World Journal of Gastrointestinal Endoscopy

Online Submissions: http://www.wjgnet.com/1948-5190office
wjge@wjgnet.com
doi:10.4253/wjge.v2.i10.335

World J Gastrointest Endosc 2010 October 16; 2(10): 335-343
ISSN 1948-5190 (online)

REVIEW

Role of pancreatic endoscopic ultrasonography in 2010

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Received: January 20, 2010 Revised: September 4, 2010
Accepted: September 11, 2010
Published online: October 16, 2010

Abstract

Endoscopic ultrasonography (EUS) was introduced 25 years ago aiming at better visualization of the pancreas compared to transabdominal ultrasonography. This update discusses the current evidence in 2010 concerning the role of EUS in the clinical management of patients with pancreatic disease. Major indications of EUS are: (1) Detection of common bile duct stones (e.g. in acute pancreatitis); (2) Detection of small exo- and endocrine pancreatic tumours; and (3) Performance of fine needle aspiration in pancreatic masses depending on therapeutic consequences. EUS seems to be less useful in cases of chronic pancreatitis and cystic pancreatic lesions. Moreover the constant improvement of computed tomography has limited the role of EUS in pancreatic cancer staging. On the other hand, new therapeutic options are available due to EUS, such as pancreatic cyst drainage and celiac plexus neurolysis, offering a new field in which new techniques may arise. So the main goal of this review is to determine the exact role of EUS in a number of pancreatic and biliary diseases.

Key words: Endoscopic ultrasonography; Fine needle aspiration; Acute biliary pancreatitis; Chronic pancreatitis; Pancreatic masses; Cross-imaging modalities

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Papanikolaou IS, Karatzas PS, Triantafyllou K, Adler A. Role of pancreatic endoscopic ultrasonography in 2010. *World J Gastrointest Endosc* 2010; 2(10): 335-343 Available from: URL: http://www.wjgnet.com/1948-5190/full/v2/i10/335.htm DOI: http://dx.doi.org/10.4253/wjge.v2.i10.335

INTRODUCTION

Endoscopic ultrasonography (EUS) was introduced 25 years ago. Its purpose was improved visualization of the pancreas, particularly in comparison with transabdominal ultrasonography whereintervening air often hampers clear and full demonstration of the organ. The role of EUS in the management of pancreatic diseases should therefore be, per definition, vital. However, systematic data evaluating the real role of EUS to investigate the pancreas are scarce. This review discusses the current evidence (in 2010) concerning the role of EUS in the clinical management of patients with pancreatic disease. Major indications of pancreatic EUS, including its role in choledocholithiasis (e.g. in acute pancreatitis), the diagnosis of endocrine tumours, as well as less pivotal indications like chronic pancreatitis, or pancreatic cancer staging, will be analyzed.

ACUTE BILIARY PANCREATITIS: ROLE OF EUS

The main goal of imaging techniques in clinical cases

of acute pancreatitis is to determine the severity of the disease, and to differentiate acute pancreatitis caused by stones of the common bile duct (CBD) from all other causes, as patients who suffer from CBD stones shall undergo emergency endoscopic retrograde cholangio-pancreatography (ERCP).

The diagnosis of CBD stones is probably one of the best indications of EUS. Results have been consistently accurate over the last years, independent of the level of stone likelihood, stone size and echo endoscope type[1]. It has been proven by a prospective randomized study, that EUS has fewer negative outcomes (10%) when compared to ERCP (40%) in patients with intermediate likelihood of bile dust stones. However, both EUS and ERCP are similarly accurate in diagnosing CBD stones in patients with acute pancreatitis[2-5].

Another indication of EUS is idiopathic acute pancreatitis (IAP)[6-8]. A prospective study from Spain has shown that EUS has great sensitivity in diagnosing cholelithiasis (including sludge) in both CBD and gallbladder. In it, 21 cases with biliary colic or recurrent pancreatitis with normal transabdominal US (performed twice) were included. The gold-standard test of ceruletide - induced aspiration and analysis was used, and proved that 100% of the patients suffered from microlithiasis. EUS diagnosed all cases but one. On the other hand, specificity data could not be derived from this study[9]. Another Spanish study recently confirmed the value of EUS in this setting. Here, 44 patients with idiopathic acute pancreatitis (IAC) were included and EUS identified the cause of IAP in 79% of patients[10]. Another study conducted in Wales, showed that EUS provides additional information in only 40.5% of patients with IAP (17 of the 42 patients included in the study)[11].

It therefore, seems possible that EUS is helpful in diagnosing CBD stones in acute pancreatitis with low to moderate likelihood. In other indications concerning acute pancreatitis, computed tomography (CT) is still the test of choice.

CHRONIC PANCREATITIS: ROLE OF EUS

The fact that EUS is quite accurate in the diagnosis of chronic pancreatitis has been shown in a variety of comparative studies[12,13]. However, as in moderate to advanced cases, other less invasive exams are available, the main interest in the gastroenterologic literature is focused on whether EUS would be capable of diagnosing the disease earlier than other tests[14,15]. In studies assessing patients with abdominal pain of possible pancreatobiliary origin, the rates of early pancreatitis have been quite high[16], so that some scepticism regarding the possible high rate of false positive diagnoses has been raised. In response to this concern, image parameters have been developed and linked to a scoring system to make the diagnosis of early chronic pancreatitis more or less likely[17]. According to up-to-date results, EUS shows good sensitivity but a weak specificity.

Two retrospective studies have tackled the issue. The first one was from Milwaukee, where 37 cases from 1993 till 1998 were diagnosed as early pancreatitis by means of EUS. These patients had negative CT results and secretin function testing. During the next 8.5 years, 67% of these patients developed signs of chronic pancreatitis in CT or secretin function testing[18]. In the second study, a group of 32 patients with normal ERCP and slightly abnormal EUS was followed-up; 69% of them developed signs of chronic pancreatitis in a mean of 18 mo[19]. The selection bias of these studies may, however, be substantial, since cases presenting again for assessment in retrospective studies are probably those with a higher likelihood of having the disease. Furthermore, these studies were undertaken in centres highly specialized in pancreatobiliary endoscopy, which could result into some referral bias.

Another area in chronic pancreatitis where the role of EUS in patients' work-up could prove important is chronic autoimmune pancreatitis. In a retrospective review of 3 cases, Levy *et al*[20] highlighted that the use of a trucut biopsy with positive immunohistochemistry for IgG4 could, in the appropriate clinical setting, spare the affected patient an unnecessary surgical intervention. However, as clearly demonstrated by the small number of patients, data on this topic are still too scarce to draw definite conclusions.

It therefore seems that EUS could play a significant role in early diagnosis of chronic pancreatitis, whereas in moderate to advanced forms of the disease, it has a more limited role. Moreover, EUS seems to be auspicious in the field of autoimmune pancreatitis.

PANCREATIC ENDOCRINE TUMOURS: ROLE OF EUS

Pancreatic endocrine tumours can be divided into two main categories:functioning and non-functioning tumours. EUS has been proven to be an excellent examination in the imaging of both categories[21-23].

In cases of functioning endocrine tumours, the diagnosis is made on the basis of laboratory tests. Imaging is used to localize the tumour for subsequent surgical removal. Moreover, pre-operative marking of the tumours has been suggested[24] but as yet has not proven as an established practice.

In contrast, non-functioning endocrine tumours are usually randomly found in transabdominal ultrasound or in abdominal CTs. EUS is the test of choice for localizing these tumours, which appear as well-demarcated, echo-poor lesions in the pancreas. EUS-fine needle aspiration (EUS-FNA) has been assessed to establish a tissue diagnosis[25-27], and further analyses from the specimens such as microsatellite loss analysis has been recently performed and is thought to be correlated to prognosis[28].

EUS is thus the gold-standard exam for localizing pancreatic endocrine tumours, but moreover offers the same potential of EUS-FNA, which in many cases can lead the management of the patient. In cases of non-

candidates for surgery, EUS-guided therapy using alcohol injection[29] can be considered, but must be weighed against potential complications, but, to date, no such evaluation has been carried out.

PANCREATIC CANCER: ROLE OF EUS

Cancers of the pancreas are usually visualized on EUS as more or less well demarcated echo-poor lesions, which - depending on their exact morphology and size - are homogeneous or inhomogeneous, with echo-rich spots or even cystic spaces[30,31]. Small pancreatic cancers can also be visualized as echo-poor and well demarcated lesions, thus resembling pancreatic neuroendocrine tumors, or may display a pattern of focal inhomogeneity. In more advanced tumour stages, pancreatic cancers become more inhomogeneous and start to infiltrate into neighboring organs, especially into large para-pancreatic vessels[32]. Before considering applying EUS, and in order to stay in line with previous consensus statements and publications of gastrointestinal endoscopy societies, the following prerequisites ought to be fulfilled: (1) Clinical consequences of applying EUS should be clear (e.g. the decision between surgery and palliation, or between a diagnosis that needs no further diagnostic and therapeutic steps, and a diagnosis that requires further tests); (2) Other modalities - i.e. mainly ultrasonography (US) or CT of the pancreas- should have established at least a tentative diagnosis that can be better characterized by EUS, or are inconclusive or negative, and the clinical suspicion remains; and (3) The suspected lesion should be accessible by endoscopy, i.e. within the reach of the echoendoscope. This is not the case when dealing with non-traversable strictures or post-operative anatomic conditions (e.g. pancreatic head in patients with Billroth Ⅱ operations).

EUS vs other imaging techniques in the diagnosis of pancreatic cancer

Nowadays, many different imaging techniques are available, and EUS is just one of the possible exams a clinician can perform. So a thorough comparison should be made in order to fully understand the value of each possible examination, especially EUS in different clinical cases. Several studies have supported the superiority of EUS when compared to other imaging modalities, especially when dealing with small tumours (e.g. < 2-3 cm)[33,34]. The potential of performing FNA during the same procedure has to be regarded as an additional advantage of EUS. Tumour detection with EUS has been remarkably high throughout the years, especially in cases of focal masses outside of fully developed chronic pancreatitis[27,35-37]. On the contrary, EUS cannot always fully visualize the pancreas, even though it scans stepwise from several stations in the duodenum and stomach.

The major advantage of imaging by means of EUS for pancreatic cancer (even in the era of recent imaging advances) seems to be its high negative predictive value (NPV)[30]. Recent data support the evidence that, on EUS performed by an expert endosonographer, absence of a circumscriptive mass can reliably exclude pancreatic cancer, especially in the setting of a low or indeterminate pre-test probability. In a retrospective report from a series of 693 patients with suspicion of pancreatic cancer, 155 of whom had a normal pancreas endosonographically, the NPV of EUS reached 100%. 135 of these 155 patients were successfully followed-up for a mean of 25 mo (range 8-48 mo). Of these, no patients developed pancreatic cancer during the follow-up period, and in 88% of these patients (i.e. 119/135) no additional work-up was required[38]. When EUS is compared to other imaging modalities, although it is not a 100% foolproof method[39-41], it still remains one of the best choices to detect a pancreatic neoplasm[30,35,42]. However, it should be emphasized that many of the studies comparing EUS and other cross-sectional imaging techniques are characterized by the absence of blinding amongst examiners, and therefore an objective assessment of the superiority of one test over another is hard[43,44]. In everyday clinical practice, the role of CT, EUS and of other available imaging tests concerning the diagnosis and staging of pancreatic cancer is, in fact, complementary.

EUS or transabdominal US in the diagnosis of pancreatic cancer?

It is widely known that transabdominal US is a cheap, efficient, radiation-free and widely available examination which efficiently demonstrates the biliary structures and the pancreas. But where pancreatic cancer is concerned, US has a variable sensitivity and specificity, which can be attributed to the miscellaneous experience of the examiners themselves and the - usually suboptimal - conditions under which the examination is performed. Nevertheless, in the hands of an experienced examiner, transabdominal US can reveal direct or indirect signs of a pancreatic malignancy, i.e. direct, such as focal hypoechoic pancreatic mass, and indirect, such as a dilated CBD(> 7 mm) with or without a dilated pancreatic duct(> 2-3 mm), liver metastases or/and ascites[30,45,46].

EUS or abdominal CT in the diagnosis of pancreatic cancer?

Many studies have been conducted to compare EUS and helical CT in pancreatic tumour detection. In many of these studies, the term "tumor" did not include exclusively solid pancreatic tumors, but also ampullary or cystic tumours as well. Regardless of the type of tumor, EUS has been proven to be more sensitive in detecting pancreatic tumors, as the overall detection rate was shown to be 97% whereas CT only reached 73%[42]. Another, more recent review, conducted a MEDLINE search (from 1986 till 2004) for studies comparing CT and EUS in pancreatic tumour detection, and found 9 papers published between 1993 and 2004. All of them concluded that EUS was more sensitive than CT, especially for pancreatic tumors smaller than 3cm in diameter. Moreover, specificity of tumor detection by means of EUS was superior or at least

equal to CT[47]. Of course, one has to take into consideration that all the above reviews have some limitations, such as the incongruity of the study design, quality and results. Also, another important fact is the constant improvement in CT imaging (contrast-enhanced multi-detector row helical CT, which appears to improve detection of smaller tumours) that has not been taken into consideration in the studies mentioned above. In spite of these limitations, current medical data still seem to support that EUS is superior to CT for the detection of pancreatic cancer[35,42,47]. It should however, be pointed-out that local expertise and availability are also factors that strongly influence which modality the clinician will finally chose in everyday practice[48].

EUS or MRI/MRCP in the diagnosis of pancreatic cancer?

Because of its high examination cost, magnetic resonance imaging/magnetic resonance cholangiopancreatography (MRI/MRCP) could be a beneficial imaging modality only if proven to be superior to EUS or CT-imaging (including multi-detector helical CT). However, according to the few existing studies, EUS has higher sensitivity than MRI/MRCP, and at the same time MRI/MRCP has been proven to produce better results than helical CT in diagnosis of pancreatic cancer. So MRI/MRCP can only play a complementary role in cases where high-quality CT- imaging shows equivocal findings, like a focal enlargement of the pancreas without a definable mass (especially when EUS is unavailable or/and chronic pancreatitis is present)[49-51].

EUS or PET in the diagnosis of pancreatic cancer?

Positron emission tomography (PET) is very helpful for the assessment of loco-regional tumour recurrence, and for distant metastases. It can also be an adjunct to CT or MRI in defining and differencing lesions (focal chronic pancreatitis vs. pancreatic neoplasia). However, when compared to EUS for pancreatic detection in a prospective study, PET was found to be less sensitive than EUS - 93% for EUS and 87% for PET[52].In addition, a retrospective study showed 98% sensitivity for EUS and 87, 5% for PET[49].

EUS-FNA in diagnosis of pancreatic cancer

EUS-FNA has offered new potential to EUS, as it allows for transmural tissue diagnosis with minimum invasion. EUS-FNA can therefore be extremely useful for various indications, such as suspected pancreatic cancer, diagnosis of pancreatic carcinoma, or differential diagnosis of pancreatic mass or smaller lesions[30,36,43,53-57]. The indications of EUS-FNA are quite controversial, except for cases where chemotherapy or radiotherapy is needed. In such cases, tissue confirmation prior to the beginning of the therapy is self-evident. On the other hand, in cases of resectable tumours, surgical resection is the treatment of choice, and EUS-FNA is meaningless[58].

The sensitivity, specificity, diagnostic accuracy, positive predictive value (PPV) and negative predictive value (NPV) of EUS-FNA vary in published studies, but are generally high (e.g. 83%, 90%, 85%, 100% and 80% respectively, in one multicenter study)[35]. In a study by Eloubeidi *et al* who reported results from a large group of 101 patients with solid pancreatic masses, even higher rates were reported. With a median of 4 needle passes, sensitivity was 95%, specificity 100%, PPV 100% and NPV 85.2%[59]. The rate of false-positive diagnoses from EUS-FNA is described as low in most papers. It has been reported that false-positive diagnoses can be caused by interpretation errors[60]. It is also evident that in most cases, only a positive diagnosis of malignancy counts, whereas there is a 15%-20% chance that a negative one is actually false-negative. A recent retrospective study reported lower rates of false-negative diagnoses of EUS-FNA. In a total of 412 cases without a mass lesion (or negative at EUS-FNA), EUS showed an NPV of 95.4%. False-negative proved to be in only 2 cases of cancer in the group of 253 patients without visible lesions (both were diagnosed as diffuse chronic pancreatitis), and 17 cases of cancer in the group of 159 patients with mass lesions, which were negative at EUS-FNA[61]. These missed cancers (around 10% in the latter group) should serve as a reminder that any negative EUS-FNA should be further investigated, and other parameters should also be taken into account (especially when the pre-test likelihood for malignancy is high).

Since EUS-FNA has been proven to be a very sensitive technique in differential diagnosis of pancreatic masses, with, in addition, very high specificity and PPV, Harewood *et al* compared EUS-FNA to other available tissue sampling techniques (CT-guided and ERCP-based). EUS-FNA was prospectively performed in 185 patients with known or suspected masses and proved to be superior to both CT- and ERCP- based tissue sampling. Moreover, in 58 patients with negative CT-guided biopsies, EUS-FNA reached 90% sensitivity for malignancy, 50% specificity for benign disease and 84% accuracy. Comparably, in 36 patients with negative ERCP- based tissue sampling, EUS-FNA presented 94% sensitivity for malignancy, 67% specificity for benign disease and 92% accuracy[62].

Performance of EUS-guided FNA of local lymph nodes in pancreatic cancer also makes sense only if a positive diagnosis would alter the management. It should also be pointed-out that only a positive result plays a significant role, whereas a negative one might mean (1) that the patient does not have lymph-node metastasis; (2) that focal (microscopic) metastasis has been missed; (3) that the puncture was technically a failure; or (4) that the lymph node examined is in fact negative, while other lymph nodes, either seen but not punctured or not seen by EUS at all, may still be positive.

EUS vs abdominal CT in pancreatic cancer staging: Competitive or complement examinations?

TNM staging: The TNM staging system for pancreatic cancer underwent major revisions in its 2002 6th revision[63]. Tumours extending beyond the pancreas, but not involving the superior mesenteric artery or the celiac axis

were deemed T3, whereas tumours involving the superior mesenteric artery or the celiac axis were defined as T4. This change in classification criteria will possibly have a positive impact on the overall staging accuracy, because the troublesome problem of differentiating T3 and T4 tumours under the prior TNM classification (i.e. based on portal vein and superior mesenteric vein involvement) is no longer present. However, most articles on the topic published up to now have not incorporated this change, therefore the controversy on the exact role of EUS remains.

EUS in loco-regional staging of pancreatic cancer

EUS has presented different percentages of correct T- and N- staging, the best of which were 93% correct T- staging and 88% correct N- staging. Because of the varying percentages, the role of EUS in loco-regional staging of pancreatic cancer is controversial[64,65]; e.g. according to a recent retrospective review, in which 89 patients were evaluated preoperatively with EUS for pancreatic adenocarcinoma, EUS was shown to achieve a lower sensitivity and specificity than those mentioned above[66].

It is noteworthy that although EUS - imaging technology is constantly improving, the sensitivity and specificity of EUS is getting worse. This can be explained by understanding the clinical management of patients. In cases of patients who suffer from unresectable disease in high-quality-cross-sectional imaging tests (usually CT), EUS is not performed. Also, patients with clearly resectable disease from CT do not undergo EUS. So the only patients who really undergo EUS - staging, are those with no clear - cut evidence of irresectability, despite optimal cross-sectional imaging studies, i.e. the most difficult cases[67]. This scepticism regarding the value of EUS-based staging was further confirmed by other studies, including careful endosonographic - histologic correlations[68-70]. On the other hand, better accuracy values have in turn been corroborated by many other studies[71-75].

Tumour resectability and vascular invasion assessment

An oft-used parameter in pancreatic cancer staging is the assessment of tumour resectability. Complete surgical resection is the only cure for patients with pancreatic carcinoma, and improvements in patient selection and surgical technique (together with decreasing peri-operative morbidity and mortality) may result in 5-year survival rates of up to 20% in patients with disease-free surgical margins. Criteria which render a pancreatic carcinoma inoperable, include size of the tumour (> 5-6 cm), presence of multiple lymph node metastases, and infiltration of major extra - pancreatic vessels (arteries)[76], but these have been questioned by quite a few surgical groups[77,78] which used other criteria of irresectability, not including the infiltration of the portal venous system, when the latter is limited. Nevertheless, the endosonographic criteria for vascular infiltration in pancreatic cancer have been a topic of a number of studies[32,75]. The proposed criteria, however, are somewhat variable and probably also involve a certain amount of inter-observer variability. One study, which showed a fairly consistent inter-observer agreement, has unfortunately only been published in abstract form[79]. Absence of a clear distance between the tumor and vessel seems to be a reliable sign of vascular infiltration; A tumour within the vessel lumen, an irregular vessel wall or unequivocal infiltration of the vessel with collaterals are all also reliable signs of vascular involvement. Intermediate findings, in which the tumor has a border at the vessel and may slightly infiltrate it, or may only adhere to the vessel by peri-tumoural inflammatory tissue, are much more difficult to interpret. This, however, is a problem not only for EUS, but probably for CT and other imaging tests as well[75]. EUS has been compared with helical CT in various studies. Many of them were summarized in a review which showed that EUS was better than CT when it came to assessment of resectability (91% *vs* 83%, $P < 0.05$), and was especially more sensitive in diagnosing vascular invasion of the portal venous system (91% *vs* 64%, $P < 0.001$)[42]. However, caution should be paid to the fact that according to the revised staging classification, invasion of veins is not regarded as a definite sign of irresectability, and many surgical teams might consider involvement of the portal vein and superior mesenteric vein as a resectable lesion. Therefore, studies before the 6th TNM-staging revision, displaying a superiority of EUS in pancreatic cancer staging compared to CT, and due to better detection of portal and splenic vein invasion, might not nowadays be as relevant as they were before 2002[32,80]. In a recent review, incorporating 4 studies comparing EUS and CT for assessment of resectability, the 2 more recent studies found no difference between CT and EUS, whereas of the other 2 previous studies, one favoured EUS and the other one favoured CT[47]. However, it should be pointed out here, that although EUS may be more accurate in staging pancreatic cancer compared to other imaging procedures, in real life, most surgeons would probably not rely on EUS alone (with the rare exception of a small tumour which can only be localized by EUS and cannot be visualized by other means)[58]. It should be acknowledged that - from a surgeon's point of view - it is not so vital to evaluate the T or N stage before resection, since neither the infiltration of other organs nor the infiltration of lymph nodes are contraindications for resections. Criteria of local irresectability of pancreatic cancer primarily include the infiltration of the celiac trunk and/or the superior mesenteric artery; EUS may therefore be of additional value if CT or MRI demonstrates a lesion close to these vessels.

In conclusion, the absolute and relative role of EUS *vs* CT in pancreatic tumour resectability remains cloudy, since the studies evaluating this role are extremely inconsistent. Their criteria are partially ill-defined, and their gold standards for diagnosis of irresectability vary considerably. This is rather disappointing in the light of many papers published, but may also simply reflect the fact that when a method requires so many studies in order to be to be shown to be useful, its value may actually be quite limited.

Endosonographic assessment of lymph nodes

The N-staging of pancreatic cancer is classified as absent

(N0) or present (N1). EUS has accuracy in N- staging around 70%, which has been improved since the appliance of EUS-FNA (xwris space)[42,45]. Although the accuracy of EUS is not very high, according to earlier studies[42,47,65] it has still been found to be superior to CT. However, recent publications show that new advances in CT (multi-detector CT or helical CT) have managed to make CT at least equivalent to EUS[47,69,71].

EUS in diagnosis and staging of pancreatic cancer: Conclusions

According to the current data, the optimal preoperative imaging, staging and tumour resectability assessment for pancreatic carcinoma remains cloudy. The two commonly used exams are EUS and CT, but the order in which EUS and CT should be performed could possibly remain indeterminate and decisions will - to some extent- rely on availability, local expertise and possible special indications (e.g. EUS-FNA), as the organisation of a large, prospective, multicenter study, necessary to resolve the controversy is virtually impossible. This is due to rapid technologic advances in imaging tests, which make timely implementation of such a study impractical. Due to its widespread availability and technological evolution, a good-quality high standard helical CT has narrowed the gap between EUS and CT, and has resulted in CT usually being performed first, especially when interpreted by an experienced radiologist. However, EUS- possibly combining electronic radial and linear imaging and/or EUS-FNA- should definitely be used in cases with indeterminate CT findings, or when EUS-FNA is deemed nessessary for diagnostic or therapeutic reasons.

HEREDITARY FORMS OF PANCREATIC CANCER: ROLE OF EUS

Any individual with a family history of pancreatic cancer should be a candidate for participation in screening programmes. These programmes include CT and EUS. In cases where abnormalities are located, ERCP with tissue sampling and/or EUS-FNA should be performed in order to decide whether the abnormality is cancer or not. Although this strategy seems to be sound enough, it has been shown that asymptomatic screening of asymptomatically high-risk individuals could possibly detect pancreatic cancer in early stages, but can also present a lot of false-positive results. In a recent study, a group of 78 high-risk individuals underwent screening tests for pancreatic cancer. 8 cases of pancreatic neoplasia were detected, and confirmed by histology over a 4-year period.However, on the other hand, 6 out of 8 of these neoplasias proved to be mucinous intraductal neoplasias[81]. Moreover, some other studies which focused on early diagnosis in suspected familial pancreatic cancer, concluded that the findings on EUS were subtle, nonspecific, and similar to those seen in patients with chronic pancreatitis[82]. Regarding cost-effectiveness, a screening test of high-risk individuals proved to be cost-effective, but only if performed centers where individuals highly experienced in endoscopic screening for pancreatic dysplasia were to be found. The reason for this is, as has been shown-; that a screening test for familial pancreatic cancer remains cost-effective only if prevalence of dysplasia is greater than 16% or the sensitivity of EUS greater than 84%[83].

UNDEFINED PANCREATIC MASSES: ROLE OF EUS

Probably the greatest challenge for EUS is differential diagnosis of an undefined pancreatic mass. The existing algorithm for uncomplicated cases with high pre-test probability for pancreatic cancer includes screening with trans-abdominal US and only if the result is elusive, performance of helical CT and/or EUS[47]. Unfortunately, there are cases in which all the above, combined with clinical and laboratory data, are insufficient to identify the nature of a pancreatic mass. A prospective study assessed EUS in differential diagnosis of focal lesions of the pancreas. 115 patients with pancreatic focal lesions were included, all patients being evaluated by EUS and with histology of the surgical specimen serving as gold standard. The study concluded that EUS, although having a high overall sensitivity, has a low specificity when dealing with diagnosis of malignancy, especially in the presence of chronic pancreatitis. In addition, EUS demonstrated a limited potential for the prediction of histologic types of lesions[84]. Whether, as concluded from a small study on 23 patients, echo-enhanced power-Doppler EUS can reliably differentiate pancreatic neoplasms and focal pancreatitis[85] remains to be seen when applied to larger patient groups.

As EUS imaging alone has been insufficient in solving these problems, new "functional,, imaging has been presented in order to improve differential diagnosis. This imaging is elastography, which is a technique recently introduced in EUS-imaging. It offers information on the mechanical properties of examined tissue by measuring mechanically-induced deformations (strain) of structures in B-mode images, in an attempt to quantify the tissue' s elasticity. This might help in the differential diagnosis between malignant and inflammatory masses. Strain is applied by pressing the EUS-transducer slightly harder against the structure's body, or simply through internal compression by pulsatile excursions of the aorta and the heart, which induce deformations of the various organs, allowing quantification and discrimination of their elasticity[86].

After initially promising experiences in differentiating nodules in various organs, elastography was tested in the differential diagnosis of pancreatic masses and lymph nodes in a multicenter setting, where 121 pancreatic masses were assessed (EUS-FNA tissue confirmation served as the reference standard). Sensitivity and specificity were 81% and 92% respectively for the pancreatic masses. However, limitations included the moderately reliable reference standard, unknown pre-test likelihoods,

and blinding, as the study has up to now only been presented in abstract form[87]. Thus, given the present state of knowledge, there are no sufficient data to prove that EUS (similarly to other imaging procedures) can efficiently solve these problems in differential diagnosis, with or without help from elastography. It seems though that pre-test likelihood plays an important role. As mentioned before, clinical assessment, including laboratory values and transabdominal US are as accurate in the differential diagnosis of pancreatic masses as sophisticated imaging procedures such as EUS, ERCP, and CT, at least in a retrospective study, in which the imaging tests were evaluated blindly[88]. Here, in order to confirm the diagnosis, one of the latter 3 examinations was used, depending on the suspected disease (and local expertise). As a general principle, imaging procedures should be performed in a stepwise fashion for specific purposes, such as exclusion of pancreatic disease and the planning of treatment in chronic pancreatitis and pancreatic cancer[88].

CONCLUSION

In conclusion, the role of EUS in the diagnosis and management of pancreatic diseases is vital Its accuracy in diagnosing or excluding CBD stones is very high and it is therefore extremely helpful in diagnosing acute biliary pancreatitis in cases with low to moderate likelihood of choledocholithiasis. Furthermore, EUS might play an important role in the early diagnosis of chronic pancreatitis, contrary to advanced forms, where its role is rather limited, and autoimmune pancreatitis where data are still insufficient. Despite developments of other cross-sectional imaging modalities, EUS remains the most sensitive method in diagnosing small pancreatic tumours, and has a pivotal role in the differential diagnosis of pancreatic masses, and exclusion of a pancreatic tumour. EUS-FNA also plays a key role in the management of patients with pancreatic cancer, providing cytological or histological diagnosis whenever clinical decision-making necessitates it. Advancement of molecular techniques, combined with EUS-guided tissue sampling might help improve the diagnostic and staging capabilities of EUS, as well as develop screening strategies for patients at high-risk of pancreatic cancer, due to familialpredisposition. Combined with its interventional and therapeutic possibilities, EUS will probably remain one of the most important examinations in improving prognosis of pancreatic cancer.

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