owing to the associated costs and morbidity. However, if high-risk groups can be defined to enrich the screened population, then EUS can potentially be used as a very effective screening tool. In 2003, the consensus reached at The Fourth International Symposium of Inherited Diseases of the Pancreas was that patients with a greater than tenfold increased risk for developing PC may benefit from screening [23]. This subgroup includes familial multiorgan cancer syndromes (e.g., Peutz–Jeghers syndrome, familial atypical multiple mole melanoma and *BRCA2* mutations with at least one case of PC within second-degree relatives), genetically driven chronic disease (e.g., hereditary pancreatitis) and familial PC kindreds (i.e., three or more first-degree relatives; or, three cases among first-, second- and third-degree relatives, with at least one being a first-degree relative) [23–25]. The use of EUS has been recommended as a screening tool by centers treating familial cancers in the USA [26–29]. However, EUS may not be the best screening test for patients with hereditary pancreatitis owing to the difficulty in searching for small tumors in parenchyma of patients with chronic pancreatitis.

Therapeutic procedures

With the advancement of technology in the echoendoscopes and the various accompanying instruments, EUS is now playing a role in therapeutic and interventional endoscopy.

Celiac plexus neurolysis/block

One of the more common EUS therapeutic procedures is celiac plexus neurolysis for the treatment of pain from unresectable PC. A recent meta-analysis demonstrated celiac plexus neurolysis to be associated with improved pain control and to reduce narcotic usage and constipation compared with standard treatment [30]. However, there was no improvement in survival, as suggested by some of the earlier studies [31]. The EUS-guided transgastric anterior approach has been demonstrated to be a safe alternative to the posterior approach, with possibly fewer complications as it does not need to traverse the pleural space and causes fewer neurological complications [32]. Other short-term complications include transient diarrhea and hypotension due to unopposed parasympathetic activity. Levy *et al.* reported the Mayo Clinic experience with EUS-guided celiac plexus neurolysis [33]. Cancer patients reported pain relief in 16 out of 17 cases (94%) when alcohol was injected, but not when steroid was used (zero out of one patient; p = 0.004). It has also been suggested that an EUS-guided transgastric approach may result in a better analgesic effect as the celiac ganglia are directly visualized and targeted by EUS, but not by the traditional approach [33].

EUS-guided fine-needle injection antitumor therapy

EUS has evolved from FNA to fine-needle injection of antitumoral agents. The most recent advance in the area of PC is the use of TNFerade [34]. TNFerade is a replication-deficient adenovector containing human TNF-α cDNA that is regulated by a radiation-inducible promoter, *Egr-1* [35]. The delivery of TNFerade into locally advanced PC using EUS fine-needle injection or a percutaneous approach were compared [36]. It was found that TNFerade was generally well tolerated, with encouraging indications of activity using both routes except for injection site pain (33 vs 0% in favor of EUS; p = 0.01). Its use in locally advanced PC is currently being evaluated in the Phase III Pancreatic Cancer Clinical Trial with TNFerade (PACT) trial [37].

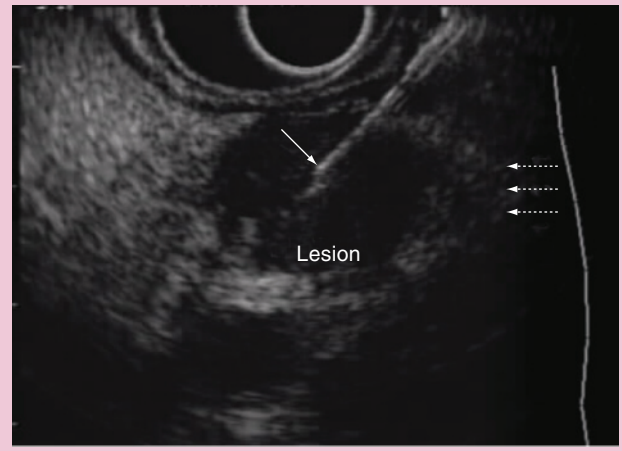

Figure 1. Endoscopic ultrasound image showing fine-needle aspiration biopsy under endoscopic ultrasound guidance using a linear echoendoscope.

Another application of EUS is in the EUS-guided placement of fiducial markers for image-guided radiation therapy (Cyberknife™; Accuray Inc., CA, USA) in the treatment of unresectable PC. The markers were traditionally being placed percutaneously, which has a similar complication profile to percutaneous organ biopsy [38]. However, placement of the fiducial markers under EUS guidance is now feasible, safe and effective [39].

Procedure-related complications

Endoscopic ultrasound is more invasive than CT, MRI or PET and is usually performed under conscious sedation. The major morbidity rate is approximately 0.05%, which is similar to diagnostic esophagogastroduodenoscopy. There is a slightly higher rate of duodenal perforation, especially if it is stenosed by PC [40]. When EUS-FNA is employed, the overall complication rate increases to 0.5–3%, which is similar to that of CT or EUS-guided FNA [41]. The major complications reported are pancreatitis and bleeding [42,43]. Eloubeidi *et al.* reported an institutional experience of 355 consecutive patients who underwent US-FNA and reported major complications in nine patients (2.5%) [44]. Three patients developed acute pancreatitis (no sequelae), three patients were admitted for management of severe pain (no sequelae), two patients were admitted for fever (one recovered after treatment with intravenous antibiotics and the other patient required surgical debridement of pancreatic necrosis) and one patient required the use of reversal medications for oversedation.

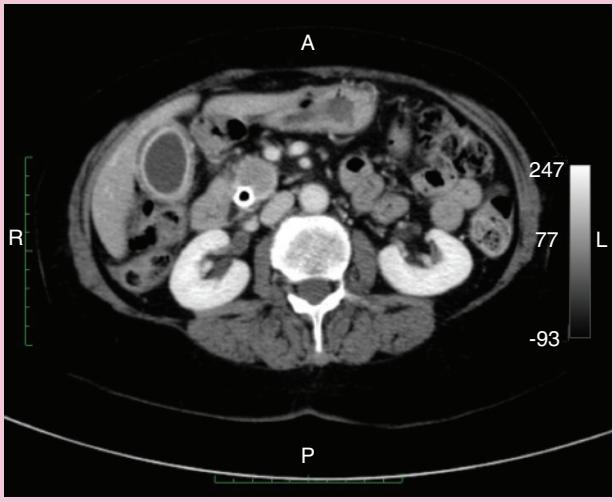

Figure 2. Multidetector CT-scan image (portal venous phase) of a 77-year-old female with a 2.5-cm pancreatic cancer tumor in the uncinate process. Note the removable metal stent *in situ* to relieve biliary obstruction.

Computed tomography

Diagnosis

For many years, multidetector CT scanning has remained the imaging modality of choice for the diagnosis of PC (Figure 2). It is widely available, noninvasive, operator independent and able to assess responses to neoadjuvant chemo- and radio-therapy when restaging prior to surgery. The only drawbacks are exposure to radiation and a remote chance of an allergic reaction to the intravenous contrast agent. The sensitivity, specificity, PPV and NPV vary widely in the literature. The newer multidetector CT scanners, which use a multiphasic pancreatic protocol, out-perform the older helical CT scanners. In the primary diagnosis of PC, sensitivity ranged from 68 to 97%, specificity ranged from 50 to 78%, PPV ranged from 88 to 100%, NPV ranged from 29 to 82% and overall accuracy ranged from 67 to 94% [7,9–12,45,46].

Staging & assessment of resectability

Assessment of staging and resectability of PC by CT has been intensely studied and several scoring systems have been proposed for predicting resectability and unresectability [7,9,17,18,45–51]. However, the definition of resectability may vary between institutions. The studies that specifically examined vascular invasion reported sensitivities of 45–67%, specificities of 94–100%, PPVs of 89–100%, NPVs of 80–88% and an overall accuracy of 83–90% [7,46,48]. The overall reported PPV for unresectability in CT is high (89–100%), although the PPV for resectability is low (45–79%). The diagnostic criteria favor specificity rather than sensitivity to avoid denying surgery to potentially resectable patients [52].

Computed tomography has limited accuracy in nodal staging because size has been used as the primary criterion (>1 cm in short axis). The reported sensitivity, specificity, PPV, NPV and accuracy are 33–37, 79–92, 56–75, 64–67 and 47–68%, respectively [7,9,46]. The sensitivity of CT in detecting metastatic disease is between 55 and 87%, and the sensitivity decreases as the size decreases [46,53,54]. CT performs poorly in the detection of peritoneal disease; therefore, diagnostic laparoscopy should be used if peritoneal disease is suspected.

Magnetic resonance imaging

Diagnosis

The role of MRI in the diagnosis of PC is still widely debated. With its limited availability in many parts of the world, it has never surpassed CT as the imaging modality of choice in diagnosis. Other drawbacks and limitations include cost, duration of the procedure and unfavorable patient characteristics, such as obesity and claustrophobia. However, MRI is noninvasive and there is no radiation or iodinated contrast involved. Moreover, MRI does not involve the procedure-related morbidity and mortality associated with ERCP. Therefore, MR cholangiopancreaticography is replacing ERCP as the diagnostic modality of choice for pathology in the biliary tree or the pancreatic duct. Schima *et al.* reported mangafodipir trisodium-enhanced MRI as having a sensitivity of 100% for the detection of discrete lesions, and the ability to differentiate cancer from noncancer with a sensitivity of 100%, PPV of 90% and NPV of 100% [45]. The overall diagnostic accuracy ranges from 62 to 91% [46,55].

Staging & assessment of resectability

The MRI approach has also been assessed for its ability to detect vascular invasion to predict PC resectability. MRI with angiography appears to be more accurate than MRI alone, with a reported sensitivity of 56–90%, specificity of 84–100%, PPV of 72–100%, NPV of 74–88% and accuracy of 74–90% [45,46,48]. The overall accuracy of detection of distant metastasis is 83–94% [46,54]. However, similarly to CT, MRI lacks diagnostic accuracy in peritoneal disease.

PET & PET/CT

Diagnosis

The use of fluorodeoxyglucose-PET as a primary diagnostic modality for PC is still uncertain and continues to be an area of current research. A pooled study of 387 patients in 2001 reported a sensitivity of 94% and a specificity of 90% [56]. A meta-analysis of 17 studies in 2004 assessing the detection of PC using fluorodeoxyglucose-PET showed the sensitivity and specificity of 92 and 68%, respectively, after positive CT, 73 and 86%, respectively, after negative CT and 100 and 68%, respectively, after indeterminate CT [57]. Therefore, it was concluded that its usefulness varies with pretest probability, results of the CT and the clinician's testing thresholds. More recent PET/CT studies showed a sensitivity of 89% and specificity of 64–88% [58–60]. The usefulness and value of PET/CT as an independent diagnostic tools still needs to be further evaluated, as a positive result only reaffirms clinical suspicion of cancer and a negative result does not exempt the patients from a more invasive diagnostic modality to obtain a tissue diagnosis due to the relatively poor specificity and NPV of PET.

Staging & assessment of resectability

Fluorodeoxyglucose-PET has been shown to be accurate and cost effective in the detection of metastatic disease in other cancers; however, its role in PC has yet to be defined. Studies have reported it to be generally accurate in detecting distant metastatic disease and more accurate than CT in detecting hepatic metastases [61,62]. With the fusion of CT, PET/CT provides more accurate anatomical information. Studies on PET/CT have demonstrated a change to the management plan due to detection of metastatic disease in 11–16% of patients [59,60]. A recent study has suggested it could be a one-stop shop for assessing resectability [63].

Endoscopic retrograde cholangiopancreatography

The ERCP method was once the primary diagnostic procedure in the evaluation of pancreatic neoplasms until the advent of high-resolution multidetector CT and MRI. However, its usefulness has become limited with the improvements in noninvasive imaging modalities, which avoid the morbidity and mortality associated with ERCP. It does, however, still have diagnostic utility in cases of periampullary tumors and intraductal pancreatic mucinous neoplasms. Newer techniques, such as the Spyglass™ Direct Visualization System and mother–daughter cholangiopancreatoscope systems [64,65], may improve diagnosis of small pancreatic ductal tumors and cholangiocarcinomas. The primary role of ERCP is now therapeutic, for example in the placement of biliary and pancreatic stents on a temporary or permanent basis.

Comparison

A systematic review of 11 studies of 678 patients by Dewitt *et al.* in 2006 found that of the nine studies that assessed tumor detection, all concluded that the sensitivity of EUS was superior to CT. Four out of five studies that assessed tumor-staging accuracy and five of the eight that assessed nodal-staging accuracy concluded that EUS was superior to CT. Among the four studies that assessed resectability, two showed no difference between EUS and CT and one favored each modality [47].

Since this meta-analysis, The MD Anderson Cancer Center reported their experience in the retrospective review of CT and EUS images in 117 patients with suspected PC [11]. They found the accuracy in the diagnosis of PC was comparable between the two modalities (85–94% for CT and 91% for EUS). Interestingly, when EUS was used in a follow-up setting, its sensitivity increased to 99% compared with CT (89–97%). More importantly, EUS was more sensitive than CT in detecting lesions of smaller than 2 cm in diameter (96 vs 89%).

Mansfield *et al.* compared CT and EUS with operative and histological findings for 84 patients in 2008 and demonstrated no significant difference in the diagnosis and agreement between the two modalities (CT sensitivity and specificity of 97 and 87%, respectively, and EUS of 95 and 52%, respectively) [66]. CT was superior in the assessment of venous invasion, but there was no difference in the assessment of resectability. The authors concluded that routine EUS should be reserved for those patients with borderline resectable disease on CT.

Difficult diagnostic scenarios & pitfalls

Small tumors & imaging negative but with high clinical suspicion

The diagnostic challenges in PC remain in early diagnosis and the diagnosis of small tumors, as tumor size is a significant prognostic variable and small tumors (<1 cm diameter) have a favorable 5-year survival rate [67,68]. Several studies have focused on small tumor detection rates. EUS has been reported to be more sensitive than CT in detecting small lesions. In the MD Anderson Cancer Center study, 27 patients had tumors smaller than 2 cm in diameter [11]. EUS had a detection sensitivity of 96% compared with 70–93% for CT. In an earlier study, Schwarz *et al.* compared CT, EUS, MRI and PET [69]. In patients with a tumor size smaller than 2 cm in diameter, EUS had the highest detection sensitivity of 100%, compared with 63% for CT.

Endoscopic ultrasound has been consistently reported to have a high NPV; therefore, it is very useful in excluding malignancies in patients with a high clinical suspicion of cancer but whose tumor is not detectable using other imaging modalities. However, in a recent publication reporting the results of the Hamburg–Eppendorf study, 412 patients with suspected PC were followed-up for a median of 14 months [70]. There were 253 patients with a 'normal' EUS appearance and no discrete lesions identified (i.e., normal or chronic pancreatitis only) and 159 patients with lesions but negative FNA results. No patients from the normal-appearance group developed cancer (zero out of 122 patients), but 1.5% of the chronic pancreatitis group (two out of 131 patients) developed cancer. In the group where the mass was seen but the FNA was negative, no patients from the cystic lesion group developed cancer (zero out of 50 patients), but 18.4% of the circumscribed solid lesion group (nine out of 49 patients), 20% of the noncircumscribed solid lesion group (five out of 25 patients) and 8.6% of the lobulated solid-lesion group of patients (three out of 35 patients) developed cancer. In this study, the sensitivity, specificity, PPV and NPV of EUS in excluding PC were 90.5, 100, 100 and 95.4%, respectively. However, although PC can be reliably excluded in patients with a normal EUS, in the subset of patients with abnormal findings, such as chronic pancreatitis and a 'benign'-appearing solid lesion despite a negative FNA result, there is still a significant risk of cancer. Therefore, these patients should be followed-up closely.

CT/MRI: enlarged head of pancreas, dilated pancreatic duct with/without dilated common bile duct

Agarwal *et al.* reported the outcome of a cohort of 110 patients with secondary signs that were only visible on CT and/or MRI (e.g., enlarged head of pancreas, and dilated pancreatic duct with or without dilated common bile duct), but without evidence of identifiable focal mass lesions or obstructive jaundice [71]. EUS was performed together with FNA biopsy if a focal pancreatic lesion was identified. Patients were followed-up with cytology and surgical pathology for a median follow-up period of 16 months. In the enlarged head of pancreas group, four out of 67 patients (6%) were diagnosed with pancreatic neoplasm (two with adenocarcinoma, one with neuroendocrine tumor and one with pancreatic metastasis). In the dilated pancreatic duct with or without common

bile duct dilatation group, five out of 43 patients (11.5%) were diagnosed with pancreatic adenocarcinoma (one false-negative diagnosis that was detected on follow-up). EUS with or without FNA had an overall accuracy of 99%. This study suggested that pancreatic neoplasms are present in a clinically significant number of patients with only radiological 'secondary signs', and that EUS is a highly accurate imaging modality in this group of patients.

Signs that may reduce the accuracy of EUS & require repeat EUS/FNA

The retrospective No Endosonographic Detection of Tumor (NEST) study was carried out to identify factors that may have contributed to the failure to detect a pancreatic neoplasm during EUS by nine experienced endosonographers [72]. Out of the 20 missed cases, 12 patients had EUS features of chronic pancreatitis, three had diffusely infiltrating cancer, two had a prominent ventral/dorsal split and one had a recent episode of acute pancreatitis. Five patients underwent repeat EUS after 2–3 months owing to clinical suspicion, and all had a pancreatic mass detected. In this cohort of patients, 17 had adenocarcinoma, one had an intraductal pancreatic mucinous neoplasm, one had a villous tumor with severe dysplasia of the pancreatic duct on histology or cytology, and one patient succumbed to their disease without a tissue diagnosis. Therefore, if there is high clinical suspicion of PC, despite EUS and other imaging methods being negative, patients should either have repeat EUS or undergo surgical exploration. The benefit and value of repeat EUS-FNA has also been shown in patients with initial negative FNA but with continuing clinical suspicion of PC [73].

Endoscopic biliary stents may reduce the accuracy of EUS

There have been conflicting results in the literature with regard to the accuracy of EUS and EUS-FNA in patients with endoscopic biliary stents *in situ*. Fusaroli *et al.* reported the accuracy of EUS staging for cancer of the pancreatic head in a cohort of 65 patients (19 with stents and 46 without) [74]. EUS T- and N-staging was compared with surgical staging. Using a multivariate model, they found that patients with stents were more likely to be incorrectly staged for both T- (odds ratio: 6.55; 95% CI: 1.69–25.49) and N-staging (odds ratio: 3.71; 95% CI: 1.11–12.45) than patients without a stent. Therefore, the authors concluded that EUS should be performed prior to stent placement. A more recent study also reported that the presence of a stent contributed to the inaccuracy of EUS in predicting R0 resection or resectability [17]. However, this was not consistent with two other recent studies, which reported similar local staging with or without endoscopic biliary stents [11,75]. Further studies are required to address this issue.

It appears that not only the accuracy of EUS may have been affected by the presence of stents; the accuracy of EUS-FNA has also been influenced. Agarwal *et al.* reported a statistically significant difference in the NPV between the two groups of patients with and without stents (22 vs 89%) [10]. This may have been secondary to the decompression of the biliary tree with a stent, making the transition of a dilated to nondilated duct more difficult to visualize. Therefore, a negative EUS-FNA cannot rule out PC in a patient with high clinical suspicion with an endoscopic biliary stent *in situ*.

Restaging after neoadjuvant therapy

A current area of research is restaging after neoadjuvant therapy in the treatment of PC. Bettini *et al.* reported restaging of 45 patients with PC after neoadjuvant chemoradiation using EUS and CT [76]. Out of the 30 patients who did not develop distant metastasis, only 12 (40%) of the patients were correctly staged when compared with surgical pathology. In total, 13 patients (43.3%) were overstaged for tumor size, and 13 patients (43.3%) were suspected to have vascular invasion that was not present at the time of surgery and pathologic examination. EUS was not reliable in assessing the response of neoadjuvant therapy owing to an intense peritumoral fibrotic reaction. Postneoadjuvant therapy CT restaging has also been shown to overestimate T-staging for the same reason [77]. Therefore, for patients in whom disease has not progressed during neoadjuvant therapy, a trial of dissection should be performed after the exclusion of peritoneal and small subcapsular hepatic metastases.

Differentiation between chronic pancreatitis & PC

Differentiation between chronic pancreatitis and PC with the presence of a pancreatic mass can be a diagnostic challenge. Moreover, chronic pancreatitis and PC quite often coexist, and the detection of PC in the background of chronic inflammation is difficult even with EUS-FNA. In the setting of chronic pancreatitis, the sensitivity of EUS-FNA in detecting cancer is lower than in a 'normal' pancreas, as even a relatively discrete lesion cannot be targeted easily [78]. Newer technology, such as EUS elastography, which measures the stiffness of tissues, is being investigated as a method to differentiate between cancer and other inflammatory conditions. However, the results are mixed and further studies are underway [79,80].

Summary of imaging for PC

The roles and relative importance of imaging modalities for PC have changed over the past few decades and continue to change with rapid technological advances in medical imaging. It is also relatively difficult to compare the techniques, even with a systematic review or a meta-analysis, because the study designs, inclusion criteria, 'gold-standard' references, quality and results are heterogeneous. The external validity of each study also differs as the referral pattern and local expertise varies. The definition of resectability may also vary between different institutions around the world. All studies have methodological limitations that potentially affect their validity, and prospective studies with state-of-the-art imaging techniques are needed to further define the role of each modality [47].

Based on the best currently available evidence, CT should be used as first-line strategy for the diagnosis, staging and assessment of resectability in PC. MRI should be reserved for patients with iodine-contrast allergy or who cannot be exposed to radiation, or for use as an adjunct to CT in patients with suspicious liver lesions that need to be better characterized. EUS should be used for local staging and assessment of resectability if PC diagnosis is inconclusive using noninvasive imaging modalities. EUS should also be used in patients with a high clinical suspicion of a lesion that has not been clearly demonstrated using

other modalities. EUS-FNA should also be the biopsy route of choice in patients where a tissue diagnosis or taking tissue from regional lymph nodes may alter the course of treatment, or if neoadjuvant treatment is contemplated. If there is disagreement between CT and EUS images, then laparotomy and surgical resection should be considered. PET/CT should be used selectively, such as when metastatic disease is suspected but has not been demonstrated with other imaging modalities.

In summary, the evidence suggests that CT, EUS, PET and MRI are complementary diagnostic modalities. The availability and local expertise of each imaging modality will also influence their use. A suggested management algorithm for patients with suspected PC is shown in Figure 3.

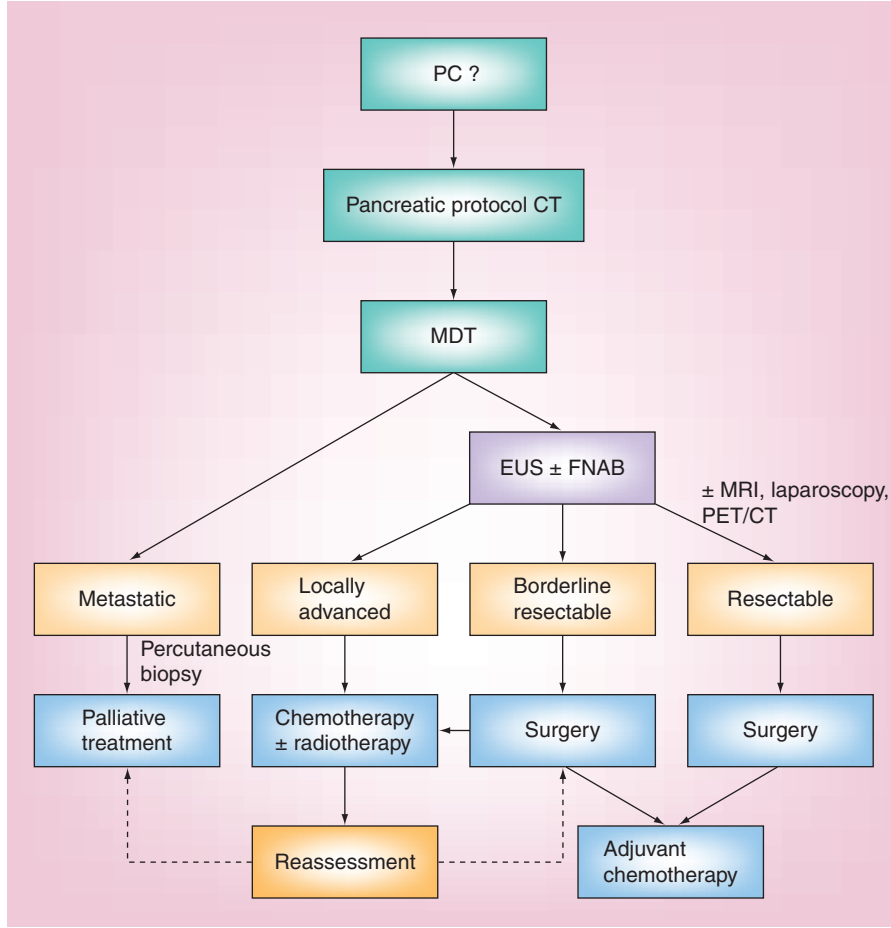

Figure 3. Suggested algorithm for the management of patients with suspected pancreatic cancer demonstrating the role of endoscopic ultrasound.
CT: Computer tomography; EUS: Endoscopic ultrasound; FNAB: Fine-needle aspiration biopsy; MDT: Multidisciplinary treatment meeting; PC: Pancreatic cancer.
Modified from [81].

Expert commentary

Pancreatic cancer is the fourth leading cause of cancer deaths in Western societies, with an overall 5-year survival of less than 5%. Accurate diagnosis and staging holds the key to the successful treatment of this disease. Considerable improvements in diagnosis and staging over the last few decades have been made possible due to the technological advances in CT, MRI and PET/CT, as well as the introduction of EUS in the late 1980s and EUS-guided FNA in the 1990s. EUS is a powerful diagnostic and staging tool in PC. It also has substantial potential for application in various PC therapeutic procedures. Significant improvements in the overall survival of PC can potentially be achieved by the development of effective early-detection strategies and defining at-risk patient populations for whom screening may be beneficial. The appropriate use of these state-of-the-art imaging modalities has the potential to improve PC patient survival through early detection and identification of suitable surgical candidates.

Five-year view

Personalization of therapy in PC

A current focus of research in cancer therapy includes the personalization of therapy based on molecular markers (i.e., biomarkers). The rationale that underpins biomarker studies is that therapeutic agents for the treatment of cancer commonly only benefit a subset of treated patients, and the delineation of cancer phenotypes based on biomarkers of therapeutic responsiveness and overall outcome can enable stratification of patients to appropriate individualized therapeutic regimens [81–86], thereby ensuring that optimal treatment is given without delay and unnecessary adverse side effects are minimized. In addition, the ongoing investigation of resistant subgroups facilitates the identification of novel, more effective therapies. Finally, the identification of prognostic markers provides the ability to inform patients of the likely outcome of their disease and their likely response to a given therapy. All of these gains improve patient management and potentially reduce morbidity and mortality. Tissue obtained from EUS-FNA provides the ideal source for biomarker analysis before patients are placed onto a tailored treatment pathway. Therefore, the use of EUS-guided FNA will become an integrated component of personalization of therapy in the future.

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Key issues

- Pancreatic cancer is the fourth leading cause of cancer-related deaths in Western societies, with an overall survival rate of less than 5%.
- Early diagnosis and accurate staging improves the overall survival rate and quality of life of patients suffering from pancreatic cancer. This can be achieved by a combination of the state-of-the-art imaging modalities (e.g., endoscopic ultrasound [EUS], CT, MRI and PET/CT).
- The role and relative importance of these imaging modalities have changed and continue to change with rapid technological advances. It is relatively difficult to compare them, even with systematic reviews or meta-analyses as the study design, inclusion criteria, 'gold-standard' reference, quality and results are heterogeneous.
- CT should be used as the first-line approach for the diagnosis and staging of, and in the assessment of resectability in, pancreatic cancer, with EUS and EUS-guided fine-needle aspiration playing a key, complementary role, particularly in difficult scenarios. Other modalities, such as MRI and PET/CT, should be used on an individual basis.
- EUS also has substantial potential in therapeutic and interventional procedures, with new applications currently being explored.

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