Therapeutic Endoscopic Ultrasound

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Endoscopic ultrasonography (EUS), since its development in the 1980s, has undergone a great deal of technological advancement in imaging, scopes with larger channels and accessories. Currently, it is possible not only to obtain tissue for histological diagnosis but also to perform therapeutic procedures that hitherto would have needed surgery with its attendant morbidity. EUS has evolved over the years and EUS-guided fine-needle aspiration for histological diagnosis has become standard practice. A wide array of interventional procedures are performed under EUS guidance including, coeliac plexus neurolysis (CPN), drainage of pancreatic and pelvic fluid collections, drainage of obstructive biliary/pancreatic ducts, and implantation of fiducial markers/radioactive seeds into gastrointestinal tumours.

Coeliac Plexus Neurolysis and Block

CPN is the injection of absolute alcohol to destroy the sympathetic plexus near the coeliac axis while coeliac plexus block (CPB) is to hinder the pain pathway by injecting triamcinolone. The former is performed in pancreatic cancer whilst the latter is undertaken in patients with chronic pancreatitis. Pain is a common symptom, with up to 90% of patients reporting pain in advanced pancreatic cancer.[1] CPN is effective in pain control in 70-90% of patients as shown in a meta-analysis.[2] However, these were radiological procedures and most adopted the posterior approach, which lead to serious complications of paraesthesia, paraplegia and pneumothorax in 1% of cases.[2] EUS has the advantage of accessing the ganglia anteriorly through the posterior stomach wall thus avoiding the spinal arteries, diaphragm and the pleura. The other notable advantages of EUS are real-time imaging, colour Doppler use to avoid vasculature and the ability to visualise the ganglia for targeted block.[3] In 1996, Wiersema and Wiersema[4] evaluated 30 patients with advanced intra-abdominal malignancy and showed that following CPN, pain scores reduced significantly compared with baseline at 12 weeks, while up to 91% of patients required the same or less pain medication and 88% of patients had persistent improvement in their pain score. Similarly, in another study of 58 patients with unresectable pancreatic cancer, EUS-guided CPN lowered pain scores in 78% at 2 weeks and a sustained response was noted until 24 weeks.[5]

Procedural Technique

The technique for EUS-guided CPB and neurolysis are identical with the only difference being the substances injected. Using a curvilinear-array echoendoscope, the region of the coeliac plexus is visualised from the lesser curve of the stomach by following the aorta to the origin of the main coeliac artery and

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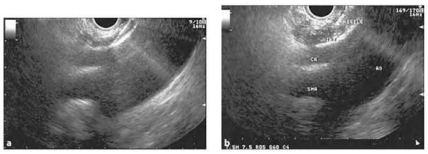
traced, using counter-clockwise rotation (Fig. 1a, b). With careful inspection it will often be possible, using slight rotational movements, to visualise directly the coeliac ganglia as elongated hypoechoic structures. A 22- or 19-G EUS-FNA needle is usually used. The tip of the needle is placed slightly anterior and cephalad to the origin of the coeliac artery or directly into the ganglia if these can be identified. Aspiration is first performed to ensure vascular puncture has not occurred. Bupivocaine is injected first, followed by alcohol (or triamcinolone for block).

Technical Considerations: There is considerable debate about injecting just anterior to the coeliac artery take off from the aorta versus injecting on either side of the coeliac artery take off. Although not proven, clinical experience suggests similar efficacy with both techniques. Also, there is increasing interest in targeting the coeliac ganglion as this can be seen clearly at EUS. Levy et al.[3] have shown in 33 patients, direct coeliac ganglia injections for unresectable pancreatic cancer or chronic pancreatitis can be performed safely. In their study, 94% of pancreatic cancer patients reported pain relief when alcohol was injected and 0% when steroid was injected. In chronic pancreatitis, 80% reported pain relief when alcohol was injected versus 38% receiving steroids.

Complications

Transient diarrhoea and orthostatic hypotension have been reported in 9 and 10-15%, respectively.[5] These are usually self-limiting and respond to conservative measures such as intravenous fluid administration. Gress et al[6] reported a complication of peripancreatic abscess in 1 of 90 patients undergoing CPB for chronic pancreatitis.



a. EUS-guided CPN being undertaken by placing the needle in the space around the coeliac artery.
b. Following injection, note the soft tissue reaction at the site of neurolysis

Pancreatic Fluid Collections

Pseudocysts occur in 10% of patients with acute pancreatitis and in patients with chronic pancreatitis following an acute exacerbation or due to ductal disruption.[7] Since 1989, when the first case was reported,[8] endoscopy has become the modality of choice for drainage of uncomplicated pancreatic pseudocysts. Various factors need to be taken into consideration prior to endoscopic drainage of pseudocysts: clinical symptoms of patients, location of the pseudocyst, presence of luminal compression at endoscopy, single or multiple fluid collections, and communication with the main pancreatic duct. EUS is a useful tool for the assessment and treatment of pancreatic fluid collections (PFCs) because of the close proximity of the stomach and duodenum to the pancreas.[9] EUS enables assessment of pseudocyst wall thickness, confirmation of size, delineate contents (clear fluid vs. walled-off pancreatic necrosis), check distance from the gastrointestinal lumen, evaluate for intervening vasculature, and sample cyst contents for analysis or perform

transmural drainage as a single-step procedure.[10-14]

Varadarajulu et al.[9] have shown that EUS alters diagnosis in 5% of cases, where cyst neoplasm was identified in cases misclassified as pseudocysts on CT imaging. At endoscopy, luminal compression is only identified in 50% of cases of PFCs.[8,15,16] EUS by virtue of its ability to identify PFC that does not cause luminal compression improves both the technical success rates (> 90%) and safety profile (complications, < 5%) of the procedure.[9,10,13] In a randomised trial, Varadarajulu et al[19] showed that blind drainage with endoscopy (gastroscopy) had a higher complication rate than under EUS guidance (12 vs. 0%) and when PFCs not amenable for drainage by endoscopy underwent crossover to the EUS cohort, all patients were drained successfully.

Procedural Technique: EUS-guided PFC drainage is performed under conscious sedation in the fluoroscopy suite with the patient in the left lateral or prone position. The patient should receive broad-spectrum antibiotics during and after the procedure to reduce the risk of infection. The PFC is first located and the contact zone between the gastric or duodenal wall is evaluated for interposed vessels using colour Doppler. After determining the optimal site for puncture, the PFC is punctured using a 19-G FNA needle and a sample of the cyst contents is aspirated and submitted for biochemical, cytological, and tumour marker analysis. If infection is suspected, a sample should be sent for Gram stain, culture and sensitivity. After passage of a 0.035-inch guidewire into the PFC, the transmural tract is sequentially dilated using a 4.5-/5-Fr ERCP cannula or a needle-knife catheter. The tract is further enlarged using a 6 or 8-mm over-the-wire biliary balloon dilator. A nasocystic drain or stent (double pigtail) is then deployed to drain the PFC. The choice between a nasocystic catheter or a stent for drainage will depend upon the density of the cyst contents. A chronic cyst with clear liquid contents can be drained with an 8.5 or 10-Fr stent alone or with two 7-Fr stents. An infected cyst mandates irrigation by nasocystic drainage catheter alongside the transmural stents.

Technical Considerations: When multiple PFCs are encountered in the same patient, the largest PFC should be drained at the index procedure. A repeat procedure is warranted for drainage of other PFCs if a patient has persistent symptoms with non-communicative fluid collection on follow-up imaging.[17]

Complications: The ability to drain the pseudocyst real-time under EUS guidance minimises the risk of complications such as perforation and haemorrhage. Intracystic haemorrhage is a rare but serious complication encountered during FNA of cyst lesions of the pancreas.[18] At EUS, the bleeding manifests as a hyperechoic area within the pseudocyst. Early identification of bleeding at EUS will enable timely intervention and thereby minimise the risk for serious adverse events.

Obstructive Bile Duct

Choledochoduodenostomy

The standard of care for patients

presenting with malignant biliary obstruction is an ERCP to place a transpapillary stent to affect bile drainage. However, technical failure is encountered in up to 10% of cases due to various factors including duodenal obstruction, anatomical variations, periampullary diverticulum and tightness of the stricture. Percutaneous transhepatic biliary drainage (PTBD) or surgical drainage are other treatment alternatives. The technical success rate for PTBD placement is 90% in a dilated intrahepatic system and 70% in a non-dilated system. The procedural morbidity for PTBD is 7% and the mortality rate is 5%. Other contraindications for PTBD include ascites and coagulopathy. Although surgical drainage is a possibility, current practice does not favour that approach as most cases are drained either by endoscopic or percutaneous means and the patient cohort are usually too unwell to undergo a major surgical intervention that has a morbidity of 66% and mortality of 32%.[19] Hence, the logical extension is to attempt drainage by means of EUS as the left intrahepatic system can be accessed via the stomach and the common bile duct (CBD) via the duodenal bulb.

Procedural Technique: After administration of intravenous antibiotics, the linear array echoendoscope is positioned in long scope position in the duodenal bulb to identify the CBD. Colour Doppler is used to exclude any intervening vasculature. A 19-G needle or needle-knife catheter is used to puncture the CBD. After removal of the stylet, bile is aspirated and contrast injected under fluoroscopic guidance to image the biliary tree. A 0.035-inch hydrophilic tip guidewire is inserted into the CBD. An ERCP cannula followed by balloon dilatation may be necessary to dilate the tract to ensure easy passage of stent. With the guidewire in place, a 7 to 10-Fr plastic stent is deployed under fluoroscopic guidance. A covered metal biliary endoprosthesis may be an alternative.

Complications: The procedural complication rate is 19 with 8% being due to focal biliary peritonitis. The advantage seems to be stent patency, which has been reported to up to a mean of 211 days at long-term follow-up.[20]

Hepaticogastrostomy

There are 19 published cases examining this concept that has demonstrated a technical success rate of 90-100% and a clinical success rate of 75-100%.[21-26]

Procedural Technique: The curved linear array echoendoscope is positioned along the cardia or the lesser curve of the stomach and after excluding the presence of intervening vasculature using colour Doppler, a dilated peripheral radical of the left intrahepatic system is accessed using a 19 or 22-G needle. After coiling a guidewire within the intrahepatic biliary ductal system, transmural dilation and stenting is undertaken as described earlier for performing a choledochoduodenostomy.

Complications: Reported complications with this technique include bile leak, infection and stent migration.

Obstructive Pancreatic Duct

Chronic pancreatitis is a debilitating

condition causing pain, exocrine and endocrine insufficiency. The latter two complications can be treated by medical means, while pain, as a symptom, can be difficult to manage. Pancreatic endotherapy is the mainstay for management of obstructive ducts and has a high success rate in expert hands. Correction of the offending factor (stone, stricture or duct disruption) leads to an improvement in symptoms in up to 80% of cases. However, ERCP can be technically challenging in a subset of patients when there is active inflammation of the duodenum, a very tight stricture, complete disruption of the pancreatic duct or severe stenosis of the minor papilla in pancreas divisum. There is also a significant minority who develop recurrent symptoms after successful endotherapy during long-term follow-up. Surgery is an effective treatment alternative in these circumstances as it has the advantage of removing the diseased part of the gland, however it involves significant morbidity and mortality.

EUS-guided pancreatic duct drainage is an attractive treatment alternative to decompress the obstructive pancreatic ductal system. The proximity of the pancreas to the posterior stomach wall makes it easy to access the main pancreatic duct under EUS guidance.

Procedural Technique: Two approaches, similar to hepatogastrostomy, have been described. The rendezvous technique and pancreatogastrostomy. For both techniques, the curved linear array echoendoscope is positioned in the stomach or duodenal bulb depending on the least distance from the transducer to the pancreatic duct. The tip of the echoendoscope should be aligned parallel to the long axis of the dilated pancreatic duct to help ease the passage of the guidewire. After excluding the presence of intervening vasculature using colour Doppler, a 19 or 22-G needle is used to puncture the main pancreatic duct. A 0.035- or 0.021-inch guidewire is inserted into the pancreatic duct and every attempt should be made to pass the wire across the papilla into the duodenum for rendezvous placement of a transpapillary stent. If this is not achievable, the guidewire should be passed retrograde to the tail of the pancreas and the transmural tract should be dilated using a 4.5-Fr cannula, needle-knife catheter or small-caliber bougie. Balloon dilatation (4-6 mm) may be necessary to dilate the tract to ensure easy passage of stent. With the guidewire in place, a transgastric 7-Fr plastic stent is deployed under fluoroscopic guidance.

Complications: Stent migration and occlusion appears to be a major problem in 20-55% of cases drained transluminally[27] and stent-induced pancreatic duct strictures have been observed on follow-up.[27] The rate of procedural complications in the four series varies between 5 and 44%, and is independent of the technique adopted for drainage.

Pelvic Fluid Collections

Pelvic fluid collections can occur due to Crohn's disease, diverticulitis, appendicitis and pelvic inflammatory diseases. More commonly they occur following pelvic surgery, in particular low

anterior resection for rectal carcinoma. The various approaches used conventionally to drain these collections are ultrasound-guided drainage via the transvaginal or transrectal route and CT-guided drainage via the transgluteal or transabdominal route. Alternatively, they can be managed surgically. The limitations with these approaches are the inability to access deep-seated collections, restriction on dilation of the tract to appropriate size, patient inconvenience, incomplete resolution, need for frequent reinterventions, and injury to surrounding vessels and nerves.[28,29] Three studies have evaluated the role of EUS-guided transrectal drainage of pelvic abscesses. While Giovannini et al.[30] used transrectal stents, Varadarajulu and Drelichman[31] used a drainage catheter with intermittent irrigation. The same author later reported a hybrid approach in which both a drainage catheter and plastic stent were deployed transrectally. While the drainage catheter was flushed and aspirated intermittently and then removed after a few days when the abscess cavity reduced in size, the stents were removed after 2 weeks.[32] Technical success in these studies was recorded in 75-100% of cases and treatment success rate was 85-100%.

Complications: No procedure-related complications were recorded in the three studies. One patient died of heart failure[31] and 25% of patients in one study[30] needed surgery because of treatment failure.

Implantation Therapy

There is a growing need for additional treatment options in cancer patients who are not surgical candidates. Due to the ability of EUS to access malignant tissue, it has the advantage of supplementing other therapeutic options that are currently available. Implantation of fiducial markers to facilitate radiotherapy and radioactive seed instillation for brachytherapy can be performed under EUS guidance.

Fiducial Implantation

Fiducials can be placed into tumours to enable more precise and targeted radiotherapy with low risk of complications. Although CT-guided placement has been attempted, EUS with its immediate access is a better option, particularly in patients with pancreatic cancer. Two studies have demonstrated a technical success rate of 84-91%.[33,34]

Complications: No immediate complications were encountered in both studies,[39,40] although 1 patient developed cholangitis after 3 weeks.

Brachytherapy

Brachytherapy is an important tool in the management of advanced pancreatic cancer and has been performed either by implanting radioactive seeds surgically or intraluminally at ERCP. As an alternative, EUS-guided brachytherapy has been performed to place radioactive iodine seeds[35] or to inject liquid-based implant into the pancreatic tumor mass.[36] Studies have demonstrated a significant improvement in pain scores in these patients. This technique needs further evaluation in multicentre trials as no survival benefit has been demonstrated and there were significant procedure-

related complications.[35]

Miscellaneous Applications

Botulinum Toxin Injection: EUS can identify the muscle layer in the lower oesophageal sphincter as a thick hypoechoic band. This allows targeted delivery of botulinum toxin to the muscle layer of the lower oesophagus in patients who are not fit for surgery or dilatation. Two studies have demonstrated technical feasibility, safety and clinical improvement in dysphagia scores.[37,38]

Tumour Localisation: EUS is known to be very sensitive in identifying small lesions in the pancreas, particularly neuroendodocrine tumours missed by CT imaging. As some of these lesions are difficult to identify at surgery, intraoperative ultrasound may be required in certain cases. EUS guided tattooing of the lesion using India ink has been advocated as a technique to facilitate their intraoperative localisation.[39-41]

Glue Injection for Vascular Bleeding: Gastric variceal bleeding is a serious complication of portal hypertension and can be difficult to treat. Blind injections with tissue adhesives have been reported with variable success rates. One of the major complications of cyanoacrylate glue injection is spread of glue to distant areas causing vascular occlusion. EUS provides a more precise approach to target the perforating veins.[43] It has been shown in one study that periodically targeted glue injections can lead to eradication of gastric varices.[44] Others have tried to use a coil to obliterate the ectopic varices.[45] In a minority of patients with non-variceal causes, the exact site of bleeding may not be easily identifiable at endoscopy.

EUS with color Doppler can identify vessels causing refractory bleeding and enables targeted therapy.[46]

Experimental Applications

Portal Vein Access: Portal vein pressures are important in the management of patients with advanced liver cirrhosis. While percutaneous and transjugular approaches are current options, four animal studies have demonstrated the feasibility and safety of portal venous access by EUS.[47,50]

Radiofrequency Ablation (RFA)

RFA is a well-established procedure for various malignant diseases to provide palliation. EUS-guided RFA is technically feasible and induces coagulation necrosis of larger areas.[51]

Conclusion

With further improvements in imaging and echoendoscope designs, more advanced and challenging interventions can be undertaken under EUS guidance with relative ease.

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