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REVIEW

Interventional endoscopic ultrasonography

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Abstract

Endoscopic ultrasonography (EUS) is the combination of endoscopy and intraluminal ultrasonography. This allows use of a high frequency transducer, which, due to the short distance to the target lesion, enables ultrasonographic images of high resolution to be obtained. Endoscopic ultrasonography is now a widely accepted modality for the diagnosis of pancreatobiliary diseases. It can be used to determine the depth of invasion of gastrointestinal malignancies, and often for visualizing lesions more precisely than other imaging modalities. The most important early limitation of EUS was the lack of specificity in the differentiation between benign and malignant changes. In 1992, EUS-guided fine needle aspiration (EUS-FNA) of lesions in the pancreas head has been made possible using a curved linear array echoendoscope. Since then, many researchers have expanded the indication of EUS-FNA to various kinds of lesions and also for a variety of therapeutic purposes. In this review, we particularly focus on the present and future roles of interventional EUS, including EUS-FNA and therapeutic EUS.

I. Introduction: development of endoscopic ultrasonography

Endoscopic ultrasonography (EUS) is a combination of endoscopy and intraluminal ultrasonography. It allows the use of a high frequency transducer with 5 to 10 MHz. Due to the short distance to the target lesion, EUS enables ultrasonographic images of high resolution to be obtained. Endoscopic ultrasonography is now a widely accepted modality for the diagnosis of pancreatobiliary diseases, for determining the depth of invasion of gastrointestinal malignancies, and often for visualizing lesions more precisely than other imaging modalities.

Rosch *et al.* stressed the advantages of EUS.[1] These include provision of clear-cut images of small and discrete changes. He also predicted the limitations of EUS, the most important of which was the lack of specificity in the differentiation between benign and malignant changes. Under the prevailing conditions of 1984, Tio *et al.* described the possibility of using the biopsy channel of an echoendoscope for cytological puncture,[2] so as to enhance the diagnostic value of EUS. In 1990, Harada *et al.* first reported the EUS-guided puncture technique using a linear array echoendocope for transesophageal puncture in two dogs.[3] In 1992, Vilmann *et al.*[4] published the first case report of EUS-guided fine needle aspiration (EUS-FNA) of a lesion in the pancreas head using a curved linear array echoendoscope.

Since then, many researchers have expanded the indications for EUS-FNA to various kinds of lesions, and also for therapeutic purposes. In this review, we describe the present place of interventional EUS in clinical practice, including the specific roles of EUS-FNA and therapeutic EUS.

II. EUS-FNA

(1) Indications and contraindications

A fundamental principle of EUS-FNA is that the information obtained should have the potential to affect patient management.[5] In addition, the indications for EUS-FNA should be guided by its diagnostic accuracy, cost effectiveness, and patient comfort and safety. Erickson[6] proposed that the following 'clear indications' for EUS-FNA: 1) Sampling of pancreatic masses when other techniques have failed, 2) Sampling of computed tomography (CT)-detected mediastinal adenopathy when other techniques have failed, 3) Sampling, at the time of diagnostic or staging EUS, of lesions that are poorly seen by or inaccessible to biopsy by other imaging modalities.

In Japan, the current indications for EUS-FNA include:[7,8] (i) differentiating between benign and malignant lesions; (ii) staging of cancer; (iii) histological evidence of malignancy before chemotherapy and/or radiation therapy.

Recently, the utility of EUS-FNA making an etiological diagnoses has been reported. Examples include characterization of histological subtypes of rare forms of pancreatic cancer,[9] inflammatory pancreatic mass[10] or autoimmune pancreatitis,[11,12]

gastrointestinal stromal tumor (GIST),[13,14] subtypes of malignant lymphoma,[15] sarcoidosis and so on. Such diagnoses are based on one or more of histological (H&E staining), immunohistochemical or genetic analysis.

According to these indications, the potential uses for EUS-FNA include,[5] (i) pancreatic mass; (ii) mediastinal lymph nodes (metastasis from esophageal and lung cancer); (iii) celiac lymph node in association with a known upper gastrointestinal (GI) cancer or in a patient suspected of having cancer or lymphomam; (iv) intra-abdominal lymph nodes in association with a known (or suspicion of) cancer; (v) peri-rectal lymph node/mass; (vi) posterior mediastinal mass of unknown etiology, and (vii) intrapleural/intra-abdominal fluid. In addition to these lesions , the indications for EUS-FNA[6,16] have been expanded to peri-pancreatic masses, submucosal masses, liver lesions, left adrenal masses, suspected recurrent cancers in and adjacent to surgical anastomosis.

Contraindications to EUS-FNA include situations in which the FNA result would not affect management, inability to clearly visualize a lesion, a tumor mass or vessel interposed in the path between the needle and target, bleeding diathesis, and risk of tumor seeding.[5,6,16]

(2) Equipment for EUS-FNA

A curved linear array echoendoscope (convex echoendocope) is usually available for EUS-FNA. This instrument generates longitudinal sector images parallel to the axis of the endoscope and is equipped with color Doppler functioning.[17] At present, the most important function of the echoendoscope is as a large instrument channel that allows not only histological biopsies to be taken, but also therapeutic applications.

Several needles have been developed. Recent models for EUS-FNA consist of a steel needle and can be lure-locked in a fixed position on the echoendoscope. The endoscopist can then advance the needle into the lesion himself or herself under ultrasonic guidance. Using the newly developed automated biopsy device, EUS FNA procedures are easier to perform and sufficient diagnostic material can be obtained more readily.[18] As to needle technology, the shapes of the tips and the diameter of the needle have been continuously developed and improved. Needles range from 19- to 22- gauge and allow a depth of penetration of up to 10 cm to be obtained[17] and recently, a 25-gauge needle is also available. A large size 19-guage trucut needle is also now commercially available.[19,20] Specimens obtained by such a trucut needle can easily be processed for immunohistochemical and gene analyses.

(3) Technique of EUS-FNA

Detailed steps of EUS-FNA procedures have been described in several articles.[21–23] Papanicolaou and Giemsa stains have been adopted as conventional cytological stains for the aspirates obtained. Sufficient tissue enables processing for HE stains, immunohistochemical stains, and flow cytometry[24] as well as gene analysis.[10,25,26]

One of the most important issues may be the introduction of rapid staining performed by a cytopathologist or cytotechnician during the procedure. Aspirated materials mixed with blood are usually prepared on slides or placed directly into a fixative for H&E staining. When a cytopathologist or cytotechnician is in attendance, the aspired material is spread onto a plate, picked up with tweezers and sprayed onto glass slides.[27] One slide is air-dried for on-site interpretation, the other slide is fixed in ethanol for Papanicolaou staining. Any remaining material goes into a fixative or cell preservative for later cell block preparation for H&E staining or immunohistochemical staining.

Erickson *et al.*[28] reported that failure to have a cytopathologist in attendance increases the number of passes, reduces definitive cytological diagnoses, prolongs procedure time, increases risk and consumes additional needles. If a cytopathologist or a cytotechnician is not in attendance, three passes should be taken through lymph nodes and five to six passes through pancreatic masses to ensure adequate cellularity in >90% of cases.[28]

Most endoscopists believe that histopathology is a more sensitive technique than cytology to obtain histological evidence of gastrointestinal cancers (esophagus, stomach and colon). Furthermore, cytology is considered unnecessary when an endoscopic biopsy is available. However, cytology (or FNA) has been reported to be an equally or more sensitive technique than histopathology in the diagnosis of breast or thyroid cancer,[29] and cytology has also been determined to be a SAFE (safe, accurate, fast and economic) technique.[30] The present authors and our colleagues previously reported that the cytology was more accurate than histopathology in EUS-FNA for the differential diagnosis of pancreatic mass lesions.[10] However, the usefulness of histopathology combined with immunohistochemical analysis to determine specific etiology has been reported.[9] Thus, a system in which both cytology and histopathology are available, needs to be developed.

With these refinements of instruments and technical skills, EUS followed by EUS-FNA is expected to be performed on a routine basis in high volume centers throughout the Asia-Pacific region and elsewhere internationally.

(4) Diagnostic accuracy and complications

High rates of adequate tissue sampling and diagnostic accuracy have been reported for EUS-FNA. Among nearly 1700 patients, the accuracy, sensitivity and specificity of EUS-FNA for pancreatic tumors were 88%, 85% and 98%, respectively.[31] Likewise, EUS-FNA for lymph nodes found a sensitivity of 92%, a specificity of 93% and an accuracy of 92%.[32]

The overall complication rate of EUS-FNA appears to be 1 to 2%.[33] The major complications reported with EUS-FNA are infections in cystic lesions, bleeding, pancreatitis, and duodenal perforation.[34] In a large multi-center trial involving 554 consecutive mass or lymph node biopsies, only 5 complications (2 perforations, 2 febrile episodes, 1 hemorrhage) were observed; none were fatal.[32] Cystic pancreatic lesions appear to have a greater risk of infective complications than solid pancreatic masses. Two deaths have been reported with EUS-FNA. One patient developed fulminant cholangitis associated with EUS-FNA of a liver metastasis, the other developed uncontrolled bleeding from a pseudoaneurysm after EUS-FNA of the pancreas.[6] The present authors have experienced EUS-FNA related severe complications, including one massive bleeding from a gastric GIST,[35] one rupture of a pancreatic pseudoaneurysm followed by massive gastrointestinal bleeding, and one acute portal vein obstruction.[36] The last two cases might possibly have been caused by acute focal pancreatitis.

The risk of acute pancreatitis after EUS-FNA of pancreatic masses has been estimated in 19 centers. It was found to have a frequency of 0.29% in a retrospective analysis, and 0.64% in prospective study.[37] Thus, although EUS-FNA for pancreatic lesions has been evaluated to be a good indicator for further treatment, largely due to the high technical reliability of pancreatic tissue sampling, the possibility of severe complications needs to be carefully considered.

III. Therapeutic EUS

Interventional procedures being developed for therapeutic use of EUS include EUS-guided drainage/ anastomosis, and EUS-guided fine needle injection. EUS-guided drainage is applied for pancreatic pseudocysts, obstructive pancreatitis, obstructive jaundice, and abdominal or pelvic abscesses. EUS-guided fine needle injection (EUS-FNI) mainly consists of EUS-guided celiac plexus neurolysis/ block, tattooing, anti-tumor injection and tumor ablation.

1. EUS-guided drainage and anastomosis

(1) EUS-guided pancreatic cyst drainage

Before any drainage procedure of pancreatic cysts, it is obviously important to distinguish different types of pancreatic fluid collections, since each type of collection differs with respect to prognosis and management. Pancreatic fluid collections complicating acute and chronic pancreatitis can be subdivided into three groups[38]: (i) acute peripancreatic fluid collections; (ii) pseudocysts; and (iii) walled-off pancreatic necrosis. Though endoscopic drainage is almost never indicated for acute peripancreatic fluid collections, it is indicated for pseudocysts and walled-off pancreatic necrosis.

(a) Pseudocyst drainage. Aspiration with a fine needle is a simple method to drain the cyst cavity without any complicated procedures. However, with this method alone the cyst tends to recur immediately. Therefore, in most cases persistent drainage is dispensable for complete reduction of the cyst cavity. In 1992, Grimm *et al.*[39] reported the first EUS-guided cyst drainage with linear array echoendoscopy in a patient with chronic pancreatitis associated with a pancreatic tail pseudocyst. Compared to endoscopic drainage of pancreatic pseudocyst under direct vision, EUS-guided cyst drainage has some advantages for identifying a pseudocyst which shows no overt protrusion 'bulge' into the gastrointestinal lumen, and also for selecting the shortest puncture pathway under real-time scan. Color Doppler images also help to avoid the inadvertent puncture of blood vessels near the cyst puncture route.

When a therapeutic echoendoscope and access to fluoroscopy are available, pancreatic pseudocyst drainage can be performed as a one-step procedure under EUS-guidance.[40] Requisite accessories for the procedure include: echoendoscope with a biopsy channel > 3.7 mm, 19-gauge FNA needle, 0.035 inch guidewire, 4.5 or 5 Fr endoscopic retrograde cholangiopancreatography (ERCP) cannula or an over-the-wire needle-knife catheter, an over-the-wire biliary balloon dilator, and 7 or 10 Fr double pigtail plastic stents. The standard technique for EUS-guided drainage of pancreatic pseudocyst is shown in Table 1.

Table 1 The standard technique for Endoscopic ultrasonography (EUS)-guided drainage of pancreatic pseudocyst

(1) Exclusion of the presence of vasculature in the path of the needle using color Doppler ultrasound.
(2) Puncture the pseudocyst under EUS-guidance using a 19-gauge fine needle aspiration (FNA) needle and insertion of a 0.035 inch guidewire through the needle and coiling of the guidewire within the pseudocyst under fluoroscopic guidance.
(3) Sequential dilation of the tract under fluoroscopic guidance by first passing a 4.5 or 5 Fr ERCP cannula over the guidewire, followed by further dilatation using a 6 or 8 mm over–the–wire biliary balloon dilator.
(4) Following dilation, insertion of two 7 or 10 Fr double pigtail stents within the pseudocyst under fluoroscopic guidance.
(5) Insertion of additional stents and a 7 or 10 Fr nasocystic drainage catheters in all patients with pancreatic abscess or necrosis for periodic flushing and evacuation of the cystic contents.

When a therapeutic echoendoscopy is not available, pseudocyst drainage can still be undertaken using a small channel convex echoendoscope by passing a 0.035 inch guidewire into the pseudocyst via a 19-gauge FNA needle. The echoendoscope is then exchanged over the guidewire for a double-channel gastroscope or duodenoscope and drainage of the pseudocyst can be completed successfully.

In the case of a pancreatic pseudocyst with a thickened wall, puncture with a 19-gauge FNA needle and dilatation of the needle tract are sometimes difficult. In such a situation, a needle-knife technique is applied for puncture of the pseudocyst. It remains controversial whether external or internal drainage should be applied to individual cases, and what conditions and timing are most appropriate for discontinuation of these draining procedures. In the presence of necrosis and purulent debris, endoscopic transmural necrosectomy is necessary in order to improve the treatment outcome.[41]

According to recent reports, EUS-guided cyst drainage is feasible in greater then 90% of the patients, and has a complication rate of less than 5%.[40] It can be concluded that EUS-guided pancreatic pseudocyst drainage is now a very effective treatment for patients with pancreatic pseudocyst.

(b) Walled off pancreatic necrosis (WOPN). Several weeks after an episode of severe necrotizing pancreatitis, necrosis can become organized into well-circumscribed areas of necrosis. Walled off pancreatic necrosis was previously described as organized pancreatic necrosis, and WOPN with infection is generally accepted as an indication for therapeutic intervention. Standard endoscopic drainage of sterile and infected WOPN has been reported to be less successful and is often considered contraindicated.[38] Endoscopic transluminal necrosectomy (ETN) added to standard endoscopic drainage with intent to remove necrotic tissue to facilitate resolution of the collection has been described; success rates vary from 80–93%.[38]

The technique of ETN is shown in Table 2. Endoscopic transluminal necrosectomy has been the first endoscopic translumenal procedure to become widely introduced in clinical practice and

can be considered one of the first Natural-orifice Transluminal Endoscopic Surgery (NOTES) procedures.

(2) EUS-guided bile duct drainage

Endoscopic biliary drainage may be unsuccessful in some patients. The alternative method of percutaneous transhepatic biliary drainage (PTBD) has a risk of complications. Wiersema *et al.*[42] first described EUS-guided cholangiopancreatography in 1996 as a diagnostic alternative in two patients with failed ERCP. Recent reports have demonstrated the feasibility of EUS-guided cholangiography with biliary stent placement in patients with failed cannulation at ERCP. Endoscopic ultrasonograhphy-guided biliary stenting includes a rendezvous technique and a direct access technique.

(a) EUS-guided biliary drainage with a rendezvous technique. EUS-guided bile duct drainage with a rendezvous technique was first described by Mallery *et al.* in 2004.[43] A rendezvous technique is feasible only when the endoscope can be advanced to the papillary orifice or to the site of surgical anastomosis for retrieval of the guidewire to undertake subsequent therapy.[44] After puncturing bile ducts, the guidewire is then advanced antegrade under fluoroscopic guidance into the small bowel via the papillary orifice. The echoendoscope is then withdrawn and the duodenoscope or colonoscope is passed so that the papilla or the anastomotic site can then be cannulated alongside the guidewire or by retrieving the guidewire into the working channel of the endoscope for further endotherapy.

Four reports[43,45–49] on EUS-guided rendezvous technique have been evaluated. Among 27 patients treated with this technique were 13 cases of pancreatic cancer, 7 of bile duct cancer or other causes of malignancy, and 7 cases of benign diseases. The site of puncture included 10 cases from duodenum and 17 from stomach. The procedure was successful in all but two cases, an overall success rate of 93%, and the complication rate was 7.4% (2/27), including individual cases of pneumoperitoneum and bile leakage, respectively. However, stent patency and late complications at long term follow-up of patients treated with this technique have not yet been reported.

(b) EUS-guided choledochoduodenostomy (EUS-CDS). EUS-CDS was first reported by Giovannini *et al.*[50] in 2001. The technique is basically similar to EUS-guided drainage of pancreatic pseudocysts, and is shown in Table 3.[51]

Eleven studies have evaluated the role of EUS-CDS.[47–57] Twenty-one cases underwent EUS-CDS, including 13 cases of pancreatic cancer, 4 cases of papilla of Vater cancer, 2 of bile duct cancer, 1 of malignant lymphoma and 1 of bile duct stone. The procedure was successful in all but 2 cases (overall technical success rate 91%). Though there were no serious procedure-related complications, comparatively high rates of complication (19%) has been reported, including 1 case of small focal bile peritonitis and 3 cases of pneumoperitoneum. Recently, the present authors have reported a comparatively long stent patency (mean: 212 days) for EUS-CDS.[57] EUS-CDS performed from the first portion of the duodenum is technically feasible without any serious complications, offering clinically effective drainage in almost all patients with comparatively long patency period.

Table 2 The technique of endoscopic transluminal necrosectomy

(1) Removal of the nasocystic catheter and all but one of the drainage stents.
(2) Under radiologic guidance, dilatation of the tract with a balloon up to 18 mm.
(3) Introduction of a therapeutic gastroscope from the dilated tract into the cavity (Fig. 1a).
(4) Use of a Dormia basket, a Roth net and/or a snare to remove necrotic tissue (Fig. 1b).
(5) Re-insertion of pigtail stents and nasocystic catheter into the cavity.

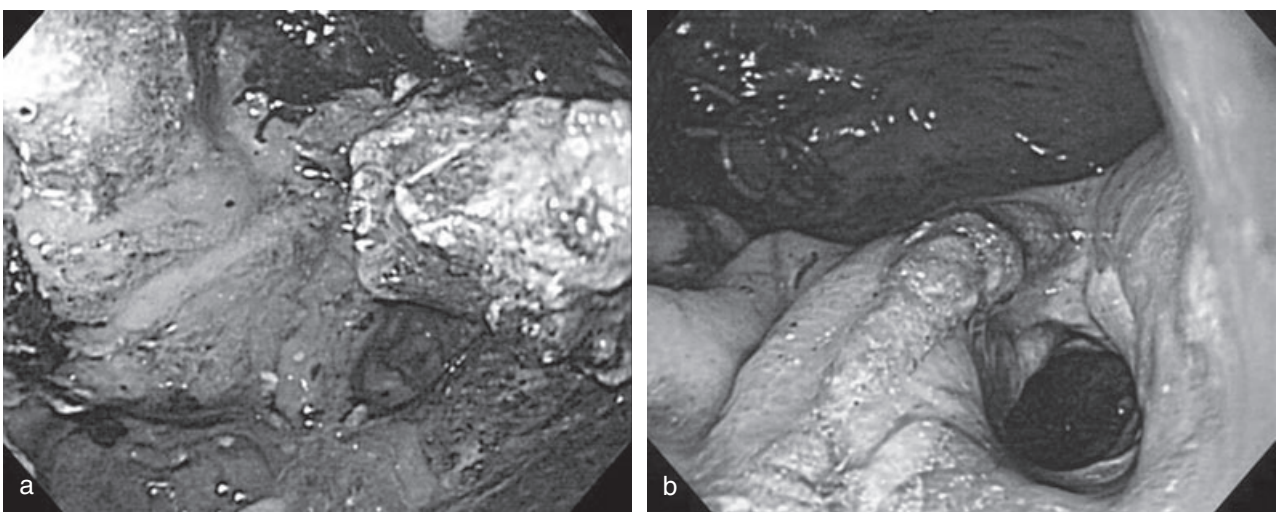

Figure 1 Endoscopic trans-luminal necrosectomy. (a) Endoscopic view of walled off pancreatic necrosis during necrosectomy, (b) Endoscopic view of dilated fistula after necrosectomy.

Table 3 The technique of endoscopic ultrasonography (EUS)-guided choledochoduodenostomy

(1) Visualization of extrahepatic bile duct from the duodenal bulb using a convex array echoendoscope with the long/pushing position (Fig. 2a).
(2) Under EUS guidance, insertion of a needle knife or a 19-gauge needle transduodenally into the bile duct.
(3) After removal of a stylet, bile aspiration and injection of contrast medium into the bile duct for cholangiography (Fig. 2b).
(4) Insertion of a 450 cm long, 0.035-inch guidewire into the outer sheath.
(5) If necessary, use of a biliary catheter or papillary balloon dilator for dilatation of the duodenocholedochal fistula.
(6) Insertion of a 5-Fr to 10-Fr biliary plastic stent or self-expandable metallic stent through the choledochoduodenostomy site into the extrahepatic bile duct (Fig. 2c,d).

(c) EUS-guided hepaticogastrostomy. The left lobe of the liver can be well visualized from the stomach by EUS, allowing EUS-FNA of hepatic lesions to be safely performed.[58,59] A similar technique to that of EUS-guided pancreatic pseudocyst drainage can be applied for EUS-guided hepaticogastrostomy. The technical success rate varies from 73–100% with an overall success rate of 84%. Complications occur in 12.5–30% of patients.[50,52,60–62] These include bile leak, bleeding, pneumoperitoneum, infection and death. Both stent occulusion and migration have been reported as late complications.[60] The procedure should not be attempted in patients with massive ascites and coagulopathy.

(3) EUS-guided pancreatic duct drainage

Pancreatic duct stenting using an ERCP technique is the first line treatment modality for management of obstructive chronic pancreatitis. EUS-guided drainage of the main pancreatic duct may be an effective treatment option for those patients in whom ERCP is technically unsuccessful and for whom surgery carries a high-risk. EUS-guided drainage of the main pancreatic duct can be undertaken either by a transluminal approach (via the stomach or duodenum) or by the rendezvous transpapillary approach.[62]

The transluminal approach and transpapillary rendezvous approach (Fig. 3) for the pancreatic duct are almost the same technique as that for bile ducts. Harada *et al.*[63] and Gress *et al.*[64] reported EUS-guided pancreatography in 1995 and 1996, respectively. In 2002, Francois *et al.*[65] first reported four cases of EUS-guided pancreaticogastrostomy; the procedures included transgastric placement of stents through the posterior wall of the stomach into a dilated, obstructed pancreatic duct through an EUS-created fistula.

EUS-guided rendezvous drainage was first reported in a single case of pancreatic duct access by Batille and Deprez in 2001.[66] Since then, another two studies using rendezvous method have been reported,[43,67] while a transluminal approach for pancreatic ducts has been reported[67,68,69] According to these reports, technical failures are mainly due to difficulty in orienting the echoendoscope along the axis of the main pancreatic duct, inability to dilate the transmural tract due to dense fibrosis, and difficulty with endotherapy due to the acute angle at which the pancreatic duct is accessed at EUS.[62] These studies showed medium-term pain relief can be obtained in 60–70% of patients following pancreatic stenting. Stent migration and/or occlusion have been reported in 20–55% of cases drained transluminally. The rate of complications has varied between 5–43%, and includes perforation, hemorrhage, pancreatitis, fever and post-procedural pain. Rendezvous drainage is more physiological and less likely to lead to retroperitoneal or intraperitoneal perforation, leakage, bleeding, or peritonitis.[70]

2. EUS-guided fine needle injection therapy

(1) EUS-guided celiac plexus neurolysis or block

EUS-guided celiac plexus neurolysis (EUS-CPN) was first reported by Wiersema *et al.* in 1996.[71] Since then, EUS-CPN has been applied for relief of intractable pain. With this technique, it is possible to observe the entire procedure in real time. Further, an anterior approach to the celiac plexus may reduce the risk of neurogenic complications. Additionally, the close proximity of the instrument to the gastric lumen allows precise needle placement and avoidance of puncture of vessels and the other organs.

The technique of EUS-CPN is similar to that of EUS-FNA except for the injection. The procedure begins with identification of the celiac trunk. The celiac plexus is located anterior and lateral to the celiac trunk take-off from the aorta. Bupivacaine (3–10 mL of 0.25%) is injected, followed by 10 mL (98%) dehydrated ethanol.[72,73] For EUS-guided celiac plexus block (EUS-CPB), a steroid (triamcinolone suspension 40 mg each side, bilaterally) is used in place of alcohol.[74]

The celiac plexus transmits the sensation of pain for the pancreas and most of the abdominal viscera. The current indication for EUS-CPN is unresectable pancreatic cancer and GI tract cancer, whereas that of EUS-CPB is abdominal pain caused mainly by chronic pancreatitis. In their study of 30 patients, Wiersema *et al.* reported a 79–88% improvement in pain score at a median follow-up of 10 weeks,[71] while Gress *et al.* reported a reduction of pain score and medication use in 55% patients with chronic pancreatitis treated with EUS-guided CPB.[74]

Recently, Levy *et al.* reported the usefulness of EUS-guided direct injection of agents into the celiac ganglia in patients with pancreatic cancer and chronic pancreatitis.[75] Using the technique of EUS-CPN to provide pain relief from pancreatic cancer has substantially increased initial response rates to more than 90%, and no major complications were encountered in this study.[75] However, celiac ganglia can be difficult to visualize in about 20% of patients, making direct ganglia injection impossible.[76]

EUS-guided CPN may be most cost-effectiveness when performed at the time of EUS-FNA. Because lower response rates have been reported, EUS-CPB should be considered investigational in patients with chronic pancreatitis.

(2) EUS-guided fine needle tattooing (EUS-FNT)

Intraoperative identification of lesions already detected on preoperative examination is sometimes difficult. Endoscopic tattooing is a very useful method to facilitate the identification of such previously detected lesions at surgery. Tattooing of pancreatic tumors, using the newly developed technique of EUS-guided fine

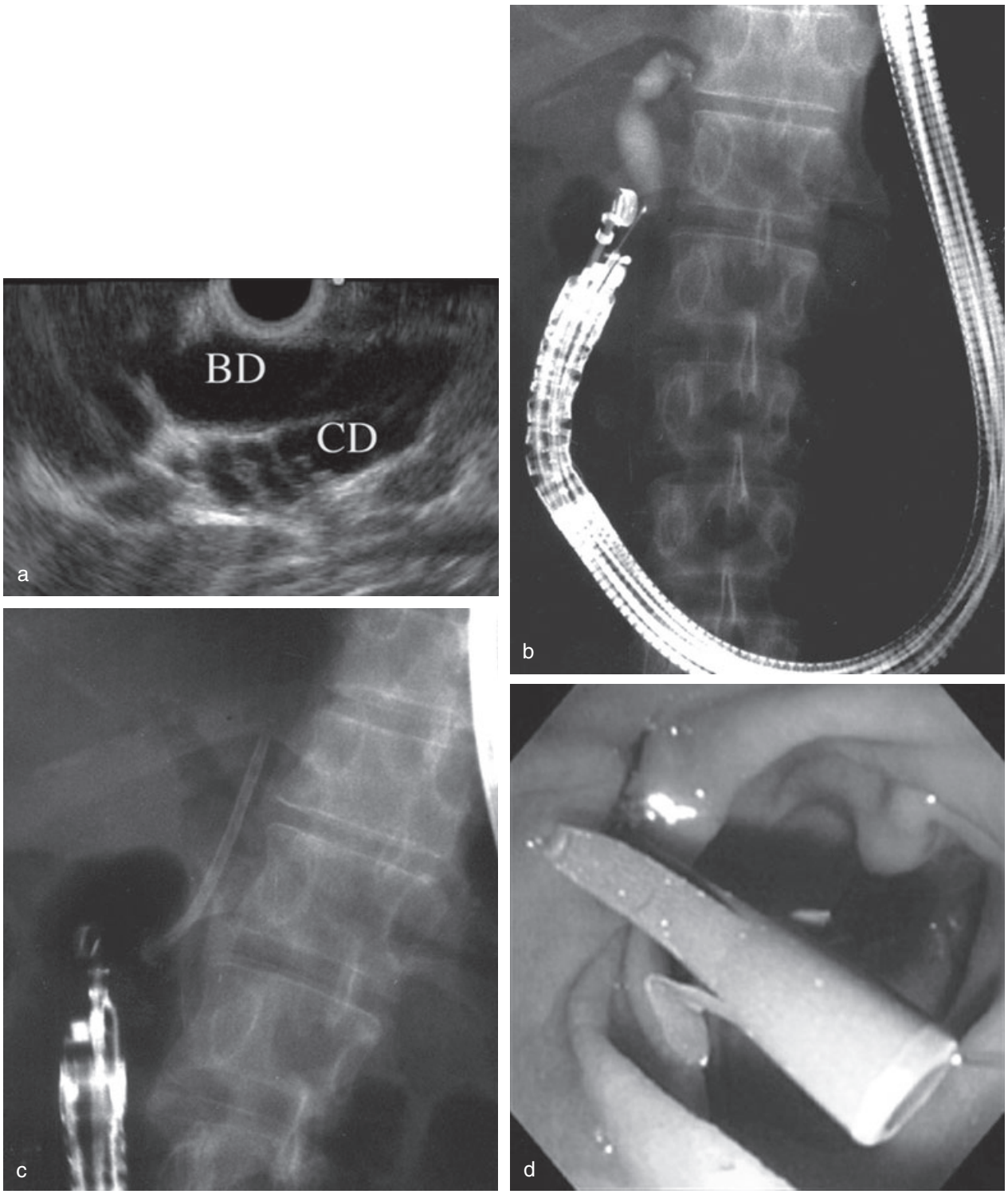

Figure 2 Endoscopic ultrasonography (EUS)-guided choledochoduodenostomy. (a) Convex echoendoscope, located in the apex of the duodenal bulb, clearly displayed the extrahepatic bile duct (CBD) and cystic duct (CD), (b) Cholangiogram obtained by EUS-guided puncture with the tip of the convex transducer directed to the hepatic hilum. The echoendoscope was observed in the long/pushing scope position, (c) Choledochoduodenostomy was accomplished using a tube stent in the apex of the duodenal bulb, (d) The stent was visible in the first portion of the duodenum.

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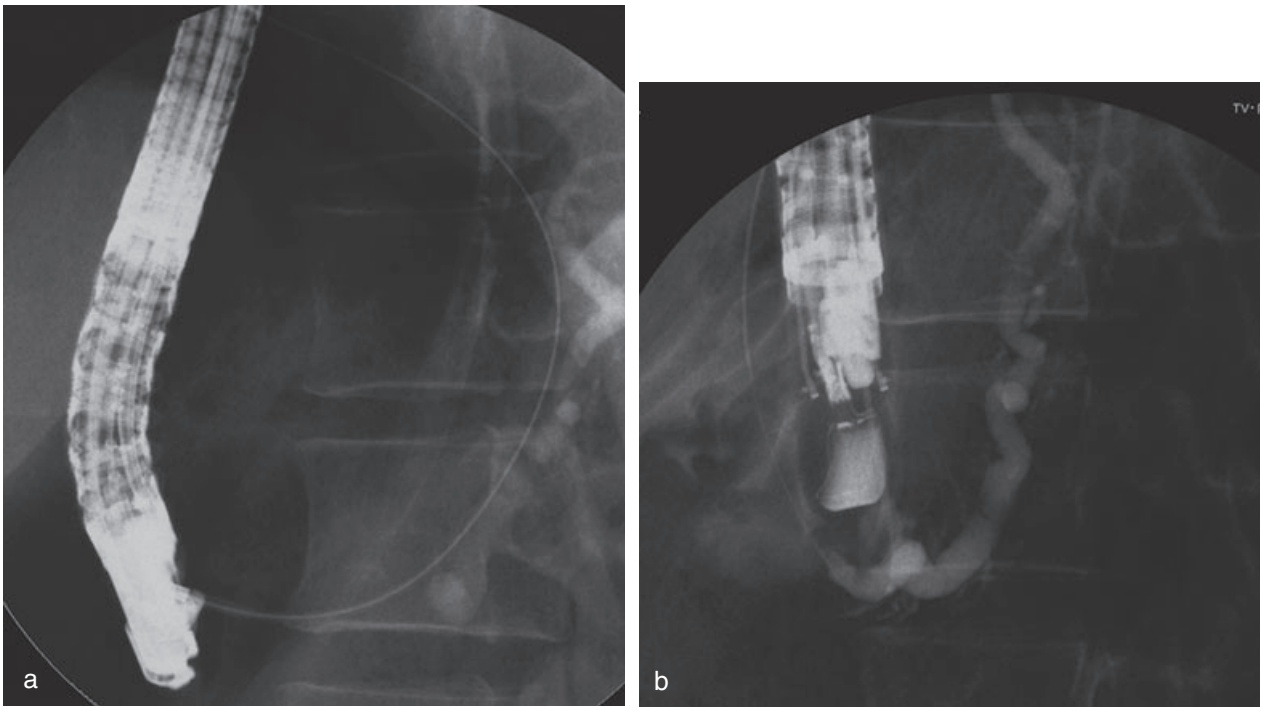

Figure 3 Endoscopic ultrasonography (EUS)-guided pancreatic access for rendezvous endoscopic retrograde cholangiopancreatograhy (ERCP) drainage in case of the stenosis of the orifice of pancreaticogastrostomy. (a) EUS-guided pancreatogram, showing the guide wire tracking diatally through the orifice of the stoma into the stomach. (b) Fluoroscopy showing the retrieval of the guide wire into the working channel of the duodenoscope.

needle injection with Indian ink was reported by Gress *et al.*[77] in 2002. Because a number of reports have noted side effects caused by Indian ink, the authors reported EUS-FNT with indocyanine green for small pancreatic tumor.[78] We have now safely performed EUS-FNT in four cases of small pancreatic tumor, including three cases of endocrine tumor and one of multiple serous cystic tumor. Farrell *et al.*[79] reported EUS-FNT with a sterile carbon-based ink for the laparoscopic preoperative localization of intraductal papillary- mucinous neoplasm (IPMN).

In summary, EUS-FNT represents a safe and useful method for preoperative marking of small pancreatic tumors. It is suggested that this technique will not only reduce operative time but also the total cost of preoperative and intraoperative tumor identification. Further trials are needed to confirm which substance provides the best efficacy and greatest safety of EUS-FNT when used to identify small pancreatic tumors.

(3) EUS-guided anti-tumor injection therapy

Injection of some materials into pancreatic cancer or other tumors under EUS guidance would seem to be an attractive treatment strategy. Materials with anti-tumor effect include ethanol and molecules with some biological anti-tumor actions.

EUS-guided ethanol injection has been used to ablate pancreatic tissue. In animal models, ethanol ablation of normal pancreatic tissue was safe and resulted in well controlled ablation.[80–82] In small case series, EUS-guided injection has been reported in pancreatic neuroendocrine tumors,[83] adrenal metastases,[84] and GIST.[85] EUS-guided ethanol injection into pancreatic cystic lesions has been reported in a couple of studies.[86] The initial trials revealed safety and effectiveness of epithelial ablation. Recently, ethanol ablation of pancreatic cystic neoplasm has been coupled with Taxol injection.[87]

The possibility of EUS-guided chemotherapy injection into solid pancreatic malignancies has been suggested by animal models. EUS-guided injection of a sustained released gel containing Taxol demonstrated effectiveness in normal porcine pancreatic tissue; there was no evidence of pancreatitis and other toxicity.[88] A similar report has demonstrated the safety of EUS-guided injection of a biodegradable polymer containing 5-fluorouracil (5FU) into the canine pancreas.[89]

Some clinical trials of EUS-guided anti-tumor injection therapy for pancreatic cancer have been reported. Chang *et al.*[90] first reported their phase 1 clinical trial of allogenic mixed lymphocyte culture (cytoimplants) in eight patients with locally advanced pancreatic cancer. This study showed the feasibility and safety of EUS-guided direct injection. The technique of EUS-guided FNI was also applied to the delivery of anti-tumor viral therapy using ONYX-015, an adenovirus that selectively replicates and kills malignant cells.[91] In this study, 2 out of 21 patients with unresectable pancreatic cancer had duodenal perforations from the rigid endoscope tip. Currently, there are no active clinical protocols evaluating cytoimplants and ONYX-015 for EUS-guided FNA.

An initial phase 1 clinical trial using TNFerade™ via EUS-guided delivery in combination with radiation therapy has been reported in patients with locally advanced pancreatic cancer.[92] TNFerade™ is a replication-deficiency adenovector cantaining the human tumor necrosis factor-alpha (TNFα) gene, regulated by a radiation-inducible promoter. A randomized control trial involving locally advanced pancreatic cancer is currently underway, comparing chemo/XRT/TNFerade™ against chemo/XRT.[93] EUS-guided injection of TNFerade™ has also been applied to the treatment of locally advanced esophageal cancer.[94] Injection of immature dendritic cells (DC)[95] into pancreatic cancer under EUS guidance was reported in 1997.

(4) EUS-guided brachytherapy and radiofrequency ablation

The delivery of ablative devices to localized malignancies has become increasingly possible through a number of developments. Goldberg *et al.* reported EUS-guided radiofrequency ablation (RFA) in the pancreas of a porcine model, using a modified EUS needle and a commercial RF needle.[96] Radiofrequency ablation could provide localized tissue ablation of a 1 cm zone from the needle catheter. One of 13 pigs developed pancreatitis.

EUS-guided brachytherapy has been reported in animal models. Through a large gauge EUS needle, radioactive seeds can be placed into the pancreas with relative safety and minimal tissue reaction. A pilot study in patients with recurrent esophageal cancer in perigastric lymph nodes[97] has demonstrated the feasibility and safety of the procedure. Following the reports of the safety of EUS-guided insertion of radioactive seeds in an animal model,[98] a recent study with radioactive iodine seeds given in conjunction with chemotherapy has demonstrated tumor remission and improvement in pain.[99] Magno *et al.* reported that EUS-guided implantation of a radiopaque marker into mediastinal and celiac lymph nodes was safe and effective in a porcine model.[100] Yan *et al.* reported EUS-guided gold fiducial insertion for image-guided radiation therapy of pancreatic cancer.[101] EUS can help guide the use of external beam radiation through the use of fiducials.

Another promising technique is photodynamic therapy (PDT). This tumor ablative technique is more selective than RFA and brachytherapy. The basis of PDT is the use of a tumor sensitizing agent that is selectively concentrated by the tumor. EUS-guided PDT guides the placement of a light catheter into the target through a large gauge EUS needle. Pre-clinical study by Chan *et al.*[102] and Tusuf *et al.*[103] both evaluated EUS-guided PDT in a pig model. They were able to ablate pancreatic and other tissue in a dose-dependent manner from 6–30 mm in diameter.

IV. Conclusion

Endoscopic ultrasound (EUS) is now indispensable imaging modality in clinical practice of gastrointestinal and pancreato-biliary diseases. Interventional EUS includes Endoscopic Ultrasound-guided Fine Needle Aspiration (EUS-FNA) and therapeutic EUS. EUS-FNA was first developed in early 1990s to enhance the diagnostic capabilities of EUS by providing additional pathological findings. The clinical utility of EUS-FNA has been widely accepted, and the number of EUS-FNA procedures has been increasing worldwide. Therapeutic EUS for various kinds of diseases has also been investigated in experimental studies and clinical trials, and some of the EUS-guided techniques are now well established. However, the others have not yet been established. Many and various kinds of interventional EUS techniques are expected to become more feasible as less invasive and safer techniques in the near future.

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