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REVIEW

Anterograde Endoscopic Ultrasound-Guided Pancreatic Duct Drainage: A Technical Review

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Abstract

The advancement of pancreatic endotherapy has increased the availability of minimally invasive endoscopic pancreatic ductal drainage techniques. In this regard, familiarity with endoscopic ultrasound-guided pancreatic duct drainage (EUS-PDD) is critical for treatment of obstructed pancreatic ductal systems, especially in nonsurgical candidates and in patients desiring a minimally invasive approach. Two distinct forms of EUS-PDD exist, viz. rendezvous-assisted endoscopic retrograde pancreatography (rendezvous-assisted ERP) and anterograde EUS-PDD. Anterograde EUS-PDD refers to transmural anterograde passage of a pancreatic drainage catheter or stent directly into the main pancreatic duct, through either the gastric or enteral wall. Rendezvous-assisted ERP should be attempted after failed conventional ERP, and anterograde EUS-PDD should be considered if rendezvous-assisted ERP fails or is not technically feasible. Common clinical scenarios that fulfil these conditions are chronic pancreatitis with high-grade main pancreatic duct obstruction, surgically altered anatomy with ductal/anastomotic obstruction, pancreas divisum, and disconnected pancreatic duct syndrome. The focus of this review article is anterograde EUS-PDD and its indications, technique, and outcomes. It also provides a summary of our own experience with this procedure, and a video demonstration of the technique.

Keywords Anterograde endoscopic ultrasound-guided pancreatic duct drainage · Pancreaticogastrostomy · Endoscopic ultrasound · Chronic pancreatitis · Pancreaticojejunostomy · Disconnected pancreatic duct syndrome

Introduction

Pancreatic endotherapy has advanced significantly in the era of therapeutic endosonography. While surgical pancreatic drainage procedures were standard of care in chronic pancreatitis (CP) with obstructed pancreatic ductal systems, the advent of endoscopic technology has allowed for more interventional endoscopic options for pancreatic ductal drainage when clinically indicated. With the improvement in imaging capabilities of endoscopic ultrasound scopes and increased experience of operators with these interventional procedures, minimally invasive endoscopic drainage options have become available for patients who require pancreatic ductal drainage.

Endoscopic ultrasound-guided pancreatic duct drainage (EUS-PDD) is a salvage procedure after technical failure of endoscopic retrograde pancreatography (ERP) and is an alternative to enteroscopy assisted-endoscopic retrograde pancreatography (EA-ERP) in case of surgically altered anatomy [1]. Two distinct forms of EUS-PDD exist, viz. rendezvous-assisted endoscopic retrograde pancreatography (rendezvous-assisted ERP) and anterograde EUS-PDD. Rendezvous-assisted ERP employs transmural and, subsequently, transpapillary/transanastomotic anterograde guidewire passage to facilitate pancreatic duct cannulation via ERP. Anterograde EUS-PDD refers to transmural anterograde passage of a pancreatic drainage catheter or stent directly into the main pancreatic duct (MPD), through either the gastric or enteral wall. Anterograde EUS-PDD should be considered if rendezvous-assisted ERP fails or is not technically feasible. The focus of this review article is anterograde

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EUS-PDD and its indications, technique, and outcomes. It also provides a summary of our own experience with this procedure, and a video demonstration of the technique.

Endoscopic Ultrasound-Guided Pancreatic Duct Drainage: Indications

Nonaccessible or nontraversable papillae/surgical anastomoses are the primary reasons for technical failure of ERP and, in turn, the main indications for EUS-PDD. Tight strictures, obstructing stones, and disconnected pancreatic duct syndrome are causes for inability to complete traditional ERP and are indications for either form of EUS-PDD.

Rendezvous-assisted ERP and anterograde EUS-PDD are the two principal forms of EUS-PDD. Understanding the distinction between the two techniques is important due to differing indications and implications, in addition to the difference in the technical difficulty of the procedures. Rendezvous-assisted ERP employs transmural anterograde guidewire passage to facilitate transpapillary/transanastomotic MPD cannulation via conventional ERP. Anterograde EUS-PDD refers to transmural, transgastric or transenteric, anterograde passage of a pancreatic stent directly into the MPD. Rendezvous-assisted ERP should be considered for therapeutics prior to anterograde EUS-PDD [2]. There are several reasons why rendezvous-assisted ERP is preferable to anterograde EUS-PDD. First, the underlying pathology is usually directly treated and transpapillary/transanastomotic drainage of pancreatic secretions is reestablished using rendezvous-assisted ERP [3]. Second, fistula formation to achieve therapeutic access to the MPD is not necessary. This translates to a theoretical decrease in risk of pancreatic injury, bleed, or leak. Inherent risk accompanies transmural fistula formation in anterograde EUS-PDD; For example, tract dilation and anterograde pancreatic stent passage in a neofistula risk leakage of gastric contents and pancreatic duct leak if fistula formation is incomplete [1]. In addition, the frequent necessity to use thermal energy in creation of the transmural fistula adds another inherent layer of pancreatic injury risk.

When considering EUS-PDD after technical failure of conventional ERP, the surgical candidacy of the patient should first be considered. Most of the conditions that are amenable to EUS-PDD are also amenable to surgical therapies, including chronic pancreatitis (CP) and anastomotic strictures. In the case of CP, surgical decompression has shown better long-term symptomatic benefit than endoscopic decompression [4]. Thus, it is reasonable to reserve EUS-PDD for suboptimal surgical candidates or for patients desiring a minimally invasive approach [4, 5]. Percutaneous image-guided pancreatic duct drainage is the alternative to EUS-PDD in nonsurgical candidates with obstructive pancreatopathy [2, 6], although our opinion is that transgastric or transenteric drainage is preferable in terms of patient comfort and decreased risk of percutaneous chronic fistula formation. Patients with a suspected malignant obstruction should first be evaluated for surgery [7, 8], although EUS-PDD may have a palliative role in select patients with malignant MPD obstruction [9].

In our opinion, all the above-mentioned issues necessitate consideration of surgical candidacy, followed by an attempt at rendezvous-assisted ERP, prior to resorting to anterograde EUS-PDD.

EUS-PDD: Contraindications

Technical contraindications for rendezvous-assisted ERP and anterograde EUS-PDD include hemodynamic instability prohibiting adequate sedation, severe thrombocytopenia (platelet count < 50,000), coagulopathy [international normalized ratio (INR) > 1.5], inability to localize the MPD using EUS, intervening structures (e.g., vasculature), and multiple MPD strictures [10, 11]. Contraindications to general endoscopy also apply to EUS-PDD.

Overview of Chronic Pancreatitis

Introduction

In available literature, chronic pancreatitis (CP) and surgically altered anatomy with anastomosis-related pathology (i.e., pancreaticojejunostomy) are among the most frequently cited clinical entities responsible for failed ERP with subsequent utilization of EUS-PDD [1–3, 5, 9, 12–19]. Given the complex natural history and management of painful CP, an overview is provided. The following overview focuses on uncomplicated painful CP (i.e., does not discuss complications of CP, such as pseudocyst, biliary stricture, and pancreatic cancer).

Natural History

Chronic pancreatitis (CP) is a condition characterized by progressive pancreatic inflammation and scarring, with ensuing structural and functional damage. Chronic pancreatic-type pain occurs in approximately half of all patients with CP [20]. The pathophysiology of pain in CP is multifaceted and incompletely understood. Prevailing theories include pancreatic ductal and interstitial hypertension and pancreatic ischemia. The association between CP pain and ductal hypertension is supported by studies showing pain relief following endoscopic and/or surgical drainage procedures [4]. Pancreatic ischemia is thought to arise from

impairment in the gland's normal hyperemic response to secretagogue-based stimulation, which occurs in the setting of reduced gland compliance from parenchymal fibrosis and MPD hypertension from obstruction [21, 22]. Other contributors to CP pain include neurogenic/neuropathic changes in the pancreas and/or peripancreatic tissues, cytokine-related inflammation from infiltrative immune cells within the pancreas, and intestinal malabsorption due to exocrine failure [20, 23].

In the setting of uncomplicated obstructive painful CP, both ERP and surgery are intended for pain relief via MPD drainage [24]. The concept of pain relief following pancreatic duct drainage is rooted in the idea that pancreatic-type pain is partly attributable to pancreatic ductal hypertension and associated parenchymal pressure. The achievement of pain relief after MPD drainage is supported by clinical evidence, but less so the basic science (i.e., PD pressure does not correlate well with pain severity; CP pain quality and severity are independent of pancreatic morphological alterations on imaging) [25, 26]. The most common etiologies of MPD obstruction in CP are strictures (47 %), strictures and stones (32 %), and isolated stones (18 %) [27].

Endoscopic Therapy

An individualized and multidisciplinary approach is recommended for the management of pain associated with uncomplicated CP. Management decisions are complex and individualized, in part because pancreatic surgery has proven superior to endoscopy in terms of long-lasting pain relief yet endoscopic therapy is performed first in many cases [4, 28]. The efficacy of a surgical approach is supported by the findings from a 2015 Cochrane review that surgery is superior to endoscopy in attainment of long-term (5-year) pain relief, and that early surgical intervention may help preserve pancreatic function [4]. However, first-line ERP is recommended after failed medical therapy by both the European Society for Gastrointestinal Endoscopy (ESGE) and by United European Gastroenterology (UEG) in most patients with uncomplicated painful CP [24, 28]. The ESGE points out that the three randomized controlled trials (RCTs) included in the 2015 Cochrane review are confounded by suboptimal endoscopic therapy and/or inclusion of mostly advanced CP patients (i.e., patients with poor predictors of endoscopic success) [24]. The ESGE argues that ERP is less invasive and does not preclude future surgery. Moreover, independent predictors of long-term (≥ 2 year) pain relief after endoscopic decompression in CP have been identified, including obstruction in the head of the pancreas [7], absent MPD stricture, short disease duration, infrequent pain flares, and abstinence from alcohol and tobacco [24, 28–32]. The ESGE and UEG both recommend consideration of surgery after an unsatisfactory response to ERP and/or in patients lacking predictors of a satisfactory endoscopic outcome [24, 28]. It is our experience that clinical response to endoscopic pancreatic ductal drainage is a predictor of successful surgical ductal drainage, specifically in patients who respond to endoscopic therapy but do not achieve long-lasting success with these therapies.

Surgical Therapy

Surgery for chronic pancreatitis is typically considered for patients who continue to have significant pain after failure of medical and endoscopic management, especially in patients lacking predictors of a satisfactory endoscopic outcome [24, 28]. As with ERP interventions, long-term pain relief is more likely to occur when surgery is performed earlier, rather than later, in the CP disease course [4, 28]. Postponement of surgical referral, until exhaustion of endoscopic options, is discouraged for this reason. Surgical goals are similar to endoscopic goals, viz. to relieve short- and long-term pain and suffering, as well as to preserve pancreatic function. CP surgical techniques are broadly categorized as drainage and/or resection. Drainage techniques relieve obstructive pancreatopathy in the setting of MPD dilation ≥ 5 mm [28]. Resection techniques remove areas of fibrotic parenchymal reorganization, independent of MPD dilation (i.e., resection techniques can be used alone or in concert with operative drainage). Operative resection techniques have been developed to target different locations of pancreatic parenchymal fibrosis (i.e., head-dominant, tail-dominant, diffuse parenchymal disease).

Lateral pancreaticojejunostomy (LPJ) is the best known operative technique for drainage of large-duct CP (i.e., MPD dilation ≥ 5-mm). The origin of LPJ can be traced back to the retrograde pancreatic drainage operation described by Peustow and Gillesby [33]. LPJ opens the MPD via anterior ductal dissection, clears the MPD of calculi, and fastens a Roux-en-Y limb of jejunum to the opened MPD. Patients with large-duct and head-dominant CP are candidates for combined operative drainage and resection, known as the Frey procedure. Lateral pancreaticojejunostomy and decortication of pancreatic head was described by Frey and Smith [34], and is essentially a combination of the LPJ (i.e., modified Peustow procedure) and subtotal pancreatic head resection (i.e., Beger procedure) [34–36]. Per the UEG, lateral pancreaticojejunostomy with a Roux-en-Y loop and Frey's procedure provide comparable pain relief in patients with painful dilated CP and a normal-sized pancreatic head. The UEG does not cite a preferred surgical technique in this setting given the low quality of evidence [28].

Head-dominant disease refers to an enlarged pancreatic head diameter > 4 cm on cross-sectional imaging [28]. Local complications of fibroinflammatory head-dominant disease include stenosis of the MPD, common bile duct (CBD),

duodenum, and/or retropancreatic vasculature (e.g., portal vein, superior mesenteric vein). Head-dominant disease is amenable to pancreaticoduodenectomy (PD; classic Whipple resection), pylorus-preserving pancreaticoduodenectomy (PPPD), and duodenum-preserving pancreatic head resection (DPPHR; Berger procedure or Frey procedure) [36]. The idea of modifying the classic Whipple surgery to preserve the pylorus (i.e., PPPD), thereby retaining the integrity of the gastric emptying mechanism, was promoted in a case series by Traverso and Longmire [37]. The idea of subtotal pancreatic head resection (i.e., DPPHR) to avoid morbidity associated with partial gastrectomy, common duct resection, and duodenectomy was reported by Beger et al. [35]. The multicenter, randomized, controlled, double-blind ChroPac trial compared long-term postoperative outcomes between PD/PPPD and DPPHR [36]. No significant difference was seen in the primary endpoint (i.e., mean quality of life within 24 months after surgery) or secondary endpoints (i.e., mortality, morbidity, new-onset exocrine and/or endocrine pancreatic insufficiency) [36].

Overview of Pancreaticojejunostomy-Related Pathology

Pancreaticoduodenectomy (classic Whipple surgery) involves multiple resections (i.e., head of the pancreas, duodenum, 15 cm of jejunum, common bile duct, gallbladder, and partial gastrectomy) and formation of three surgical anastomoses (i.e., gastrojejunostomy, hepaticojejunostomy, and pancreaticojejunostomy). The incidence of long-term pancreaticojejunostomy stricture (PJS) following pancreaticoduodenectomy resection for benign disease reportedly ranges from 5 to 10 % [38, 39]. Symptoms of PJS may include abdominal pain, steatorrhea, and recurrent acute pancreatitis [40]. Endoscopic management of pancreaticojejunostomy-related adverse events (AEs), including PJS and pancreatic fistula, is challenging given that the pancreaticojejunostomy may be endoscopically unreachable or unidentifiable.

Enteroscopy-assisted ERP (EA-ERP) is the conventional first-line therapy for post-Whipple-surgery pancreatic intervention at most tertiary centers due to its excellent safety profile and because of more widespread procedural familiarity [1]. However, EA-ERP is known for a technical success rate that has been reported to be as low as 8 % [41]. In some cases of altered surgical anatomy (e.g., post-Whipple resection), Chen et al. argue that select tertiary centers should consider replacing EA-ERP with EUS-PDD as first-line therapy for management of post-Whipple pancreatic pathology. Chen et al. compared EUS-PDD [anterograde ($n=40$), rendezvous-assisted ERP ($n=3$)], with enteroscopy-assisted ERP ($n=35$), following Whipple surgery. EUS-PDD was superior to EA-ERP in terms of technical success [92.5 versus 20 %; $p<0.001$ (successful pancreatography, duct access with stricture dilation, and/or stent placement)] and clinical success [87.5 versus 23.1 %; $p<0.001$ (partial and complete symptom resolution)]. The safety profile of EA-ERP [AEs 2.9 % ($n=1$); $p<0.001$] was better than EUS-PDD [AEs 37.5 % ($n=15$); $p<0.001$], and no major AEs occurred in either group. Chen et al. reason that the perceived (relative) safety of EA-ERP, compared with EUS-PDD, is likely confounded by its low technical success rate. Before the inception of EUS-PDD, surgical revision would frequently follow failed EA-ERP in a post-Whipple patient.

EUS-PDD: Techniques

Choosing a Technique

EUS-guided pancreatic duct drainage (EUS-PDD) is indicated for surgically altered anatomy (i.e., unreachable native papilla or surgical anastomosis) or failed conventional endoscopic retrograde pancreatography (ERP). EUS-PDD comprises two principal drainage techniques: rendezvous-assisted ERP and anterograde EUS-PDD [1, 42, 43]. Rendezvous-assisted ERP is preferred over anterograde drainage because underlying ductal pathology is directly treated and native ductal anatomy is preserved [2]. However, the clinical/endoscopic scenario dictates which EUS-PDD technique is required. Rendezvous-assisted ERP is not feasible if the papilla or pancreaticoenteric anastomosis is endoscopically inaccessible or impassable with a guidewire [10]. Examples in which anterograde transpapillary guidewire passage (i.e., rendezvous-assisted ERP) might fail include high-grade pancreaticojejunostomy strictures, disconnected pancreatic duct, and completely obstructing pancreatic ductal stones that have failed extracorporeal shock wave lithotripsy (ESWL). A prophylactic antibiotic (e.g., fluoroquinolone) should be administered before and after EUS-PDD [42].

EUS-Guided Pancreatography

EUS-guided attainment of MPD access (i.e., EUS-guided pancreatography) precedes both rendezvous-assisted ERP and anterograde EUS-PDD. Following endosonographic localization of the MPD using a linear echoendoscope, transgastric (or transenteric) puncture is performed using a sharp (19-gauge) aspiration needle. Use of a 22-gauge needle is discouraged as the associated 0.018- or 0.021-inch guidewire may have insufficient caliber for optimal traction during subsequent tract dilation and stent insertion [1]. Moreover, a 22-gauge needle renders contrast injection and guidewire exchange more difficult, and the

theoretical risk of guidewire shearing is greater. The best site for transgastric MPD access is typically between the gastric body and cardia [11]; however, the small bowel may be utilized for transmural access in cases of surgically altered anatomy [1]. The linear echoendoscope should be aligned parallel to the MPD to mitigate inadvertent guidewire passage into a MPD side-branch [42]. Parallel scope orientation also allows easier application of traction when the fistula is being created and devices are being advanced over the guidewire. Pancreatogram is obtained via contrast medium injection under fluoroscopy. We typically utilize half-strength contrast medium (contrast diluted 1:1 with sterile water), as this allows easier injection of the contrast medium through the 19-G needle.

Rendezvous-Assisted ERP

Two prerequisite conditions must be met for successful rendezvous-assisted ERP. First, the native papilla (or pancreaticoenteric anastomosis) must be endoscopically accessible with a duodenoscope, pediatric colonoscope, or balloon-assisted enteroscopy (BAE). Second, anterograde transpapillary or transanastomotic guidewire passage is necessary to perform subsequent ERP.

With regard to guidewire advancement during the rendezvous technique, a higher-caliber guidewire (e.g., 0.035 inches) is more likely to pass through an area of high-grade obstruction. Passage of a thick guidewire through a sharp needle risks stripping the guidewire membrane, so caution should be exercised. We typically utilize a 0.025-inch guidewire, as this allows easier device exchange over the guidewire, and less theoretical risk of guidewire membrane shearing. Upon advancement of the guidewire into the small bowel, the needle and echoendoscope are exchanged for a duodenoscope (if normal anatomy) versus a pediatric colonoscope or enteroscope (if surgically altered anatomy). Unlike the anterograde approach, the rendezvous technique is a two-step procedure because of endoscope exchange. The endoscope is advanced to the native papilla or pancreaticoenteric anastomosis. The protruding guidewire is then grasped with a snare or biopsy forceps, and the guidewire is withdrawn through the endoscope working channel. Once guidewire control is achieved, retrograde pancreatic cannulation may be achieved via advancement of the cannulation catheter over the guidewire. Alternatively, next-to-the-wire pancreatic cannulation can be performed, where the cannulation catheter is used to cannulate next to the existing anterograde-placed guidewire, rather than the catheter being advanced over the guidewire. Rendezvous-assisted ERP culminates in transpapillary/transanastomotic stent placement.

Anterograde EUS-PDD

Anterograde EUS-PDD is performed when the papilla or surgical anastomosis is endoscopically inaccessible or when anterograde transpapillary/transanastomotic guidewire passage is impossible due to high-grade ductal/anastomotic obstruction or pancreatic ductal disruption. In other words, anterograde EUS-PDD is performed when rendezvous-assisted ERP is impossible. Transmural stent placement with fistula formation distinguishes anterograde EUS-PDD from rendezvous-assisted ERP. Transmural stent placement can be transgastric or transenteric.

Tract dilation may be necessary to facilitate anterograde stent passage over the guidewire. Tract dilation refers to dilation of the gastric wall, pancreatic parenchyma, and MPD. Non-cautery-assisted devices (e.g., cannula, tapered catheter, dilation balloon, or biliary dilation catheters) are recommended for normal pancreatic parenchyma to avoid cautery-induced injury. Risks associated with non-cautery-assisted devices include leaks, perforation, and bleeding arising from axial or radial dilation forces [42]. Cautery-assisted devices (e.g., needle-knife, cystotome) may prove more efficacious when pancreatic parenchyma is hardened from fibrosis related to chronic scarring and chronic pancreatitis.

Anterograde stent placement can be categorized as (1) transpapillary/transanastomotic or (2) transmural (transluminal). Anterograde transpapillary/transanastomotic stenting is contingent on guidewire (and stent) traversal across the obstruction, and therefore is only applicable to cases of papilla/anastomotic inaccessibility (i.e., rendezvous-assisted ERP should always be performed if the papilla/anastomosis is accessible and anterograde transpapillary/transanastomotic guidewire passage is possible). When anterograde transpapillary/transanastomotic drainage is performed, the distal end of the stent should terminate in the small bowel and the proximal tip within the gastric lumen (i.e., "ring drainage" or gastropancreatojejunostomy) [19]. Ring drainage facilitates future stent exchanges while theoretically maximizing drainage and minimizing stent migration risk. Ring drainage also theoretically reduces risk of stent-induced pancreatic ductal injury from a stent tip lodged within the wall of the MPD.

Anterograde transmural stenting is used if the guidewire cannot bypass the obstruction, such that the distal and proximal tip lie within the MPD and stomach, respectively (Fig. 1a, b). Stent options include straight and double-pigtail plastic stents, as well as fully covered self-expanding metal stents [9]. Uncovered stents are relative contraindicated due to risk of leakage [10]. Also, uncovered stents are technically difficult to remove or replace, due to tissue ingrowth. Following placement of a transmural pancreatic stent, a tract forms between the MPD and the associated gastroenteric lumen. This fistula tract can be dilated and used for further

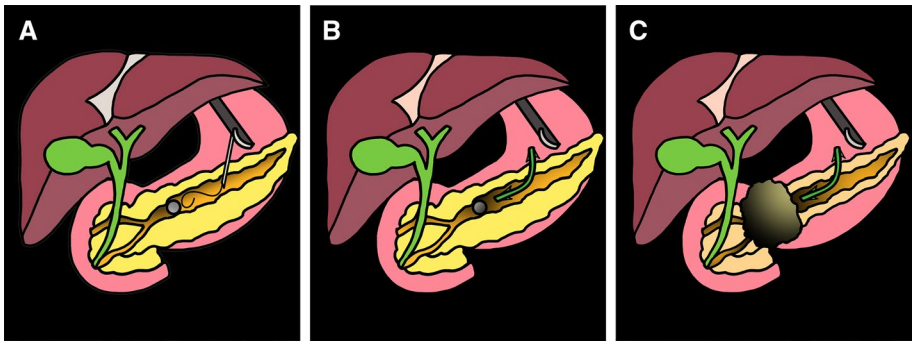

Fig. 1 **a** Illustration of transgastric anterograde guidewire passage through an aspiration needle in chronic pancreatitis with an obstructing calculus in the genu of the MPD. An echoendoscope is depicted in the stomach. The guidewire is unable to traverse the MPD obstruction; therefore, rendezvous-assisted ERP is not an option, and anterograde stenting must be performed for pancreatic ductal drainage. **b** Illustration of anterograde EUS-PDD in chronic pancreatitis (CP). A plastic pancreatic stent is seen traversing the endoscopically created pancreaticogastrostomy. The distal tip of the plastic pancreatic stent is within the MPD and directed towards the head of the pancreas. The proximal tip of the plastic pancreatic stent is within the gastric body. **c** Illustration of anterograde EUS-PDD in disconnected pancreatic duct syndrome (DPDS). Pancreatic necrosis is depicted in the neck and body of the pancreas, with proximal MPD dilation (i.e., proximal disconnected MPD). A plastic pancreatic stent is seen draining the disconnected pancreatic duct segment via the endoscopically created pancreaticogastrostomy. In cases of complete MPD abruption, drainage (stenting) of the disconnected duct segment is impossible via conventional or rendezvous-assisted ERP. Utilization of anterograde EUS-PDD in cases of DPDS can potentially spare the patient surgery (e.g., distal pancreatectomy) and/or percutaneous image-guided pancreatic duct drainage

therapeutic intervention, such as wire-guided basket retrieval of stones, pancreatoscopy-associated electrohydraulic lithotripsy (EHL), and/or holmium laser lithotripsy.

Anterograde EUS-PDD: Elective Stent Exchange

Unless anterograde EUS-PDD is performed as a bridge to surgery, repeat endoscopy with stent exchange should be considered after the index procedure [14, 15]. In a study of 36 cases of anterograde EUS-PDD, Tessier et al. [14] encountered 31 total episodes of stent dysfunction (stent obstruction or migration) among 20 patients (55 %) at a median time of 195 days (6.5 months) after the index procedure. Tessier et al. responded by changing their practice to offer repeat endoscopy with stent exchange (caliber upsizing) or insertion of a second stent within the existing transmural fistula. In contrast, Will et al. [18] did not perform elective stent exchanges among the 26 patients who underwent successful anterograde drainage on first attempt. Spontaneous stent dislocation occurred in 4 of these 26 patients during a median follow-up of 285 days (9.5 months). Will et al. reasoned that stent-induced ductal damage had not been reported in cases of anterograde EUS-PDD; therefore, stent exchange is best dictated by the clinical and radiographic response to index drainage.

It is our practice to perform elective stent exchanges following the index anterograde EUS-PDD (Table 2). Besides mitigating the risk of stent dysfunction, elective stent exchange can widen the aperture of the endoscopically created transmural fistula (i.e., via exchange with a larger-caliber stent or via placement of additional indwelling stents). Widening the transmural fistula can facilitate more definitive endoscopic therapy (e.g., anterograde pancreatoscopy for impacted MPD stones).

An issue of concern to our team is the "life" of the endoscopically created fistula. It remains unclear how long these fistulas remain patent after indwelling stent removal. Long-term follow-up studies are required to assess endoscopic fistula longevity. At this time, we recommend continued anterograde therapy, until the papilla/anastomosis is traversable (in cases where the papilla/anastomosis is reachable). Anterograde guidewire traversal of the papilla/anastomosis can facilitate traditional retrograde transpapillary drainage, thereby mitigating concerns of transmural fistula closure. Anterograde transpapillary/transanastomotic guidewire passage may be technically impossible in the setting of an unreachable papilla/anastomosis, or in cases of disconnected pancreatic duct syndrome (Fig. 1c).

Literature Review of Anterograde EUS-PDD

This literature review is specifically meant to examine anterograde EUS-PDD, which is distinct from rendezvous-assisted ERP. Table 1 summarizes the 13 available case series and cohort studies that include data on anterograde EUS-PDD with stent placement. Per the available information, anterograde drainage was attempted 155 times. Technical success is defined as successful stent placement on initial or repeat attempt. The overall technical success of

Table 1 Literature review of anterograde EUS-PDD with stent placement

Ref.	Patients	Technique [no. attempted interventions]	Technical success (%)	Clinical success (%)	Adverse events (%) [no. cases]
François et al. [12]	4	Anterograde [4]	4/4 (100)	3/4 (75)	0/4 (0)
Kahaleh et al. [13]	12	Anterograde [12]	10/12 (83)	N/A	2/12 (17) Bleeding [1] Perforation, contained [1]
Tessier et al. [14]	36	Anterograde [36]	33/36 (92)	25/33 (76)	2/36 (6) Bleeding, hematoma [1] Pancreatitis, pseudocyst [1]
Brauer et al. [5]	8	Anterograde [4] Rendezvous [4]	4/4 (100) 3/4 (75)	2/4 (50) 2/3 (67)	0/4 (0) 0/4 (0)
Ergun et al. [15]	20	Anterograde [15] Rendezvous [5] EUS-PDD [anterograde and rendezvous]	13/15 (87) 5/5 (100)	10/13 (77) 3/5 (60)	N/A N/A 2/20 (10) Bleeding [1] Pancreatic fluid collection [1]
Shah et al. [16]	22	Anterograde [14] Rendezvous [16]	10/14 (71) 9/16 (56)	N/A N/A	2/14 (14) Pancreatitis [1] Pneumoperitoneum [1] 2/16 (12.5) Pancreatitis [2]
Vila et al. [16]	19	Anterograde [5] Rendezvous [14]	2/5 (40) 9/14 (64)	N/A N/A	1/5 (20) Pseudocyst [1] 4/14 (29) Pancreatitis [4]
Fujii et al. [3]	43	Anterograde [unknown] Rendezvous [unknown] EUS-PDD [43]	18/__ (N/A) 14/__ (N/A) 32/43 (74)	N/A N/A 27/29 (93)	N/A N/A 16/43 (37) Abdominal pain [13] Abscess [1] Guidewire shaving [1] Pancreatitis [1]
Kurihara et al. [2]	14	Anterograde [3] Rendezvous [16]	3/3 (100) 11/16 (69)	3/3 (100) 11/11 (100)	0/3 (0) 1/16 (6) Pseudocyst [1]
Will et al. [18]	83	Anterograde [unknown] Rendezvous [unknown] EUS-PDD [83]	30/__ (N/A) 22/__ (N/A) 52/83 (63)	30/30 (100) 22/22 (100)	N/A N/A 24/83 (29) Aspiration [1] Abscess [4] Bleeding [6] Pancreatitis [6] Perforation [1] Perigastric fluid [3] Pressure ulcer [2] Retention cyst [1]
Oh et al. [9]	25	Anterograde [25]	25/25 (100)	25/25 (100)	5/25 (20) Abdominal pain [4] Bleeding [1]
Tyberg et al. [19]	80	Anterograde [unknown] Rendezvous [unknown] EUS-PDD [80]	57/__ (N/A) 14/__ (N/A) 71/80 (89)	N/A N/A 65/71 (92)	N/A N/A 16/80 (20) Abdominal pain [3] Bleeding [1] MPD leak [1] Pancreatitis [6] Perforation [1] Pancreatic fluid collection [4]

Table 1 (continued)

Ref.	Patients	Technique [no. attempted interventions]	Technical success (%)	Clinical success (%)	Adverse events (%) [no. cases]
Chen et al. [1]	40	Anterograde [37] Rendezvous [3] EUS-PDD	34/37 (92) 3/3 (100)	29/34 (85) 3/3 (100)	N/A N/A 15/40 (37.5) Abdominal pain [13] Abscess [1] Pressure ulcer [1]
Total	406	Anterograde [155] Rendezvous [58] EUS-PDD [206]	138/155 (89) 40/58 (69) 155/206 (75)	127/146 (87) 41/44 (93) 92/100 (92)	Anterograde [12/103] (12) Rendezvous [7/50] (14) EUS-PDD [73/266] (27)

References: Available case series and cohort studies of interventional anterograde EUS-PDD (i.e., excluded studies containing only rendezvous-assisted ERP and/or EUS-guided pancreatogram; excluded single case reports)

Patients: Total number of patients included in the study (i.e., the number of patients who underwent any form of EUS-PDD)

Technique [no. attempted interventions]: The number of attempted EUS-PDD *interventions (*stenting) within each study cohort. "Anterograde," aka anterograde EUS-PDD, refers to transmural pancreatic stent placement. "Rendezvous," aka rendezvous-assisted ERP. "EUS-PDD" refers to both anterograde EUS-PDD and rendezvous-assisted ERP (i.e., data from this sub-row are listed when separate information on anterograde drainage is not available within a study). Studies by Fujii et al. [3], Will et al. [18], and Tyberg et al. [19] did not separate the number of attempted interventions according to anterograde EUS-PDD and rendezvous-assisted ERP

Technical success: Successful stent placement on initial or repeat attempt, separated by anterograde and rendezvous technique. Overall technical success provided for studies by Fujii et al. [3], Will et al. [18], and Tyberg et al. [19] (i.e., technical success not divided by anterograde and rendezvous techniques)

Clinical success: Partial or complete resolution of symptoms or the clinical problem (e.g., cessation of recurrent acute pancreatitis following stenting of pancreaticojejunostomy stricture), separated by anterograde and rendezvous technique. Overall clinical success provided for studies by Fujii et al. [3] and Tyberg et al. [19] (i.e., clinical success not divided by anterograde and rendezvous techniques). Clinical success not available for Kahaleh et al. [13], Shah et al. [16], and Vila et al. [16]

Adverse events [no. cases]: Total number of anterograde EUS-PDD- and rendezvous-assisted ERP-related adverse events. Studies by Ergun et al. [15], Fujii et al. [3], Will et al. [18], Tyberg et al. [19], and Chen et al. [1] did not separate AEs according to anterograde or rendezvous technique; the collective adverse events for both anterograde and rendezvous techniques are provided for these studies. Accounts for AEs of all severity (mild to severe), occurring anytime relative to the procedure (i.e., intraprocedural and immediate-to-extended). AEs are separated by anterograde and rendezvous technique only in Shah et al. [16], Vila et al. [16], and Kurihara et al. [2]

anterograde drainage was 138/155 (89 %). Studies by Fujii et al. [3], Will et al. [18], and Tyberg et al. [19] did not separate the number of attempted interventions according to anterograde and/or rendezvous drainage techniques; therefore, these three studies (i.e., 206 attempts at EUS-PDD) are excluded from the composite technical success calculation for anterograde drainage. Clinical success is defined as partial or complete resolution of symptoms or the clinical problem (e.g., resolution of pancreatic fistula following anterograde MPD stent placement). The overall clinical success of anterograde drainage was 127/146 (87 %). Studies by Fujii et al. [3], Tyberg et al. [19], Kahaleh et al. [13], Shah et al. [16], and Vila et al. [16] either did not distinguish clinical success by anterograde and rendezvous drainage techniques, or did not report clinical success; therefore, these five studies (i.e., 97 anterograde drainage technical successes) are excluded from the composite clinical success calculation for anterograde drainage.

Adverse events associated with anterograde EUS-PDD occurred in 12/103 (12 %) of intervention attempts. Reported adverse events included abdominal pain (4), bleeding (3), pancreatitis (2), pseudocyst (2), and perforation (1). Studies by Ergun et al. [15], Fujii et al. [3], Will et al. [18], Tyberg et al. [19], and Chen et al. [1] did not separate adverse events according to anterograde and rendezvous technique; therefore, these five studies are excluded from the composite adverse events calculation for anterograde drainage. The adverse events rate (anterograde and rendezvous drainage) for these five (excluded) studies together was 73/266 (27 %). Although Chen et al. [1] did not separate adverse events according to anterograde and rendezvous technique, 37/40 (92.5 %) of attempted EUS-PDD utilized the anterograde technique (37 attempts), as compared with 3 attempts at rendezvous drainage. Therefore, the reported AE rate of 15/40 (37.5 %), including abdominal pain (13), abscess (1), and mucosal pressure ulcer from stent friction (1), mostly pertains to the anterograde technique.

Our Experience with Anterograde EUS-PDD

We currently perform anterograde EUS-PDD in poor surgical candidates who have failed conventional ERP and rendezvous-assisted ERP. Table 2 outlines our experience with

Table 2 Anterograde transgastric EUS-PDD (authors' experience)

Case	Age/sex	Indication	MPD size (BOP)	Needle (gauge)	Wire (inches)	Tract dilation	Stent	Elective stent exchange	Technical success	Clinical success	Adverse events
1	66/M	Technical failure of ERP and rendezvous-assisted ERP in painful chronic calcific pancreatitis	10.5 mm	19G	0.025	Needle-knife	5×9	Yes	Yes	Yes	None
2	55/M		5 mm	19G	0.025	None	3×9	Yes	Yes	Yes	None
3	52/F		8 mm	19G	0.025	None	5×7	Yes	Yes	Yes	None
4	59/M		1.4 cm	19G	0.025	Needle-knife	5×13	Yes	Yes	Yes	None

Case: Case number

Age/sex: Age and sex of patient

Indication: Painful chronic calcific pancreatitis was the indication for (initial) conventional endoscopic retrograde pancreatography (ERP). Technical failure of ERP was the indication for rendezvous-assisted ERP. Technical failure of rendezvous-assisted ERP was the indication for anterograde EUS-PDD

MPD size (BOP): Diameter of the main pancreatic duct (MPD) located in the body of the pancreas (BOP)

Needle (gauge): Size (gauge) of the aspiration needle used to obtain transmural MPD access

Wire (inches): Width of the guidewire in inches

Tract dilation: Whether transmural tract dilation was performed to facilitate anterograde stent insertion

Stent: Measurements (French×centimeters) of the plastic pancreatic stents with internal barbs that were used to form the final pancreaticogastrostomy

Elective stent exchange: Whether subsequent stent exchange(s) occurred following the index drainage procedure

Technical success: Successful stent placement on initial or repeat attempt

Clinical success: Partial or complete resolution of symptoms or the clinical problem

Adverse events: Periprocedural or postprocedural adverse events of any severity

four cases of anterograde EUS-PDD. All four cases were performed for the same indication: failed ERP and failed rendezvous-assisted ERP, in the setting of painful chronic calcific pancreatitis. Proximal MPD obstruction from calculi was present in all cases. Figure 2a–d shows fluoroscopic images from case 4 (Table 2), in which anterograde EUS-PDD was performed for an unusually dilated MPD (1.4 cm). Video 1 provides a narrated video demonstration of anterograde EUS-PDD from case 1 (Table 2).

Conclusions

Anterograde EUS-PDD should be considered as a therapeutic option in select patients in high-volume tertiary centers. Candidates for anterograde EUS-PDD include poor surgical candidates, and/or patients desiring a minimally invasive approach, (1) after technical failure of conventional ERP and rendezvous-assisted ERP in cases

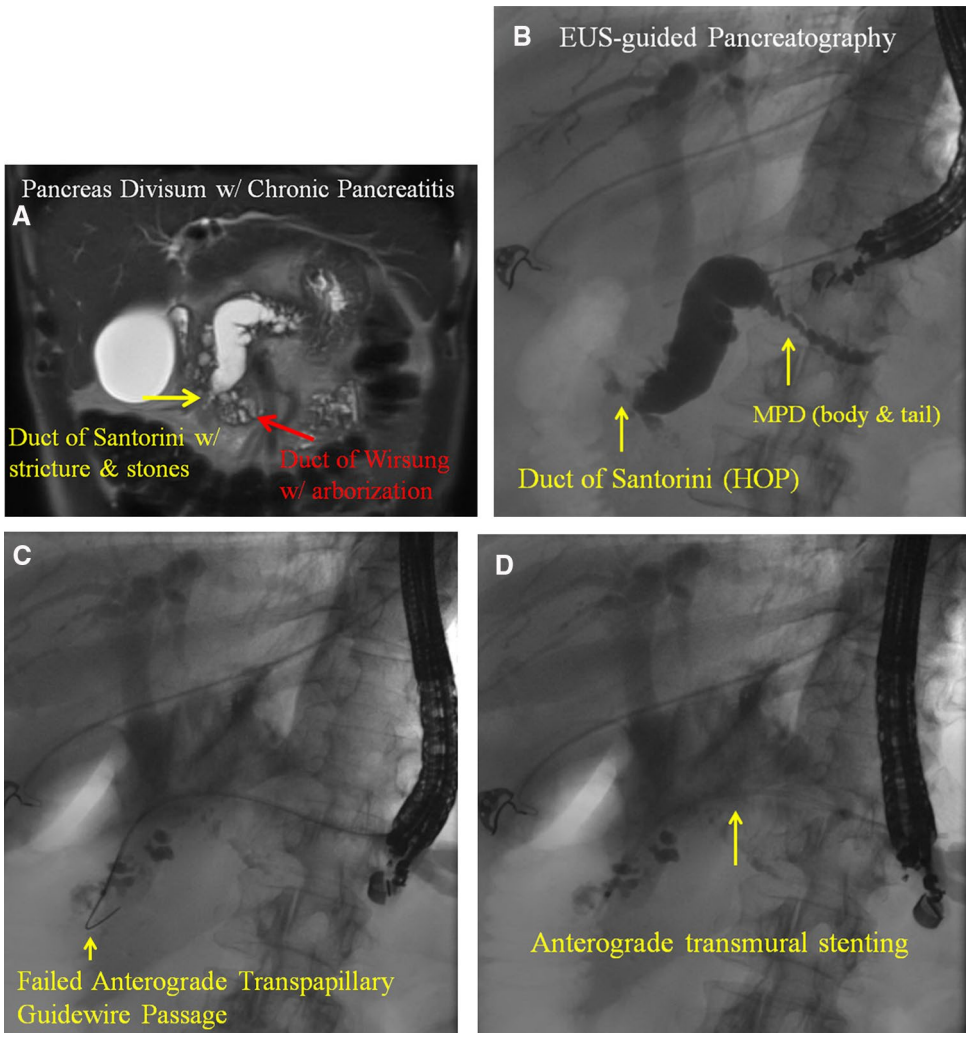

Fig. 2 **a** Magnetic resonance cholangiopancreatography (MRCP; coronal view; T2-weighted) demonstrating pancreas divisum with chronic pancreatitis. The duct of Santorini is extremely dilated to 1.4 cm. A ductal narrowing (outflow obstruction) is present near the minor papilla (yellow arrow). The proximal MPD is tightly strictured. The duct of Wirsung, in the setting of pancreas divisum, is identifiable by its arborization (red arrow). **b** Fluoroscopic view of EUS-guided pancreatography. Transgastric puncture of the MPD, and pancreatography, is performed using a 19-gauge aspiration needle and contrast medium, dilated 1:1 with sterile water. An outflow obstruction is present in the duct of Santorini adjacent to the minor papilla (labeled), with upstream dilation of the MPD to 1.4 cm. The proximal MPD (body and tail labeled) is narrowed and irregular, likely the result of strictures and stones. **c** Fluoroscopic view of failed anterograde transpapillary guidewire passage. The 0.025-inch guidewire cannot traverse the high-grade obstruction near the minor papilla. Without anterograde transpapillary guidewire passage, rendezvous-assisted ERP is impossible, and anterograde stenting can be performed. **d** Fluoroscopic image immediately following successful anterograde transgastric stent placement. A 5-Fr × 13-cm plastic pancreatic stent with internal barbs forms the pancreaticogastrostomy. The distal end of the stent is located next to the MPD obstruction, and the proximal end of the stent is located within the gastric lumen

of normal luminal anatomy, or (2) after technical failure of, or as an alternative to, enteroscopy-assisted ERP (EA-ERP) in cases of surgically altered anatomy. Common clinical scenarios that fulfil these conditions are chronic pancreatitis with high-grade MPD obstruction, surgically altered anatomy with ductal/anastomotic obstruction, pancreas divisum, and disconnected pancreatic duct syndrome.

EUS-PDD is technically difficult with limited indications; thus, it is only described in retrospective studies with relatively small sample sizes. Future studies should focus on distinguishing anterograde from rendezvous drainage, as technique and technical difficulty differ between the two approaches. Also, long-term studies and a higher volume of cases are required to assess longevity of fistula patency following drainage catheter removal in cases of untreatable ductal obstruction. We encourage collaboration between high-volume tertiary centers to answer the multitude of questions regarding this effective and minimally invasive approach.

Compliance with ethical standards

Conflict of interest Drs. Matthew Krafft and John Nasr report no disclosures related to industry.

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