World Journal of Gastroenterology

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DOI: 10.3748/wjg.v20.i24.7808

World J Gastroenterol 2014 June 28; 20(24): 7808-7818
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (14): Pancreatic cancer

Applications of endoscopic ultrasound in pancreatic cancer

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Author contributions: All authors contributed equally to the intellectual conception of the manuscript and approved the final version; Luz LP and DeWitt JM performed extensive literature research and drafted the article; AL-Haddad MA and Sey MSL revised the manuscript critically.

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Received: November 2, 2013 Revised: January 15, 2014
Accepted: February 16, 2014
Published online: June 28, 2014

Abstract

Since the introduction of endoscopic ultrasound guided fine-needle aspiration (EUS-FNA), EUS has assumed a growing role in the diagnosis and management of pancreatic ductal adenocarcinoma (PDAC). The objective of this review is to discuss the various applications of EUS and EUS-FNA in PDAC. Initially, its use for detection, diagnosis and staging will be described. EUS and EUS-FNA are highly accurate modalities for detection and diagnosis of PDAC, this high accuracy, however, is decreased in specific situations particularly in the presence of chronic pancreatitis. Novel techniques such as contrast-enhanced EUS, elastography and analysis of DNA markers such as k-ras mutation analysis in FNA samples are in progress and might improve the accuracy of EUS in the detection of PDAC in this setting and will be addressed. EUS and EUS-FNA have recently evolved from a diagnostic to a therapeutic technique in the management of PDAC. Significant developments in therapeutic EUS have occurred including advances in celiac plexus interventions with direct injection of ganglia and improved pain control, EUS-guided fiducial and brachytherapy seed placement, fine-needle injection of intra-tumoral agents and advances in EUS-guided biliary drainage. The future role of EUS and EUS in management of PDAC is still emerging.

Key words: Pancreatic ductal carcinoma; Pancreatic neoplasm; Endoscopic Ultrasound-Guided Fine Needle Aspiration; Endosonography; Endoscopic ultrasound guided fine-needle aspiration

Core tip: Applications of endoscopic ultrasound (EUS) in pancreatic cancer are emerging. We review the role of EUS in the detection, diagnosis and staging of pancreatic cancer. The introduction of recent novel techniques such as contrast-enhanced EUS, elastography and analysis of DNA markers in fine-needle aspiration samples might improve the accuracy of EUS. In addition, we review therapeutic application of EUS including celiac plexus interventions, fiducial and brachytherapy seeds placement, fine needle injection and EUS-guided biliary drainage.

Luz LP, Al-Haddad MA, Sey MSL, DeWitt JM. Applications of endoscopic ultrasound in pancreatic cancer. *World J Gastroenterol* 2014; 20(24): 7808-7818 Available from: URL: http://www.wjgnet.com/1007-9327/full/v20/i24/7808.htm DOI: http://dx.doi.org/10.3748/wjg.v20.i24.7808

INTRODUCTION

With the introduction of endoscopic ultrasound guided fine-needle aspiration of pancreatic masses by Vilmann *et al*[1] (EUS-FNA), endosonography has assumed an increasing role in the management of pancreatic ductal adenocarcinoma (PDAC). In this review, our objective is to discuss the various applications of EUS and EUS-FNA in PDAC. Initially, its use for detection, diagnosis and staging, including newly described techniques as

contrast-enhanced EUS, elastography, and use of DNA markers will be described. Finally, the use of therapeutic EUS procedures including celiac plexus neurolysis and emerging therapies as fine-needle injection, implantation of fiducials and brachytherapy seeds will be discussed.

DETECTION AND DIAGNOSIS OF PANCREATIC CANCER

Detection of pancreatic cancer

EUS is the most sensitive nonoperative imaging test for the detection of malignant pancreatic lesions, with a reported sensitivity between 87%-100%[2-11]. EUS is markedly superior to transabdominal ultrasound (reported sensitivity between 64%-91%)[2-5,7] and has also been shown to be superior to computed tomography (CT) (sensitivity 66%-86%) for the detection of pancreatic masses in studies which compared both techniques[3-8,10,11]. EUS is clearly superior to conventional CT[3-5,8] and a few studies comparing EUS and multidetector-row CT (MDCT) for detection of pancreatic tumors demonstrated the superiority of EUS as compared to 4-row CT[10,11]. Agarwal *et al*[10] showed a sensitivity of 100% for EUS in the diagnosis of cancer compared to 86% for MDCT in a retrospective cohort of 81 patients with PDAC. DeWitt *et al*[11] reported similar findings in a prospective cohort of 80 patients with PDAC, showing that the sensitivity of EUS 98% statistically superior to MDCT 86% for detection of PDAC. There are scant comparisons between EUS and MRI for tumor detection with at least one study showing superiority of EUS[6] and one study showing superiority of magnetic resonance imaging (MRI)[9]. Future studies comparing EUS and 3.0 or higher Tesla MRI are necessary to further define the roles of each imaging modality in the diagnosis of pancreatic masses.

EUS is particularly useful for identification of small tumors that are not visualized by other imaging modalities[3,6,10-12] For tumors ⩽ 30 mm in diameter, EUS was found to have a sensitivity of 93% compared to 53% for CT and 67% for MRI[6]. In a recent retrospective cohort by Wang *et al*[12], which included 116 patients with clinical presentation suspicious for PDAC and inconclusive MDCT findings, EUS showed a sensitivity of 87% and an accuracy of 92% in diagnosing pancreatic neoplasm. With thinner slice imaging and precisely timed contrast administration coupled with multiplanar reconstruction, pancreas protocol CT may now be able to identify small pancreatic masses that previously may have been undetected by conventional or even single detector dual-phase imaging[11]. EUS should be performed in all patients with obstructive jaundice or unexplained pancreatic and/or bile duct dilations in whom CT or MRI do not definitively identify a pancreatic lesion, both to detect any tumor and to exclude non-neoplastic diseases.

EUS may fail to identify a true pancreatic mass in patients with chronic pancreatitis, a diffusely infiltrating carcinoma, a prominent ventral/dorsal split or a recent episode (< 4 wk) of acute pancreatitis[13]. In a study of 80 patients with clinical suspicion of PDAC and a normal EUS, Catanzaro *et al*[14] found that no patient with a normal pancreatic EUS developed cancer during a follow-up period of 24 mo. Therefore, a normal pancreas by EUS examination essentially excludes PDAC although follow-up EUS or other studies should be done in the setting of chronic pancreatitis due to potentially impaired visualization. Acoustic shadowing caused by an indwelling biliary or pancreatic stent may also interfere with visualization of a small pancreatic mass. However, a recent retrospective study by Ranney *et al*[15] did not show any difference in the diagnostic yield or technical difficulty of EUS-FNA of visualized pancreatic masses in the presence of a biliary stent (plastic or metal).

Imaging-based technologies such as contrast-enhanced EUS (CE-EUS) may be used to differentiate PDAC from other benign or malignant lesions. In this procedure, an intravenous contrast agent is administered at time of EUS and microbubbles are detected in the microvasculature of pancreatic tumors during real-time evaluation. Adenocarcinomas show hypo-enhancement while neuroendocrine tumors and pseudotumoral chronic pancreatitis are iso- or hyper-enhancing. Numerous contrast agents are available including first generation contrast agents such as Levovist and second generation such as Sonovue and Sonazoid. In a recent meta-analysis including 1139 patients, the pooled sensitivity and specificity of CE-EUS for the differential diagnosis of pancreatic adenocarcinoma were 94% and 89%, respectively[16]. This study found that a hypoenhanced lesion by CE-EUS was a sensitive and accurate predictor of adenocarcinoma. In the United States, routine use of CE-EUS is limited by its high cost and the lack of both agent availability and expertise with this technique.

Another emerging technology used to differentiate benign from malignant masses is EUS elastography. This technology provides real-time evaluation of tissue stiffness and is based on the premise that there is less strain when hard tissues are compressed compared to soft tissues[17]. As malignant lesions are generally harder than normal adjacent tissue, measuring strain might aid classification of pancreatic masses. Results from 2 recent meta-analyses demonstrated a high pooled sensitivity of 95%-97% but a low pooled specificity of 67%-76%, respectively, for differential diagnosis of solid pancreatic masses[18,19]. Elastography might provide complementary information to EUS, potentially increasing the yield of EUS-FNA, and assist endosonographers to improve targeting of FNA[18]. Limitations of this technique include limited availability, difficulty controlling tissue compression by the endosonographer, presence of motion artifacts, and unclear stiffness cut-off values for pancreatic masses[19].

Elastography and contrast-enhanced imaging may be combined during the same procedure. Săftoiu *et al*[20] sequentially combined CE power Doppler with real-time elastography in 21 patients with chronic pancreatitis and 33 patients with PDAC undergoing EUS examination. The sensitivity, specificity, and accuracy of combined information provided by both tests to differentiate hypo-

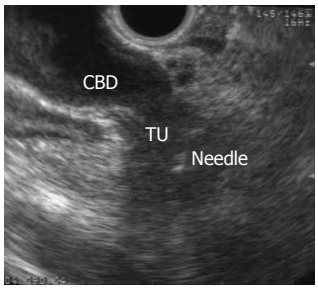

Figure 1 Endoscopic ultrasound guided fine-needle aspiration of pancreatic mass in a patient with painless jaundice.

vascular hard masses suggestive of pancreatic carcinoma were 75.8%, 95.2%, and 83.3%, respectively, with a positive predictive value and negative predictive value of 96.2% and 71.4%, respectively.

Diagnosis of pancreatic cancer

EUS-FNA of a pancreatic mass was first described in 1992[1] and is currently the preferred method to sample pancreatic mass lesions, having largely replaced intraoperative sampling or biopsies under CT or US guidance. EUS-FNA is performed using the linear array echoendoscope, as the ultrasound transducer at its distal tip allows needle advancement under real-time guidance once the target is identified (Figure 1). EUS-FNA of a suspected metastatic site from PDAC (ascites, distant metastatic lymph node, omental nodule or a suspicious liver lesion) should be performed first. If those are negative for malignancy then either the suspected tumor or a regional lymph node may be sampled.

EUS-FNA has excellent accuracy. Two recent meta-analyses reported a pooled sensitivity for the diagnosis of malignancy based on cytology of 85% and 89%, and a pooled specificity of 98% and 99%, respectively[21,22]. EUS-FNA of unresectable pancreatic cancer therefore is routinely performed where available but its use in patients with resectable pancreatic cancer remains controversial when neoadjuvant therapy is not planned.

EUS-FNA of pancreatic masses is overall a safe procedure. A recent systematic review by Wang *et al*[23] of 8246 patients with pancreatic lesions reported complications in 60 (0.82%) patients. Pancreatitis occurred in 36/8246 patients, of which 75% where mild. One patient with severe pancreatitis died, with an estimated pancreatitis-related mortality rate of 2.78%. The overall rate of pain, bleeding, fever and infection were 0.38%, 0.10%, 0.08% and 0.02% respectively.

Peritoneal seeding of tumor cells following EUS-FNA has been reported in up to 2.2% of patients but appears to be less than CT-guided FNA (16.3%)[24]. EUS-FNA did not increase the risk of peritoneal carcinomatosis in pancreatic masses in a comparison of 161 patients who underwent Endoscopic retrograde cholangiopancreatography (ERCP) alone with 56 who also underwent EUS-FNA[25]. Beane *et al*[26], compared overall and recurrence-free survival of patients with PDAC who underwent distal pancreatectomy, and found no difference between the 179 patients included who underwent preoperative EUS-FNA as compared with the 59 patients who did not. In addition, in a recent study, the risk of gastric/peritoneal recurrence after preoperative EUS-FNA was evaluated in 256 patients diagnosed with malignant pancreatic neoplasms who underwent surgery with curative intent, and it was found that EUS-FNA was not associated with increased needle track seeding[27].

Despite excellent accuracy and a low incidence of major complications, EUS-FNA of pancreatic masses has several limitations. Despite excellent sensitivity, negative predictive value of EUS-FNA for pancreatic tumor remains limited at 55%-65%[10,21]. Therefore, a negative or nondiagnostic FNA does not completely exclude the possibility of malignancy. Secondly, the presence of chronic pancreatitis decreases the diagnostic accuracy of EUS-FNA[28,29]. The presence of chronic pancreatitis may also hinder cytological interpretation of pancreatic FNA, decreasing sensitivity of EUS-FNA[30]. Third, EUS-FNA for pancreatic cancer has a false-positive rate of 1.1%, usually in patients with chronic pancreatitis[31].

The presence and experience of an on-site cytopathologist also impacts the accuracy of EUS-FNA[22,32] In a recent meta-analysis, which included 34 studies and 3644 patients, rapid on-site evaluation was a significant determinant of accuracy of EUS-FNA in the diagnosis of pancreatic masses[22]. The optimal number of EUS-FNA passes has been evaluated by 2 studies[32,33], which reported that at least 5-7 passes for pancreatic masses should be performed to maximize diagnostic yield. This information may prove helpful to endosonographers performing EUS-FNA when rapid pathology interpretation is unavailable.

A variety of commercially available FNA needles is available which range in size from 19 to 25 gauge (G). In a recent meta-analysis, 25-G needle was associated with a higher sensitivity but comparable specificity to the 22-G needle in 1292 patients with solid pancreatic lesions[34]. In another meta-analysis, 25-G needles appeared to have an advantage in adequacy of passes as compared to 22-G needles, without difference in accuracy, number of passes or complications[35]. Interestingly, 25-G needles were associated with less technical failures compared to 22-G needles when sampling pancreatic head and uncinate process lesions in some studies, and therefore should be considered first in those cases[36,37].

Due to its inherent rigidity, 19-G needles have been rarely used in the duodenum. Recently, a needle made of nitinol has been developed with enhanced flexibility to overcome these limitations (Flex 19, Boston Scientific, Natick, MA). The first report on the use of this needle included 38 patients, 32 of those with pancreatic head/uncinate lesions. Transduodenal FNA yielded adequate samples for cytological analysis in all 32 patients, without technical failures or procedure related complications[38].

EUS-FNA with use of DNA markers

In order to improve the diagnostic yield of EUS-FNA of pancreatic masses, analysis of abnormal genes in EUS-FNA samples is being investigated. The most studied

marker is κ-ras. A prospective study including 394 pancreatic masses found that the combination of κ-ras mutation analysis with cytopathology increased the sensitivity of EUS-FNA from 87% to 93% and the accuracy from 89 to 94%[39]. Recently, a meta-analysis of 8 prospective studies (931 patients) assessing the accuracy of k-ras mutation analysis in the diagnosis of PDAC reported a pooled sensitivity and specificity of 77% and 93%, respectively. When combined with EUS-FNA alone, the addition of k-ras mutation testing improved sensitivity from 81% to 89% but decreased specificity from 97% to 92% for the diagnosis of PDAC. Among inconclusive EUS-FNA cases, k-ras mutation analysis reduced the false-negative rate by 56% and increased false positive rate by 11%[40]. The addition of other somatic mutations as p53 and p16 to K-ras mutation analysis has been shown to increase the sensitivity of PDAC detection to up to 100% in cases where FNA was inconclusive in one study[41]. Detection of chromosomal abnormalities by fluorescence in situ hybridization (FISH) analysis has also been recently investigated in the detection of pancreatic cancer. In combination with cytopathology, the use of FISH analysis to detect polysomy of chromosomes 3, 7, and 17 and deletion of 9p21 improves sensitivity of EUS-FNA from 61% to 85%[42]. Presently, in view of the high accuracy of standard FNA, together with elevated price and reduced availability of these genetic tests, it appears that its use in EUS-FNA samples should be limited to research protocols and in cases with inconclusive specimens.

EUS and staging of PDAC

Suspected malignant tumors of the pancreas should be assigned a TNM staging based on the most current American Joint Committee on Cancer staging classification, which describes the tumor extension (T), lymph node (N) and distant metastases (M) of tumors, respectively. If the tumor is limited to the pancreas, it is either a T1or T2 lesion. If the tumor is smaller than 2 cm it is a T1, if it is larger is a T2. In case the lesion extends beyond the pancreas, it is either a T3 or T4 lesion. Tumors extending to the celiac artery or superior mesenteric artery are considered T4 lesions, and tumors involving any other of the surrounding pancreatic structures as portal vein, ampulla or duodenal wall but the celiac or superior mesenteric artery are classified as T3. The distinction between T3 and T4 is important, as T4 lesions with involvement of celiac or superior mesenteric arteries is considered unresectable for curative intent. Reported accuracies of T staging by EUS range from 63%-94%[4-6,8,11,43-57]. Nodal (N) metastases are classified as absent (N0) or present (N1); including peripancreatic, gastro-hepatic or celiac malignant appearing lymph nodes. The accuracy of EUS for N-staging of pancreatic tumors ranges from 41%-86%[4-6,8,11,44,58]. Malignant echofeatures for detection of metastatic lymph nodes include size greater than 1 cm, hypoechoic echogenicity, sharp distinct margins, and round shape. If a lymph node has all four echofeatures, there is an 80%-100% chance of malignant invasion[59,60]. The sensitivity of EUS alone for the diagnosis of metastatic adenopathy in pancreatic PDAC is 28%-92%[5,6,44,49,51,52,54,55], however most report sensitivities under 65%. Metastatic lymph nodes that do not have all four endosonographic features described above[59] may therefore incorrectly assumed to be benign. Specificity of EUS alone for the diagnosis of metastatic adenopathy in PDAC is 26%-100%[5,6,44,49,51,52,54,55], however most report specificities above 70%. It is presumed that the addition of EUS-FNA of suspicious lymph nodes may increase specificity however there are little data that describe the impact of the addition of EUS-FNA to EUS alone. Routine EUS-FNA of peritumoral lymph nodes with pancreatic head cancers may not be necessary as those nodes are removed en-bloc with the surgical specimen. As presence of malignant celiac lymph nodes might preclude surgery, detailed survey of this region should be done at the time of preoperative EUS staging.

For detection of non-nodal metastatic cancer, CT and MRI are superior to EUS due to both anatomic limitations of normal gastrointestinal anatomy and the limited range of EUS imaging. Although the entire left and caudate hepatic lobes might be seen by EUS imaging in most patients, a portion of the right lobe may not be visualized by EUS. EUS clearly cannot replace but may supplement other modalities for staging of hepatic metastases. EUS might, however, detect and sample small hepatic lesions missed by other imaging modalities[61-63]. The sensitivity of EUS-FNA for benign and malignant liver masses reportedly ranges from 82%-94%[61,64] and the diagnosis of liver metastases from pancreatic cancer generally precludes surgical resection[64]. EUS may also identify and sample ascites either previously detected or undetected by other imaging studies[65,66]. Identification of malignant ascites and liver metastases by EUS-FNA is associated with poor survival following diagnosis[67]. Therefore, routine examination of the perigastric and duodenal spaces for ascites should be incorporated in the staging of every pancreatic mass.

THERAPEUTIC EUS APPLICATIONS

EUS and fiducials

Fiducials are inert radiographic markers implanted into a target tumoral lesion for both localization and tracking during image-guided radiation therapy (IGRT). This technique depends on reference points by which the lesion is identified and tracked during radiation therapy. Fiducials have been traditionally implanted by percutaneous or surgical approach. The use of EUS-guided fiducial placement was first described by Pishvaian *et al*[68] in a case series including 13 patients, 7 with PDAC. Technical success was achieved in 94%. Since then, several series reported successful EUS-guided implantation of fiducials in the pancreas (Figure 2), including more than 180 patients with technical success > 90%[38,69-73]. Reported complications were uncommon and included cholangitis in a case in which prophylactic antibiotics were not used),

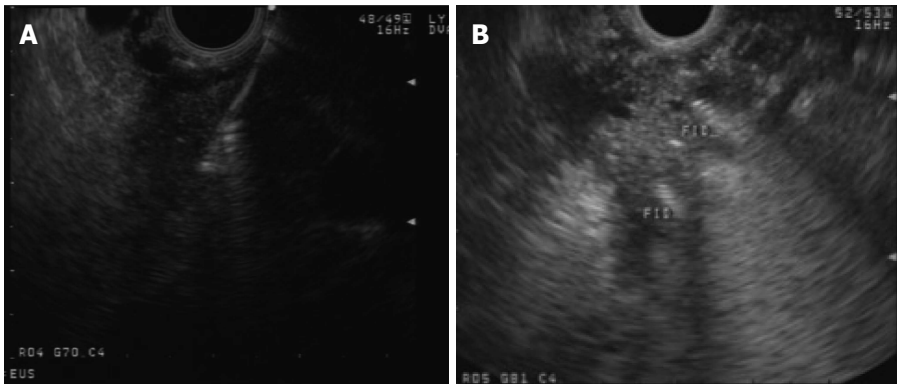

Figure 2 Endoscopic ultrasound guided deployment (A) and view (B) of fiducials in a pancreatic head mass.

mild pancreatitis, minor bleeding and fiducial migration requiring repeat procedure.

Traditional fiducials are cylindrical gold seeds that can be loaded in a 19G needle. More modern coil design fiducials can be loaded into a 22G needle and in theory coil design might reduce migration. However, this was not confirmed in a recent retrospective series including 39 patients with PDAC (103 fiducials). In this study, comparison of both types of fiducials showed no difference in migration and in addition traditional cylindrical fiducials were significantly more visible during IGRT[73]. In summary, EUS placement of fiducials appears a feasible and safe technique; its practice, however, will depend on local availability of EUS expertise and IGRT.

EUS and brachytherapy

Instead of placing an inert radiologic marker, brachytherapy involves the insertion of a radioactive seed directly into the pancreatic tumor for localized therapy. Currently the most common radioactive seed used clinically is iodine-125, which has a half-time of 59.7 d and tissue penetration of 1.7 cm[74]. Currently there are only 3 case series reporting EUS-guided brachytherapy in PDAC. In the pilot study by Sun *et al*[75], in 15 patients with advanced PDAC median survival was 10.6 mo, with 27% partial response and a mean number of 22 iodine-125 seeds per patient. Technical success was 100%; local complications including pancreatitis and pseudocyst occurred in 3 patients, also hematological toxicity without clinical sequelae occurred in 3 patients. In the subsequent series by Jin *et al*[76], a median number of 10 seeds were placed in 22 patients with advanced PDAC. Dose calculation was based on tumor volume from reconstructed three dimensional CT images. Although placement under EUS guidance was successful in all patients with no major complications, only three achieved partial remission at 4 wk and no improvement in survival was shown. However, pain was significantly reduced 1 and 4 wk after the procedure. The most recent larger series by Du *et al*[77] included 100 patients with advanced PDAC who underwent brachytherapy with EUS guided implanted iodine-125 seeds. Pain scores dropped dramatically after one week post implantation, and maintained significant lower until the third month. The same group also used iodine-125 as a neurolytic agent in 23 patients undergoing EUS-guided CPN for unresectable PDAC[78]. At week 2.82% of patients had a reduction in pain score on a visual analogue scale and the mean narcotic consumption had decreased. This effect lasted until the study conclusion at 5-mo follow-up when only 2 patients were still alive. The authors postulate that iodine-125 may be a superior neurolytic agent compared to ethanol due to its longer half-life and deeper tissue penetration, although this has yet to be confirmed in a controlled clinical trial. The limited data so far for brachytherapy is encouraging, as it appears feasible and safe and might have some benefit in pain control in patients with locally advanced PDAC. Survival benefit, however, was not yet shown. Larger studies are needed to further evaluate this technique, including assessment of patient safety studies as well as safety of handling and storing radioactive material at endoscopy suites.

EUS-guided celiac plexus interventions

Patients with PDAC commonly develop abdominal pain that can be debilitating. Celiac plexus neurolysis (CPN) is a chemical splanchnicectomy of the celiac plexus that can be used to treat pain caused by PDAC. It can be performed by percutaneous, surgical or EUS-guided approach. EUS is well suited for identification of the celiac plexus due to the close approximation of the gastric wall with the origin of the celiac artery. EUS-CPN was first described in 1996 in 30 patients with intra-abdominal malignancy (25 with PDAC) who were treated with injection of bupivacaine and 98% absolute alcohol. Pain scores were significant lower compared with baseline at 2, 4, 8 and 12 wk after EUS-CPN[79]. Next, a prospective study including 58 patients with inoperable PDAC found that EUS-CPN provided significant decline in pain scores in 78% patients[80]. In a meta-analysis of randomized controlled trials of EUS-CPN for PDAC in 283 patients, Puli *et al*[81] reported 80% of patients experienced at least partial pain relief. Although the authors could not determine whether EUS-CPN reduced narcotic requirements due to heterogeneous reporting in the included studies, an earlier meta-analysis by Yan *et al*[82] reported a significant reduction in narcotic use with non-EUS guided CPN. Similar

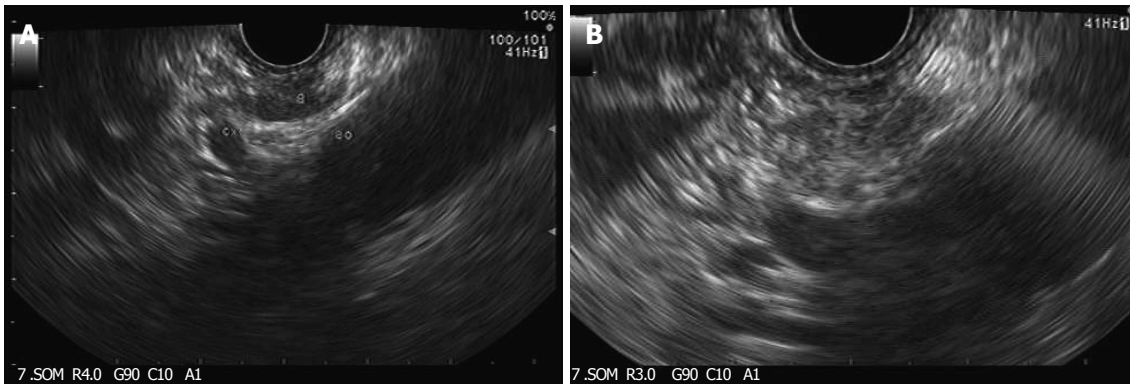

Figure 3 Celiac ganglia identified during endoscopic ultrasound (A) and injected during neurolysis under endoscopic ultrasound guidance (B).

findings were reported in a more recent Cochrane meta-analysis which combined studies evaluating EUS-guided and percutaneous CPN[83]. In a double-blind, controlled trial by Wyse *et al*[84], which included 96 patients with advanced PDAC, early EUS-CPN provided greater pain relief as compared with conventional therapy at 1 mo and significantly greater at 3 mo. Morphine consumption was similar in both groups at 1 mo but tended toward lower consumption at 3 mo in the neurolysis group.

Over the past decade, advancements in echoendoscope designs have permitted the accurate identification of celiac ganglia and interest has developed in direct ganglia injection to improve the efficacy of CPN (Figure 3A and B)[85]. In a recent randomized controlled study, celiac ganglion neurolysis was more effective than celiac plexus neurolysis in relieving pain (73.5% *vs* 45.5%, respectively; $P = 0.026$)[86].

EUS guided CPN is a safe procedure and complications are uncommon. Diarrhea (4%-15%) and orthostasis (1%) can occur due to disruption of the autonomic nervous system are usually mild and transient. A paradoxical increase in pain may occur in up to 9% of cases but generally resolves over several days[80]. Recently, serious complications including paralysis due to anterior spinal cord infarction[87,88], death from necrotic gastric perforation[89] or celiac artery thrombosis with infarction[90,91] have been reported.

EUS and fine needle injection

EUS-guided fine-needle injection (EUS-FNI) is an emerging method, which involves direct intra-tumoral delivery of therapeutic agents into pancreatic tumors under EUS guidance. This technique offers theoretic potential to deliver high dose concentration while minimizing systemic side effects.

In the pilot study by Chang *et al*[92], a single injection of allogeneic mixed lymphocyte culture (cytoimplant) was delivered by EUS-FNI in 8 patients with unresectable PDAC. The technique was feasible and not associated with substantial toxicity. In this series, median survival was 13.2 mo and two patients had partial response and one had a minor response. Subsequently, Hecht *et al*[93] reported the use of EUS-FNI of ONYX-015 (a gene-deleted replication-selective adenovirus that preferentially targets malignant cells) in 21 patients with locally advanced PDAC without significant liver metastasis. Patients underwent 8 sessions of EUS-FNI and the final treatments were given in combination with systemic gemcitabine. In this study, mean survival was 7.5 mo, and there were 2 partial regressions, 2 minor responses and 6 patients with stable disease. Nevertheless, there were serious complications including 2 duodenal perforations and 2 patients with sepsis, therefore limiting the use of EUS-FNI of this agent.

EUS-FNI of immature dendritic cells was reported by Irisawa *et al*[94] in a series with 7 patients with metastatic PDAC who previously failed gemcitabine. Mean survival was 9.9 mo. There were 3 partial responses, 2 patients with stable disease and no serious reported complications. Also Hanna *et al*[95] reported EUS-FNI of BC -819, a DNA plasmid that has the potential to treat PDAC that overexpresses H19 gene, in 6 patients with advanced PDAC. There were 3 partial responses and no serious reported complications.

TNFerade biologic is a replication-deficient adenoviral vector that expresses tumor necrosis factor α (TNF-α) under control of the Egr-1 promoter, which is inducible by chemotherapy and radiation In a phase I / II study, EUS or percutaneously guided intra-tumoral TNFerade biologic with 5-fluorouracil and radiotherapy was well tolerated and showed promising results in 50 patients with locally advanced PDAC[93]. Successively, a randomized multicenter trial, TNFerade biologic was compared with standard of care (SOC) in 304 patients with locally advanced PDAC. TNFerade was injected intratumorally by either EUS-guided approach or percutaneous transabdominal approach. Results showed that the addition of TNFerade to SOC was well tolerated, however did not prolong survival in patients with locally advanced PDAC. In addition, in the TNFerade arm of the study, multivariate analysis showed that TNFerade injection by EUS approach, rather than a percutaneous transabdominal approach was a risk factor for inferior progression-free survival. It is possible that greater variability existing in EUS operator skill across the participating institutions compared to the more straight forward percutaneous

transabdominal approach technique might have resulted in reduced efficacy in the EUS group[96]. EUS-FNI although promising, up to now did not show noteworthy results in the treatment of PDAC.

EUS-guided biliary drainage

ERCP is the procedure of choice for bile duct stenting in obstructive jaundice in patients with advanced PDAC. When ERCP is not possible due to failed cannulation, altered upper gastrointestinal tract anatomy, a distorted ampulla, gastric outlet obstruction, a periampullary diverticulum or in situ enteral stents, EUS-guided biliary drainage (EGBD) has been used as a minimally invasive alternative to surgical biliary bypass or percutaneous transhepatic biliary drainage (PTBD)[97].

Two main approaches for EGBD have been used: direct transluminal stenting (hepaticogastrostomy or choledochoduodenoscopy, without accessing the papilla) and a rendezvous technique (wire placed into intrahepatic or extrahepatic biliary duct, passed through the papilla and retrieved by a duodenoscopy for biliary interventions). A third approach, EUS-guided antegrade transpapillary biliary stent placement, has also been described[98,99]. Case-series from expert tertiary centers suggest that EGBD can be performed with high therapeutic success (87%) but is associated with 10%-20% mild to moderate morbidity and rare serious adverse events[97,100-110]. Rendezvous technique appears to be the safest[110,111], however can only be attempted in whom the papilla or choledocho-enteric anastomosis is accessible by endoscopy. In addition, rendezvous biliary drainage either fail or is not possible in at least 25% of patients, is associated with prolonged procedure times and may lead to acute pancreatitis[97,102,107,108]. Transluminal stenting can be complicated by stent migration or occlusion, bile leak, cholangitis, hemobilia, pneumoperitoneum and bile peritonitis[104-106,111,112]. EUS-guided hepaticogastrostomy is potentially applicable to patients with duodenal obstruction or prior gastric surgery, however it can only be attempted when the left intra-hepatic system is dilated[111]. EUS-guided choledochoduodenostomy can be attempted only in patients with a native anatomy (intact duodenal bulb) and an intact biliary tree[112]. EGBD by using either rendezvous or directly transluminal technique requires needle puncture *via* an intrahepatic or an extrahepatic route in an non-obstructed patient with normal upper GI anatomy. It appears that extrahepatic route is preferable and safer than intrahepatic access, whether EGBD is performed by rendezvous or direct transluminal stenting[97,105,109,110].

Recently Park *et al*[110] reported a single-operator, non-randomized prospective study evaluating technical and functional success and adverse event rate of a treatment algorithm using a modified technique of "enhanced guidewire manipulation" for EGBD, performed at same-session after failed ERCP in 45 patients with malignant or benign biliary obstruction. Results of this approach showed a technical and functional success of 95% and overall adverse event rate of 11%, including pancreatitis, focal bile peritonitis, limited pneumoperitoneum, intraperitoneal stent migration and biloma.

Artifon *et al*[113] reported the first prospective randomized comparison between EGBD (choledochoduodenoscopy) and PTBD, in 25 patients with unresectable malignant biliary obstruction who failed ERCP (13 patients EGDB *vs* 12 patients in the PTBD group). In this small study, both groups had similar technical and clinical success, complication rate, cost and quality of life.

EGBD is a safe and effective alternative after failed ERCP, whether performed by rendezvous or direct luminal stenting. Although limited data suggests equivalency to PTBD, larger studies are needed to confirm those results. EGBD ideally should be performed by high skilled endoscopists trained in both ERCP and EUS, and should be limited to expert tertiary centers, where surgery and radiology back-up are available in case of adverse events.

CONCLUSION

EUS and EUS-FNA are highly accurate modalities for detection, diagnosis and staging of PDAC. This high accuracy is decreased, however in specific situations most notably in the presence of chronic pancreatitis. Newly techniques including contrast-enhanced EUS, elastography and detection of DNA markers are in progress and might improve the accuracy of EUS in the detection of PDAC in the setting of chronic pancreatitis. EUS and EUS FNA have recently progressed from a diagnostic to a therapeutic technique in the management of PDAC. Evolving therapeutic applications include celiac plexus interventions, fiducial and brachytherapy seeds placement, fine needle injection and EUS-guided biliary drainage. The future role of EUS and EUS in management of PDAC is still emerging.

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ISSN 1007-9327