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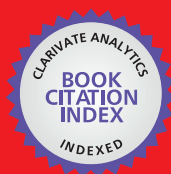
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Endoscopic Ultrasound in Pancreatic Cancer: The New Perspective

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1. Introduction

Pancreatic cancer is one of the most deadly forms of cancer worldwide, with median survival of less than 6 months and a 5-year survival rate of 35%. Endoscopic ultrasound (EUS) was first introduced for assessment of pancreatic pathology more than 30 years ago, as transabdominal imaging yields limited information. EUS has a role in the detection, staging and sampling of pancreatic tumor. Curative-intent surgery, chemotherapy, and radiation therapy of pancreatic cancer are all performed more frequently in patients with EUS evaluation [1]. Palliative EUS-guided treatments are also possible. However, a recent large observational study reported no influence on survival [2].

2. Detection

The detection rate for pancreatic tumors by EUS is 90-100%, with good detection for tumors less than 2 cm in diameter, but EUS does not definitively rule out the presence of malignancy. In certain situations EUS may give false-negative results, especially when there is concomitant chronic pancreatitis, if the examination is performed too soon after an acute episode of acute pancreatitis, or in the presence of diffusely infiltrating carcinoma or a prominent ventral/dorsal split [3]. For patients with false-negative endoscopic ultrasound fine-needle aspiration (EUS-FNA), the risk for malignancy is higher when vascular involvement or lymph nodes are seen, with a mean of 66 days until diagnosis [4].

EUS vs CT

Two studies showed that the detection of small pancreatic tumors (diameter less than 3 cm) by EUS is better than by CT or MRI (accuracy 93% vs 53% vs 67%) [5] or than by CT or US

(accuracy 100% vs 94% vs 65%) [6]. The size of tumors less than 3 cm in diameter is assessed better by EUS than the size of larger tumors (90% vs 30%) [7].

When a mass is not visible on CT, with enlargement of the pancreatic head or dilatation of the pancreatic duct, but without obstructive jaundice, EUS can reliably identify a pancreatic mass in 7-9% of cases [8-11]. If combined bilio-pancreatic dilation is present with obstructive jaundice, the prevalence of pancreatic malignancy is 85% [12]. The risk of positive findings on EUS is higher in patients with weight loss, hyperbilirubinemia, or dilation of the common bile duct [13]. If there is no dilation of the pancreatic duct in a suspected pancreatic mass, the prevalence of malignancy is 17% [14].

EUS vs MRI. Studies carried out before 2000 showed a clear superiority of EUS over MRI in tumor detection [15]. Even after advances in MRI technology, and despite excellent sensitivity of MRI (87-91%), EUS remained superior to MRI [16], albeit non-significantly so in one study [17].

EUS vs PET.EUS is more sensitive than PET in the detection of pancreatic cancer (93% vs 87%) [18]. Another study found similar sensitivities for EUS, CT, and US, with a negative predictive value of 82% on EUS [19]. Due to the high costs, however, EUS is not routinely used for detection.

EUS vs IDUS.Intraductal endoscopic ultrasound (IDUS) identifies the wall of the pancreatic duct as a hyperechoic layer and the surrounding neoplastic tissue as a hypoechoic area. IDUS yielded impressive sensitivity (100%) and specificity (91.7%) for differentiation between pancreatic cancer and chronic pancreatitis in patients with localized stenosis of the main pancreatic duct. The same study compared IDUS with EUS, CT, and ERCP, which had sensitivity of 92.9%, 64.3%, and 85.7% and specificity of 58.3%, 66.7%, and 66.7%, respectively. Another study compared IDUS, EUS, CT, and ERCP, and found higher sensitivities (75% vs 50%, 37%, and 37%, respectively) but lower specificities (67%, 67%, 33%, and 67%) [20]. However, a recent study revealed no difference between EUS and IDUS in pancreatic tumor detection, with sensitivity of 81-89% and specificity of 74-88% [19].

3. Staging

Pancreatic cancer typically has the EUS appearance of a heterogeneous hypoechoic mass with irregular margins, but based on this aspect only 55% are correctly diagnosed [21]. Lymph nodes appear as hypoechoic structures, round and well delineated, usually over 1 cm in diameter. They are found in the peri-aortic space, in peripancreatic locations, in the liver hilum, in the celiac region, or in the mediastinum (in around 10% of the cases). A positive periductal hypoechoic sign, defined as patchy hypoechoic areas adjacent to a dilated pancreatic duct, was predictive for malignancy with accuracy of 80% [22].

The first studies used the 1987 TNM staging, which considered stage T3 as the involvement of adjacent vessels (both arteries and veins) and of neighboring organs, and found T staging accuracy of 73-94% [23-26]. Later studies used the 1997 TNM classification, which defined

Figure 1. T4 tumor of the pancreatic body. The hypoechoic lesion with invasion of the celiac trunk and gastric wall.
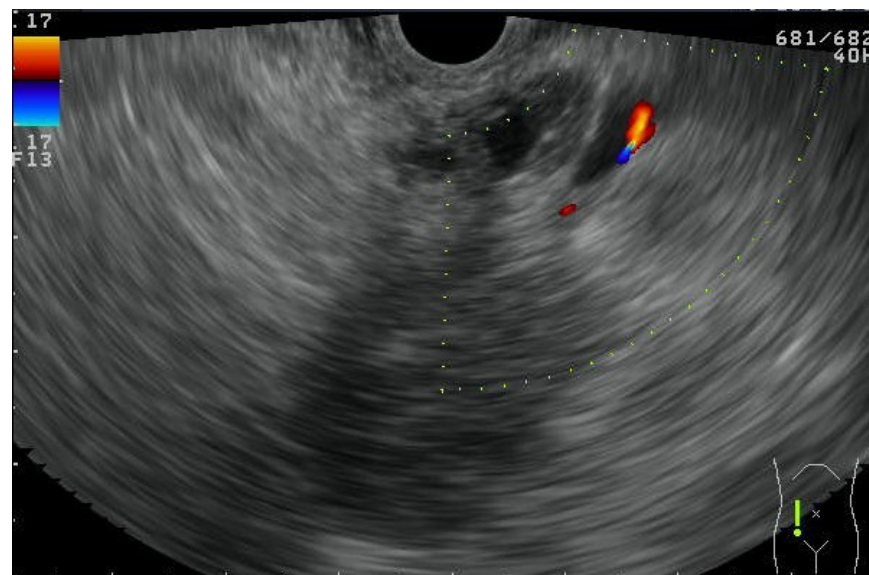

Figure 2. T3 tumor of the pancreatic body. The hypoechoic lesion invades splenic vein and produces the dilation of the Wirsung duct.

invasion of the portal vein, celiac trunk, and mesenteric vessels as stage T4. The results for T stage accuracy were poorer: 61- 74% for stage T3 and 78-88% for stage T4 [7,16,27,28,29]. Currently the 2002 TNM classification is being used. This includes invasion of superior mesenteric artery or celiac artery as stage T4, representing a criterion for irresectability. Using this latest classification, accuracy rises to 85% for T stage and 72% for N stage [30-31](Table 1).

Vascular invasion is the main factor in resectability. Typical findings are the loss of the sonographic interface between the echogenic vessel and the parenchyma, a tumor within the vessel lumen, or the presence of collateral circulation. However, the overall sensitivity when

Primary tumor(T)	
T0	No evidence of primary tumor
T1	Tumor limited to the pancreas, ≤ 2 cm in greatest dimension
T2	Tumor limited to the pancreas, > 2 cm in greatest dimension
T3	Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery
T4	Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)
Regional lymph node(N)	
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
Distant metastasis(M)	
M0	No distant metastasis
M1	Distant metastasis

Table 1. TNM Classification for Pancreatic Cancer

using this criterion is modest (43%), with specificity of 91%. In a study published at the turn of the century, the positive and negative predictive values for the parameters chosen to diagnose portal venous involvement were as follows: 42% and 33% for irregular tumor-vessel relationship, 36% and 34% for visualization of tumor in the vascular lumen, 80% and 28% for complete vascular obstruction, and 88% and 18% for collateral vessels [32].

Initial comparative studies of EUS versus surgery indicated that portal vein invasion, but not encasement of the superior mesenteric artery, was reliably assessed by EUS [32-34]. A meta-analysis on pancreatic and peri-ampullary malignancies published in 2007 concluded that EUS diagnoses vascular invasion with sensitivity of 73% and specificity of 90% [35]. Recent data based on images obtained with newer digital echoendoscope, indicate good results for superior mesenteric vessel invasion or hepatic artery invasion [36]. Globally, the accuracy of vascular invasion is 83-93% [36,37].

EUS vs CT. In an early study that compared conventional CT with mechanical EUS and surgical exploration, the results were in favor of EUS, with a global accuracy of 85-98% vs 30-86% for T staging and of 72-84% vs 52-68% for N staging [5,18,24,37,38,40]. In a series of 53 surgical patients, EUS had better accuracy than multidetector CT (67% vs 46%) for T stage and similar results for N stage (44% vs 47%) [29]. A systematic review of 11 prospective studies concluded the superiority of EUS for detection [31] and this was confirmed in recent studies [30]. Newer data show better assessment of arteries, including the superior mesenteric artery, and better assessment of resectability by digital linear EUS than by CT [36,40]. Furthermore, EUS has a significant threefold advantage over CT with regard to T stage and an even higher significant advantage with regard to N stage [40].

Vascular invasion was predicted better by EUS assessment than by conventional CT evaluation (93-100% vs 45-62%) [37,38]. EUS evaluation of portal vein invasion had results superior to those of US, CT, or angiography (93% vs 67%, 74%, and 79% respectively) [41]. Also, assessment of the portal vein and of the superior mesenteric vein invasion by EUS was better than by CT [18]. However, another study showed that radial EUS predicted resectability in only 46% of cases and that T and N staging accuracy were 69% and 54% [27]. Moreover, other studies found better [15,28] or similar [42] resectability accuracies for CT. The current recommendation is to use EUS for situations where invasion is doubtful as assessed by CT. One study recommended both EUS and CT evaluation for arterial invasion [30], but this would represent a huge volume of investigations and high costs.

EUS vs MRI. The accuracy of MRI for T and N staging is 89% and 76% respectively. Arterial involvement seemed to be best evaluated by MRI in one study on 59 patients [16], but further studies are needed before MRI can be performed routinely in patients with pancreatic cancer.

EUS vs PET. Understaging using EUS and PET was comparable (25% vs 27%) in a small study of 48 surgically explored patients [43], but routine PET examination is not indicated.

EUS vs US. Although hypoechoic masses can be seen during US examination, together with dilation of the pancreatic duct or common bile duct, the accuracy of US in pancreatic cancer diagnosis is modest (sensitivity 67%, specificity 40%) [32]. US and MRI are not accurate enough for the prediction of staging and resectability; CT should be used for this purpose [44].

4. Endoscopic ultrasound fine-needle aspiration

EUS-FNA is indicated for obtaining specimens for cytology and histopathology with regard to palliative radiochemotherapy and for differential from other nodular pancreatic lesions such as chronic pancreatitis nodules, autoimmune pancreatitis, pancreatic metastasis, or neuroendocrine tumors.

The accuracy of diagnosis by FNA is 85-95% and depends on several factors: the type of needle, the number of passes, the presence of cytopathologist in the room, the technical quality of processing, and the experience of the pathologist.

Type of needle. The main advantage of EUS-FNA is the use of thin needles -- 19G, 22G, and 25 G -- to yield cytological smears or core specimens. The Tru-Cut needle and histological needles have the advantage of obtaining tissue samples which maintain the architecture of the pancreas, thus facilitating interpretation by the pathologist, especially for non-adenocarcinoma tumor types or inflammatory masses [45,46]. Cytological smears are associated with description of atypia in 1-14% of cases, similar to reports for thyroid cytology; however, the risk of malignancy in pancreatic smears is higher (25-100%) [47]. The combination of smears and core specimens revealed the diagnosis in 90-100% of cases [45,46,48] and the recommendation of the European Society of Gastrointestinal Endoscopy (ESGE) is to try to obtain material for histology routinely [49]. The overall pancreatic tissue-sampling rate for cytology using 22G needles is variable compared with histology

(82-93% vs 84-87%), while the overall diagnostic accuracy of histology on each pass is only 60% for the 25G needle and 75% for the 22G needle [50].

The accuracy of diagnosis for pancreatic masses using 22G needles is up to 95% [51]. A meta-analysis compared the 22G and 25G needles for pancreatic and peripancreatic masses showed non-significant differences in sensitivity (78% vs 91%), and 100% specificity, with no difference in the number of passes or complications [52]. Repeating EUS-FNA in the case of initial negative cytology increases the diagnostic yield [53-55].

Because the 19G aspiration needles are more rigid [56,57], they are not routinely recommended for head pancreatic biopsies [49]. However, the diagnostic accuracy for body/tail pancreatic lesions is better with 19G needles than with 22G needles [57,58], especially for the differential diagnosis of pancreatic masses.

Tru-Cut biopsy using 19G EUS-TCB needles is recommended when EUS-FNA is nondiagnostic owing to insufficient biopsy material, but cannot be used so readily in the antrum, fundus, and duodenal bulb, where the echoendoscope is angulated [59]). The tendency is to replace the 19G EUS-TCB needle with the flexible 19G needle (Flex 19, Boston Scientific, Natick, MA) or the 19G or 22G histological needle (ProCore, Wilson-Cook, Ireland). A comparison of 22G needles and histological 22G needles reported better diagnostic accuracy for 22G needles [60]. Likewise, a 25G needle showed high sensitivity of 96% when three passes were done [61].

The yield for malignancy is similar with or without use of a stylet (87% vs 83%) [62-64], but in some studies sample adequacy was significantly better when a stylet was used (75% vs 87%) [62]. Also. The amount of blood in the sample was greater when the stylet was used (75% vs 52%) [62-64]. Although no conclusion has yet been drawn, the ESGE recommendations leave it to the discretion of the endosonographer whetherto use a stylet or not [49].

The current recommendation of the ESGE is to use suction for solid masses [49]. Moreover, a prospective comparative trial showed better diagnostic accuracy when suction was applied (85% vs 75%), but more blood was present in the case of sampling with suction [65].

Most studies have used a standard back and forth technique for sampling. In a randomized trial comparing the fanning and standard techniques, the diagnostic accuracy was non-significantly different, although better in the fanning technique (76% vs 96%), with a lower number of passes to establish the diagnosis and better sensitivity after the first pass [66].

Number of passes. The current recommendation for EUS-FNA of solid pancreatic masses is at least five passes with a 22G needle [49]. In a retrospective study, a mean of two passes with combined histology and cytology provided adequate tissue for pancreatic mass diagnosis [45]. When Tru-Cut biopsy is done, more than two passes are usually necessary to improve diagnostic accuracy [67].

Presence of a cytopathologist. It is not clear whether the presence of a cytopathologist improves the diagnostic accuracy over 90%. The cytopathologic on-site rapid assessment of smear slides is reported to be better than that of monolayer prepared slides [68]. The first large prospective study (540 patients) which included cytopathologic assessment found that the agreement

between cytopathology and final diagnosis was very good, but the presence of the pathologist did not significantly increase the accuracy of the diagnosis [69]. Thus, the presence of a cytopathologist does not always guarantee better results.

Features of lesion. The presence of features of chronic pancreatitis was associated with lower accuracy of EUS-FNA for the differential diagnosis of pancreatic masses (73% vs 91%) and may necessitate a higher number of passes to establish the diagnosis [70]. The presence of stents (either plastic or metallic) usually does not impede EUS-FNA [71-73], although the stent has to be placed at least one day before performing EUS-FNA [72]. There is no difference in diagnostic accuracy between lesions less or more than 3 cm in diameter [74], although one study found sensitivity as low as 40% for tumors less than 1 cm in diameter [75].

5. Differential diagnosis of pancreatic masses

A recent meta-analysis found that the sensitivity and specificity of EUS-FNA in differential diagnosis are 86% and 95%, respectively [76]. New imaging methods, such as elastography and contrast-enhanced EUS (CEUS), are considered additive to EUS-FNA in the differential diagnosis of pancreatic masses. Molecular analysis of the specimen obtained by FNA can also help in discrimination of pancreatic masses. Needle-based confocal laser endomicroscopy to provide real-time imaging at microscopic level for pancreatic cancer is still also under evaluation.

Elastography

This method assesses the elasticity of tissue during the ultrasound examination. The blue aspect of pancreatic adenocarcinoma is on elastography due to hard desmoplastic tissue, while the soft normal tissue is red [77]. Based on the elastography pattern, the sensitivity and specificity for differentiation of benign and malignant pancreatic lesions were 92.3% and 80.0% respectively, compared to 92.3% and 68.9% for the conventional B-mode images [78], and the overall accuracy for diagnosis of malignancy was 94% [79]. The hue histogram analysis of elastographic images differentiated malignant from benign nodules (cut-off point: 175) with sensitivity, specificity, and accuracy of 91.4%, 87.9%, and 89.7% respectively [80,81]. Using a second-generation US machine for elastography, the strain ratio can be calculated, comparing the strain value of the mass to a strain value from a control area in the region under study. A strain ratio of 4.65 and elasticity of 0.27% were the cut-off points for differentiation of pancreatic cancer from inflammatory masses [82]. Higher strain ratios were diagnostic for malignancy with an accuracy of 98% [83,84]. Three recent meta-analyses found sensitivity of 95-99%, specificity of 69-76%, and accuracy of 89-96% [85-87]. The combination of power Doppler CEUS and elastography yielded global accuracy of 83%, with better specificity than elastography alone [88].

Contrast-enhanced EUS

The principle of the CEUS technique is based on visualization of microvessels inside the pancreatic tumor; their presence was found useful for predicting efficacy of chemotherapy [89].

The initial indication was achievement of better delineation of pancreatic nodules or better visualization of vascular involvement. However, these aspects seem not to be improved and many studies of CEUS have focused on differential diagnosis of pancreatic masses. The contrast agents are microbubbles of gas included in a hydrophilic shell. The initial studies used Levovist, which is rapidly destroyed in pulmonary capillaries. Second-generation contrast agents, such as Sonovue, Sonazoid, or Definity, have a better lifetime in the vascular flow and are able to pass the pulmonary capillaries. Hypoenhancement on CEUS is considered suggestive of adenocarcinoma, due to the presence of a high proportion of desmoplastic tissue within the tumors, with few microvessels. Using a high mechanical index and Doppler CEUS, the hypovascular aspect was suggestive of adenocarcinoma in 83-94% of patients [88,90-94]. Motion artifacts and blooming effect are frequent, however, and this method has been replaced by harmonic CEUS. This latter procedure uses frequencies resulting from non-linear oscillation of microbubbles, and the low mechanical index of the ultrasound machine allows subtraction of the tissue-derived signal from the microvessel of the tumor [95]. The qualitative interpretation of the contrast image as hypoenhanced was diagnostic for adenocarcinoma in 80-95 % of patients, presenting the prospect of successful diagnosis in the case of false-negative EUS-FNA [96-98](Figure3). Also, CEUS seemed superior to CT scan in detecting lesions under 2 cm in diameter [98].

Figure 3. A hypoenhanced lesion of the head of the pancreas during the arterial phase of constrast uptake suggestive for pancreatic adenocarcinoma.

In total, a meta-analysis of both power Doppler and harmonic CEUS showed that hypoenhancement was associated with pooled sensitivity of 94% and specificity of 89% [99]. Qualitative interpretation can be subjective, however, and quantification of contrast uptake is expected to yield new information with improved accuracy. We used a hue histogram analysis and noted that a hypoenhanced aspect can occur even in severe chronic pancreatitis, but the level of contrast enhancement compared with surrounding tissue is much lower in adenocarcinoma than in chronic pancreatitis [100]. Using specialized software to interpret contrast data, our results were confirmed in another study where time to peak (TTP) was associated with

sensitivity of 93% and specificity of 89% [101]. Using Sonazoid in 91 patients, the CEUS accuracy for detection of pancreatic cancer increased from 84% to 94% with quantitative analysis of TTP [102]. Compared with autoimmune pancreatitis, maximum intensity gain rather than TTP was confirmed as significant for pancreatic cancer contrast uptake [103]. In a comparative study of different methods in 58 patients, specificity and sensitivity were 73.7% and 61.5% for B-mode endosonography; 94.7% and 33.4% for elastography; 84.2% and 76.9% for harmonic CEUS; and 89.5% and 92.3% for power Doppler CEUS. These latter results need further evaluation due to artifacts in the power Doppler CEUS procedure [104].

Linear 3D endoscopic ultrasound, considered as a potential means of improving visualization of vessel involvement, allows the reconstruction of tumor volume, but further technical improvement of ultrasound equipment is necessary to establish the practical importance of this technique [105,106].

Digital image analysis can obtain high diagnostic accuracy (94-97%) [107-109]. Detection of chromosomal abnormalities by fluorescence in-situ hybridization (FISH) analysis is useful when the cytology is inconclusive [110].

Molecular analysis of EUS-FNA samples is expected to improve the accuracy of diagnosis. Kras mutation occurred in 10 of 11 cases of pancreatic adenocarcinoma in which DNA amplification was successful, but in none of 16 patients with autoimmune pancreatitis. However, the fractional allelic loss did not differ between the two groups [111]. Another large study (n = 394 EUS-FNA samples) found 87% Kras mutations in pancreatic adenocarcinoma and only 3% in inflammatory masses and improved the accuracy of cancer diagnosis by 6% [112]. A recent meta-analysis showed that Kras detection in inconclusive EUS-FNA cases reduces the false-negative rate by 55.6%, with a false-positive rate of 10.7%, and the combined modality increases diagnostic accuracy from 80% to 88% [113].

In indeterminate pancreatic masses, the combination of Kras mutation detection and serum CA19-9 showed better sensitivity than serum CA19-9 alone (81% vs 54%) [11]. Identification of telomerase activity in pancreatic mass samples increased the sensitivity from 85% to 100%, maintaining 100% specificity [114].

6. Treatment

EUS can be used for direct antitumor therapy by injection, ablation, fiducial implantation to guide radiotherapy, pain treatment, and treatment of jaundice.

6.1. Antitumor therapy

Intratumoral injection for pancreatic cancer has been performed in several trials. Vaccination with dendritic cells as immunotherapy is considered a potential anti-cancer tool, and OK-432 represents a maturation stimulus for dendritic cells [115]. One early trial used concomitant immunotherapy with EUS-guided injection of OK-432, followed by intravenous infusion of lymphokine-activated killer cells stimulated with anti-CD3 monoclonal antibody. The

investigators hypothesized that apoptotic cells induced by gemcitabine treatment could release tumor antigens slowly over time and that this stimulates dendritic cells to process and present tumor antigens [116]. The results were encouraging in five patients, but further studies are needed [117]. Immature dendritic cells and OK-432 were preoperatively injected intratumorally in nine patients with resectable pancreatic cancer; there were no complications, and survival was prolonged in only one patient with distant metastasis [115].

Allogeneic mixed lymphocyte cultures (cytoimplants) were injected in four patients who then survived for a mean 13.2 months, with two partial responses and one minor response. The main side effect was low-grade fever responsive to acetaminophen. No further investigation ensued [118].

Weekly injection of ONYX-015 (dl1520), an E1B-55kD gene-deleted replication-selective adenovirus that preferentially replicates in and kills malignant cells, was performed in 21 patients with irresectable pancreatic adenocarcinoma. More than half had progressive disease and developed treatment toxicity. Sepsis was noted in two patients, and duodenal perforation was seen when the injection was delivered transduodenally [119].

TNFrade is a replication-deficient adenovector containing human tumor necrosis factor (TNF)-α gene, regulated by a radiation-inducible promoter Egr-1 (early growth response). The advantage of this approach is the potential to maximize local antitumor activity and to minimize systemic toxicity. Five once-weekly intratumoral injections of TNFrade before radiotherapy and continuous infusion of 5-FU were reported as beneficial in the management of inoperable pancreatic cancer [120,121], but the phase III randomized controlled trial showed no survival advantage (6.8 months vs 7 months) [122].

EUS-guided local injection for anaplastic carcinoma with chemosensitivity to paclitaxel was associated with complete tumor response 2 years later [123].

6.2. EUS-guided tumor ablation

EUS-guided Tumor ablation, a minimally invasive technique allowing selective ablation of tumor masses, might improve the efficacy of neoadjuvant treatments in patients not suitable for any other kind of treatment. Local ablative therapies such as radiofrequency ablation, photodynamic therapy, and brachytherapy have been applied in animal models or humans.

Tumor destruction by radiofrequency ablation (RFA) results in a scar, surrounded by normal tissue, which shrinks in the course of time. The pancreas is thermosensitive and usually responds with inflammation followed by edema, fibrotic and sometimes cystic transformation. The potential advantage of ablation under EUS control is guidance by real-time imaging into a deeply located target such as the pancreas which is extremely difficult to reach by a percutaneous approach. Moreover, the established precision of EUS in the measurement of the location and size of pancreatic masses could be used to estimate and follow up the area of ablation and then to avoid damage of surrounding structures.

The first report of EUS-guided RFA in the pancreas was in a porcine model, using a modified EUS needle and a commercial RF needle. RFA provided localized tissue ablation in a 1-cm

zone from the needle catheter. One of the 13 pigs developed pancreatitis [124]. Carrara demonstrated the feasibility and efficacy of EUS-guided RFA using a Cryotherm probe in 14 pigs, with good results in spleen and liver [125]. Other investigators found the technique to be safe in the pig model, with minimal evidence of fat necrosis in intrapancreatic and/or extrapancreatic adipose tissue [126,127].

The EUS-guided RFA technique was recently successfully applied in 16 patients, but in another 6 patients either the wall or the tumor was too stiff to permit passage of the Cryotherm probe. No pancreatitis was noted in the successful group, although an increase in amylases was seen in 3 of the 16 patients [128,129]. However, the impact on survival or tumor size needs further evaluation.

Ablation with a neodymium:yttrium-aluminum-garnet laser was tried in a porcine model, following the results in hepatocellular carcinoma, and no major complications were noted [129].

EUS-guided photodynamic therapy (PDT) with the photosensitizing agent porfimer sodium was used in an animal model again and the extension of necrosis was found to be related to the light dose applied, but no human study has yet been conducted due to lack of controlling the area of necrosis, similar to laser ablation [130].

EUS-guided intraoperative interstitial brachytherapy had a moderate local tumor effect and showed some clinical benefit in one third of 15 patients, with some severe hematological complications, pancreatitis, and pseudocyst formation, but without serious clinical sequelae [131]. Another study involving EUS-guided implantation of seeds in local advanced adenocarcinoma showed improvement in pain control, but no survival benefit [132].

6.3. EUS fiducial implantation

EUS guidance can also be used for the placement of radio-opaque fiducial markers in or near the tumor. Fiducials define the tumor border and serve to guiding radiotherapy. Fiducials vary in shape -- spheres, coils, seeds, etc. -- and their EUS visibility varies [133]. They are deployed into the mass by using the 19G or the less stiff 22G needle, by means of a stylet, or by injecting sterile water into the needle. A mean number of 2-4 fiducial markers per patient have to be placed [134]. The "ideal fiducial geometry" was studied in 77 patients and the placement of fiducials judged to be better by surgery than by EUS; however, this geometry was unnecessary for successful tracking and delivery of radiation [135].There is migration of 0.8-2 mm in relation to bony landmarks [133,136], and in one study the procedure had to be repeated in 7% of the patients [137]. However, no migration-related complications have been reported to date.

6.4. Pain palliation by EUS-guided celiac plexus neurolysis

The NCCN guidelines version 2.2012 for pancreatic adenocarcinoma recommend EUS-guided celiac plexus neurolysis (EUS-CPN) for the treatment of severe tumor-associated pain. In the case of jaundice caused by an unresectable pancreatic head tumor, biliary drainage should be offered first, then EUS-CPN if pain persists. Relative contraindications to EUS-CPN include difficult access owing to anatomical distortion from previous surgery or congenital malfor-

mations. The absolute contraindications for EUS-CPN are the same as for any other invasive procedure: coagulopathy, platelets < 50 000, and patients who are unable or unwilling to cooperate [138].

The mean rate of pain alleviation is 72-80%, with a much lower rate of complete pain response [139-141]. The post-neurolytic residual pain could be related to non-visceral pain owing to invasion of the muscles or surrounding connective tissue. The bilateral technique on both sides of the celiac trunk was associated with a rate of pain alleviation of 45-88% [142-144], while the central technique, with injection above the celiac trunk, showed 68-72% alleviation [145,146]. To date, only one randomized controlled trial has compared the central and bilateral techniques of EUS-CPN; it found no difference in duration of pain relief (11 vs. 14 weeks), complete pain relief (2/29 vs. 2/21 patients), or reduction in pain medication (9/29 vs. 7/21 patients) [147,148]. The choice between central and bilateral EUS-CPN remains difficult, depending on the personal skills and experience of the individual endosonographer. We have achieved good results with the central technique, which we consider easier to perform [148].

EUS-guided direct ganglia neurolysis resulted in better pain alleviation than bilateral injection [149,150]; but no randomized study has yet compared these two techniques. No difference in pain alleviation was noted between injection of 10 or 20 ml alcohol [149].

Pain reduction was more effective and the need for increased opioids was prevented in patients without radiochemotherapy compared with patients who had radiochemotherapy [151]. The benefit of repeated EUS-CPN was studied in 24 patients and results were less encouraging. The rate of successful pain relief was much lower than for the first EUS-CPN (29% vs. 67% at 1-month follow-up), and disease progression was a factor which limited the response [152].

The predictors of pain alleviation were found to be lack of ganglia visualization [153], direct invasion of celiac ganglia, and leftward diffusion of the neurolytic agent [145]. The pain was also less severe, albeit not significantly so, for tumors located in the body or tail of the pancreas, for large tumors, and for patients with severe pain at presentation [153].

Nowadays the potential immediate complications, such as hypotension, tachycardia, pain enhancement, severe bleeding, and paraplegia, are considered rare. The late side effects include diarrhea, hypotension, fever, and paraplegia [154]. Several severe side effects have been reported, e.g., permanent lower paraplegia due to spinal cord infarction [155,156], hepatic, splenic, and renal infarction [157], and lethal perforation of aorta and stomach [158].

6.5. Palliative EUS-guided treatment of jaundice

Palliative EUS-guided treatment of jaundice should be offered as an effective alternative for percutaneous transhepatic biliary drainage when ERCP fails and surgery is not indicated. One approach is transduodenal in combination with ERCP (rendez-vous technique), with reported technical success rates of 75-100% [159,160]. EUS-guided choledochoduodenostomy with transluminal stenting is successful in 75-88% of cases [161-164], while the transgastric approach has a success rate of 65-100% [165-167]. Recently, cholecysto-antrostomy has been described as an ideal alternative if the patient has duodenal strictures with or without a duodenal metal

stent and a non-dilated intrahepatic bile duct [168-169]. When duodenal stenosis is also present, double duodenal and biliary drainage by ERCP or EUS can be performed [170].

All these procedures are technically challenging and should be attempted only by very experienced endosonographers at a high-volume center for bilio-pancreatic pathology. Complications are frequent, occurring in 18-23% of cases, and are represented by pneumo-peritoneum, bile peritonitis, cholangitis, bleeding, pancreatitis (in the rendez-vous approach), and stent migration (Table 2). The existing data are from single very experienced centers; further prospective multicentric results are awaited.

Author, year	No. of patients PC / total	Technical success rate	Functional success rate	Patency (days)	Complications
Song [161]	9/15 CDS	13/15	13/13	264-CDS	Pneumoperitoneum-2 Cholangitis-1 Stent migration -4
Shah[159]	70 CDS	86%(75% rendez-vous)			Pancreatitis-5, hematoma-1, bile leak-1, bacteremia -1,pneumoperitoneum-1, perforation-1
Kim[165]	9-CDS 4-HGS	12/13	11/12		Pneumoperitoneum-2 Peritonitis-2 Migration-3
Park[166]	57	55/56	49/55	132-HGS 142-CDS	Pneumoperitoneum-7 Bile peritonitis-2 Bleeding-2 Migration-4
Kim[160]	15 CDS	15/15	12/15		Acute pancreatitis-1
Park [171]	9HGS 5CDS	14/14			Migration-1
Hara[172]	18- CDS	17/18	17/17	272	Peritonitis-1 Hemobilia-1
Artifon [173]	3 CDS-metal				
Ang [174]	2 CDS-plastic				
Iwamuro [175]	7 CDS				Bile peritonitis-2 Obstruction-1
Siddiqui[176]	9CDS	8/9			Pneumoperitoneum-1 Pain-1
Belletruti [177]	4CDS 2HGS	6/7		102	

Author, year	No. of patients PC / total	Technical success rate	Functional success rate	Patency (days)	Complications
Nguyen-Tang [178]	5HGS	5/5			
Hanada[179]	4CDS	4/4			
Brauer[163]	12 -4 CDS (8pancreatic mass)	11/12			
Bories[167]	11HGS	10/11		213	Obstruction-1(plastic) Biloma-1 Cholangitis-1 Migration-1
Kahaleh[180]	13 HGS 10 CDS	21/28			Pneumoperitoneum-2 Bile leakage-1 Bleeding-1
Yamao[181]	2 CDS				
Puspok [182]	5CDS 1HGS	6/6			Acute cholecystitis-1
Mallery [183]	6CDS	5/6			
Burmester[164]	4CDS	3/4			

PC, pancreatic cancer; CDS, choledochoduodenostomy; HGS, hepaticogastrostomy

Table 2. Studies of EUS-guided biliary drainage.

7. Screening of pancreatic cancer

Multislice CT detection of pancreatic cancers less than 2 cm in diameter has sensitivity of 70-80% [184,185] and that of MRI is higher [186], but EUS can detect almost twice lesions compared to other imaging methods [184,187]. For patients with elevated CA19-9, the use of EUS detected cancer in only 0.9% of patients, with the result that the cost of detecting one pancreatic adenocarcinoma was $41,133 [188]. An initial study from the National German Familial Pancreatic Cancer Registry noted potential precursors of pancreatic cancer in 4 of 182 examinations of patients from families with familial pancreatic cancer, based on EUS and MRI, and the authors concluded that screening is not justified due to the high costs and the psychological stress to the persons concerned [189].

Screening by EUS and/or MRI is important for first-degree relatives (FDRs) of patients with PC from a familial PC kindred with at least two affected FDRs; patients with Peutz-Jeghers syndrome; and carriers of p16, BRCA2, and hereditary non-polyposis colorectal cancer (HNPCC) mutations with at least one affected FDR [190]. Another study which investigated

a high-risk population by means of EUS found a 6.8% rate of adenocarcinomas in the body and tail of the pancreas; two of the three patients had N1 tumors [186].

8. Conclusion

EUS is useful for the detection of pancreatic cancers less than 3 cm in diameter and for the staging of cases in which CT is inconclusive. EUS-FNA establishes the tumor type with high accuracy and a very low rate of complications, and it is useful for differential diagnosis. EUS-guided palliative treatments include neurolysis and therapy of jaundice, but intratumoral ablative therapy needs further evaluation. Screening in high-risk groups should take advantage of EUS evaluation.

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