

# Endoscopic ultrasonography for pancreatic cancer: current and future perspectives

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**Abstract:** A suspected pancreatic lesion can be a difficult challenge for the clinician. In the last years we have witnessed tumultuous technological improvements of the radiological and nuclear medicine imaging. Taking this into account, we will try to delineate the new role of endoscopic ultrasound (EUS) in pancreatic imaging and to place it in a shareable diagnostic and staging algorithm of pancreatic cancer (PC). To date the most accurate imaging techniques for the PC remain contrast-enhanced computed tomography (CT) and EUS. The latter has the highest accuracy in detecting small lesions, in assessing tumor size and lymph nodes involvement, but helical CT or an up-to-date magnetic resonance imaging (MRI) must be the first choice in patients with a suspected pancreatic lesion. After this first step there is place for EUS as a second diagnostic level in several cases: negative results on CT/MRI scans and persistent strong clinical suspicion of PC, doubtful results on CT/MRI scans or need for cyto-histological confirmation. In the near future there will be great opportunities for the development of diagnostic and therapeutic EUS and pancreatic pathology could be the best testing bench.

**Key Words:** Endoscopic ultrasound; pancreatic cancer; multidetector helical computed tomography; fine-needle aspiration; pancreatic cyst; neuroendocrine tumor



Submitted Dec 14, 2012. Accepted for publication Jan 18, 2013.

doi: 10.3978/j.issn.2078-6891.2013.002

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## Introduction

One of the most important task of pancreatic endoscopic ultrasound (EUS) remains diagnosis and staging of pancreatic cancer (PC), the most deadly of all gastrointestinal (GI) malignancies, the fourth leading cause of cancer-related deaths in the United States, with a very poor prognosis. The 5-years survival rate is less than 5% (1). PC is a major health problem for several reasons: aggressive behaviour of the tumor, relative frequency that appears to be increasing, approximately 30,000 new cases in 2002 and about 32,000 in 2004 were diagnosed in the United States (1). Unluckily, most patients present late in the history of their disease with advanced cancer either locally or with metastatic spread (2). Even though surgery represents the only chance for cure, at the time of diagnosis only 10% to 25% (in the more optimistic series) of PC patients will be amenable to potentially curative resection (3) and in this case the prognosis

remains dismal (4). This is demonstrated by a 5-year survival not above 20% after surgical resection (5). Furthermore, if we consider the high costs of major pancreatic surgery not only in terms of money but also morbidity and mortality even in the most experienced surgical hands (6,7), it is clear that all efforts must be oriented towards the need of an early diagnosis and to reliably identify patients who really can benefit from major surgical intervention. A study indeed found that a complete resection with negative margins can be achieved in almost half of patients with suspicion of locoregional PC, when state-of-the-art preoperative imaging was used (8).

Pancreatic tumors have always represented a complex dilemma for clinicians and diagnostic imaging and, currently, there is no consensus on the optimal preoperative imaging modality for diagnosis and staging assessment of patients with suspected or proved locoregional PC. This brought us

during the years to a complex range of diagnostic proposals.

Three steps are crucial in clinical practice: first you must find the lesion (detection), secondly you must make a differential diagnosis between benign and malignant pancreatic masses and once the diagnosis of PC is established you need the most accurate preoperative staging to select patients that can benefit from curative resections. Modern imaging techniques such as transabdominal ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI) and EUS are less invasive and less costly than surgery. For years EUS has been claimed to be the best currently available technique for imaging the pancreas, but in the last ten years we have witnessed tumultuous and galloping technological improvements of the radiological and nuclear imaging techniques. Taking into account the rapid increase in the sensitivity and accuracy of these new technologies, in a narrative review we analyzed current and future perspectives of EUS in the management of PC.

Other important and challenging tasks of pancreatic EUS are represented by:

(I) the differential diagnosis of solid pancreatic masses (auto-immune pancreatitis, chronic pancreatitis, solid-cystic dystrophy of the duodenal wall, neuroendocrine tumor, pancreatic metastasis);

(II) differential diagnosis and surveillance of pancreatic cystic lesions;

(III) detection, diagnosis and staging of neuroendocrine tumors (NETs) of the duodenopancreatic area;

(IV) diagnosis of parenchymal and ductal changes of chronic pancreatitis (CP);

(V) the setting of idiopathic acute pancreatitis (AP) in order to define an aetiology, to identify patients that can take advantage of an endoscopic treatment (endoscopic retrograde cholangiopancreatography or ERCP) and to predict severity of the AP.

To identify all publications considered appropriate to discuss this issue, a MEDLINE search of all studies published from 1965 to 2012 was conducted. The final date of the MEDLINE search was November 25, 2012. The following medical subject headings were used: pancreatic cancer, pancreatic cyst, neuroendocrine tumor, endoscopic ultrasound, echoendoscopy, EUS, fine-needle aspiration, and FNA. The search was also performed using reference lists from published articles. The titles of these publications and their abstracts were scanned in order to eliminate duplicates and irrelevant articles.

### The challenge of EUS

EUS is one of the most important innovations that have

occurred in GI endoscopy during the last 30 years. This technique has been introduced in the early 1980s (9), just to overcome difficulties in visualization of the pancreas on transabdominal US. It has been for many years a mere imaging modality, but the development of new electronic instruments with linear or sector scanner allowed the visualization in the echographic field of a needle coming out from the operative channel of the echoendoscope so guiding the needle in the target lesion both within and outside the GI wall. So we witnessed in the early 1990s at the birth of interventional EUS, both diagnostic and therapeutic.

For many years EUS has been advocated as the best available technique for imaging the pancreas and the extra-hepatic biliary tree. High resolution images of the main pancreatic duct and surrounding parenchyma can be achieved and structures as small as 2-3 mm can be distinguished thanks to the small distance between the transducer and the gland, that allows to use higher frequency probes, from 7.5 to 20 MHz, with lower penetration depth but more elevated spatial resolution (10). EUS, compared with transabdominal US, CT and MRI, has a superior parenchymal resolution, that gives reason for the results of several studies establishing the higher sensitivity of EUS (98%) in the diagnosis of PC in comparison to all the other imaging modalities, i.e., US (75%), CT (80%), even with pancreatic protocols, angiography (89%) and so on (11,12). The results of EUS were even better in small tumors, less than 3 cm, where sensitivity of US and CT decreased to only 29% (11). However, the introduction of multidetector helical CT (MDHCT) has today revolutionized the field of pancreatic imaging and “has created a new dimension of temporal and spatial resolution” reaching a sensitivity of 97-100% and a non-resectability prediction near to 100% (13). Also MRI, developed in the early 1990s, has known great improvement in technology and softwares in the last ten years, with the addition of magnetic resonance cholangiopancreatography (MRCP) and MR angiography. The reported sensitivity of MRI ranges from 83% to 87% with a specificity from 81% to 100%. Given the increasing sensitivity of MDHCT and the high cost of MRI, the latter to date should not be considered the first choice in PC diagnosis and staging, even though MRI may be useful in the detection and characterization of non-contour-deforming pancreatic masses and it is more sensitive than CT in the detection and characterization of small liver metastases and peritoneal and omental metastases (10,14).

In the last ten years EUS had to bear the weight of the rapidly evolving technology of radiological imaging modalities and finally also the advent and the evolution of nuclear imaging such as positron emission tomography (PET) (15) and the integrated approach PET/CT, aimed to

overcome the major disadvantage of PET scan, that is the limited anatomical information (16).

In short, the development of modern imaging modalities have limited or almost annulled the advantages of EUS in terms of sensitivity, accuracy for T and N staging, prediction of resectability (i.e., detection of vascular infiltration) in the preoperative evaluation of PC. Multiple published studies with discordant results compared EUS and CT or other imaging modalities in the diagnosis or detection, staging and prediction of resectability of suspected or known PC (12). For example in the study of Schwarz *et al.* the diagnosis of periampullary tumors could be achieved with high sensitivity by EUS (97%) and spiral CT (90%) (17). For small tumors the most sensitive method remains EUS, which correctly predicted all lesions <2 cm. When comparing accuracy rates for resectability, EUS was the leading modality, but the difference with spiral CT was not significant. In a systematic review, comparing EUS and CT for the preoperative evaluation of PC, the authors concluded that literature is heterogeneous in study design, quality and results (18). There are many methodologic limitations that potentially affect the validity. Overall, EUS is superior to CT for detection of PC, for T staging and for vascular invasion of the spleno-portal confluence. The two tests appear to be equivalent for N staging, overall vascular invasion and resectability assessment. The optimal preoperative imaging modality for the staging and assessment of resectability of PC remains undetermined. Prospective studies with state-of-the-art imaging are needed to further evaluate the role of EUS and CT in PC. In this challenge EUS has been mainly supported by the advent of interventional EUS (EUS-guided fine-needle aspiration or EUS-FNA). In contrast to the very high sensitivity previously shown, specificity of EUS is limited, especially when inflammatory changes are present. The ability to perform EUS-FNA may overcome some of the specificity problems encountered with EUS in distinguishing benign from malignant lesions, allowing an improvement of EUS accuracy, mainly as a result of enhanced specificity, without losing too much in sensitivity (12). To tell the truth also the negative predictive value of 100% for EUS in pancreatic tumors must be in some way mitigated: in a multicenter retrospective study were identified 20 cases of pancreatic neoplasms missed by nine experienced endosonographers. Factors that caused a false-negative EUS result included chronic pancreatitis, a diffusely infiltrating carcinoma, a prominent ventral/dorsal split and a recent (<4 weeks) episode of AP. The authors suggested that if a high clinical suspicion of PC persists after a negative EUS, a repeated examination after 2-3 months may be useful for detecting an occult pancreatic neoplasm (19).

Anyway we should refrain from the idea that investigations only exist to compete with one another, but instead we should accept that different technologies often provide complementary information which ultimately result in optimum patient care. An overriding principle of care should be that patients should first undergo the least invasive, harmful and most widely available investigation. Moreover we must consider that EUS can not define distant metastases, it is still not universally available and highly operator dependent. So spiral CT or better MDHCT must today be the initial study of choice in patients with a suspected pancreatic lesion.

### Current role of EUS in pancreatic cancer diagnosis

Starting from the above mentioned concepts we will propose a diagnostic algorithm in case of a suspected PC, trying to place EUS in shareable and evidence-based positions inside this algorithm. As already mentioned, in case of a clinical suspicion of PC, the initial study should be performed with a spiral or multidetector CT: if there is a PC with distant (hepatic for instance) metastases, there is no place for EUS. CT scan can be negative for pancreatic pathology: in this case we must search for other causes accounting for patient's symptoms, but if the suspicion of pancreatic disease remains strong we must proceed to EUS: if endosonography depicts a pancreatic lesion, we can biopsy it (EUS-FNA) or just refer the patient to the surgeon or propose a follow-up of the detected lesion, if EUS diagnosis leans towards a benign process. If pancreatic EUS is negative we can reasonably exclude a pancreatic disease. This is why EUS is the test with the best negative predictive value for the pancreas that approaches 100% (19).

Second scenario: the CT scan shows some doubtful pancreatic changes or inconclusive imaging such as small (<2 cm) masses, fullness, enlargement or prominence of the gland. The clinical significance of these indeterminate CT findings is not established, however in a clinical setting with a proper suspicion of PC they are very worrisome. Also in this case EUS is indicated and again we can rely on its high negative predictive value (20), with the possibility of real-time EUS-guided FNA that has been demonstrated useful for overcome EUS specificity problems in the differential diagnosis between malignancy and inflammation (20,21).

Third scenario: CT imaging is positive for PC. Contrast-enhanced MDHCT is highly accurate for the assessment of PC staging and resectability (22) and we can be facing a resectable tumor or not. In the first case the patient can go straight to surgery, even if some authors, in order to most reliably identify patients who might really benefit

from major surgical intervention, recommend EUS to be performed as second staging modality (10,23). A cost minimization analysis strengthened the sequential strategy, MDHCT followed by EUS, in potentially resectable cancers (22). If both methods confirm resectability the patient is referred to the surgeon and there is general agreement between experts and literature that FNA is not necessary for resectable cancers. Anyway in some cases one can argue that not all pancreatic tumors are ductal adenocarcinomas: endocrine neoplasias, lymphomas, solid-papillary tumors, metastatic cancer, such as metastases from breast, kidney, adrenal gland and so on can be found in the pancreas and they may have varying prognostic outcomes and may require different treatment approaches. In this case, if there is any imaging or clinical doubt about the nature of the mass, FNA could be advisable even in the presence of a resectable pancreatic mass. On the other hand if MDHCT shows a non-resectable pancreatic tumor, histological or cytopathological confirmation is needed in order to address the patient to protocols of palliative radio- or chemo-therapy (10,24). In very few cases is also described that EUS can recover the patient for surgery demonstrating that MDHCT overstaged the tumor.

### **When do we need cytological or histological diagnosis?**

There is only one answer to this question: when the obtained information can change patient management. So we need cyto-pathological confirmation:

(I) in patients with unresectable pancreatic masses or anyway not eligible for surgery prior to start palliative radio- or chemo-therapy (this is the main indication for pathological confirmation in PC) (10,24);

(II) when we have some justified doubts that the resectable pancreatic mass is not a ductal adenocarcinoma but a different type of tumor amenable to different therapeutic strategies (25);

(III) when the patient or sometimes also the surgeon wish to have a cytopathological confirmation of cancer before engaging in a major surgical intervention;

(IV) in the differential diagnosis between carcinoma and mass forming pancreatitis.

The differentiation between a malignant and an inflammatory tumor especially in a setting of CP is very challenging. This is one of the main limitations of EUS, which is also observed with all other imaging modalities. It restricts the value of EUS for one of the most frequent differential diagnostic dilemmas in pancreatic diseases. The positive predictive value of EUS for PC in patients with concurrent CP was only 60% (26). In this case histological

confirmation may be of outstanding value, but also EUS-FNA showed some limitations in presence of CP, in particular a lower sensitivity in comparison to patients without chronic inflammation (73.9% vs. 91.3%,  $P=0.02$ ) (27). The authors suggest some tips for improving the yield of pancreatic mass EUS-guided FNA in the setting of CP: multiple FNA passes, repeated procedures, on-site cytologic interpretation, sampling of suspicious non-pancreatic lesions, such as lymph nodes or liver lesions, use of core-biopsy needles, the cooperation of an experienced pancreatic cytologist. The impact of an expert cytopathologist on diagnosis and treatment of pancreatic lesions in current clinical practice is well demonstrated: in a series of 106 EUS-FNA sensitivity increased from 72% to 89% due to the cytopathologist experience (28). In this difficult challenge EUS can be assisted by new technological advances such as contrast-enhanced (CE) imaging that increased sensitivity and specificity of EUS in discriminating between focal pancreatitis and PC, from 73% to 91% and from 83% to 93%, respectively (29). Another new tool that could demonstrate to be useful in this setting is EUS elastography. Allowing the visualization of tissue elasticity distribution it could help in the differential diagnosis of focal pancreatic masses or in the differentiation of benign and malignant lymph nodes or various solid tumors. Possibly it will help EUS-FNA in targeting less fibrous areas inside the lesion of interest (30). It uses a hue color map (red-green-blue) to display the stiffness of the tissue (31,32): recent data with quantitative, second-generation EUS elastography, demonstrate its usefulness for differential diagnosis of solid pancreatic masses, allowing for a quantitative and objective assessment of tissue stiffness, which indicates the malignant or benign nature of the pancreatic lesion. A good reproducibility of the results was proven (32).

### **How to obtain samples for cytopathological or histological confirmation in pancreatic masses**

Non surgical pancreatic cyto-histological samples can be obtained either endoscopically by means of EUS or ERCP guidance or percutaneously by CT or US guidance. ERCP-directed brush cytology has a low sensitivity between 33% and 57% and a specificity between 97-100% (33-35). Even adding ERCP-directed biopsies the sensitivity does not exceed 70% (34,35). In a prospective study, Rosch *et al.* compared ERCP-guided brush cytology, ERCP-directed biopsies and EUS-FNA for diagnosis of biliary strictures. Biliary stenoses of undeterminate origin remained a difficult challenge, but EUS-guided FNA has been demonstrated superior to ERCP-guided techniques for pancreatic lesions (43% vs. 36%) (36). Percutaneous FNA or core biopsy of

the pancreas via CT and transabdominal US has a success rate of 65% to 95% for detecting malignancy (37-40) and it is considered safe, with a mortality rate for abdominal biopsies of 1:1,000 (38,41). The development of instruments with electronic linear or sector scanners, equipped with color Doppler technology permitted FNA for cytology specimens guided by means of EUS. We performed a systematic review and a meta-analysis of the literature in order to evaluate the accuracy of EUS-FNA in the diagnosis of cancer in solid pancreatic masses (42): counting atypical results as positive, we found a sensitivity of 0.88 (95% CI: 0.847-0.929) and a specificity of 0.960 (95% CI: 0.922-0.998); counting atypical results as negative, sensitivity was 0.812 (95% CI: 0.750-0.874) and specificity 1. The updated data literature confirms that EUS-FNA is highly accurate in diagnosis of cancer in solid pancreatic masses (43,44). The most weighted factors affecting the accuracy are on-site cytopathological evaluation and lesion size (44). A recent Japanese study reported that with four needle passes, in absence of on-site cytology, it can be obtained a sensitivity of 93% and a specificity of 100% in the cytopathological diagnosis of solid pancreatic lesions (45). During the last ten years EUS-FNA was established as a low risk diagnostic tool in PC. The complication rate of EUS-FNA is considered to be very low, ranging between 0.3% and 1.6% (20,46-48). Controversy has arisen about the preferred method of choice to obtain pancreatic diagnostic tissue: the percutaneous approach with CT/US guidance or the EUS-guided endoscopic one. To our knowledge, till now there are only retrospective studies (49,50) and one prospective, randomized study (51) comparing the performance of percutaneous CT/US-guided FNA with EUS-guided FNA in pancreatic lesions. A retrospective analysis suggested that the sensitivity of CT-FNA was superior to EUS-FNA (71% *vs.* 42%) (49), while another retrospective study found an equivalent accuracy between EUS-FNA, CT/US-FNA and surgical biopsies (50). In the only prospective, randomized, crossover trial EUS-FNA resulted numerically, though not quite statistically, superior to CT/US FNA for the diagnosis of PC (51).

So why should we choose EUS-guided sampling instead of CT/US-FNA? Indeed some arguments in favour of this choice exist and can be summarized as follow:

(I) the ability to sample lesions (including lymph nodes) too small to be identified by other methods;

(II) concern about cutaneous and peritoneal seeding: a study from Micames *et al.* showed lower frequency of peritoneal seeding in patients with PC diagnosed by EUS-FNA *vs.* percutaneous FNA (52); a shorter needle path, the use of smaller needles and the ability to biopsy the lesion through a segment of the GI wall, which becomes part of

the resected specimen, in case of surgery, can minimize the risk of needle-tract seeding;

(III) the possibility of targeting more confidently small lesions adjacent to vessels, using the color Doppler capability or lesions located in seats difficult to be reached percutaneously;

(IV) the provision of sometimes remarkable additional diagnostic and staging information through the EUS examination;

(V) there are some initial data about the superior cost-effectiveness of EUS-guided FNA in the evaluation of pancreatic head adenocarcinoma compared with CT-FNA and surgery (53).

Finally, the true strength of EUS in a patient with suspected PC is the possibility to offer a really "all inclusive" service; it can in a single step:

(I) detect the lesion (diagnosis);

(II) assess the local extent and vascular invasion of the tumor (staging and resectability assessment);

(III) if the tumor is deemed unresectable, biopsy the lesion for cytopathological confirmation (EUS-FNA);

(IV) if the patient is symptomatic, treat the pain (coeliac plexus neurolysis) or even the jaundice (EUS-guided biliary drainage) (palliative treatment).

At our institution as well as in other centers all around the world we are witnessing a clear trend toward increasing referrals for pancreatic EUS-FNA with a parallel decrease in referrals for percutaneous FNA. EUS-FNA is perceived by physicians to be superior to CT/US-FNA and is already the preferred choice in some realities (23,51).

### Current role of EUS in the differential diagnosis and surveillance of pancreatic cystic lesions

EUS can help us in detecting some morphological changes characteristic for malignancy, like thick wall, thick septations, macroseptations, mural nodules, presence of mass, but can also supply information on the surrounding pancreatic tissue and pancreatic duct anatomy, suggestive for CP or can define the communication of the cystic lesion with the pancreatic duct (54). Current literature data tell us that the EUS accuracy for differentiating malignant *vs.* non-malignant in this clinical setting ranged from 43% to 93%, with an interobserver agreement of 50% (55,56), pancreatic duct anatomy is best visible by secretin MRCP. Thus, EUS alone is not sufficient for clinical decision making, but EUS role today is no more limited to imaging alone: EUS-FNA can give some help in the characterization of pancreatic cystic lesions. EUS-FNA may provide more information: cytology and viscosity, amylase level, CEA and molecular analysis on the aspirated fluid (56-59). It is a relatively safe procedure

with a complication rate of 2.2% (mostly pancreatitis) (60,61). By means of EUS-FNA we can localize the cystic lesion, define its morphology, direct the needle to the cystic wall, mural nodules, debris, septations or associated mass. In this respect we can use various needles (25, 22, 19 gauge needle or Trucut needle), one to 3 passes and we must give the patient prophylactic antibiotics. Resuming current literature data (56-59), today we know that in the aspirated fluid the interpretation of parameters should be as reported below:

(I) CEA levels;

(i) <5 ng/mL: serous cystadenoma or pseudocyst;

(ii) >800 ng/mL: mucinous cystic adenoma (MCA) or cancer;

(iii) CEA is the most accurate marker for differentiating mucinous from non-mucinous cysts but it cannot distinguish intraductal papillary mucinous neoplasm (IPMN) from MCA or benign from malignant mucinous cyst.

(II) High amylase;

(i) Pseudocyst and IPMN;

Furthermore we know that cytology is quite insensitive for both diagnosis and detection of malignancy and "EUS-FNA-Surgical Correlation" accuracy ranged between 55% and 97%.

About biochemical analyses on the aspirated cystic fluid new tools and possibilities are represented by immuno-molecular analysis (K-ras, p53, mucins pattern, telomerase, PCNA, VEGF, MMP-7 and so on) (62). We published that high levels of chromogranin A in the aspirated fluid can help in the diagnosis of neuroendocrine pancreatic cystic tumor (63). Data from US (64,65), Spain (66,67) and our group (68) seem to demonstrate that cytology samples obtained by echobrush had superior diagnostic yield compared to EUS-FNA and cytology brushings are more likely to provide an adequate mucinous epithelium specimen than standard FNA, but be careful about possible serious complications, reported with the echobrush, from 0% to 22.7%, i.e., acute pancreatitis, severe bleeding, minor bleeding, self-limited abdominal pain or minor abdominal discomfort. Also 1 death is reported in one series (66). A cost-effective analysis for asymptomatic incidental solitary cystic pancreatic tumors demonstrated that risk stratification of malignant potential by EUS-FNA and cyst-fluid analysis was most effective (69).

In conclusion, in defining the nature of a pancreatic cystic lesion CT, MRI and EUS morphology may not be enough, EUS-FNA may be of some help, combining cytology, CEA and amylase levels in the aspirated fluid. Trucut biopsy is feasible but today we don't have any data about the role of the new pro-core needle. We know that the echobrush is feasible, it can give us some better result compared to standard FNA, but complication risks must be

considered. For the initial setup EUS and secretin MRCP are the best. Management decision should be individualized based on surgical candidacy, expertise and life expectancy. MRCP +/- EUS are the best for follow-up (70).

### Current role of EUS in detection, diagnosis and staging of neuroendocrine tumors of the duodenopancreatic area

NETs of the duodeno-pancreatic area pose various problems in terms of diagnosis, detection, staging and treatment. Correct preoperative diagnosis, detection and staging are mandatory in these cases, to select treatment options, type of surgical intervention and to optimize the curative approach itself, limiting time and complexity of surgical intervention, thus contributing to an improvement in results of surgery. In this clinical scenario the main endoscopic technique is represented by EUS. In the past, the only endoscopic procedure that had a role in the diagnosis of NETs of the pancreas was the ERCP, which today has completely lost any diagnostic role (replaced by magnetic resonance cholangiography and by EUS), but it has kept an exclusively operative space when drainage of the biliary tree or the pancreatic ductal system is necessary. The EUS characteristics of pancreatic NETs are in most cases represented by a homogeneous echo-pattern, often hypoechogenic, rarely non-homogeneous, with cystic or calcified areas, whilst margins are clear in over 84% of patients, sometimes having a hypoechogenic border (71). In several studies, albeit with small numbers due to the rarity of the disease, EUS demonstrated high sensitivity and specificity in diagnosing NETs of the pancreatic-duodenal area, with correct detection between 57% and 89% (71-74). Sensitivity is between 80% and 90% for tumors discovered in the pancreas, whilst it drops to 30-50% for lesions located outside the pancreas, mainly gastrinomas of the duodenal wall. The most sensitive technique for detecting these latter lesions remains intraoperative endoscopic transillumination (approximate 83%) and duodenectomy can increase sensitivity by a further 15% (75). Even though it is an extremely operator-dependent procedure and its diffusion is not completely adequate, EUS has proven to be an accurate means of preoperatively detecting small NETs of the pancreas, it is the most sensitive preoperative detection and staging technique in this clinical field and it should be used at an early diagnostic stage, as it has also proven to be cost-effective (less expensive, time saving, reduced morbidity compared with other more invasive procedures).

It must be said, however, that advancement of radiologic techniques over the last few years, especially the MDHCT,

but also MRI, in terms of software and hardware, has been enormous and in the more recent comparative studies between EUS and multi-phase spiral CT the difference in sensitivity between the two methods, for example in localizing pancreatic insulinomas, would appear to be reset to zero, even though there are few comparative data reported in the literature to prove this. It can therefore be asserted that the most efficient tool for detecting insulinomas of the pancreas is a combined imaging protocol that consists of both MDHCT and EUS (76,77).

Preoperative detection of gastrinomas continues to be a problem, mainly because over the years they have often been reported as having an extrapancreatic site (up to 50% of cases). The pancreatic localization is not, as previously believed, almost exclusively in the head (the so-called gastrinoma triangle), but they are increasingly detected in the body/tail of the pancreas. Lesions located in the duodenal wall are smaller than those in the pancreas (9.6 vs. 28.7 mm). There are no data in the literature to confirm that spiral CT for gastrinomas has filled the sensitivity gap of EUS, as occurred for insulinomas. The EUS sensitivity for the detection of pancreatic gastrinomas is between 75% and 94%, for peripancreatic lymph nodes it is between 58% and 82%, whilst it drops to 11-50% for gastrinomas of the duodenal wall (77). Problems return again in the MEN-1 syndrome, where many tumors are small in size (1.1 cm) and they are often multiple (median 3.3 lesions/patient). In this clinical setting an EUS follow-up carried out for 8 years on 13 MEN-1 patients, revealed the onset of pancreatic tumors in 11 cases (78). It would seem that an aggressive screening programme with EUS in these patients, leading to early surgical treatment, could improve prognosis (79-81), but there is no agreement in the literature. Nevertheless, various papers demonstrated the efficacy of EUS in detecting and following small endocrine tumors of the pancreas in asymptomatic patients with MEN-1 syndrome (78-81).

The electronic linear scanning instruments introduced in the 1990s, made it possible to perform EUS-guided FNA, with increased EUS specificity for example in the diagnosis of pancreatic carcinoma and metastatic lymph node involvement (20). Some papers have been published demonstrating the usefulness of EUS-guided FNA also for the diagnosis of functioning NETs of the pancreas (80) and functioning and non-functioning NETs (82-88). As for pancreatic carcinoma, the superiority of EUS-FNA versus CT-FNA has been also demonstrated for pancreatic NETs (88). The possibility to predict biologic behaviour and outcome by means of molecular biology techniques applied to the EUS-FNA cell sample has also been described. This approach allows to limit the number of false positive findings of the morphologic EUS test alone, which may be

due to intra- or peri-pancreatic lymph nodes or splenosis nodules. A methylene blue tattoo can be made with EUS-guided injection on a small NET of the pancreas in order to facilitate intraoperative localization. Both linear and radial new generation electronic EUS scopes enable application of pulsed colour and power Doppler functions, more recently associated with the use of ultrasound contrast media. These techniques can help in localization and differential diagnosis of small hypervascular pancreatic nodules (89).

### A look in the near future

IntraDuctal UltraSound (IDUS) and 3-Dimensional IDUS will perhaps add something to the already high performances of EUS in diagnosis and staging of biliary and pancreatic diseases (90). A new frontier in diagnosis and therapy could be opened by a new technique, named Endoscopic Ultrasound Retrograde CholangioPancreatography (EURCP) (91), that with some needed technological advances will allow us to put together in the same instrument the diagnostic accuracy of EUS and EUS-FNA with the therapeutic possibilities of ERCP and EUS. With such an instrument in experienced hands we can predict that the benefits to the patients and the health care system will be substantial. Today EUS is following the same way as endoscopy, i.e., to cross the bridge between a mere diagnostic technique and a therapeutic modality. In this view EUS can guide or better will guide in the near future a number of therapeutic procedures, such as ablative techniques (92,93), injection therapies (94,95), creation of digestive anastomoses (96,97). Regrettably these new techniques have progressed very slowly till now for several reasons (small number of operative endosonographers, very little incentive by manufacturers to put substantial resources into EUS and accessories development because the market is too small, the competition of CT, MRI and vascular interventional radiology).

### Conclusions

To date the most accurate imaging techniques for the pancreas remain CE MDHCT and EUS. They provide the most cost-effective and accurate modalities for diagnosis and staging of most cases of pancreatic diseases. CE spiral CT or better MDHCT must today be the initial study of choice in patients with suspected PC. It has replaced digital subtraction angiography for evaluation of vascular infiltration and has similar or higher accuracy than EUS in assessing locoregional extension and vascular involvement. EUS has the highest accuracy in detecting small lesions, in assessing tumor size and lymph nodes involvement. After

CE spiral CT or MDHCT or MRI as the first diagnostic tool, it remains the need of EUS as a second step in several cases: negative results on CT/MRI scans and persistent strong clinical suspicion of PC, doubtful results on CT or MRI scans, need for cyto-histological confirmation. However it remains true that the choice of diagnostic and staging modalities varies among different centers depending on the local availability of the high-end imaging techniques and operators expertise. As far as the evolution of EUS-guided therapeutic procedures is concerned, to our view, there will be in the near future great opportunities for the development of diagnostic and therapeutic EUS and pancreatic pathology will be the best testing bench for the new era of EUS.

### Acknowledgements

*Disclosure:* The authors declare no conflict of interest.

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**Cite this article as:** De Angelis C, Brizzi RF, Pellicano R. Endoscopic ultrasonography for pancreatic cancer: current and future perspectives. *J Gastrointest Oncol* 2013;4(2):220-230. doi: 10.3978/j.issn.2078-6891.2013.002