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Role of endoscopic ultrasound in the diagnosis of pancreatic cancer

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not being ruled out of a potentially beneficial resection. The accuracy for N staging with EUS is 64%-82%. In unresectable cancers, EUS also plays a therapeutic role by means of treating oncological pain through celiac plexus block, biliary drainage in obstructive jaundice in patients where endoscopic retrograde cholangiopancreatography is not affordable and aiding radiotherapy and chemotherapy.

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Core tip: In this article, the role of endoscopic ultrasonography as a diagnostic, staging and therapeutic procedure in patients with pancreatic cancer is discussed and all the current knowledge on this subject is summarized, providing the reader with a quick update.

Abstract

Endoscopic ultrasonography (EUS) with or without fine needle aspiration has become the main technique for evaluating pancreatobiliary disorders and has proved to have a higher diagnostic yield than positron emission tomography, computed tomography (CT) and transabdominal ultrasound for recognising early pancreatic tumors. As a diagnostic modality for pancreatic cancer, EUS has proved rates higher than 90%, especially for lesions less than 2-3 cm in size in which it reaches a sensitivity rate of 99% vs 55% for CT. Besides, EUS has a very high negative predictive value and thus EUS can reliably exclude pancreatic cancer. The complication rate of EUS is as low as 1.1%-3.0%. New technical developments such as elastography and the use of contrast agents have recently been applied to EUS, improving its diagnostic capability. EUS has been found to be superior to the recent multidetector CT for T staging with less risk of overstaging in comparison to both CT and magnetic resonance imaging, so that patients are

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INTRODUCTION

Pancreatic cancer is the fourth leading cause of cancer-related death in men and the first leading cause in women, with an approximate incidence of ten per 100000 population per year^[1,2].

Multiple-imaging modalities are used in combination in the diagnosis and staging of pancreatic cancer: transabdominal ultrasound, computed tomography, magnetic resonance and endoscopic retrograde cholangiopancreatography (ERCP).

The prognosis of pancreatic cancer is dismal, with a 1 and 5 year survival rate at all stages at diagnosis of 24% and 5%, respectively, according to the latest from the American Cancer Society^[3]. Without treatment, the average survival of patients with pancreatic cancer is four months^[4]. Endoscopic ultrasound (EUS) could be a good imaging technique for a better selection of patients for an effective curative treatment.

In addition, by the time pancreatic cancer manifests symptoms that demand medical attention, it has already spread to the point of unresectability in nearly 80%-90% of patients because of metastatic disease^[4,5]. It is especially in these patients where the therapeutic spectrum of EUS is growing. Treatment of oncological pain through celiac plexus block, biliary drainage in obstructive jaundice in patients where ERCP is not affordable and aiding radiotherapy and chemotherapy are some examples of this.

Therefore, EUS has several roles in the widespread sphere of pancreatic cancer. The introduction of EUS in the 1980s was received with great enthusiasm because of the improved information it could provide on the pancreas by overcoming the limitations associated with the use of transabdominal ultrasound. EUS with or without fine needle aspiration (FNA) has been shown to be a cost-effective technique for evaluating pancreatobiliary disorders, particularly where others have failed^[6], and has a higher diagnostic yield than positron emission tomography (PET), computed tomography (CT) and transabdominal ultrasound for recognizing early pancreatic tumors^[1,2].

Pancreatic cancer diagnosis can be made with accurate sensitivity and specificity by EUS because of its inherent advantage of a high-frequency transducer placed in close proximity to the tumor which provides a high resolution image, especially with the incorporation of contrast enhanced images in the last years, making possible a differential diagnosis with other pathologies, such as chronic pancreatitis and neuroendocrine tumors^[7], and a histological confirmation using EUS-FNA

THE ROLE OF EUS FOR DIAGNOSIS OF PANCREATIC CANCER

Numerous studies indicate that EUS is highly sensitive for the detection of pancreatic tumors with rates higher than 90%^[8], especially for lesions less than 2-3 cm in size in which it reaches a sensitivity rate of 99% *vs* 55% for CT^[9,10]. Although the sensitivity for tumor detection is high, it is also important to note that it has a very high negative predictive value (NPV)^[11,12]. This is quite important for clinicians because it means that EUS could reliably exclude pancreatic cancer. On the other hand, this evidence comes from one study only and certain conditions explained further on in the text may hinder a diagnosis of pancreatic cancer.

EUS also has the ability to provide FNA which has made it essential in the evaluation of patients with solid pancreatic lesions since most patients require a tissue di-

agnosis before treatment.

Certain tumor extrinsic conditions exist that may hinder the identification of pancreatic cancer^[13]: chronic pancreatitis with a severe inhomogeneous echotexture, diffuse infiltration by tumor, prominent ventral/dorsal division and acute pancreatitis lasting less than 4 wk.

THE ROLE OF EUS IN THE DIFFERENTIAL DIAGNOSIS OF PANCREATIC CANCER

Differential diagnosis of solid pancreatic masses remains a challenge. Dynamic contrast-enhanced CT is the most widespread imaging technique for this purpose and has been considered the most comprehensive tool for diagnosis and surgical staging of pancreatic malignancies^[5]. Despite all the advances with the multidetector helical CT scan, differential diagnosis between mass-forming chronic pancreatitis, ductal adenocarcinoma and autoimmune pancreatitis based on only CT image is still difficult^[14,15].

Magnetic resonance imaging (MRI) could also be useful in the differentiation of pancreatic solid masses but several studies have demonstrated that is less sensitive than CT and EUS^[16,17]. The administration of secretin during magnetic resonance cholangio-pancreatography can be useful, enhancing the image of the main pancreatic duct, providing pancreas function and duct shape information as dilation^[18].

Currently, ERCP has no clinical role in the diagnosis and staging of pancreatic cancer. Indirect findings such as combined dilation of the bile and the pancreatic duct or abrupt cutoff in the main pancreatic duct or a solitary long stricture of the pancreatic duct could raise suspicion of malignant disease but may also be observed in chronic pancreatitis.

PET is an image modality which relies upon detection of functional activity rather than lesion size alone. Tumors have enhanced glucose uptake and normal pancreas has low glucose utilization rate, fluorodeoxyglucose labelled with radioactive fluorine (¹⁸FDG-PET) readily accumulates in malignant cells and can be detected by a PET camera^[19]. However, the role of ¹⁸FDG-PET in evaluation of primary pancreatic adenocarcinoma has not been established in evaluating tumor response to neoadjuvant chemoradiotherapy or in the evaluation of recurrent disease after surgical resection.

EUS is considered to be one of the most accurate methods for diagnosis of inflammatory, cystic and neoplastic diseases of the pancreas^[4,20,21] and recent studies recommend it for the differential diagnosis of solid pancreatic masses, although accuracy in differentiation between benign inflammatory masses and malignant tumors of pancreas has not been higher than 75%^[22-27].

In a study by Eloubeidi *et al*^[28], 101 patients with solid pancreatic masses underwent an average of 4 needle passes with EUS-FNA, resulting in a sensitivity of 95%, specificity of 95%, positive predictive value (PPV) of 100% and NPV of 85.2%.

EUS-FNA can be made using different types of

needles. Small calibre needles (25 G) have a similar cytology yield as large calibre needles (19 G) with less blood contamination and the advantage of greater flexibility for difficult-to-reach areas such as the uncinate process^[29]. The prospective study by Sakamoto *et al*^[30] showed that 25-gauge was the best choice of needle for cytological diagnosis of solid pancreatic lesions and, in cases in which a histological diagnosis is desired, the 22-gauge FNA needle and 19-gauge trucut needle may be an advantage in head/uncinate and body/tail lesions, respectively.

On-site cytopathology for some investigators is deemed a superior standard of care with the provision of opportunity for real-time interpretation of samples^[31,32] so that it improves the diagnostic yield of EUS-FNA independent of the number of needle passes undertaken for tissue sampling^[33]. If this cannot be provided, 5-6 passes for pancreatic masses and 2-3 passes for peripancreatic lymph nodes and metastases will provide the maximum yield^[34]. Also, having an experienced cytopathology technician or to specifically train a EUS nurse to prepare and determine cellular adequacy for each sample^[33] is helpful in these cases. In cases in which initial cytology is indeterminate or non-diagnostic, the literature supports reattempting EUS-FNA and combining routine cytology with fluorescence in situ hybridization (FISH) and K-ras/p53 analysis to improve the diagnostic yield. This combination yields 87.9% sensitivity, 93.8% specificity, 96.7% PPV, 78.9% NPV and 89.8% accuracy in the Reicher and colleagues retrospective study^[35]. FISH plus K-ras analysis correctly identified 60% of atypical FNAs with a final malignant diagnosis.

EUS is considered a safe procedure with complication rates as low as 1.1%-3%^[36]. Commonly reported complications include bleeding (1%-4%), pancreatitis (1%-2%), perforation (0.03%)^[37] and rarely tumor seeding after EUS-guided FNA^[38-42]. The risk of tumor seeding along the needle tract has been a concern especially in Japan. Although the reported incidence of tumor seeding after EUS-FNA is scarce, the indication of EUS-FNA for small lesions located at pancreas body/tail where the aspiration route will not be included in the resection area needs to be carefully considered. When pancreatic head lesions are evaluated by FNA, there is a theoretical risk of cancer seeding, but this has never been reported after EUS-FNA because after a Whipple procedure, the potential sites of seeding are removed. As for patients with unresectable disease, most die of disease progression before any seeding is detected. If the decision is to proceed to EUS-FNA, patients must be fully aware of the remote risk of seeding to the gastric wall^[39]. There are two cases of tumor seeding along a EUS-FNA tract in pancreatic adenocarcinoma and both were pancreatic tail adenocarcinomas^[39,40]. The only other two reports related to tumor seeding after EUS-FNA were peritoneal dissemination after EUS-FNA of pancreatic intraductal papillary mucinous neoplasia^[41] and metastatic melanoma^[42]. Whether this risk is increased by the needle size or number of passes remains uncertain.

The sensitivity of EUS-FNA for malignancy in pa-

tients with chronic pancreatitis is lower compared to when the surrounding parenchyma is normal^[27,43-47]. Studies by Fristcher-Ravens *et al*^[27] and Varadarajulu *et al*^[44] found a sensitivity of 54% and 73.4% in parenchymas with chronic inflammation *vs* 89% and 91.3% in normal parenchyma respectively ($P = 0.02$). A systematic review of 53 studies estimated a NPV of EUS-FNA in the diagnosis of pancreatic adenocarcinoma as 60%-70%^[48] which makes a new function mandatory in cases where the first EUS-FNA has been benign. The Procore® histology needle has been designed in order to optimize tissue sampling of EUS-FNA, allowing a histological evaluation with an overall accuracy of 89.4% in solid pancreatic lesions^[49].

Recently, quantitative EUS elastography (QE-EUS) has been developed in an attempt to make the elastography interpretation less subjective than the old qualitative EUS-elastography. In the Iglesias-Garcia *et al*^[23] study with 86 patients with solid pancreatic masses, the strain ratio (ratio of elasticity in the target area over soft referent tissue) was significantly higher among patients with malignant pancreatic tumors compared to those with inflammatory masses. Normal tissue showed a mean strain ratio of 1.68 (95%CI: 1.59-1.78), inflammatory masses 3.28 (95%CI: 2.61-3.96) and pancreatic adenocarcinoma 18.12 (95%CI: 16.03-20.21) ($P < 0.001$). The sensitivity and specificity of the strain ratio for detecting pancreatic malignancies in solid masses using a cut off value of 6.04 were 100% and 92.9% respectively, higher rates than obtained with qualitative elastography (100% and 85.5% respectively)^[50].

Contrast-enhanced EUS (CEH-EUS) is performed with the application of contrast agents. Numerous US contrast agents (UCAs) are commercially available. Levovist®, the first agent for general use, is made of a galactose microcrystal filled with air bubbles which, shattering under a high sound pressure, emits pseudo-Doppler signals. With the development of second UCAs (Sonovue® and Sonazoid®) which contain inert gases with low solubility in water, the stability and duration of the contrast and real-time vascular images have been increased. The risk for drug allergy is small because of the small molecular weight of microbubbles and they are also applicable for patients with liver and renal dysfunctions because it is excreted by exhalation^[51,52]. Most carcinomas, neuroendocrine tumors and inflammatory pseudotumors are simply depicted as hypoechoic masses, but the use of contrast agents in EUS has been shown to improve the characterization of the vasculature inside the organ of interest, to better delineate such hypoechoic masses. According to published reports, hypoenhancing masses were regarded as a sign of malignancy in CEH-EUS. The first feasibility study reported good values of sensitivity, specificity and accuracy for the differential diagnosis between adenocarcinoma and focal chronic pancreatitis^[53]. This was further confirmed in two other studies by Sakamoto *et al*^[54] and Dietrich *et al*^[55] in which adenocarcinomas showed hypoenhancement compared with neuroendocrine tumors and pseudotumoral (mass-forming) pancreatitis, which

showed isoenhancement or hyperenhancement. Fukusawa *et al*^[56] reported a prospective study, concluding that in most cases of pancreatic adenocarcinoma, CEH EUS exhibits a hypoperfusion pattern compared with the adjacent normal pancreatic tissue, whereas autoimmune pancreatitis/chronic pancreatitis exhibits iso-perfusion and pancreatic neuroendocrine tumors (PNET) exhibit a hyperperfusion pattern^[56]. Fusaroli *et al*^[57] found that a hypo-enhancing mass with an inhomogeneous pattern diagnosed pancreatic adenocarcinoma with a sensitivity of 96% and more accuracy than standard EUS. Hyper-enhancement specifically excluded adenocarcinoma (98%), although with a low sensitivity. Seicean *et al*^[58] introduced the use of quantitative CEH-EUS for differential diagnosis between pancreatic cancer and chronic pancreatitis, with the index of contrast uptake lower in adenocarcinoma compared to cases with mass-forming chronic pancreatitis. Also, using pulsed Doppler could help with the differential diagnosis between adenocarcinomas and chronic pseudotumoral pancreatitis. Pancreatic adenocarcinomas show mainly arterial-type signals and chronic pseudotumoral masses show both arterial-type and venous-type signals^[59]. The first meta-analysis that summarized the available evidence of the diagnostic performance of CEH-EUS for the differential diagnosis of pancreatic adenocarcinomas showed that CEH-EUS had a pooled sensitivity of 94% (95%CI: 91-95) and a pooled specificity of 89% (95%CI: 85-92), so finding a hypoenhancing lesion was a sensitive and accurate predictor of pancreatic adenocarcinoma^[60]. The variation in this study in comparison with Fusaroli *et al*^[57] may have occurred because more patients with severe chronic pancreatitis were enrolled in the Fusaroli *et al*^[57] study, which may have altered the enhanced pattern of pancreatic adenocarcinomas. Severe forms of chronic pancreatitis mean less intense intralesional "parenchymographic" enhancement and fibrosis resulting in decreasing vascular flow^[62-64]. Iglesias-Garcia *et al*^[65] compared the aforesaid QE-EUS to CEH-EUS. The authors concluded that the diagnostic accuracy of QE-EUS in pancreatic masses is superior to CEH-EUS and, furthermore, that addition of CEH-EUS does not significantly increase the diagnostic accuracy of QE-EUS.

THE ROLE OF EUS IN STAGING OF PANCREATIC CANCER

Surgery is the only curative treatment for pancreatic cancer. Statistics for survival in pancreatic cancer, where 5 year survival rates are as low as 10%-25% after a successful surgery^[66,67], have been changing because of identification of appropriate candidates for surgery by a good staging, approaching a 5 year survival rate of 40% if margins and nodes are negative and the resection is made by experienced surgeons^[68,69].

However, even with the newest diagnostic workup, pancreatic cancer at laparotomy is often found to be more advanced than originally thought^[70,71].

Currently, the preferred modality for pancreatic can-

cer staging and assessing resectability is CT because its low cost and high availability^[72] and MRI for preoperative assessment of pancreatic cancer, with an accuracy of 86% *vs* 71% even with comparable sensitivity of MRI for detecting pancreatic cancer (88%-96%)^[73].

EUS has been found to be superior to the recent multidetector CT (MDCT) for T staging^[74-77], with less risk of overstaging in comparison to both CT and MRI^[78] so that patients are not being ruled out of a potentially beneficial resection. In a recent study, the sensitivity of EUS was higher than MDCT but MDCT was more specific, especially in the assessment of vascular invasion. The correct decision could be achieved in 63% in patients with either MDCT or EUS, in 9% of patients with EUS alone and in 14% of patients with MDCT alone, but the success rate rises to 86% when they are used in combination^[79].

The accuracy for N staging with EUS is 64%-82%^[80]. Only one study found that EUS is also better than CT for N-staging (93.1% *vs* 87.5% respectively), but most of the studies have found no difference between CT and EUS in predicting resectability in relation to node involvement^[74,78-81]. Criteria for the identification of lymph node metastasis are used in different studies: spherical shape, hypoechoic node, well delineated boundaries and 10 mm diameter or more. These criteria normally are not enough and EUS-FNA is often required.

EUS has been found to be better at peripancreatic and periceliac lymphadenopathy detection (87.5%), and vascular infiltration (90%), especially for mesenteric vessels that also have a higher ability to correctly predict surgical resectability^[82-84]. EUS has shown a good ability to detect vascular invasion, showing low sensitivity in the superior mesenteric artery (17%) and celiac artery (50%), although the portal venous system was correctly assessed by EUS in 95% of cases, compared with angiography (85%) and CT (75%)^[85,86]. However, differently from radial EUS, linear EUS can show arterial vessels longitudinally using a linear image and both the celiac and superior mesenteric arteries are easily followed from the stomach. A recent prospective study by Tellez-Avila *et al*^[87], in which the accuracy of linear-EUS and CT to determinate vascular invasion is evaluated in 50 patients with pancreatic cancer, EUS is a very good option to detect vascular invasion and is especially sensitive for arterial invasion (PPV EUS 100% *vs* PPV CT 60%).

Tumor conditions may also affect the accuracy of EUS staging^[88], such as peritumoral inflammatory changes and attenuation of ultrasound beam in large tumors. For this reason, tumors smaller than 3 cm in size are more accurately staged with EUS.

THE ROLE OF EUS AS PALLIATIVE TREATMENT OF PANCREATIC CANCER: THERAPEUTIC OPTIONS

In patients with advanced unresectable disease, chemotherapy, radiation or a combination of both may positively influence overall survival and quality of life. The

therapeutic spectrum of EUS has turned endoscopy into an integral component of palliative treatment in patients with inoperable disease. EUS offers access to lesions in different parts of the pancreas, including anatomical regions that are difficult to approach percutaneously.

CELIAC PLEXUS NEUROLYSIS

Pain is one of the most prevalent symptoms in pancreatic cancer at presentation (75%) and its incidence increases as the disease advances to more than 90% of patients^[89]. Pain control is the main therapeutic goal for clinicians in palliative care of pancreatic cancer patients and the conventional management with high doses of narcotics and the inherent adverse effects may further impair quality of life^[90-92].

Before 2010, celiac plexus neurolysis (CPN) was considered an effective technique for controlling pain and reducing narcotic requirements in patients with pancreatic cancer^[89-93]. However, a recent meta-analysis of five randomised controlled trials documented a fair response to CPN with an overall reduction in the visual analog pain scores^[89]. A recent systematic review that aimed to determinate its efficacy and safety in reducing pancreatic pain found that the statistical evidence of the superiority of CPN over analgesic therapy or reducing opioid use was weak^[94,95]. On the other hand, a recent randomised trial of early EUS guided CPN concluded that early EUS-CPN provides better pain relief in patients with painful, inoperable pancreatic adenocarcinoma and may prevent progressive increases in morphine consumption compared with conventional management, especially in patients who do not receive chemotherapy and/or radiation therapy, so they recommend it to be considered during diagnostic and staging EUS in all patients with predicted survival of several months where a confirmation of painful, locoregional and inoperable pancreatic cancer is obtained^[95]. Despite better pain control, early EUS-CPN did not produce a demonstrable improvement in quality of life, but this was not a study powered to look for effects on quality of life.

BILIARY DRAINAGE

EUS-guided biliary drainage (EUS-BD) has been described as an alternative method to achieve internal biliary drainage in those patients in whom ERCP is not feasible. EUS-guided cholangiopancreatography (ESCP) was first described by Wiersema *et al*^[96] in 1996. ESCP using either direct access or a rendezvous technique has shown a technical success between 75%-100%^[97-100], although complications can reach up to 20%, especially in the early phase of the learning curve of the procedure^[101].

ESCP can be performed through different routes (transgastric, transduodenal) and with different techniques (rendez-vous, hepaticogastrostomy, choledocoduodenostomy)^[102]. In the rendezvous technique, the bile duct is punctured with a 19 or 22 G needle under EUS guidance and a wire is antegradely guided through any

stricture and across the papilla under fluoroscopic guidance. The echoendoscope is then removed, leaving the wire in place, and the procedure is completed with a duodenoscopy.

In hepaticogastrostomy and choledocoduodenostomy, the bile duct is punctured, preferably with a 19 G needle, a wire is guided into the bile duct and, after dilation of the transmural tract, a plastic or metallic stent is inserted.

EUS-GUIDED RADIOFREQUENCY ABLATION

EUS-guided radiofrequency ablation (EUS-RFA) has been successfully tested in two porcine studies for ablation of both lymph nodes^[103] and the pancreas^[104]. RFA was performed with a EUS adapted probe which was inserted through the lumen of a FNA needle. At histological analysis, the ablation effect was limited to the lesions and a direct correlation was seen between probe length and length and diameter of the necrosis.

EUS-FNI FOR TUMOR ABLATION AND INTRATUMORAL DRUG DELIVERY

EUS-FNI has made the intratumoral delivery of ethanol, chemotherapy as paclitaxel^[105] or biological agents^[106] possible in a precise real time tumor visualisation. Several studies have proved that it is a promising and safe technique, but validation in larger studies over longer follow-up periods is necessary.

EUS GUIDED RADIATION THERAPY

In a recent study with 22 patients with pancreatic cancer in which an average of 10 radioactive iodine-125 seeds were implanted under EUS guidance, the authors noticed a decrease in pain during the week following brachytherapy but there was no long-term survival benefit^[107]. Recent reports concluded that EUS is safe for fiducial placement in pancreatic tumors^[107] and for submucosal injection of tantalum for identification of the tumor during radiation and surgery^[108].

In conclusion, EUS plays an important role in the diagnosis of pancreatic cancer, including FNA with cytological or histological confirmation. Staging of pancreatic cancer is crucial and CT and EUS are the cornerstones of staging, currently providing the more accurate results. Furthermore, EUS also has a therapeutic role, providing biliary drainage when it is not feasible with ERCP and pain relief. EUS can also have future applications on pancreatic cancer management.

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