MINI REVIEW

The place of endoscopic ultrasound in bilio-pancreatic pathology

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Available online 25 June 2010

Summary The place of endoscopic ultrasound (EUS) in malignant pathology of the pancreas is two-fold: (1) EUS is the best examination for the diagnosis of small tumours (<3 cm in diameter). Its sensitivity is greater than that of CT scan, percutaneous ultrasound or magnetic resonance imaging (MRI) and is equal to that of endoscopic retrograde cholangiopancreatography (ERCP) without sharing its invasive character; (2) EUS is also indicated in the assessment of locoregional extension of tumours judged resectable by tomodensitometric (TDM) (scanner) data. The performance of EUS seems to be greater than other imaging techniques for the diagnosis of vascular and lymph node invasion although recent studies report less good results than those of studies in 1992 to 1994, particularly for vascular involvement. Nevertheless, EUS cannot affirm the malignant or benign character of these pancreatic masses. The development over the last 20 years of linear sector-based EUS has enabled us to perform guided biopsies of such lesions. EUS-guided biopsy is today the best technique for obtaining the histology of a pancreatic mass, with a sensitivity of 85 to 87%. Furthermore, it also has a non-negligible impact on the deciding the treatment particularly in the case of adenocarcinomas (ADKP) not visible to TDM (scanners). This is currently of importance because trials are being developed of preoperative radio-chemotherapy for resectable lesions. Probably in the next future, contrast-enhanced EUS (CE-EUS) and elastography will improve the results of EUS and will be necessary for a precise local staging before treatment.

Introduction

Endoscopic ultrasound (EUS) of the digestive tract is a relatively recent technique since the first publications date from the early 1980s. The history of EUS can be divided into two parts, the first in the 1980s to 1990s, where EUS was essentially descriptive. During this period, EUS enabled us to better define the degree of locoregional extension of cancers of the oesophagus, stomach, pancreas [1] and rectum. It also enabled the diagnosis of stones of the common bile duct to be made in a less invasive manner than by endoscopic retrograde cholangiopancreatography (ERCP). But it rapidly became apparent that the specificity of the EUS images was low (around 50 to 60%), particularly for the diagnosis of neoplastic ganglions and pancreatic...
masses. The appearance in 1991 of sector-based linear probes enabled EUS-guided biopsies (EUSGB) to be made of these lesions [2]. This has enabled the specificity of EUS to increase significantly, particularly for the diagnosis of cancerous lesions (now about 95%).

Endoscopic ultrasound and staging of pancreatic cancer

The place of EUS in malignant pathology of the pancreas is two-fold:

- EUS is the best technique for the diagnosis of small tumours (<3 cm in diameter). Its sensitivity is greater than that of tomodensitometric (TDM), percutaneous ultrasound (US) or magnetic resonance imaging (MRI) and equal to that of ERCP without sharing its invasive character. Nevertheless, the specificity of EUS for differentiating a nodule of chronic pancreatitis (CP) from an adenocarcinoma (ADKP) remains poor;
- EUS is also indicated in the assessment of locoregional extension of tumours judged resectable on the basis of TDM. The performance of EUS seems superior to that of other imaging techniques for the diagnosis of vascular and lymph node (LN) involvement although recent studies report less favourable results than do studies dating from 1992 to 1994.

We are going to study the results of ultrasonic endoscopy in the assessment of resectability of pancreatic ADKP and compare these results with those of conventional examinations (percutaneous US, TDM [scanner], MRI and angiography).

Classification by endoscopic ultrasound of cancers of the pancreas

An EUS examination in the context of assessing the locoregional extension of a pancreatic tumour aims to answer these five questions:

- Is there venous involvement (portal vein, superior mesenteric vein, splenic vein)?
- Is there arterial involvement (superior mesenteric artery, celiac artery)?
- Is there LN involvement?
- Are there signs of peritoneal carcinosis (surge of ascites)?
- Are there secondary lesions on the left lobe of the liver?

The responses to these five questions will enable the tumour to be classified as:

- T1: tumour limited to the pancreatic gland without vascular involvement;
- T2: tumour exceeding the limits of the pancreatic gland without vascular involvement;
- T3: invasive tumour with an arterial or venous vascular structure;
- N0: no LN involvement;
- N1: presence of LN that appear to be malignant;
- M0: no distant LN or visceral metastasis or sign of peritoneal carcinomatosis;
- M1: distant LN: celiac node for tumour of the head, interaortico-caval LN, mediastinal LN.

Tumours classed as T3N0 or N1 must be considered non-resectable although it is accepted that the criteria of non-resectability are very variable from one surgical team to another. This is because some teams carry out resections/reconstruction of the portal vein if it is affected, although no increased survival has been reported with this type of surgical technique.

Role of endoscopic ultrasound in the diagnosis of pancreatic adenocarcinoma

EUS is the most appropriate exploration for the diagnosis of small tumours (<3 cm in diameter) of the pancreas. Its sensitivity is greater than that of CT scan, percutaneous US and MRI and similar to ERCP without the invasive component. Nevertheless, the specificity of EUS for distinguishing between a CP nodule and ADKP remains poor (60 to 75%). The major problem is the diagnosis of an ADKP that develops on CP because it is very difficult to recognize with certainty the malignant character of a hypoechoic area within CP tissue. Positive diagnosis requires a biopsy specimen.

For the diagnosis of pancreatic tumours, two studies have demonstrated that EUS is superior to helicoidal CT scan for small tumours measuring less than 25 mm. The first study reported by Midwinter et al. [3] compared 58 patients who underwent a helicoidal CT scan and an EUS. This study showed that EUS is more precise for the diagnosis and the location of small-sized pancreatic tumours less than 25 mm in diameter, and that EUS provides comparable results for diagnosis of invasion of the superior mesenteric or portal veins.

The second study by Bender et al. [4] used linear EUS in 65 patients with suspected pancreatic lesions on the helicoidal CT scan. EUS confirmed the pancreatic lesion in 33 patients and found a normal pancreas in the 32 others. When compared with the surgical findings, the specificity of EUS for the diagnosis of pancreatic cancer was significantly higher (P < 0.005) than that of the helicoidal CT scan (88% vs. 41%).

Finally, another study by Mertz et al. [5] compared positron emission tomography (PET) for the assessment of locoregional extension of pancreatic carcinoma. Sensitivity for diagnosis of pancreatic cancer was 93% with EUS, 87% for PET and only 53% for helicoidal scan. EUS was more sensitive than helicoidal scan for the diagnosis of portal invasion. Finally, PET diagnosed four metastatic localizations unrecognized with the CT scan. These authors concluded that EUS + PET combination was superior for the diagnosis and extension assessment of cancer of the pancreas.

Summarizing, today EUS is the best exploration for the diagnosis of small-sized pancreatic tumours; it is however still the second intention examination after helicoidal CT scan. The specificity of EUS for the diagnosis of pancreatic tumours is better than other explorations, a specificity that is further improved with addition of guided biopsy.
Results of endoscopic ultrasound by comparison with imaging methods for the assessment of locoregional extension of cancers of the pancreas

Evaluation of the T and N by endoscopic ultrasound: data from the literature

Data in the literature show that the reliability of EUS for locoregional staging of pancreatic cancer is 80 to 85% for tumoral staging and 72 to 75% for LN staging. These results were reported by Rösch et al. in 1995 in a series of 250 patients [6—16]. Accuracy of T staging was 80% and N staging was 72%.

In all these studies, the EUS data have been compared to the results of surgical exploration. Generally speaking, EUS will correctly classify a tumour of the pancreas in 80% of cases as regards the lesion itself and will correctly evaluate the ganglionic involvement in 72% of cases.

Moreover, the reliability of EUS does not vary according to the stage of the pancreatic lesion [17].

<table>
<thead>
<tr>
<th>Stage</th>
<th>Number of patients</th>
<th>Correct EUS staging</th>
</tr>
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<tbody>
<tr>
<td>T1</td>
<td>24</td>
<td>80%</td>
</tr>
<tr>
<td>T2</td>
<td>67</td>
<td>81%</td>
</tr>
<tr>
<td>T3</td>
<td>75</td>
<td>85%</td>
</tr>
<tr>
<td>N0</td>
<td>79</td>
<td>76%</td>
</tr>
<tr>
<td>N1</td>
<td>142</td>
<td>81%</td>
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</tbody>
</table>

Finally, EUS seems to be the best examination for evaluating the local extension of a cancer of the pancreas [17].

<table>
<thead>
<tr>
<th>Staging</th>
<th>Number of patients</th>
<th>EUS (%)</th>
<th>Ultrasound (%)</th>
<th>TDM (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T staging</td>
<td>82</td>
<td>35</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td>N staging</td>
<td>143</td>
<td>68</td>
<td>42</td>
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Evaluation of the vascular involvement

Invasion of the portal system. The early studies showed an 85% reliability. More, recently Rösch reported in 1995 [16] his experience where the reliability was close to 70 to 75%. The problem is the interpretation of the loss of the interface between the tumour and the wall of the portal vein. It’s very difficult to determine whether the loss of this interface results from tumour invasion or is simply an inflammatory reaction [3,10,12—14,16,18—20].

Arterial invasion. Few studies are to be found in the literature evaluating the performance of EUS in the evaluation of arterial involvement. Only three studies report the results of EUS in overall figures [“vascular involvement”] [11,12,21].

It would be difficult to assess the superior mesenteric artery with mechanical rotating probes. In their study of superior mesenteric region, Rösch et al. were only able to visualize this area in 75% of cases. It’s easier to assess this region with linear electronic probes.

Nodal invasion. The last problem is that of nodal extension, particularly in cases with an obstructive jaundice where inflammatory nodes of the hepatic pedicle are frequently encountered. The problem is even more difficult when EUS is performed after insertion of a biliary stent. Of course, in case of distant LN as mediastinal or aortico-caval LN an EUSGB is mandatory to differentiate inflammatory than malignant nodes.

The development of helicoidal CT scan has modified the data reported in the literature up through 1995. Legmann et al. compared EUS and helicoidal CT scan in 30 patients in assessing resectability. The authors found no difference between the two methods for diagnostic sensitivity (100% vs. 92%), positive resectability (93% vs. 93%), and finally negative resectability (86% vs. 100%). EUS could be more interesting for the diagnostic of distal nodal invasion particularly for celiac nodes for tumours of the head of the pancreas and lomboaortic nodes. Quite obviously, only guided biopsy can confirm tumour invasion of a LN.

Finally, EUS can evidence signs of peritoneal carcinomatosis such as minimal ascitis effusion around the stomach or the duodenum. This sign is pathognomonic for peritoneal carcinomatosis with a sensitivity around 85% in the absence of portal vein thrombosis. EUS provides also a precise assessment of the left liver and in certain case can evidence small metastasis less than 1 cm that can go unnoticed on CT scan.

Place of biopsy-guided by endoscopic ultrasound in solid tumours of the pancreas

The development of EUS has enabled us to have a more accurate picture of the spread of pancreatic tumours. Nevertheless, EUS is not able to confirm the malignant or benign character of such pancreatic masses. The development of the linear sector-based EUS technique over the last 8 years has enabled us to perform guided biopsies of these lesions [22—27].

Technique

Biopsies are performed at the end of US endoscopy examinations, the patient lying down on their left side. Neuroleptanaesthesia is generally necessary. The biopsy technique is quite simple, and takes place in the following sequence:

- the lesion is positioned on the needle’s exit path;
- the stylet is withdrawn, then the needle is inserted into the tumour. The operator can visualize the tip of the needle by US enabling its correct position in the lesion to be verified;
- aspiration is performed with the aid of a 20ml syringe as the needle makes to-and-fro movements within the tumour. One to three passages are usually necessary in order to obtain a micro-biopsy. It is currently possible to obtain micro-fragments of tissues in about 90% of cases with the Vilmann-Hancke type of needle, which is 22 gauge and 12 cm long. The micro-biopsies are obtained in the following manner:
  - all of the sample contained within the needle is withdrawn using a foam stylet that is introduced into the needle,
  - the sample is then placed in formaldehyde or cetylamine then completely enclosed in paraffin wax.

In contrast to American teams, we do not systematically administer an antibiotic injection after taking a sample.
At the end of the examination, it is necessary to monitor patients for at least 3 hours. Biopsies guided by EUS can be done on an outpatient basis in the majority of cases.

The main limits of the technique are size of lesion below 5 mm, depth of the lesion greater than 6 to 7 cm compared with the probe and a blood clotting problem (PT < 60%, platelets < 80,000/mm³).

Indications and results

Data from the literature

Our experience is based on around 1500 samples we have taken up to now. Samples have been taken from LN and mediastinal, celiac and pelvic masses, from sub-mucosal membrane tumours, from gastric linitis tumours with negative endoscopic biopsies and from pancreatic tumours. The best results are obtained from LN, anastomotic recurrences of tumours and extrinsic compressions in addition to pancreatic tumours. For the latter, the efficacy of EUSGB is best for lesions of small diameter (<4 cm). This is because the larger cancers are the site of necrosis and/or of intratumour fibrosis, both of which prevent good samples from being obtained.

If a “micro-biopsy” is obtained, it enables a more accurate histological diagnosis to be made and an accurate characterisation of the tissue in about 80% of cases of diagnosis of malignancy.

Furthermore, certain teams recommend the presence of an anatomical pathologist in the theatre in order to ensure the high quality of the sample.

No mention was found in the literature concerning the risk of spreading the cancer with this sampling technique.

The results quoted in the literature show an overall sensitivity of the technique varying between 76 and 91%, a specificity of 84 to 100% and a reliability of 78 to 94%. A prospective study [2] investigating 457 patients from four centres (Indianapolis, Copenhagen, Marseilles and Orange in California) was published. In the course of this study, the sensitivity of the biopsy was statistically better for LN (94%) and extra-luminal tumours (86%) than for parietal lesions (sub-mucosal tumours and large gastric folds) (61%; P < 0.001). On the other hand, there was no difference concerning the specificity for these three groups of lesions.

Another multicentre study carried out by the same centres concerned EUSGB of pancreatic tumours [28]. This study involved 164 patients; the average diameter of the lesions varied between 28.5 and 41.3 mm. The sensitivity, the specificity, the positive predictive value (PPV) and the negative predictive value (NPV) for the diagnosis of cancer of the pancreas turned out respectively to be 83%, 90%, 100% and 80% and the diagnostic reliability was 85%.

Impact of endoscopic ultrasound-guided biopsies on the process of diagnosis and/or therapy when faced with a solid tumour of the pancreas

The most important question is to know whether performing an EUSGB is able to modify the process of diagnosis and/or therapy. Concerning the process of diagnosis, it seems to be accepted that an EUSGB is the least aggressive technique (five minor complications in 457 samples, three of which were directly attributable to the biopsy: two episodes of fever that responded to antibiotics and one haemorrhage during the biopsy of a pancreatic cyst). The biopsies had been to obtain a characterisation of the tissue [2].

Moreover, EUSGB seem indispensable for pancreatic tumours, particularly those only visible to EUS. This is because the transgastric or transduodenal route of entry diminishes the risk of spread and for tumours of the head of the pancreas, the biopsy path will be operated at the time of the cephalic duodeno-pancreatectomy.

Regarding solid pancreatic masses, what is the impact of EUS on the treatment decided on? It is probably less than that which is reported in the literature. This has to do with the low specificity of EUS images and it is only due to guided biopsy that EUS will have a considerable impact on the treatment decision. We have carried out a prospective study [29,30] on the impact of EUSGB on 174 patients suffering from a pancreatic mass, and formed the following conclusions: 174 patients (90 M and 84 F) of average age 66 years have had a EUSGB for a solid pancreatic mass. Twenty lesions were sited in the uncinate process, 43 in the head region, 31 in the isthmus area, 41 in the body and 39 in the tail of the pancreas. The average diameter of the tumours was 29 mm (extremes: 8 to 40 mm) and 39 patients presented with a lesion of less than 20 mm in diameter. In each lesion upon which a biopsy was performed, one sample was taken for cytological study and one sample for micrhistological study. The patients’ dossiers were discussed by a medical team comprising gastroenterologists, surgeons, oncologists, radiologists and specialists in radiotherapy in order to decide how the result of the EUSGB might affect the choice of treatment.

The sensitivity, the specificity and the reliability of the EUSGB for the diagnosis of malignancy were respectively 87.2, 100 and 87.9%. In 143 cases, the EUSGB revealed a malignant tumour (107 ADKPs, 28 neuroendocrine tumours [NET], seven pancreatic metastases and one primitive lymphoma of the pancreas). In seven cases it revealed objects whose appearance was compatible with CP, on three occasions it showed an abscess following acute pancreatitis. In 21 cases, the EUSGB did not contribute to diagnosis, 19 of these were in ADKP, in one case a somatostatinoma and in one case a pancreatic sarcoma. Of the seven EUSGBs suggesting a CP nodule, five were confirmed by surgery and two by the course of the disease (absence of change followed by regression at 24 or 36 months). The diagnosis of pancreatic abscess was confirmed by the aspiration of pus and by the disappearance of the image 3 months later on a follow-up EUS. The result of the EUSGB modified or influenced treatment of the 28 NETs, the seven pancreatic metastases, the three abscesses, two of seven CP nodules and 70 of 107 ADKP that were not visible on TDM examination; this came to a total in 110/174 cases (63.2%). EUSGB is today the best technique for obtaining the histology of a pancreatic mass with a sensitivity of 85 to 87%. Furthermore, it also has a non-negligible impact on deciding what treatment to follow, particularly in cases of ADKP not visible to TDM. This is particularly important these days because trials are being developed of preoperative radio-chemotherapy for resectionable lesions.

More recently, we have published our results on 1544 patients having had an EUS-fine needle aspiration (FNA) [31], the result of the biopsy was confirmed either by surgical investigation or coelioscopy, or by the evolution and the
follow-up of the patients. A complication occurred in 15 patients (0.97%) it was about nine feverish episodes, about five acute pancreatitis and of one bleeding.

It is to be noted that only one of the four pancreatitis required a hospitalization of more than a week and complicated of a pseudo-cyst. All the feverish episodes answered an antibiotherapy (association of amoxicillin, clavulenic acid and of ciprofloxacin).

Finally, bleeding consisted of a wirsungorragia after EUS-FNA of a pancreatic tumour; this one had no hemo-dynamic consequence and did not require any transfusion, it stopped spontaneously.

As regards results, for the diagnosis of malignancy, sensitivity, specificity, predictive positive value, predictive negative value and the accuracy of EUS-FNA were respectively 84.6, 98.4, 99.6, 54.7 and 86.9% for the 1544 patients.

For the pancreatic (N = 534), we were interested only in the solid tumours, the cystic lesions were excluded from this study. EUS-FNA allowed to diagnose an ADKP in 331 cases, an endocrine tumour in 76 cases, a pancreatic metastasis in 28 cases, a nodule of CP in 25 cases, an pancreatic abscess in 17 cases, a pancreatic sarcoma in four cases, a primitive pancreatic lymphoma in five cases and a squamous cell carcinoma of the pancreas in three cases. Finally, in 45 cases, EUS-FNA was not contributory.

For these solid tumours of the pancreas, concerning the diagnosis of malignancy, sensitivity, specificity, accuracy of EUS-FNA were respectively 89.8, 98.8 and 90.1%. The 45 patients whose biopsy was not contributory, were operated and the pathologic resected specimen examination showed an ADKP in 28 cases, an endocrine tumour in three cases, a pancreatic sarcoma in one case and in 13 cases a nodule of CP.

Besides, EUS-FNA modified the treatment of 242 pancreatic tumours. It was about 91 ADKPs not diagnosed on CT or MRI and of 151 other masses, which were not ADKPs (76 endocrine tumours, 28 metastases, 25 CP, 17 abscess, four sarcomas, five lymphomas and three squamous cell carcinomas).

Globally, EUS-FNA has modified diagnosis and therapeutic decision in 1081 patients over the 1544 is in 70.1% of cases.

As regards the solid pancreatic masses, the impact of the echoendoscopie on the therapeutic decision is now well clarified in the literature [32–34]. Nevertheless, in our series, we show that this impact is rather important because it concerns 268 of 534 patients presenting a pancreatic mass, notably by showing an other histology than ADKP (endocrine tumour, pancreatic metastasis), but especially, it allowed to confirm the diagnosis of pancreatic cancer in 91 patients whose tumour had not been diagnosed with the conventional techniques (CT and MRI).

It seems so today that EUSGB is the best technique to obtain the histology of a pancreatic mass and that it also has a not unimportant impact on the therapeutic decision, notably in case of ADKP not seen in by Ct. Being this at present mattering because of the development of preoperative protocols of radio-chemotherapy for resectable tumours [35].

To summarize: we are talking about a simple technique, which can be performed after the linear sector-based EUS technique has been learned. It is currently possible to obtain material by biopsy in about 80 to 85% of cases, enabling the tissue to be characterised. The development of therapeutic protocols for preoperative radio-chemotherapy [30] for resectable pancreatic ADKPs requires a pre-treatment pancreatic biopsy to be taken. EUS with an electronic linear probe enables an accurate assessment of the degree of spread to be made at the same time, together with a guided biopsy of the lesion. The technique has a sensitivity of approximately 85% and does not carry the risk peritoneal spread described with the percutaneous route. Moreover, this biopsy enables lesions only visible to EUS to be characterised and cannot only be used for ADKPs.

**Future developments of pancreatic endoscopic ultrasound**

Two future developments are promising as elastography EUS and the use of US contrast agents.

**Endoscopic ultrasound elastography**

The introduction of EUS represented a major advance in the diagnosis and staging of gastrointestinal malignancies. In addition to providing imaging of tumours and enhancing TMN (malignancy [large node on CT]) staging, EUS also provides guidance for FNA and biopsies of undiagnosed masses and LN suspicious for malignant invasion, providing further diagnostic and staging information. However, FNA is technically demanding and multiple punctures of LN or masses are sometimes required to obtain sufficient tissue for histologic assessment. In addition, when several LN appear suspicious, the choice of which to puncture is not always clear. Current sonographic criteria for malignant LN (round, hypoechogenicity, diameter >1 cm, and distinct margins) are helpful in targeting lesions, but problems exist with specificity and overlap of these features with benign LN. For further consideration is the fact that pancreatic masses have a wide differential diagnosis that includes benign and malignant etiologies, and FNA of the pancreas is associated with a small, but not insignificant, risk of pancreatitis [36]. Hence, the ability to evaluate masses and LN more accurately prior to their puncture in an effort to aid in targeting lesions for FNA and possibly reduce complications would be welcomed by echoendoscopists. At least two strategies have been developed with these goals in mind: contrast-enhanced endosonography and sonoelastography.

**Theory and technical aspects of sonoelastography**

Sonoelastography is based on the knowledge that some diseases, such as cancer, lead to a change of tissue hardness (i.e., the so-called elasticity modulus) and is an outgrowth of the well-known breast US fremitus technique [37–39], during which the patient is asked to hum while color or power Doppler is used to examine the breast. Softer portions of the breast vibrate more in response to the humming, while cancers and other firm masses vibrate less and thus are seen as areas of decreased color, even if they are isoechoic on the ordinary B scan. Elastography examines the elastic properties of tissues by applying a slight compression to the tissue and comparing an image obtained before and after this compression. The before and after data are then compared, using a cross-correlation technique to determine...
the amount of displacement each small portion of tissue undergoes in response to the compression applied by the US transducer [40–42]. The elasticity modulus, i.e., the tissue elasticity distribution, can be calculated from the strain and the stress of the examined structures. While the strain field can be estimated from the radio frequency signals returned from tissue structures before and after compression, it is impossible to measure the stress field directly within the tissue. Another problem is that the compression of harder tissue structures is often followed by a lateral displacement of these structures [42]. It is nearly impossible to represent the volume of this sideslip with conventional 2-D methods, but its calculation is indispensable for an accurate determination of the tissue elasticity of the examined structures. To overcome these problems, the extended combined autocorrelation method has been developed, which allows the reconstruction of the tissue elasticity of the examined structures on the basis of the 3-D finite element model. The new technique enables highly accurate estimation of the tissue elasticity distribution and adequate compensation of sideslips. The elasticity imaging can be performed with the sonoelastography module that can be integrated into the platform of the Hitachi EUB-8500 system (Hitachi Medical Systems Europe, Zug, Switzerland).

Procedure technique and criteria
As with traditional color Doppler imaging, EUS tissue elasticity imaging is performed with conventional EUS probes and does not require additional instruments (e.g., for measuring pressure or producing vibrations). The vibrations and compressions are provided physiologically by vascular pulsation and respiratory motion. The calculation of tissue elasticity distribution is performed in real time and the examination results are represented in color superimposed over the conventional B-mode image.

To date, the majority of clinical research involving sonoelastography has been focused on the evaluation of breast masses. Three different patterns have been identified in elastograms of breast cancers: a well-defined, very hard (dark) mass or nodule; a moderately hard mass or nodule containing much harder (darker) foci within it; and a very dark or hard central core surrounded by a somewhat softer or less dark peripheral component [38]. Although with conventional US or EUS fibrosis generally appears as hyperechogenic regions with posterior acoustic shadowing (an appearance also seen in cancers), in elastography, it generally appears as a uniform, moderately hard region with no distinct foci of increased hardness. Preliminary work in breast tissue elastography has shown that it can correctly classify most benign and malignant masses [40].

Data on endoscopic ultrasound sonoelastography
A recent European study on EUS elastography has evaluated 222 patients [43]. The aim of this prospective multicentre study was to evaluate the ability of EUS elastography to distinguish benign from malignant focal pancreatic masses and LN and to compare the results with the conventional B-mode images and final histology.

The study results show that EUS elastography has high sensitivity, specificity and accuracy and a much higher specificity than conventional B-mode images to differentiate between benign and malignant focal pancreatic lesions. Using our current scoring system, 15.7% of the cases still obtain an elastography score equal to 3 indicating tissue difficulty to classify as benign or malignant. However, 84% of these cases with an elastography score equal to 3 turned out to be malignant and we believe that the soft tissue parts of these focal lesions on elastography represent necrotic areas in an ADKP (N = 15) or a hypervascularised area in an endocrine tumour (N = 1). Hence, an elastography score equal to 3 should be considered as malignant in our opinion.

There were seven false-negative cases (five ADKP and two NET) that may be explained in a similar way: the presence of abundant necrotic or vascular tissue resulted in an elastographic pattern mainly consisting of soft tissue. By contrast, the false positive cases in our study (N = 6) might represent patients with (early) CP having areas of hard fibrotic nodules. Unfortunately, lack of surgical specimens in these patients cannot confirm this hypothesis. However in a recent publication by Janssen et al. the elastographic patterns of the normal pancreas and the pancreas affected by inflammatory or focal disease were studied. They concluded that elastography does not distinguish between CP and tumours because of their similar fibrous structure. This implies that EUS elastography will not be able to help target suspicious lesions and improve the rather low accuracy of EUS-FNA in patients with CP.

In distinguishing benign from malignant focal pancreatic lesions, EUS elastography does not replace tissue confirmation and we believe that EUS elastography should not be used as a first line examination in the evaluation of focal pancreatic lesions. However, when facing (repeated) negative EUS-FNA or technical problems to perform EUS-FNA, the interpretation of the EUS elastographic images could help orientate the diagnosis and influence the decision making for surgery when the lesion is suspicious on elastography or justify a follow-up when the elastographic images are in favour of a benign lesion.

For both pancreatic masses and LN EUS elastography might also help guiding the puncture in a non-necrotic part of the suspicious lesion when there is presence of necrotic tissue as in advanced cancer.

One of the main criticisms of the EUS elastography is the variability of the elastographic image and the difficulty of interpretation [44]. However, our interobserver study showed a satisfying interobserver concordance for the differentiation between benign and malignant pancreatic masses and LN (kappa = 0.725).

In the absence of pathologic assessment of surgical specimen, we considered the EUS-FNA result as a gold standard. Although the specificity of EUS-FNA is close to 100% [23–27] it has the potential to miss micro-invasion of malignancy into LN or to give false-negative results in a necrotic pancreatic lesion. However, we consider it as representative of daily practice particularly when it is combined with an adequate clinical and imaging follow-up period.

To overcome the difficulty in classifying the EUS elastography score equal to 3 or B as benign or malignant, we are currently evaluating the next generation of elastography software. This new software provides a quantitative histogram analysis of the elastographic images and has already proven to be useful in the evaluation of LN [18].
The potential role of EUS elastography to help detect and differentiate sub-mucosal tumours as well as any other solid masses situated nearby the gastrointestinal tract has still to be evaluated. The exact role of EUS elastography in patients manifesting symptoms suggestive of CP with equivocal EUS (three features or fewer) has still to be validated [45].

**Endoscopic ultrasound and ultrasound contrast agents**

Diagnosis between ADKPs and nodular CP is problematic. All methods of diagnosis are limited. Histology is the standard, but even biopsy can be difficult because cancers can produce a marked fibrotic reaction or necrosis, and give false results. For ERCP, sensitivity and specificity are, respectively, 85 and 66% when there is a stenosis of the main pancreatic duct [46]. Magnetic resonance cholangiopancreatography (MRCP) has a similar sensitivity and specificity for detecting pancreatic cancer or CP as that of ERCP.

Nevertheless, sensitivity is yet perfectible and MRCP gives a correct differentiation between malignant and benign lesions in 58% of cases [47,48]. MRCP remains an expensive procedure, is time consuming, and is available only in a few centers.

There are few studies about contrast-enhanced EUS (CE-EUS). In one of the first studies, Bhutani et al. [49] evaluated the utility of SHU508 A (Levovist®) and concluded it could potentially improve the accuracy of EUS in the diagnosis of malignant vascular invasion, in detection of occult pancreatic neoplasms, and in the diagnosis of vascular thrombosis. Subsequently, Hirooka et al. [50] studied the presence or absence of enhancement of different lesions with Albunex® in 37 patients. An enhancement of the lesion was observed in 100% of the patients with islet cell tumour, in 80% with intraductal papillary mucinous tumour (IPMT), in 75% with CP, and no enhancement effect was observed in the patients with carcinoma. All patients underwent angiography, and comparison between images of CE-EUS and angiographic images showed similar results, except for three patients (two IPMT and one CP) in whom angiograms were hypovascular, but enhancement effect was observed on EUS images. Finally, Becker et al. [51] showed their experience in 23 patients with another contrast agent (FS 069 Optimon®) and evaluated CE-EUS as a method of differentiating inflammation and carcinoma based on perfusion characteristics. Markedly hyperperfused lesions were considered as inflammatory pseudotumours, whereas hypoperfused lesions compared to surrounding tissue were considered as carcinomas. Sensitivity for differentiation of pancreatic carcinoma vs. inflammatory changes was 94%, specificity was 100%, PPV was 100%, NPV was 88%. These results are very similar to ours [52] (sensitivity: 90.9%, specificity: 88.8%, PPV: 88.2%, and NPV: 91.4%). In our study [52], we also studied hyperechoic lesions (supposed not to be a pancreatic ADK), and sensitivity was 88.8%, specificity was 90.9%, PPV was 91.4%, and NPV was eight88.2%. In future, CE-EUS could allow us to have a direct and reliable result (malignant or not) without waiting several days for histological findings. Perhaps it could also save time and money in limiting the use of expensive EUS needles. CE-EUS could be an interesting complement to EUS-FNA concerning diagnosis accuracy. EUS-FNA sensitivity and diagnosis accuracy are, respectively, 75 to 92% and 79 to 92% [53–58]. First reason, EUS-FNA is not realizable in 6 to 9% of cases owing to vessel interpositions, duodenal stenosis, and tumoral hardness, particularly in CP. Then, sensitivity of the EUS-FNA is limited by uninterpretable material (bleeding or noncellular samples) ranging from 9 to 19%. Totally, the lack of sensitivity of EUS-FNA ranges from 8 to 25% of cases [51]. In our work [52], sensitivity and diagnostic accuracy of this technique were comparable to cytopathology results guided by EUS (sensitivity 90.9%, specificity: 88.8%, PPV: 88.2%, and NPV: 91.4%). From a more general point of view, 97% of hyperechoic lesions were malignant tumours (30 ADKP, one endocrine tumour, one pancreatic lymphoma, one pancreatic metastasis from colonic cancer). Therefore, CE-EUS could appear like a reliable and complementary tool for EUS-FNA in detection and classification of pancreatic lesions when EUS-FNA is impossible or biopsy uninterpretable. CE-EUS could improve accuracy and allow us to propose an appropriate treatment (surgery, follow-up, chemotherapy, etc.).

CE-EUS could allow us to differentiate malign tumour from pseudotumoral nodule. CP is also a limiting factor for diagnosis of pancreatic masses. Several works have attempted to establish EUS imaging criteria (without tissue sampling) for the discrimination of benign inflammatory pseudotumours and tumours. Despite the high resolution of EUS, it does not provide reliable differentiation of benign and malignant lesions of the pancreas [59]. Fritscher-Ravens et al. [19,34] found that sensitivity of EUS-FNA in patients with a focal pancreatic lesion without CP was 89%, while it was only 54% in patients with CP. Nevertheless diagnosis of EUS-FNA influenced clinical management in nearly half of patients [60]. CE-EUS could also play an important part in the case of lesions occurring within CP. Indeed, in the study of Hocke et al. [46,50], ADKP developed on CP was non-enhanced after contrast injection. Conversely, pseudotumoral nodule (benign masses) (91%) in CP was hypervascularized after sonovue injection.

CE-EUS could be useful in the case of negative results after EUS-FNA. In early studies, NPV of EUS-FNA was around 75%, but most recent studies found NPV between 26 and 44% [51–57]. In the work from Oshikawa et al. [61], the rate of patients with negative results of the first biopsy, but with malignant tumour diagnosed a second time with a new puncture or with surgery, was 47%.

To conclude, NPV of pancreatic EUS-FNA is 30 to 33%. Theoretically, a new puncture is mandatory to be sure that it is normal tissue. We can also imagine that CE-EUS could avoid this second procedure. With regard to false-negative results of Sonovue®, we found three ADKPs that presented hyperechoic aspect (enhancement contrast pattern). Two were poorly differentiated ADKP and the third was associated with IPMT. This suggests that poorly differentiated ADKP could have different vascularity of well-differentiated ADKP. These results were similar to studies with CE-EUS [62,63]. Differences in histology, such as histological differentiation grade, amount of fibrosis, and obliteration of blood vessels in the tumour, may be associated with differences in enhancement behavior.

Concerning CE-EUS and endocrine tumours, there is only one case report using Levovist® that seemed to be a useful
Bilio-pancreatic neoplasia: Place of EUS

443

diagnostic method for precise localization of small insulinoma [64]. In our study [52], 87.5% (7/8) of endocrine tumours had a strong contrast-enhancement pattern, indicating hypervascular lesions. These results were similar to CE-EUS [59,62,63,65]. These vascular images differed from those of almost all pancreatic ductal carcinomas. Thus, differentiation of enhancement pattern on CE-EUS between pancreatic ADKPs and endocrine tumours is useful in the diagnosis of these lesions. In addition, “standard” EUS is already known to have a great value for localizing endocrine pancreatic tumours because of its excellent capacity to visualize small lesions and tumour vascularization at the same time [66,67]. Therefore, we are authorized to think CE-EUS could increase sensitivity of diagnosis of pancreatic tumours.

Regarding IPMT, in our study [3], the only benign tumour was hyperechoic, whereas in malignant IPMT, one was hypoechoic and another was hyperechoic. In CE-EUS studies, malignancy could be associated with contrast-enhancement. For Sofuni et al. [62], all (four patients) with IPMT showed hypervascularity of the nodules inside the tumours. For Nagase et al. [63], two of the five IPMT had solid components within the tumours and they were positive for enhancement effects. All five patients with IPMT underwent surgical resection and pathologic examination revealed malignancy in the two lesions with solid components and positive enhancement. For Itoh et al. [68], when the patients with carcinoma were compared with those with adenoma, the postenhancement intensity was significantly higher in the carcinoma group. CE-EUS could be useful for the differential diagnosis of benign and malignant IPMT.

The small number of patients with IPMT in each study did not allow conclusions.

Metastatic lesions of the pancreas are rare, between 5 to 10% [59], but an important cause of focal pancreatic lesions. There is only one description of one case of kidney metastasis analyzed in CE-EUS [60]. Our work [52] is the first in the literature that describes the enhancement pattern of pancreatic metastasis in CE-EUS. All metastasis except one (4/5; 80%) showed an echo-enhancement pattern, probably proving their hypervascularization. The only pancreatic metastasis non-enhanced was from colonic cancer. CE-EUS could provide a contribution to the differential diagnosis between a primary pancreatic carcinoma and a pancreatic metastasis, and therefore can have a decisive influence on the selection of appropriate therapeutic strategies (chemotherapy rather than surgery, for example). However, histology remains the standard in the differential diagnosis of pancreatic tumours.

Conclusion

EUS is actually the best and the less invasive method for the diagnosis of small pancreatic tumour, the development of EUSGB has increased the specificity of the technique and showed that all pancreatic mass aren’t “ipso facto” an ADKP (about 70% of ADKP and 30% of other histology). The role of EUSGB will increase in the future with the development of preoperative treatment for resectable pancreatic cancer. The future development of the use of US contrast agents will increase the capability of this technique.

Conflict of interest statement

The author has not declared any conflict of interest.

References


