Pancreatic Cancer Imaging: The New Role of Endoscopic Ultrasound

Claudio De Angelis¹, Alessandro Repici², Patrizia Carucci¹, Mauro Bruno¹, Matteo Goss¹, Lavinia Mezzabotta¹, Rinaldo Pellicano¹, Giorgio Saracco¹, Mario Rizzetto¹

¹GastroHepatology Department, ‘San Giovanni Battista’ Hospital, University of Turin. Turin, Italy.  ²Gastroenterology Unit, IC Humanitas. Rozzano (MI), Italy

Summary

Pancreatic cancer is the most deadly of all gastrointestinal malignancies and has a very poor prognosis. Unfortunately, most patients present late in the course of their disease and, at the time of diagnosis, only 10 to 25% of patients will be eligible for potentially curative resection. Efforts must be oriented towards an early diagnosis and towards reliably identifying patients who can really benefit from major surgery. A suspected pancreatic tumor can be a difficult challenge for the clinician. In the last ten years, we have witnessed notable technological improvements in radiological and nuclear imaging. Taking this into account, we will try to delineate the new role of endoscopic ultrasound (EUS) in pancreatic tumor imaging and to place EUS in a shareable diagnostic and staging algorithm. To date, the most accurate imaging techniques for pancreatic neoplasms remain contrast-enhanced computed tomography and EUS. EUS has the highest accuracy in detecting small lesions, in assessing tumor size and lymph node involvement, but helical CT must still be the first choice in patients with a suspected pancreatic tumor. However, after this first step, there is a place for EUS as a second diagnostic level in several cases: negative results on CT scan and persistent strong clinical suspicion of pancreatic cancer, doubtful results on CT scans or the need for cytohistological confirmation. In the near future, there will be great opportunities for the development of diagnostic and therapeutic EUS and pancreatic cancer could be the best testing ground.

Introduction

Pancreatic cancer is the most deadly of all gastrointestinal malignancies, the fourth leading cause of cancer-related deaths in the United States and has a very poor prognosis; almost all pancreatic cancer patients will die from this disease. The 5-year survival rate is less than 5% [1]. Pancreatic cancer is a major health problem for several reasons: the aggressive behavior of the tumor and the relative frequency which appears to be increasing; approximately 30,000 new cases in 2002 and about 32,000 in 2004 were diagnosed in the United States [1]. Unfortunately most patients present late in the course of their disease with advanced cancer either locally or with metastatic spread [2, 3]. Even though surgery represents the only chance for cure, at the time of diagnosis only 10 to 25% (in the more optimistic series) of pancreatic cancer patients will be eligible for potentially curative resection [3, 4, 5, 6] and the prognosis remains dismal even for patients with potentially curative resections. This is clearly demonstrated by a 5-year survival rate which does not surpass 20% even after surgical resection [7, 8, 9]. Furthermore if we consider the high cost of
major pancreatic surgery, not only in terms of money but also in terms of morbidity and mortality even in the most experienced surgical hands [10, 11], it is clear that all our efforts must be oriented towards the need for an early diagnosis and towards reliably identifying patients who really can benefit from major surgical intervention. A recent study [12] indeed found that we could achieve a complete resection with negative margins in almost half of 53 patients with suspicion of locoregional pancreatic cancer when state-of-the-art preoperative imaging is used.

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 proven locoregional pancreatic cancer. Over the years, this has led to a complex range of diagnostic proposals which are summarized in Figure 1. Nevertheless, sometimes we need all the same cytological and histological confirmation.

A suspected pancreatic tumor can be a difficult challenge for the clinician; 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 pancreatic cancer is established, you need the most accurate preoperative staging to select patients which can benefit from curative resections. Modern imaging techniques such as transabdominal ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI) and endoscopic ultrasound (EUS) are less invasive and less costly than surgery. For years, EUS has been considered to be the best available technique for imaging the pancreas but, in the last ten years, we have witnessed notable technological improvements of the radiological and nuclear imaging techniques which have arrived in rapid succession. Taking into account the rapid increase in the sensitivity and accuracy of these new technologies, we will try to delineate the new role of EUS in pancreatic tumors imaging and to place EUS in a shareable diagnostic and staging algorithm.

**The Challenge of EUS**

EUS has been one of the most important innovations which have occurred in gastrointestinal endoscopy during the last 25 years. It has extended the range of possibilities for endoscopic diagnosis, supplying the endoscopist with the unequalled opportunity of seeing not only the mucosal surface but within and beyond the wall of the gastrointestinal tract (Figure 2).
EUS was introduced in the early ‘80s [13, 14, 15] to overcome difficulties in visualization of the pancreas on transabdominal US. For many years, it was a mere imaging modality, but the development of new electronic instruments with linear or sector scanners allowed the visualization in the echographic field of a needle emerging from the operative channel of the echoendoscope thus guiding the needle in the target lesion both within and outside the gastrointestinal wall. Therefore, in the early ‘90s, we witnessed the birth of both diagnostic and therapeutic interventional EUS.

For many years, EUS has been advocated as the best available technique for imaging the pancreas. 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 due to the small distance between the transducer and the gland which allows the use of higher frequency probes, from 7.5 to 20 MHz, with lower penetration depth but more elevated spatial resolution [16]. One of the more relevant advantages of EUS compared with other imaging techniques, such as transabdominal US, CT and MRI, was the superior parenchymal resolution (Figure 3). This accounts for the results of several studies in the ‘90s which established the greater sensitivity of EUS (98%) for diagnosing pancreatic cancer in comparison to all the other imaging modalities, i.e. US (75%), CT (80%, even with pancreatic protocols), angiography (89%) etc. [17, 18, 19, 20]. The results of EUS were even better in small tumors, less than 2 or 3 cm in size, where the sensitivity of US and CT decreased to only 29% [17, 18, 19]. 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 of nearly 100% [21, 22]. MRI, developed in the early 90’s, has also enjoyed great improvement in technology and software in the last ten years, with the addition of 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, magnetic resonance imaging to date should not be considered the first choice in pancreatic cancer diagnosis and staging even though MRI may be useful in the detection and characterization of non-contour-deforming pancreatic masses, more sensitive than CT in the detection and characterization of small liver metastases and peritoneal and omental metastases [16, 23].

Therefore, in the last ten years, EUS has had to bear the weight of the rapidly evolving technology of radiological imaging modalities and finally also the advent [24] and the evolution of nuclear imaging such as positron emission tomography (PET) and the integrated PET/CT approach, aimed at overcoming the major disadvantage of PET scan (i.e., the limited anatomical information) [25, 26, 27].

In this challenge, EUS has mainly been supported by the advent of interventional EUS (EUS-FNA). In contrast to the very high sensitivity previously shown, the specificity of EUS is limited, especially when inflammatory changes are present. 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 sacrificing too much in terms of sensitivity [28].

In short, the development of modern imaging modalities has limited or almost annulled the advantage of EUS in terms of sensitivity,
accuracy for T and N staging and prediction of resectability (i.e., detection of vascular infiltration) in the preoperative evaluation of pancreatic cancer. Multiple published studies [12, 29, 30, 31, 32, 33, 34] with discordant results have compared EUS and CT or other imaging modalities used in detecting or diagnosing, staging and prediction of resectability of suspected or known pancreatic cancer. For example, in the study of Schwarz et al. [34], the diagnosis of periampullary tumors could be achieved with high sensitivity by EUS (97%) and spiral CT (90%). For small tumors the most sensitive method remains EUS which correctly predicted all lesions less than 2 cm. When comparing accuracy rates for resectability, EUS was the leading modality, but the variance when compared with spiral CT was not significant. In a recent systematic review of DeWitt et al. [35] comparing EUS and CT for the preoperative evaluation of pancreatic cancer, the authors concluded that the literature is heterogeneous in study design, quality and results. There are many methodological limitations which potentially affect validity. Overall, EUS is superior to CT for detecting pancreatic cancer, for T staging and for vascular invasion of the splenoportal confluence. The two tests appear to be equivalent for N staging, overall vascular invasion and assessment of resectability. The optimal preoperative imaging modality for the staging and assessment of resectability of pancreatic cancer remains undetermined. Prospective studies with state-of-the-art imaging are needed to further evaluate the role of EUS and CT in pancreatic cancer. Furthermore, we should refrain from the idea that investigations only exist to compete with one another, but, instead, accept that different technologies often provide complementary information which ultimately results in optimal patient care. An overriding principle of care should be that patients should first undergo the least invasive, least harmful and most widely available examination [36]. Moreover, we must consider the fact that EUS can not identify distant metastases, is still not universally available and is, to a high degree, operator dependent. Thus spiral CT, or better MDHCT, must today be the initial study of choice in patients with suspected pancreatic tumors.

**Current Role of EUS in Pancreatic Cancer Diagnosis**

Starting from the above-mentioned concepts, we will propose a diagnostic algorithm in the case of suspected pancreatic cancer, trying to place EUS in shareable and evidence-based positions inside this algorithm. It is summarized in Figure 4. In this chapter, we will discuss some clinical scenarios in order to better understand the diagnostic algorithm. As we have already mentioned, in the case of clinical suspicion of pancreatic cancer, the initial study of choice should be a spiral or multidetector CT; if there is a pancreatic cancer with distant (hepatic for instance) metastases, there is no place for EUS in this clinical setting. In the first scenario, otherwise, the CT scan can be negative for a pancreatic pathology; in this case we must search for other causes to account for the patient’s symptoms, but if the suspicion of pancreatic disease remains strong, you must proceed to EUS. If EUS shows a pancreatic lesion, you can biopsy it (EUS-FNA), just refer the patient to a surgeon or propose a follow-up of the detected lesion if the EUS diagnosis leans towards a benign process. If pancreatic EUS is negative, you can...
reasonably exclude pancreatic disease. This is why EUS is the test with the best negative predictive value for the pancreas [37], approaching 100%.

In the second scenario, the CT scan shows some doubtful pancreatic changes or inconclusive imaging such as small (less than 2 cm) masses, fullness, enlargement or prominence of the gland. The clinical significance of these indeterminate CT findings has not been established; however, in a clinical setting with a suspicion of pancreatic cancer, they are very worrisome. In this case, EUS is also indicated and again we can rely on its high negative predictive value [38], with the possibility of real-time EUS-guided FNA which has been demonstrated to be useful for overcoming EUS specificity problems in the differential diagnosis between malignancy and inflammation [28, 38].

In the third scenario, CT imaging is positive for pancreatic cancer. Contrast-enhanced MDHCT is highly accurate for the assessment of pancreatic cancer staging and resectability [39]. If the tumor is deemed resectable, the patient can go straight to surgery, even if some authors, in order to reliably identify patients who might really benefit from major surgical intervention, recommend EUS to be performed as a second staging modality [16, 40]. A cost minimization analysis strengthened the sequential strategy, MDHCT followed by EUS, in potentially resectable cancers [39]. If both methods confirm resectability, the patient is referred to the surgeon and there is general agreement between experts and the literature that FNA is not necessary for resectable cancers. Moreover, in some cases, one can argue that not all pancreatic tumors are ductal adenocarcinomas: endocrine neoplasias, lymphomas, solid-papillary tumors, metastatic cancers, such as metastases from the breast, kidney, adrenal gland etc. can be found in the pancreas and they may have varying prognostic outcomes and require different treatment approaches. In this case, if there is any imaging or clinical doubt about the nature of the mass, FNA may be advisable even in the presence of a resectable pancreatic mass [16, 41]. On the other hand, if MDHCT shows a non-resectable pancreatic tumor, histological or cytopathological confirmation is needed in order to guide the patient to protocols of palliative radio- or chemotherapy [16, 42]. In a few cases, it has also been shown that EUS rendered the patient available for surgical resection, demonstrating that MDHCT overstaged the tumor.

To tell the truth, a negative predictive value of 100% for EUS in pancreatic tumors cannot be completely trusted; in a multicenter retrospective study [43] 20 cases of pancreatic neoplasms missed by nine experienced endosonographers were identified. Factors which can cause a false-negative EUS result include chronic pancreatitis, diffusely infiltrating carcinoma, a prominent ventral/dorsal split and a recent (less than 4 weeks) episode of acute pancreatitis. The authors suggest that, if a high clinical suspicion of pancreatic cancer persists after a negative EUS, a repeated examination after 2-3 months may be useful for detecting an occult pancreatic neoplasm.

**When Do We Need Cytological or Histological Diagnosis?**

There is only one answer to this question, namely when the information obtained can change patient management. Therefore, we need cytopathological confirmation:

1. in patients with unresectable pancreatic masses or not eligible for surgery prior to starting palliative radio- or chemo-therapy (this is the main indication for pathological confirmation in pancreatic cancer) [16, 42];
2. 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 [41];
3. when the patient, or sometimes also the surgeon, wishes to have a cytopathological confirmation of the cancer before engaging in a major surgical intervention;
4. for a differential diagnosis between carcinoma and mass forming pancreatitis.
The differentiation of a malignant from an inflammatory tumor, especially in a setting of chronic pancreatitis, 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 in one of the most frequent differential diagnostic dilemmas in pancreatic diseases. The positive predictive value of EUS for pancreatic cancer was only 60% in patients with concurrent chronic pancreatitis [44]. In this case, histological confirmation may be of outstanding value, and EUS-FNA also showed some limitations in the presence of chronic pancreatitis, in particular, a lower sensitivity in comparison to patients without chronic inflammation (73.8% vs. 91.3%, P<0.02) [45]. The authors suggest some tips for improving the yield of pancreatic mass EUS-guided FNA in the setting of chronic pancreatitis: more FNA passes, repeating the procedure, on-site cytologic interpretation, the sampling of suspicious non-pancreatic lesions, such as lymph nodes or liver lesions, the use of core-biopsy needles and the cooperation of an experienced pancreatic cytologist. The impact of an expert cytopathologist on the diagnosis and treatment of pancreatic lesions in current clinical practice is well demonstrated in a series of 106 EUS-FNAs [46]; sensitivity increased from 72 to 89% due to the experience of the cytopathologist. In this difficult challenge EUS can be assisted by new technological advances such as contrast-enhanced imaging which increased the sensitivity of EUS in discriminating between focal pancreatitis and pancreatic cancer from 73 to 91% and the specificity from 83 to 93% [47] (Figure 5). Another new tool which, in the near future, could be useful in this setting is EUS elastography [48]. Allowing the visualization of tissue elasticity distribution, it may help in the differential diagnosis of focal pancreatic masses or in the differentiation of benign and malignant lymph nodes or various solid tumors. It could help EUS-FNA in targeting less fibrous areas inside the lesion of interest.

Figure 5. Contrast-enhanced EUS: a small hypo-echoic mass in the pancreatic head without any color-Doppler signal, showing a notable early vascular flare after intra-venous injection of an echo-contrast medium which suggests the neuroendocrine nature of the lesion.

How to Obtain Samples for Cytopathological or Histological Confirmation in Pancreatic Masses

Non-surgical pancreatic cytohistological 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 ranging from 33% to 57% and a specificity ranging from 97% to 100% [16, 49, 50, 51]. Even when ERCP-directed biopsies are added, the sensitivity does not exceed 70% [49, 50]. In a recent prospective study, Rosch et al. [15] compared ERCP-guided brush cytology, ERCP-directed biopsies and EUS-FNA for the diagnosis of biliary strictures. Biliarystenoses of indeterminate origin remain a difficult challenge, but EUS-guided FNA has been demonstrated to be superior to ERCP-guided techniques for pancreatic lesions (60% vs. 38%). Percutaneous FNA or a core biopsy of the pancreas using CT and transabdominal US has a success rate of 65 to 95% for detecting malignancies [52, 53, 54, 55] and is considered safe, with a mortality rate for abdominal biopsies of 1:1,000 [53, 56]. The development of instruments with electronic linear or sector scanners, equipped with color Doppler technology made FNA for cytology specimens guided by means of EUS possible. In the last ten years EUS-FNA was established as a low risk diagnostic tool in pancreatic cancer (Figure 6). Recently, we performed a systematic review and meta-
analysis of the literature in order to evaluate the accuracy of EUS-FNA in the diagnosis of cancer in solid pancreatic masses [57]; counting the atypical results as positive, we found a sensitivity of 0.880 (95% CI: 0.847-0.929) and a specificity of 0.960 (95% CI: 0.922-0.998); counting the atypical results as negative, the sensitivity was 0.812 (95% CI: 0.750-0.874) and the specificity was 1. Data in the literature on more than 1,880 patients demonstrated that EUS-FNA is highly accurate in diagnosing cancer in solid pancreatic masses. The complication rate of EUS-FNA is considered to be very low, ranging from 0.3 to 1.6% [28, 58, 59, 60]. Controversy has arisen about which is the preferred method of choice for obtaining pancreatic diagnostic tissue: the percutaneous approach with CT/US guidance or the endoscopic EUS-guided approach. To our knowledge, until now, there have only been retrospective studies [61, 62] and one prospective, randomized study [63] comparing the performance of percutaneous CT/US-guided FNA to EUS-guided FNA in pancreatic lesions. One retrospective analysis [61] suggested that the sensitivity of CT-FNA was superior to EUS-FNA (71% vs. 42%) while another retrospective study [62] found an equivalent accuracy between EUS-FNA, CT/US-FNA and surgical biopsies. In the only prospective, randomized, crossover trial [63] EUS-FNA was numerically, though not statistically, superior to CT/US FNA for the diagnosis of pancreatic cancer.

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

1. the ability to sample lesions (including lymph nodes) too small to be identified by other methods;
2. concern about cutaneous and peritoneal seeding: a study by Micames et al. [64] showed a lower frequency of peritoneal seeding in patients with pancreatic cancer diagnosed by EUS-FNA vs. percutaneous FNA; a shorter needle path, the use of smaller needles and the ability to biopsy the lesion through a segment of the gastrointestinal wall which becomes part of the resected specimen in case of surgery, thus minimizing the risk of needle-tract seeding;
3. the possibility of more confidently targeting small lesions adjacent to vessels using color Doppler capability or targeting lesions located in sites difficult to reach percutaneously;
4. the possibility of occasionally obtaining diagnostic and staging additional and remarkable information through a EUS examination;
5. there are some initial data about the superior cost-effectiveness of EUS-guided FNA in the evaluation of pancreatic head adenocarcinoma as compared to CT-FNA and surgery [65].

Finally, the true strength of EUS is the possibility of offering to patients and referring physicians a really ‘all-inclusive’ service. In a patient with suspected pancreatic cancer, EUS can, in a single step:

1. detect the lesion (diagnosis);
2. assess the local extent and vascular invasion of the tumor (staging and resectability assessment);
3. biopsy the lesion for cytopathological confirmation (EUS-FNA) if the tumor is deemed unresectable;
4. treat the pain (celiac plexus neurolysis) or even the jaundice (EUS-guided biliary...
drainage) (palliative treatment) if the patient is symptomatic.

However, at our institution, as well as in other centers all around the world, we are witnessing a clear trend toward an increased number of 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 centers [40, 63].

A Look in the Near Future

Intraductal ultrasound (IDUS) (Figure 7) and 3-dimensional IDUS will perhaps add something to the already high performance of EUS in the diagnosis and staging of biliary and pancreatic diseases [66]. A new frontier in diagnosis and therapy could be opened by a new technique, called endoscopic ultrasound retrograde cholangiopancreatography (EURCP) [67] which, with some necessary technological advances, will allow us to have the diagnostic accuracy of EUS and EUS-FNA and the therapeutic possibilities of ERCP and EUS in the same instrument (Figure 8). With such an instrument in experienced hands we can predict that the benefits both to patients and to the health care system will be substantial [67, 68]. Today EUS is going the same way as endoscopy, i.e. crossing the bridge between a mere diagnostic technique and a therapeutic modality. As such, EUS can or, better, will guide a number of therapeutic

![Figure 7. Intraductal ultrasound (IDUS): the miniprobe is inside a slightly dilated main pancreatic duct with a small collateral duct (a.). The miniprobe is inside the Wirsung duct and shows a small communication between the Wirsung and a complex cystic lesion (IPMN, branch type) (b.). The miniprobe in a dilated main pancreatic duct inside the pancreatic head shows a stone in the adjacent bile duct (c.).](image)

![Figure 8. Endoscopic ultrasound retrograde cholangiopancreatography (EURCP): the future challenge of putting together in the same instrument the diagnostic EUS capabilities with the therapeutic possibilities of EUS and ERCP.](image)

![Figure 9. Future possibilities of therapeutic EUS: ablative techniques.](image)
procedures in the near future, such as ablative techniques [69, 70, 71, 72, 73] (Figure 9), injection therapies [74, 75, 76, 77, 78, 79] (Figure 10) and the creation of digestive anastomoses [80, 81, 82, 83, 84, 85, 86] (Figure 11). Regrettably these new techniques have progressed very slowly until now for several reasons (a limited number of operative endosonographers, very little incentive by manufacturers to put substantial resources into the development of EUS and necessary accessories because the market is too small and the competition of CT, MRI and vascular interventional radiology).

**Conclusions**

To date, the most accurate imaging techniques for pancreatic cancer remain contrast-enhanced MDHCT and EUS. They provide the most cost-effective and accurate modalities for the diagnosis and staging of most cases of pancreatic malignancies. Contrast-enhanced spiral CT or better MDHCT must today be the initial study of choice in patients with a suspected pancreatic tumor. It has replaced digital subtraction angiography for the 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 node involvement. After contrast-enhanced spiral CT or MDHCT as the first diagnostic tool, there remains the need for EUS as a second step in several cases: negative results on CT scan and a persistently strong clinical suspicion of pancreatic cancer, doubtful results on CT or MRI scans and the need for cytohistological confirmation.

However, the fact remains that the choice of diagnostic and staging modalities varies among different centers depending on the local availability of high-end imaging techniques and operator expertise.

As far as the evolution of EUS-guided therapeutic procedures is concerned, in our opinion, there will be great opportunities for the development of diagnostic and therapeutic EUS in the near future and pancreatic cancer will be the best testing bench for the new era of EUS.

**Keywords** Biopsy, Fine-Needle; Diagnostic Imaging; Endosonography; Pancreatic Neoplasms; Tomography, Spiral Computed

**Abbreviations** EURCP: endoscopic ultrasound retrograde cholangiopancreatography; IDUS: intraductal ultrasound; MDHCT multidetector helical computed tomography

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Correspondence
Claudio De Angelis
Echoendoscopy Service and GEP Neuroendocrine Tumors Center
Department of GastroHepatology
San Giovanni Battista Hospital
University of Turin
C.so Bramante, 88
10126 Torino
Italy
Phone: +39-011.633.5558/5208
Fax: +39-011.633.5927
E-mail: eusdeang@hotmail.com; eusdeang@yahoo.it

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