Evolution of Pancreatic Endotherapy

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KEYWORDS

- Pancreatic endotherapy
- Therapeutic endoscopic retrograde cholangiopancreatograhy
- Therapeutic endoscopic ultrasound • Pancreatic pseudocyst • Walled-off necrosis
- Pancreatic strictures • Pancreatic calculi

KEY POINTS

- Therapeutic endoscopic retrograde cholangiopancreatography (ERCP) and EUS are important tools for managing complications of pancreatitis and have significantly reduced the need for surgery.
- ERCP with transpapillary stenting remains key to managing pancreatic duct leaks. However, in more complex cases, therapeutic EUS or a multidisciplinary approach with interventional radiology can be helpful.
- EUS-guided antitumor therapy remains investigational, although shows potential in palliation and cure of pancreatic neoplasms.

INTRODUCTION

The pancreas was described circa 300 BC by the Greek physician Herophilus of Chalcedon during his decades of scientific dissections of human cadavers.[1,2] The organ was named circa 100 AD by Rufus of Ephesus from the Greek words *pan*, "all" and *kreas*, "flesh." It was not until the nineteenth century that physiologists began to recognize the pancreas' role in digestion and physicians began to describe pancreatic diseases. Microscopically verified cases of pancreatic adenocarcinoma were reported as early as 1858 and by the end of the nineteenth century, the signs and symptoms of cancer at the head of the pancreas were well known. In 1889, Mering and Minkowski found that extirpation of the pancreas in dogs caused glycosuria and diabetes. That same year, Fitz characterized the signs, symptoms, and complications of acute pancreatitis, thus establishing it as a disease entity.[1]

For more than a century, the treatment of pancreatic diseases fell almost exclusively within the purview of surgeons. In 1841, Wandesleben performed a pseudocyst drainage—the first documented pancreatic surgery. By 1867, Lucke reported the first

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successful resection of a pancreatic cystic tumor. In the late nineteenth century, surgeons began debating the management of acute pancreatitis—whether conservative versus surgical treatment and furthermore whether early versus late surgery was favorable. Surgery prevailed as the treatment of choice until 1927 when the discovery of serum amylase revealed milder forms of pancreatitis that could respond to nonoperative therapy. This discovery, along with the recognition that surgical mortality rates were as high as 50% to 78%, shifted the treatment paradigm to a more conservative approach. In the 1960s, surgeons again began advocating for extensive pancreatic resections for patients with severe acute pancreatitis who had high mortality rates with medical treatment alone.[3,4] In recent decades, the pendulum swings of pancreatitis management have been less extreme.

As medical technology has expanded, so too have new treatments for pancreatic diseases. Although endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic ultrasound (EUS) were introduced initially as diagnostic tools, they quickly evolved into therapeutic tools for treating pancreatic diseases. As such, in recent decades, gastroenterologists have had an increasingly important role in managing pancreatic diseases. The current article discusses the changing landscape of pancreatic endotherapy because therapeutic ERCP and EUS were introduced and because they have evolved to treat different diseases.

Endotherapy for Etiologies of Pancreatitis

In 1968, McCune reported the first endoscopic cannulation of the ampulla of Vater in living patients (**Table 1**). He used a fiberoptic duodenoscope and taped a small tube to the scope that allowed passage of a cannula that could be maneuvered into the ampulla. Citing a 25% cannulation rate and difficulty positioning the scope in the duodenum, McCune recognized the need for improved endoscopic instruments.[5] The following year, Oi helped develop a side-viewing duodenoscope that included a working channel with an elevator that improved manipulation of the cannula and presented the first ERCP at an international conference.[6] During the next few years, increased experience with ERCP led to higher cannulation rates, reported between 74% and 96%.[7] Finally in 1974, the first endoscopic sphincterotomy (ES) was performed, thus marking the beginning of therapeutic ERCP.[8]

Gallstone pancreatitis

Opie postulated in 1901 that gallstones that migrated and became impacted in the distal common bile duct (CBD) could impair pancreatic duct (PD) secretions, cause bile reflux into the PD, and lead to pancreatic inflammation.[9] However, it was not until the 1950s that biliary stone disease became widely recognized as a common cause of pancreatitis.[10] For decades, abdominal exploration with choledochotomy was the standard treatment of CBD stones.[11] After ERCP with ES was introduced, it was used in conjunction with nasobiliary catheters, biliary stents, balloons, and mechanical lithotripsy and became the procedure of choice for choledocholithiasis after cholecystectomy.[8]

Recurrent acute pancreatitis

With the widespread use of ERCP, anomalies of the PD were increasingly recognized as possible causes of recurrent acute pancreatitis (RAP). For the next 2 decades, an abundance of literature exploring the use of ES and endoprosthesis for management of these conditions emerged. These have been described below.

Pancreas divisum. Pancreas divisum is a common anatomic variant in which the pancreatic buds fail to fuse in utero, resulting in predominant drainage of pancreatic

Table 1
Timelines in pancreatic endotherapy

	Author, Year, and Reference
Pancreas divisum	
Minor papilla sphincterotomy to treat RAP in pancreas divisum	Cotton,[13] 1978
Minor papilla stents to treat RAP in pancreas divisum	McCarthy et al,[16] 1988
Choledocholcele	
Endoscopic snare removal of choledochocele	Deyhle et al,[19] 1974
Endoscopic sphincterotomy of choledochocele	Siegel,[20] 1981
Sphincter of Oddi disorder	
RCT demonstrating lack of efficacy of endoscopic sphincterotomy for type III SOD	Cotton et al,[24] 2014
Pancreatic pseudocyst	
Endoscopic transgastric needle aspiration of pseudocyst	Rogers,[31] 1975
Endoscopic cystoenterostomy via conventional transmural drainage	Kozarek et al,[33] 1985
Endoscopic cystoenterostomy with nasocystic drain left for irrigation	Sahel et al,[34] 1987
EUS-guided pseudocyst drainage	Wiersema,[40] 1996
Fully covered self-expanding stents used for pseudocyst drainage	Talreja et al,[42] 2008
Lumen-apposing metal stents invented	Binmoeller,[43] 2004
Cautery-enhanced lumen-apposing metal stents introduced	Teoh,[44] 2014
Walled-off necrosis	
Endoscopic drainage of walled-off necrosis	Baron et al,[47] 1996
Direct endoscopic necrosectomy	Seifert et al,[49] 2009
RCT demonstrating (1) low mortality rates with conservative management, (2) superiority of step-up therapy compared to surgical open necrosectomy for infected walled-off necrosis or peripancreatic necrosis	van Santvoort et al,[50] 2011
Dual-modality drainage	Ross et al,[52] 2014
Pancreatic duct leaks and disconnected duct syndrome	
Transpapillary drains or stents used to treat:	
Pancreatic duct leaks, some complicated by pancreatic fluid collections	Kozarek et al,[54] 1991
Pancreatic duct leaks complicated by ascites	Kozarek,[55] 1992
Pancreatic duct leaks complicated by pancreaticoenteric fistulae	Wolfsen et al,[56] 1992
Pancreatic duct leaks complicated by external pancreatic fistulae	Kozarek et al,[57] 1997
Disconnected duct syndrome managed with:	
Combination of transpapillary drainage, cystenterostomy, or nasocystic catheter	Deviere et al,[60] 1995
1. Outside-in technique 2. EUS-guided pancreaticobulbostomy	Arvanitakis et al,[61] 2007

(*continued on next page*)

Table 1
(*continued*)

	Author, Year, and Reference
1. Inside-out technique 2. Reconnecting disconnected ducts	Irani et al,[62] 2012
Pancreatic calculi	
ERCP with basket stone retrieval	Inui et al,[63] 1983
ERCP with pancreatic sphincterotomy, stenting, pancreatoscopy with basket stone retrieval	Fuji et al,[64] 1985
Extracorporeal shock wave lithotripsy with ERCP	Sauerbruch et al,[66] 1987
ERCP with electrohydraulic lithotripsy	Howell et al,[72] 1999
Pancreatic duct strictures	
Retrospective study describing pancreatic stent placement associated with ductal changes, including stenoses	Kozarek,[39] 1990
Prospective study demonstrating efficacy of multi-stent placement for strictures refractory to single-stent placement	Costamagna,[76] 2006
EUS-guided pancreaticogastrostomy	Francois et al,[80] 2002
Celiac plexus block and neurolysis	
EUS-guided celiac plexus neurolysis	Wiersema & Wiersema,[83] 1996

fluid through the minor papilla.[12] Although most patients are asymptomatic, studies have shown that pancreas divisum is more prevalent in cases of unexplained RAP,[12,13] which may be due to increased intraductal pressures caused by minor papilla stenosis.[12] In 1978, Cotton performed the first minor papilla sphincterotomy to treat pancreatitis in patients with pancreas divisum.[13] Subsequent studies reported that patients with RAP who had pancreas divisum had fewer episodes of pancreatitis, fewer hospitalizations, and improvement in pain after minor papilla sphincterotomy.[14,15] In 1988, McCarthy and colleagues published the first experience of placing PD stents across the minor papilla in pancreas divisum with RAP and found that this was associated with fewer pancreatitis flares.[16] The efficacy of these interventions suggests that, at least in a subset of patients with pancreas divisum, endotherapy aimed at improving flow across the minor papilla is beneficial. However, randomized prospective trials aimed at delineating the effect of ES on pancreas divisum have been challenging to execute.[17] Thus, controversy remains about whether and which these patients benefit from pancreatic endotherapy with ES and stenting.

Choledochocele. In 1915, Wheeler first described a choledochocele after performing an exploratory laparotomy for workup of jaundice and discovering a small cyst at the orifice of the CBD.[18] Since that time, choledochoceles have been defined as cystic dilations of the intraduodenal portion of the distal CBD and have been distinguished from duodenal duplication cysts as having direct communication to the CBD, lack of fusion with the duodenal wall, and lack of a muscle layer beyond the muscularis mucosa.[18] Also known as type III choledochal cysts, choledochoceles have been associated with RAP.

Choledochoceles were previously treated surgically with excision or sphincteroplasty. However, the advent of ERCP has obviated surgery. Endoscopic removal of a choledochocele was documented as early as 1974, and the first use of ES for treatment was reported in 1981.[19,20] In 1992, a case series reported 7 patients with choledochoceles and RAP who underwent ES with complete resolution of symptoms.[21] Since that time, ES has remained primary treatment of choledochoceles.

Papillary stenosis and Sphincter of Oddi disorder. In 1887, Oddi described the anatomy of the muscle at the papilla of Vater and thereafter suggested that contraction of this muscle could lead to jaundice.[22] In the early 1900s, there was increasing recognition that Sphincter of Oddi (SO) abnormalities were associated with clinical presentations involving recurrent abdominal pain, elevated liver function tests, or even RAP.[1,22,23] With ERCP, sphincter of Oddi manometry (SOM) became a nonsurgical possibility and was reported as early as 1975.[24] The increasing use of SOM helped define parameters of normal transpapillary pressures and identify sphincter of Oddi disorders (SODs).

For the next few decades, ERCP was used to diagnose and treat SODs. In 2004, a review on SOD found that patients with papillary stenosis benefitted most consistently from ERCP with ES.[25,26] ERCP has been less beneficial in other SODs. In a landmark trial, Cotton and colleagues investigated patients with pancreaticobiliary-type pain after cholecystectomy who did not have significant laboratory or imaging findings. In this multicenter trial, patients were randomized to sphincterotomy versus sham. Patients in the sphincterotomy group with elevated pancreatic sphincter pressures were further randomized to biliary sphincterotomy alone or both biliary and pancreatic sphincterotomies. The results demonstrated that no clinical subgroups benefitted from sphincterotomy more than others and that sphincterotomy did not reduce disability related to pain.[27] This led to a change in the classification of SODs with the 2016 Rome IV criteria discarding “types I, II, and III SOD” and instead adopting “functional pancreatic (or biliary) sphincter disorder.”[28]

Although ES remains the primary treatment of choice for papillary stenosis, it is not indicated for all patients with SOD. The use of SOM has also been greatly reduced, with its applicability limited to identifying hypertensive sphincters and assessing response to ES.[25,26]

Endotherapy for Complications of Pancreatitis

Pancreatic pseudocyst

Pancreatic pseudocysts (PP) are a common complication of pancreatitis that may require treatment if they become infected or symptomatic (see **Table 1**). For most of the 1900s, surgical cystoenterostomy was the primary method of PP drainage.[3,29] In the 1970s, ultrasound, computed tomography (CT), and fluoroscopic guided percutaneous drainage of PP were introduced as nonsurgical management alternatives.[30] Endoscopic drainage methods took longer to surface. In 1975, Rogers described the first transgastric needle aspiration of a PP through the biopsy channel of an endoscope.[31] However, it was not until 1984 that Hershfield and colleagues reported using ERCP to cannulate the minor papilla and incidentally found that it connected to a PP. During the procedure, he aspirated amylase-rich fluid and found that the PP had resolved on repeat imaging.[32]

In 1985, more intentional efforts of endoscopic PP drainage were reported in 4 patients who either failed surgery or were not surgical candidates. The procedure consisted of using a duodenoscope and diathermic needle-knife to create a fistulotomy between the PP and stomach or duodenum, whichever location appeared more amenable to drainage on earlier imaging. Two patients had complete PP resolution.[33] In 1987, Sahel and colleagues used a similar technique that relied on visualizing a bulge in the duodenal wall to identify the PP and then performing ERCP to determine the relationship between the PP and duodenum. After creating a cystoduodenostomy, a nasocystic drain was left in place for irrigation. They reported good results in 64% of patients.[34] This technique of relying on a visible bulge to create a cystoenterostomy became known as conventional transmural drainage (CTD).[29,35,36] In the late 1980s, experience with endoscopic PP drainage was growing. With the combination of CTD and nasocystic drains used for irrigation, PP drainage success rates were reported as greater than 96%.[29]

In the early 1990s, endoscopic drainage of PPs shifted in 3 manners. First, 2 case series reported successful use of plastic biliary stents to maintain the patency of the cystoenterostomy. This internal drainage method was as an improved alternative that would avoid discomfort of a nasal catheter and would result in the extinction of external nasocystic drainage.[37,38] Second, endoscopists began exploring the efficacy of ERCP with transpapillary PP drainage—with PD sphincterotomy and stent or drain placement into the duct. This method of drainage had high success rates, although it raised concerns of possible stent-related ductal changes (discussed later).[39] Finally, in the 1990s, the development of linear-array echoendoscopes with an accessory channel opened the doors to the possibility of EUS-guided therapeutic procedures.

In 1992, Grimm and colleagues demonstrated the utility of EUS in identifying an optimal puncture site for PP drainage close to the gastric or duodenal wall. In his report, a needle, guidewire, and catheter were advanced into the pseudocyst under EUS guidance before switching to a therapeutic duodenoscope for stent placement.[40] In 1996, Wiersema improved on this technique by using a new prototype linear-array echoendoscope with an elevator and a larger instrument channel that could create a cystoduodenostomy and place a stent without exchanging for a duodenoscope.[40] This was the first description of complete EUS-guided PP drainage, which would prove to have greater technical success than CTD and was a safe alternative for those without visible luminal compression[41] (**Fig. 1**).

Recognizing that many patients originally described as having pseudocysts actually had walled-off necrosis (WON). Over the years, new techniques were developed to optimize “PP” drainage including placing multiple stents and improving dilation of cystoenterostomies. In 2008, a larger shift was seen in the management of PPs. Although the use of self-expandable metal stents (SEMS) for PP drainage was first reported in 1994 in a patient with an infected pseudocyst, fully covered SEMS (FCSEMS) were not yet available, and the patient was left with a permanent uncovered SEMS. In 2008, a case series reported using FCSEMS to drain pancreatic fluid collections (PFCs) and demonstrated 78% clinical success with complete resolution of the PFCs.[42,43] Multiple subsequent studies used FCSEMS for drainage of PFCs but complications included stent migration, clogging, and exposed stent ends causing tissue trauma, bleeding, and perforation. In 2004, lumen-apposing metal stents (LAMS) were introduced as a solution to these complications. With bilateral double-walled flanges in a dumbbell shape, the tissue walls could be held in close apposition and minimize the risk of migration. Electrocautery-enhancement of the LAMS has further improved deployment of these stents to minimize leakage and maximize safety of PFC drainage.[43,44]

Management of PP has evolved during the last 50 years. EUS-guided cystgastrostomy has proven to be superior to surgical cystgastrostomy in reducing the length of stay, reducing cost, and improving quality of life for patients.[45] As such, EUS-guided drainage has remained the preferred management for symptomatic PP with LAMS demonstrating higher clinical success rates, lower adverse event rates, and reduced need for percutaneous drainage when compared with plastic stents.[46]

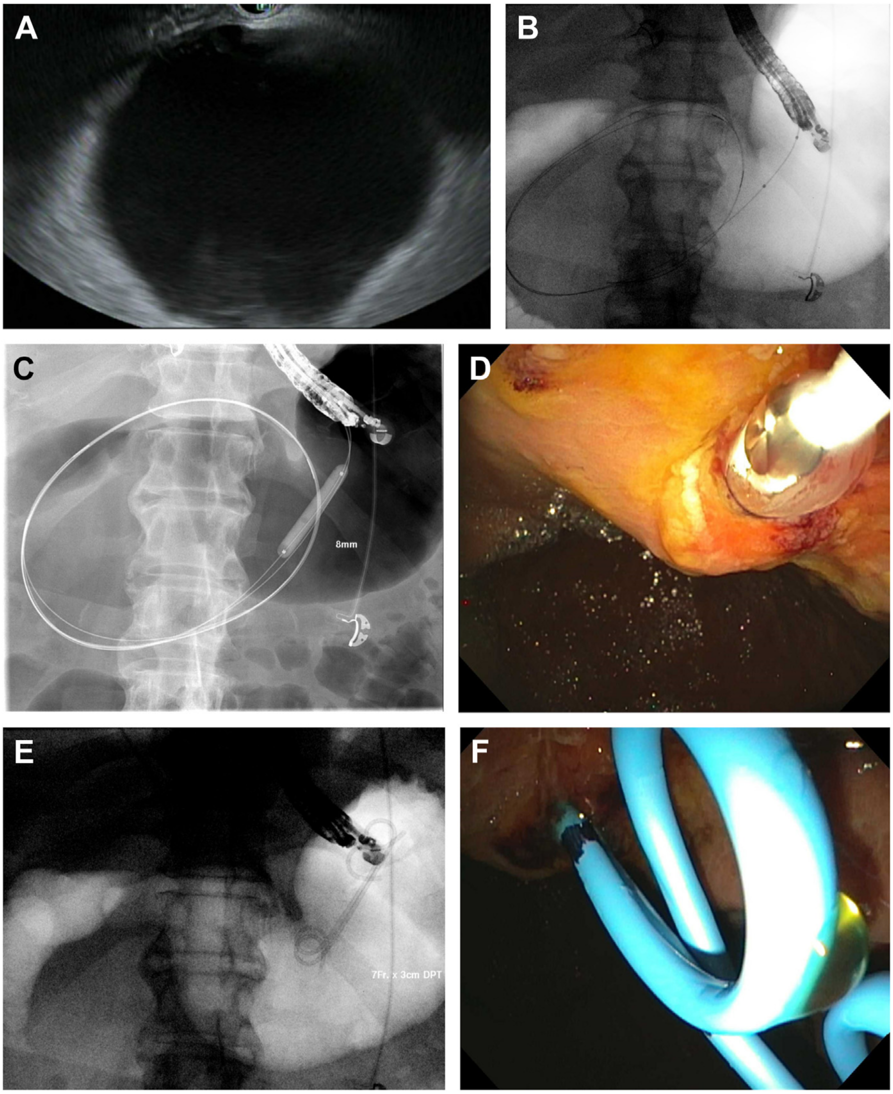

Fig. 1. EUS-guided drainage of a PP with double pigtail stents. (*A*) EUS view of PP before drainage. (*B*) After needle puncture, a dilating catheter is advanced over a guidewire into the PP. (*C, D*) The tract between the stomach lumen and guidewire is dilated, fluoroscopic and endoscopic views, respectively. (*E, F*) Two double pigtail stents are left in place, fluoroscopic and endoscopic views, respectively.

Walled-off necrosis

WON, a complication of acute necrotizing pancreatitis, can require drainage if infected or symptomatic.[45] Historically, surgical necrosectomy was considered the only management option.[47] However, because experience with endoscopic drainage of PP increased, similar techniques were applied to the management of WON. In 1996, Baron and colleagues published the first experience of endoscopic drainage of WON. The protocol used ERCP to assess the integrity of the PD then CTD was performed to create a tract into the WON collection, followed by dilation and stent placement. After 2 patients developed infection, the protocol was modified to include leaving a nasobiliary tube in the WON collection for irrigation until the collection resolved. Nine out of 10 patients whose collections were successfully entered achieved complete drainage, thus establishing the feasibility of endoscopic drainage of WON.[47] Endoscopists have since use this method as a prototype for entry into and debridement of WON collections with various endoscopic tools. Although CTD of WON can have high success rates, most endoscopists agree that EUS-guided access is superior in establishing a safe puncture site and minimizing risks of injury to adjacent vessels or organs.[41,48]

In the 2000s, natural orifice transluminal endoscopy emerged as a promising hybrid of surgical and endoscopic procedures. During this time, Seifert and colleagues described obtaining transgastric or transduodenal access into the retroperitoneal cavity for direct endoscopic necrosectomy (DEN). In long-term follow-up, 80% of patients had initial clinical success and 84% of these had sustained clinical improvement although 10% required retreatment. Complications included bleeding, perforation of necrosis into the abdominal cavity, fistula formation, air embolization, and pancreatitis. Furthermore, 7 patients died within 30 days and long-term follow-up included another 7 patients who died.[49]

With increasing treatment modalities available, including percutaneous drainage and video-assisted retroperitoneal debridement, the Dutch Pancreatitis Study Group sought to determine the optimal approach to managing WON. In this multicenter prospective trial, 639 patients with necrotizing pancreatitis were managed conservatively unless they had suspected or confirmed infected WON or peripancreatic necrosis. As such, 88 patients underwent either surgical open necrosectomy or a step-up approach with percutaneous drainage followed, if necessary, by minimally invasive necrosectomy. The study found that 62% of patients with necrotizing pancreatitis could be managed conservatively with low-mortality rates. For those with infected WON, the step-up group had lower rates of short-term and long-term complications than the surgical group.[50] Subsequent studies investigating endoscopic versus surgical step-up approaches demonstrated lower complication and mortality rates with endoscopy.[51]

Given the efficacy of both percutaneous and endoscopic drainage methods, it did not take long for dual-modality drainage (DMD) to be introduced. In 2014, our institution reported the first series of 117 patients who underwent DMD for symptomatic and infected WON.[52] These patients first underwent percutaneous drainage of the WON with interventional radiology (IR) and immediately afterward underwent either CTD or EUS-guided drainage with dilation and stent placement into the necrosum. Based on clinical course, some patients required irrigation through and upsizing of the percutaneous drain. With clinical improvement, the drains were capped and imaging was repeated to ensure that the collection did not recur before drain removal. At the time of publication, 103 patients completed treatment and had drains removed. Although this study demonstrated favorable clinical outcomes, this approach requires a collaborative relationship between gastroenterology and IR and reliable follow-up because the median duration of follow-up was 750 days.[52]

Although the initial WON drainage was performed with plastic stents, current guidelines recognize LAMS as superior in providing better egress of necrotic material[51] (**Fig. 2**). Furthermore, both endoscopic and percutaneous drainage are recommended as first-line nonsurgical approaches while DMD is reserved for more complicated WON. Notably, DEN is reserved for patients who do not respond to other nonsurgical approaches.[53]

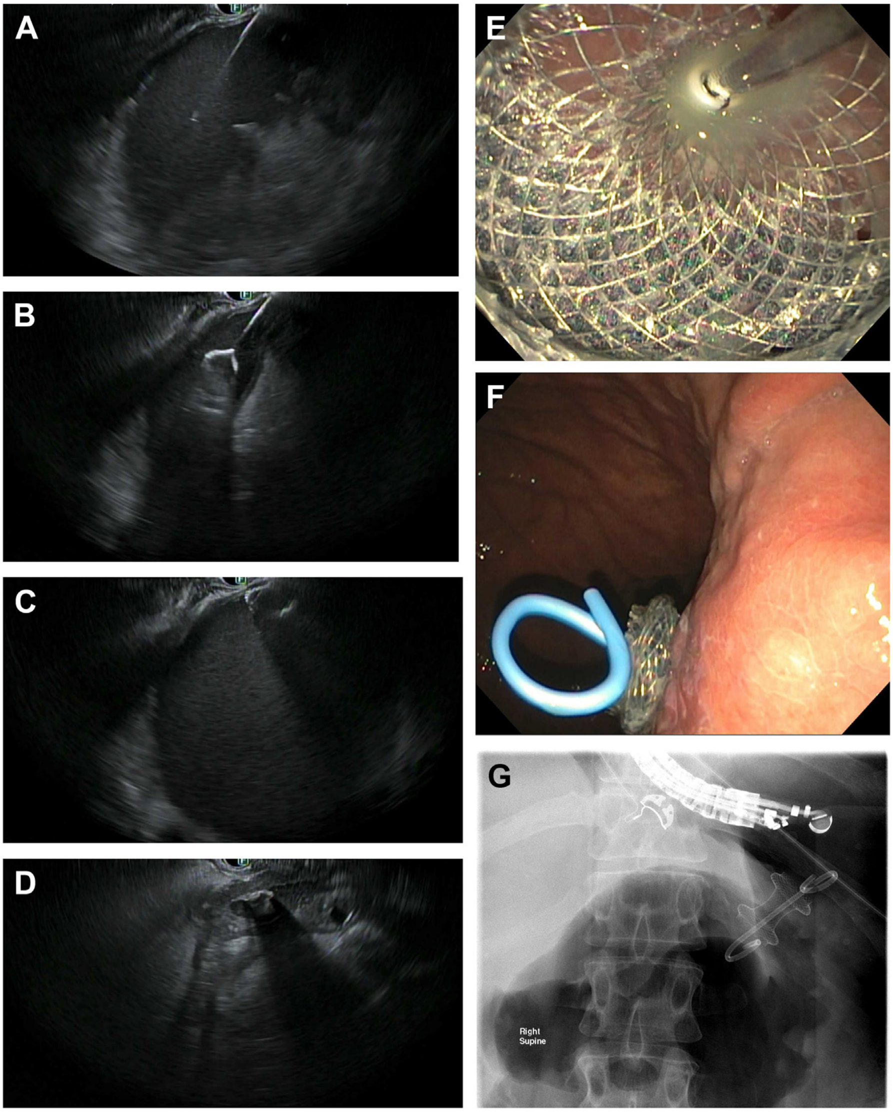

Fig. 2. EUS-guided drainage of WON with lumen apposing metal stent (LAMS) and a double pigtail stent within. *EUS views*: (*A*) Needle puncture through initial WON collection. (*B*) Distal flange of LAMS is deployed into collection. (*C*) Distal flange is retracted tightly against wall of WON. (*D*) Collection is notably smaller after more than 1L of fluid has drained. *Endoscopic views*: (*E*) Proximal flange of LAMS is deployed into the stomach lumen. (*F*) A double pigtail stent is placed within the LAMS. *Fluoroscopic view*: (*G*) Cystgastrostomy formed with LAMS and double pigtail stent within.

Pancreatic duct leaks and disconnected duct syndrome

PD leaks can develop as sequelae from pancreatitis, malignancy, abdominal trauma, or after abdominal surgery. Although minor leaks can resolve with conservative management, severe leaks often require interventions. Depending on the direction of location and flow, leaks can cause internal fistulae (including PP, WON, ascites, pleural effusion, pancreaticoenteric fistula) or external pancreatic fistulae (EPFs). Although some leaks may result from a partial disruption of the PD, complete disruptions can lead to disconnected duct syndrome (DDS) where the distal gland becomes isolated from the proximal gland—orphaned tail syndrome. Previously a surgical problem, PD leaks have been increasingly managed in a multidisciplinary fashion between gastroenterology and IR.

As previously described, ERCP with transpapillary stenting has been used in isolation or in conjunction with other modalities for management of PP and WON. Our institution has had a long history managing complications of PD leak with transpapillary stenting. In 1991, we used transpapillary drains or stents to successfully treat 16 of 18 patients with PD disruption, including 12 with PFCs[54] (**Fig. 3**). In 1992, we described the first endoscopic treatment of patients with PD leaks resulting in high-amylase ascites who responded to transpapillary stenting and paracentesis.[55] The same year, we demonstrated efficacy of endoscopic transpapillary stenting in managing pancreaticoenteric fistulae that developed after patients with PFCs underwent percutaneous drainage.[56] In 1997, our group first reported using transpapillary stents for treating EPFs caused by PD leaks.[57] Since these initial descriptions, other studies have demonstrated transpapillary drainage as a safe and effective method for treating these sequelae of PD leaks with the best results obtained if the leak is partial and can be bridged by the stent.[48]

With DDS, endoscopic management is less straightforward because the upstream pancreas and duct are not in communication with the papilla. Because the isolated pancreas continues to secrete exocrine juices freely into the abdominal cavity, a PFC will often form. If a PFC is present and persistent, CTD or EUS-guided drainage can be performed. Contrary to the management of other PFCs, transmural stents for DDS should be left in place to maintain an outflow tract and prevent recurrence.[48,58] However, if metal stents are initially used, they should be exchanged for plastic stents to minimize complication rates.[59]

In 1995, Deviere and colleagues published the first experience of endoscopic management of DDS and related PFCs using transpapillary drainage, cystoenterostomy, or nasocystic catheter drainage. Most patients required a combination of these treatments and 12 of 13 patients had resolution of PFCs.[60] Since this study, many hybrid approaches have been used to manage DDS and its complications. In 2007, Arvanitakis used transpapillary drainage combined with other techniques to treat EPF in

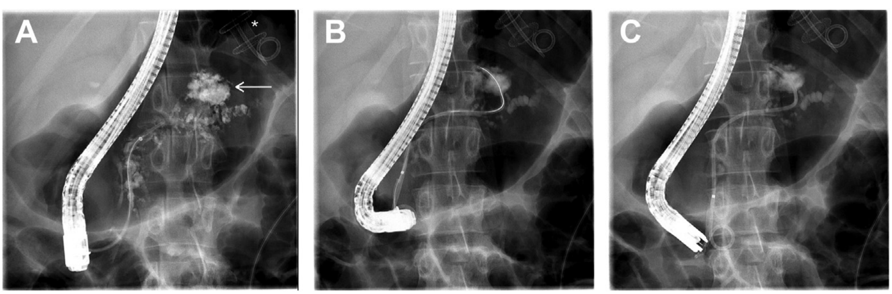

Fig. 3. Transpapillary stenting of PD leak complicated by new fluid collection. (*A*) Contrast injection of PD reveals dilated main duct with prominent side branches and a leak in the distal body of the pancreas (*arrow*), distinct from earlier WON collection that had been resolved with a lumen apposing metal stent and double pigtail stent within (*asterisk*). (*B*) Guidewire access is obtained into the new fluid collection. (*C*) A transpapillary stent is deployed to drain the PFC.

patients with DDS.[61] This included the first description of the outside-in technique where a needle and catheter were advanced over a guidewire that had been threaded through the EPF orifice (outside) to a site closely apposed to the stomach or duodenum wall (in). After a puncture was made, the needle, catheter, and guidewire were advanced into the duodenal or gastric lumen, where guidewire was retrieved by the scope, allowing endoscopic placement of a plastic stent from the lumen into the EPF tract. Another novel technique described was EUS-guided pancreaticobulbostomy, where EUS was used to access the dilated duct of the orphaned pancreas and a stent was placed from the duodenal bulb into the duct. Using these techniques along with PFC drainage, the EPF resolved in 15 of 16 patients.[61]

In 2012, our institution used the outside-in technique and described 2 other novel rendezvous techniques to treat EPF in DDS patients. First, the inside-out technique used EUS to find a site for a needle to advance from the stomach (inside) toward a preexisting drain placed within the EPF tract (out). After a guidewire was advanced through the needle into the EPF tract, the guidewire was secured externally. With access obtained, the newly created fistula was dilated before stents were placed between the stomach and EPF tract. The second technique of reconnecting the disconnected ducts was only possible in patients who were previously able to demonstrate both downstream (toward the head) and upstream (toward the tail) ducts on fistulograms. In this technique, IR injected contrast through a preexisting drain within the EPF tract, allowing full visualization of both duct segments. Then, a wire was passed from the cutaneous end of drain, past the duct disruption site, and through the ampulla. On the duodenal end, an endoscopist captured the wire and used it to guide a papillotome through the downstream duct and into the fistulous tract, which had been unsuccessful on earlier ERCPs. With visualization of the upstream duct, the wire could then be advanced toward the tail and facilitate balloon dilation and transpapillary stent placement. All patients had EPF closure without recurrence.[62]

Managing DDS and its complications is challenging. Although some groups have had success with transpapillary drainage alone, often a multimodality approach is required, and this may be in the form of transmural drainage, a rendezvous technique, or EUS-guided pancreaticoenterostomy. Current management is less streamlined and a multidisciplinary approach with surgery and IR is important.

Pancreatic calculi

Pancreatic calculi are sequelae of chronic pancreatitis that can obstruct PDs, lead to ductal hypertension, and cause pain (**Fig. 4**). In 1891, Pearce reported the first surgical stone removal.[10] In 1983, Inui and colleagues documented the first ERCP with stone extraction,[63] although Michel Cremer performed this earlier (*J. Deviere, personal communication*). In 1985, Fuji and colleagues described performing ERCP with ES in 10 patients with pancreatic calculi. In one patient, direct pancreatoscopy was used to facilitate basket retrieval of pancreatic calculi. In 3 patients, pancreatic stent placement was used to facilitate PD drainage. In total, 9 patients had improvement of pain.[64] This report was perhaps the first documented transpapillary pancreatic stent placement and validated the use of basket stone retrieval for pancreatic calculi. Shortly thereafter, balloon catheters were introduced as another method of extracting PD stones.[65]

In the following decade, endoscopists managed pancreatic calculi with ES, intraductal lavage, fragmentation with forceps, stone retrieval baskets, stone retrieval balloons, and dilating or stenting the main duct if strictures were present.[35] However, larger stones were not always amenable to these treatments. In 1987, Sauerbruch and colleagues demonstrated extracorporeal shock wave lithotripsy (ESWL) as an

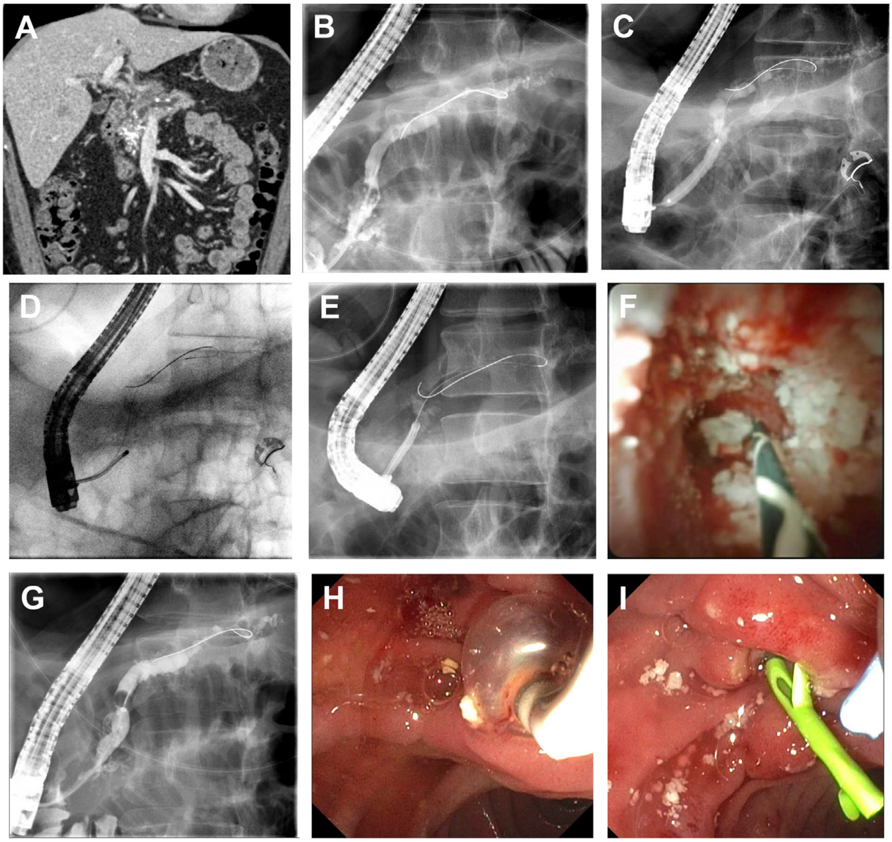

Fig. 4. Endoscopic management of a patient with chronic calcifying pancreatitis after undergoing ESWL. (*A*) CT scan before ESWL demonstrating multiple large stones in the head of the pancreas. (*B*) After ESWL, contrast injection demonstrates multiple filling defects and a stricture in the head of the pancreas. (*C*) After a pancreatic sphincterotomy is performed, the stricture in the head of the pancreas is dilated. (*D*) Basket stone retrieval is attempted but unable to advance past the stones. (*E*) A pancreatoscope is passed into the main PD. (*F*) Stones are visualized and EHL is performed, yielding stone fragments. (*G, H*) An extraction balloon is used to remove stone fragments, fluoroscopic and endoscopic views, respectively. (*I*) A stent is placed in the PD to facilitate further drainage.

effective method of breaking down biliary stones. The next year, the same group used ESWL to treat a patient with an obstructing PD stone who did not respond to earlier ERCP with ES.[66] Imaging after ESWL demonstrated successful disintegration of the stone, which was later removed with ERCP. Since this first experience, many studies have validated ESWL with ERCP as an effective strategy for managing larger pancreatic calculi, leading to long-term improvement in pain, reduced use of narcotics, and fewer hospitalizations.[67–69] Currently, the American Society for Gastrointestinal Endoscopy recommends ESWL as adjunctive therapy for symptomatic patients with pancreatic calculi refractory to standard endoscopic stone extraction techniques.[67]

Laser lithotripsy (LL) is another tool used for the fragmentation of large stones. In 1990, our institution reported using LL on a patient with chronic calcific pancreatitis (CCP) who failed surgical stone extraction and had an obstructive main duct calculus requiring surgical placement of a percutaneous pancreatostomy drainage catheter. Under endoscopic and fluoroscopic guidance, LL was applied directly to the stone and a transpapillary PD stent was left for drainage. The patient had complete resolution of pain, closure of the pancreaticocutaneous fistula, and no recurrent calculi.[70] Since this initial experience, a few case series have reported using pancreatoscopy-guided LL for pancreatic stone fragmentation with good results in patients who have failed ESWL but overall experience is still limited with LL.

Electrohydraulic lithotripsy (EHL) is another form of stone fragmentation that is less utilized than ESWL. EHL was first used to treat biliary stones in the mid-1970s. In 1992, the first experience of intraoperative EHL for pancreatic stones was reported in 2 patients with CCP who required lateral pancreaticojejunostomies.[71] During each operation, EHL allowed stone fragmentation under direct visualization, which facilitated subsequent stone extraction. In 1999, Howell and colleagues described using a 10F endoscope that could pass through the accessory channel of a therapeutic duodenoscope into the PD. Through the accessory channel of the 10F endoscope, an EHL probe was able to advance to the pancreatic stone, and EHL of the stone was performed under direct visualization. Five of 6 patients in this study had partial or complete PD clearance and relief of pain.[72] Similar success of pancreatoscopy with EHL has been seen with the Spyglass Direct Visualization System, a single-operator cholangiopancreatoscopy system.[73]

Management of PD calculi has evolved since the 1980s. In addition to standard ERCP techniques of balloon and basket stone extraction, ESWL, LL, and EHL have emerged as effective tools for stone fragmentation. Because data on intraductal lithotripsy are limited, ESWL is currently considered first-line in the management of larger stones.[67]

Pancreatic duct strictures

Benign PD strictures resulting from inflammation or fibrosis of the pancreas can cause upstream ductal hypertension, leading to pain or pancreatitis flares.[67] Endoscopic management of strictures has been documented as early as 1983 with ERCP with balloon dilation and 1986 with ES and pancreatic stent placement.[73,74] As previously described, pancreatic stents and drains were increasingly used in the late 1980s for indications including PD leaks and pancreas divisum. In 1990, our institution examined the long-term effects of PD stents that were placed for various diseases. Stents used were 5 to 7F and were exchanged at a mean of 4 months. We found that 36% of patients had ductal changes related to either stent occlusion, direct stent trauma, or side branch occlusion. These ductal changes included ductal dilation, irregular stenoses, and side branch ectasia—findings similar to those seen in chronic pancreatitis.[39] This study raised the concern that stent placement is not risk-free and highlighted the importance of determining the best protocols for PD stent placement.

For many years, standard treatment of PD strictures included dilation and insertion of a single plastic stent across a dominant stricture.[74,75] In 2006, a study challenged the paradigm of single-stent placement. Costamagna and colleagues reported a prospective study on patients with symptomatic PD strictures refractory to single-stent placement. Patients underwent balloon dilation followed by insertion of the maximum number of stents allowed by the stricture. The median number of stents placed through the major and/or minor papilla was 3. Although all patients developed temporary abdominal pain, they subsequently remained asymptomatic while the stents were in place. Of 19 patients, 84% had resolution of their strictures.[76] These results suggest that multiple plastic stenting can be effective and safe for refractory pancreatic strictures.

Many initial studies used stents of varying sizes between 5 F and 11.5 F. In 2009, a retrospective study reviewed patients who underwent PD stent placement for chronic pancreatitis and found that those with size 10 F stents had significantly fewer hospitalizations for abdominal pain when compared with those with size 8.5 F or smaller.[77] More recently, there has been growing interest in using FCSEMS to treat PD strictures. A meta-analysis including 19 studies with a total of 300 patients treated with FCSEMS reported a 91% pooled stricture resolution rate with a 6% recurrence rate. Although the results are promising, there was significant heterogeneity between the studies.[78] In a recent prospective study using soft FCSEMS to treat painful PD strictures, the technical success rate was high (97%) but the primary efficacy rate was low (26%) and there were high rates of stent migration (48%) and serious adverse events (31%). Further studies will be needed to determine the efficacy of FCSEMS.[79]

In patients with tight strictures that may preclude deep cannulation of the papilla, ERCP with transpapillary stenting may be challenging. In 2002, EUS-guided pancreaticogastrostomy was described as a technique for decompressing upstream-dilated PDs when ERCP was unsuccessful. In this procedure, an echoendoscope was used to guide a needle into the upstream-dilated PD. Under fluoroscopy, contrast injection demonstrated the duct, and a guidewire was then inserted to facilitate dilation of the tract and stent placement.[80] Since this initial description, other case series have described EUS-guided drainage of the PD. Studies with long-term data have reported complete or major pain relief in 70% to 90% of patients but the probability of remaining pain-free can drop over time.[81] Stent migration and occlusion rates have ranged between 20% and 55%.[81]

Over the years, the management of PD strictures has centered on dilation and stent placement. When single stents are placed, size 10F or larger are recommended. When strictures are refractory to single-stent placement, multistent placement can be considered.[67] Although studies have not been performed to assess duration of stent placement, some experts recommend planned exchanges every 6 months.[81] Of note, when encountering PD strictures, brushings for cytology should be considered to rule out underlying malignancy.[67,81]

Celiac plexus block and neurolysis

Despite endotherapy for pancreatic strictures and stones, pain management for chronic pancreatitis patients is often difficult. Since percutaneous transposterior celiac plexus block (CPB) was first described in 1914,[82] CPB has evolved with changing technology and has been performed under CT, fluoroscopic, and transcutaneous ultrasound guidance. In 1996, EUS-guided celiac plexus neurolysis (CPN) was first documented in patients with pain from pancreatic cancer or intra-abdominal metastases, with up to 88% experiencing pain improvement.[83] Although CPN and CPB differ in the injection solution, the technique is similar, and this initial experience demonstrated feasibility and safety of EUS-guided CPB.

Despite similarity in technique, CPN and CPB are not equally efficacious in treating pain for patients with pancreatic cancer and patients with chronic pancreatitis, respectively. Two meta-analyses reported that CPB provides temporary pain relief in 51% to 59% of chronic pancreatitis patients while CPN provides pain relief in 73% to 80% of patients with pancreatic cancer. Adverse events reported have included transient diarrhea, orthostasis, retroperitoneal abscess formation, and spinal cord infarction.[67,82,84] As such CPB should not be considered first-line treatment of chronic pancreatitis pain and should only be considered in patients with severe pain affecting quality of life or recurrent hospitalizations. However, CPN is generally accepted as a relatively effective method of pain control for patients with pancreatic cancer and has been suggested to have greater benefit when used earlier as opposed to as salvage therapy.[85]

Endotherapy for Pancreatic Neoplasms

In the last 2 decades, EUS has expanded its application and played an active role in the management of pancreatic neoplasms (**Table 2**). The following section discusses EUS-guided radiotherapy, tissue ablation, and antitumor injections. Although some of these techniques are promising, they remain experimental and require further studies to delineate their utility.

Endoscopic ultrasound-guided radiotherapy

Stereotactic radiotherapy is a treatment that delivers external radiation into tumors by using real-time image guidance.[86] Fiducials are radiographic markers that serve as reference points for stereotactic radiotherapy and were initially placed surgically or percutaneously.[87] In 2006, EUS guidance was successfully used to place fiducials in patients with mediastinal and abdominal lesions.[86] Since this experience, many centers have reported EUS-guided placement of fiducials into pancreatic neoplasms. Although generally safe, migration can occur with tumor treatment and inflammation, and there is a 1% risk of minor bleeding.[87]

Although fiducials facilitate external radiotherapy, brachytherapy exposes tumors to internal radiotherapy. In EUS-guided brachytherapy, radioactive seeds are implanted into or adjacent to tumor and release radiation that induces tissue injury and tumor ablation.[87,88] In 2006, EUS-guided implantation of iodine-125 seeds was reported in 15 patients with unresectable pancreatic adenocarcinoma. Seven patients had partial or minor response and complications occurred in 20% of patients, including 3 who developed pancreatitis.[89] Although there have been a few other studies on EUS-guided brachytherapy, these have been limited by a small number of subjects and lack of a control group.[87]

Endoscopic ultrasound-guided radiofrequency ablation

Radiofrequency ablation (RFA) is a minimally invasive technique that generates localized heat to induce thermal necrosis of targeted tissue.[87] Experience with RFA began in animal models and later was used intraoperatively in humans. In 2015, EUS-RFA was successfully used in 6 patients with pancreatic cystic neoplasm (PCN). Two patients had complete resolution of the cysts and 3 had 48% reduction in size.[90] In a

Table 2
Investigational endotherapy for pancreatic neoplasms

Endotherapy	Year of Initial Experience (Reference Number)	Potential Pancreatic Disease Applications
EUS-guided fiducial placement	Pishvaian et al,[86] 2006	Unresectable pancreatic cancer
EUS-guided brachytherapy	Sun et al,[89] 2006	Unresectable pancreatic cancer
EUS-guided radiofrequency ablation	Pai et al,[90] 2015	PCNs, PNETs, unresectable pancreatic cancer
EUS-guided ethanol ablation	Gan et al,[95] 2005	PCNs, PNETs
EUS-guided immunotherapy injection	Chang et al,[99] 2000	Unresectable pancreatic cancer
EUS-guided chemotherapy injection	Levy et al,[100] 2016	Unresectable pancreatic cancer

Abbreviations: PCN, pancreatic cystic neoplasm; PNET, pancreatic neuroendocrine tumor.

subsequent larger series of 17 PCNs, 11 had complete disappearance, and one had a diameter reduced by greater than 50% 1 year after treatment; all 12 had complete resolutions of mural nodules.[91]

EUS-RFA has also had favorable results with pancreatic neuroendocrine tumors (PNETs). In the larger series cited above, 12 of 16 PNETs disappeared 1 year after treatment. These results were validated in a meta-analysis of 12 studies that included 61 patients, reporting a 96% efficacy rate without differences noted between functional and nonfunctional PNETs (NF-PNETs).[92]

Although EUS-RFA is associated with 10% risk of abdominal pain,[93] it has overall proved promising for treating pancreatic neoplasms. Few studies have demonstrated safety and feasibility of using EUS-RFA for unresectable pancreatic cancer; however, these have yet to demonstrate an impact on disease progression and survival.[93]

Endoscopic ultrasound-guided ethanol ablation

Ethanol is an ablative agent that causes cell death by inducing cell membrane lysis, protein denaturation, and vascular occlusion.[94] In 2002, EUS-guided ethanol ablation was first used to treat liver metastases.[87] By 2005, EUS-guided ethanol ablation was reported in 23 patients with PCNs with 35% achieving complete resolution within 12 months; the ethanol concentration ranged between 5% and 80%.[95] Later studies used 80% to 100% ethanol and reported PCN resolution rates widely ranging between 9% and 85% with inconsistent results regarding whether cyst type or size affect clinical response.[96]

EUS-guided ethanol ablation has also been used to treat PNETs. In 2006, EUS-guided ethanol ablation of a symptomatic insulinoma led to the resolution of hypoglycemic episodes and of the PNET on imaging. Other limited case reports using EUS-guided ethanol ablation for symptomatic insulinomas have reported similar favorable responses.[97] Additionally, in a study that included 10 NF-PNETs, EUS-guided ethanol ablation was able to achieve complete response in 6 and incomplete response in 3.[98]

Although EUS-guided ethanol ablation has shown promise in treating pancreatic neoplasms, it is currently reserved for patients who are not surgical candidates or for those who refuse surgery. Further studies are needed to determine its efficacy on different types of PCNs and to standardize treatment protocols (ie, ethanol concentration, number of treatments).

Endoscopic ultrasound-guided antitumor injections

Although the previously discussed EUS-guided treatments have focused on PCNs and PNETs, EUS-guided antitumor injections have been directed at treating pancreatic cancer. In 2000, the first EUS-guided immunotherapy was performed in 8 patients with advanced unresectable pancreatic cancer. These cancers were injected with a lymphocytic culture that could theoretically produce cytokines and activate antitumor effector cells. Only 2 patients had partial tumor response.[99] Other EUS-guided immunotherapy injections have been performed with dendritic cells and TNFerade (a recombinant agent that delivers tumor necrosis factor alpha [TNF-α] to cancer cells). Neither has been shown to have significant benefit.[87]

EUS-guided chemotherapy injection has shown more promise in treating pancreatic neoplasms. Initial experience with chemotherapy injection was with either gemcitabine or paclitaxel and was performed as an adjunct to EUS-guided ethanol ablation for PCNs. These studies suggested a higher rate of complete resolution of PCNs with chemotherapy injection as compared with ethanol injection alone.[96] In 2016, EUS-guided injection of gemcitabine was performed in patients with inoperable locally advanced pancreatic cancer who were receiving conventional chemoradiation. In this study, 20% of patients with unresectable stage III disease were downstaged and underwent R0 resection.[100] Further studies are needed to assess safety and efficacy of EUS-guided antitumor injections.

SUMMARY

In the last half century, endotherapy for pancreatic diseases has evolved considerably. With more accessory tools available, both ERCP and EUS have grown in their therapeutic capabilities in managing pancreatic disease and have reduced the need for surgery. Although the management of pancreatitis and its complications has been stagnant in the last 2 decades, endotherapy for pancreatic neoplasms is only in the early stages of development and has shown potential for both palliation and cure.

CLINICS CARE POINTS

- Symptomatic or infected PFCs can be safely drained with EUS-guided cystoenterostomy.
- WON should be managed conservatively. However, if the WON becomes infected or symptomatic, endoscopic and percutaneous step-up therapies have been showed to have lower complication and mortality rates when compared with surgical approaches. Furthermore, DMD has favorable clinical outcomes but requires collaboration with IR and reliable patient follow-up.
- Complications of PD leaks can be treated with endoscopic transpapillary stenting or drainage. However, the management of DDS often requires the addition of therapeutic EUS techniques or a multidisciplinary approach with IR.
- When large pancreatic calculi cannot be managed with traditional endoscopic extraction methods, stone fragmentation with ESWL, LL, and EHL can be considered.
- Although endoscopic transpapillary stenting is used to treat PD strictures, long-term observations suggest that PD stenting can induce changes including ductal dilation, stenoses, and side branch ectasias.
- EUS-guided CPB and neurolysis differ in the injection solution used but have been used to treat pain for chronic pancreatitis and patients with pancreatic cancer, respectively. However, CPB should not be considered first-line treatment of chronic pancreatitis pain.
- EUS-guided antitumor therapy remains investigational, although shows potential in palliation and cure of pancreatic neoplasms.

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REFERENCES

1. Busnardo AC, DiDio LJ, Tidrick RT, et al. History of the pancreas. American journal of surgery 1983;146(5):539–50.
2. Wiltse LL, Pait TG. Herophilus of Alexandria (325-255 B. C.). The father of anatomy. Spine (Phila Pa 1976) 1998;23(17):1904–14.
3. Navarro S. The art of pancreatic surgery. Past, present and future. The history of pancreatic surgery. Gastroenterol Hepatol 2017;40(9):648 e1–e648, e11. El arte de la cirugia pancreatica. Pasado, presente y futuro. doi:.
4. O'Reilly DA, Kingsnorth AN. A brief history of pancreatitis. J R Soc Med 2001;94(3):130–2.

5. McCune WS, Shorb PE, Moscovitz H. Endoscopic cannulation of the ampulla of vater: a preliminary report. Ann Surg 1968;167(5):752–6.
6. Wallace MB, Fockens P, Sung JJY. Gastroenterological endoscopy. Thieme 2018;xix:418.
7. Cotton PB. Cannulation of the papilla of Vater by endoscopy and retrograde cholangiopancreatography (ERCP). Gut 1972;13(12):1014–25.
8. Buscaglia JM, Kalloo AN. Pancreatic sphincterotomy: technique, indications, and complications. World J Gastroenterol 2007;13(30):4064–71.
9. Behrns KE, Ashley SW, Hunter JG, et al. Early ERCP for gallstone pancreatitis: for whom and when? J Gastrointest Surg 2008;12(4):629–33.
10. Andersen DK, Frey CF. The evolution of the surgical treatment of chronic pancreatitis. Ann Surg 2010;251(1):18–32.
11. Sherman S, Hawes RH, Lehman GA. Management of bile duct stones. Semin Liver Dis 1990;10(3):205–21.
12. Guo A, Poneros JM. The Role of Endotherapy in Recurrent Acute Pancreatitis. Gastrointest Endosc Clin N Am 2018;28(4):455–76.
13. Cotton PB. Congenital anomaly of pancreas divisum as cause of obstructive pain and pancreatitis. Gut 1980;21(2):105–14.
14. Lehman GA, Sherman S, Nisi R, et al. Pancreas divisum: results of minor papilla sphincterotomy. Gastrointestinal endoscopy 1993;39(1):1–8.
15. Kozarek RA, Ball TJ, Patterson DJ, et al, Brandabur JJ, Raltz SL. Endoscopic approach to pancreas divisum. Digestive diseases and sciences 1995;40(9):1974–81.
16. McCarthy J, Geenen JE, Hogan WJ. Preliminary experience with endoscopic stent placement in benign pancreatic diseases. Gastrointest Endosc 1988;34(1):16–8.
17. Cote GA, Durkalski-Mauldin V, Williams A, et al. Design and execution of sham-controlled endoscopic trials in acute pancreatitis: Lessons learned from the SHARP trial. Pancreatology 2022. https://doi.org/10.1016/j.pan.2022.12.011.
18. Law R, Topazian M. Diagnosis and treatment of choledochoceles. Clin Gastroenterol Hepatol 2014;12(2):196–203.
19. Deyhle P, Schnaars P, Meyer HJ, et al. [Electrosurgical removal of a choledochocele through an endoscope introduced by mouth (author's transl)]. Dtsch Med Wochenschr 1974;99(3):71–2. Perorale endoskopisch-elektrochirurgische Abtragung einer Choledochocele.
20. Siegel JH, Harding GT, Chateau F. Endoscopic incision of choledochal cysts (choledochocele). Endoscopy 1981;13(5):200–2.
21. Martin RF, Biber BP, Bosco JJ, et al. Symptomatic choledochoceles in adults. Endoscopic retrograde cholangiopancreatography recognition and management. Arch Surg 1992;127(5):536–8, discussion 538-9.
22. Guelrud M. Papillary stenosis. Endoscopy 1988;20(Suppl 1):193–202.
23. Toouli J. What is sphincter of Oddi dysfunction? Gut 1989;30(6):753–61.
24. Gregg JA, Carr-Locke DL. Endoscopic pancreatic and biliary manometry in pancreatic, biliary, and papillary disease, and after endoscopic sphincterotomy and surgical sphincteroplasty. Gut 1984;25(11):1247–54.
25. Petersen BT. An evidence-based review of sphincter of Oddi dysfunction: part I, presentations with "objective" biliary findings (types I and II). Gastrointestinal endoscopy 2004;59(4):525–34.
26. Petersen BT. Sphincter of Oddi dysfunction, part 2: Evidence-based review of the presentations, with "objective" pancreatic findings (types I and II) and of presumptive type III. Gastrointest Endosc 2004;59(6):670–87.

27. Cotton PB, Durkalski V, Romagnuolo J, et al. Effect of endoscopic sphincterotomy for suspected sphincter of Oddi dysfunction on pain-related disability following cholecystectomy: the EPISOD randomized clinical trial. JAMA 2014;311(20):2101–9.
28. Cotton PB, Elta GH, Carter CR, et al. Rome IV. Gallbladder and Sphincter of Oddi Disorders. Gastroenterology 2016. https://doi.org/10.1053/j.gastro.2016.02.033.
29. Cremer M, Deviere J, Engelholm L. Endoscopic management of cysts and pseudocysts in chronic pancreatitis: long-term follow-up after 7 years of experience. Gastrointest Endosc 1989;35(1):1–9.
30. Barkin JS, Smith FR, Pereiras R Jr, et al. Therapeutic percutaneous aspiration of pancreatic pseudocysts. Dig Dis Sci 1981;26(7):585–6.
31. Rogers BH, Cicurel NJ, Seed RW. Transgastric needle aspiration of pancreatic pseudocyst through an endoscope. Gastrointestinal endoscopy 1975;21(3):133–4.
32. Hershfield NB. Drainage of a pancreatic pseudocyst at ERCP. Gastrointestinal endoscopy 1984;30(4):269–70.
33. Kozarek RA, Brayko CM, Harlan J, et al. Endoscopic drainage of pancreatic pseudocysts. Gastrointest Endosc 1985;31(5):322–7.
34. Sahel J, Bastid C, Pellat B, et al. Endoscopic cystoduodenostomy of cysts of chronic calcifying pancreatitis: a report of 20 cases. Pancreas 1987;2(4):447–53.
35. Huibregtse K, Schneider B, Vrij AA, et al. Endoscopic pancreatic drainage in chronic pancreatitis. Gastrointest Endosc 1988;34(1):9–15.
36. Kozarek RA, Patterson DJ, Ball TJ, et al. Endoscopic placement of pancreatic stents and drains in the management of pancreatitis. Ann Surg 1989;209(3):261–6.
37. Binmoeller KF, Seifert H, Walter A, et al. Transpapillary and transmural drainage of pancreatic pseudocysts. Gastrointestinal endoscopy 1995;42(3):219–24.
38. Smits ME, Rauws EA, Tytgat GN, et al. The efficacy of endoscopic treatment of pancreatic pseudocysts. Gastrointestinal endoscopy 1995;42(3):202–7.
39. Kozarek RA. Pancreatic stents can induce ductal changes consistent with chronic pancreatitis. Gastrointestinal Endoscopy 1990;36(2):93–5.
40. Wiersema MJ. Endosonography-guided cystoduodenostomy with a therapeutic ultrasound endoscope. Gastrointestinal endoscopy 1996;44(5):614–7.
41. Adler JM, Sethi A. Interventional Endoscopic Ultrasonography in the Pancreas. Gastrointest Endosc Clin N Am 2018;28(4):569–78.
42. Talreja JP, Shami VM, Ku J, et al. Transenteric drainage of pancreatic-fluid collections with fully covered self-expanding metallic stents (with video). Gastrointest Endosc 2008;68(6):1199–203.
43. Binmoeller KF, Nett A. The Evolution of Endoscopic Cystgastrostomy. Gastrointest Endosc Clin N Am 2018;28(2):143–56.
44. Teoh AY, Binmoeller KF, Lau JY. Single-step EUS-guided puncture and delivery of a lumen-apposing stent for gallbladder drainage using a novel cautery-tipped stent delivery system. Gastrointest Endosc 2014;80(6):1171.
45. Fisher JM, Gardner TB. Endoscopic therapy of necrotizing pancreatitis and pseudocysts. Gastrointest Endosc Clin N Am 2013;23(4):787–802.
46. Yang J, Chen YI, Friedland S, et al. Correction: Lumen-apposing stents versus plastic stents in the management of pancreatic pseudocysts: a large, comparative, international, multicenter study. Endoscopy 2019;51(11):C5.

47. Baron TH, Thaggard WG, Morgan DE, et al. Endoscopic therapy for organized pancreatic necrosis. Gastroenterology 1996;111(3):755–64.
48. Varadarajulu S, Rana SS, Bhasin DK. Endoscopic therapy for pancreatic duct leaks and disruptions. Gastrointest Endosc Clin N Am 2013;23(4):863–92.
49. Seifert H, Biermer M, Schmitt W, et al. Transluminal endoscopic necrosectomy after acute pancreatitis: a multicentre study with long-term follow-up (the GEPARD Study). Gut 2009;58(9):1260–6.
50. van Santvoort HC, Bakker OJ, Bollen TL, et al. A conservative and minimally invasive approach to necrotizing pancreatitis improves outcome. Gastroenterology 2011;141(4):1254–63.
51. Yasuda I, Takahashi K. Endoscopic management of walled-off pancreatic necrosis. *Dig Endosc*. Mar 2021;33(3):335–41.
52. Ross AS, Irani S, Gan SI, et al. Dual-modality drainage of infected and symptomatic walled-off pancreatic necrosis: long-term clinical outcomes. Gastrointest Endosc 2014;79(6):929–35.
53. Baron TH, DiMaio CJ, Wang AY, et al. American Gastroenterological Association Clinical Practice Update: Management of Pancreatic Necrosis. Gastroenterology 2020;158(1):67–75 e1.
54. Kozarek RA, Ball TJ, Patterson DJ, et al. Endoscopic transpapillary therapy for disrupted pancreatic duct and peripancreatic fluid collections. Gastroenterology 1991;100(5 Pt 1):1362–70.
55. Kozarek RA, Jiranek GC, Traverso LW. Endoscopic treatment of pancreatic ascites. American Journal Of Surgery 1994;168(3):223–6.
56. Wolfsen HC, Kozarek RA, Ball TJ, et al. Pancreaticoenteric fistula: no longer a surgical disease? J Clin Gastroenterol 1992;14(2):117–21.
57. Kozarek RA, Ball TJ, Patterson DJ, et al. Transpapillary stenting for pancreaticocutaneous fistulas. J Gastrointest Surg 1997;1(4):357–61.
58. Larsen M, Kozarek R. Management of pancreatic ductal leaks and fistulae. J Gastroenterol Hepatol 2014;29(7):1360–70.
59. Verma S, Rana SS. Disconnected pancreatic duct syndrome: Updated review on clinical implications and management. Pancreatology 2020;20(6):1035–44.
60. Deviere J, Bueso H, Baize M, et al. Complete disruption of the main pancreatic duct: endoscopic management. Gastrointestinal endoscopy 1995;42(5):445–51.
61. Arvanitakis M, Delhaye M, Bali MA, et al. Endoscopic treatment of external pancreatic fistulas: when draining the main pancreatic duct is not enough. American Journal of Gastroenterology 2007;102(3):516–24.
62. Irani S, Gluck M, Ross A, et al. Resolving external pancreatic fistulas in patients with disconnected pancreatic duct syndrome: using rendezvous techniques to avoid surgery (with video). Gastroenterol Endosc 2012;76(3):586–93, e1-3.
63. Inui K, Nakae Y, Nakamura J, et al. A case of non-calcified pancreatolithiasis which was removed by endoscopic sphincterotomy of the pancreatic duct. Gastroenterol Endosc 1983;25(8):1246–53.
64. Fuji T, Amano H, Harima K, et al. Pancreatic sphincterotomy and pancreatic endoprosthesis. Endoscopy 1985;17(2):69–72.
65. Ponsky JL, Duppler DW. Endoscopic sphincterotomy and removal of pancreatic duct stones. Am Surg 1987;53(10):613–6.
66. Sauerbruch T, Holl J, Sackmann M, et al. Disintegration of a pancreatic duct stone with extracorporeal shock waves in a patient with chronic pancreatitis. Endoscopy 1987;19(5):207–8.

67. ASoP Committee, Chandrasekhara V, Chathadi KV, et al. The role of endoscopy in benign pancreatic disease. Gastrointest Endosc 2015;82(2):203–14.
68. Rosch T, Daniel S, Scholz M, et al. Endoscopic treatment of chronic pancreatitis: a multicenter study of 1000 patients with long-term follow-up. Endoscopy 2002; 34(10):765–71.
69. Kozarek RA, Brandabur JJ, Ball TJ, et al. Clinical outcomes in patients who undergo extracorporeal shock wave lithotripsy for chronic calcific pancreatitis. Gastrointest Endosc 2002;56(4):496–500.
70. Feldman RK, Freeny PC, Kozarek RA. Pancreatic and biliary calculi: percutaneous treatment with tunable dye laser lithotripsy. Radiology 1990;174(3 Pt 1): 793–5.
71. Tanaka M, Yokohata K, Kimura H, et al. Intraoperative endoscopic electrohydraulic lithotripsy of pancreatic stones. Int J Pancreatol 1992;12(3):227–31.
72. Howell DA, Dy RM, Hanson BL, et al. Endoscopic treatment of pancreatic duct stones using a 10F pancreatoscope and electrohydraulic lithotripsy. Gastrointest Endosc 1999;50(6):829–33.
73. van der Wiel SE, Stassen PMC, Poley JW, et al. Pancreatoscopy-guided electrohydraulic lithotripsy for the treatment of obstructive pancreatic duct stones: a prospective consecutive case series. Gastrointest Endosc 2022;95(5): 905–914 e2.
74. Nguyen-Tang T, Dumonceau JM. Endoscopic treatment in chronic pancreatitis, timing, duration and type of intervention. Best Pract Res Clin Gastroenterol 2010;24(3):281–98.
75. Talukdar R, Reddy DN. Pancreatic Endotherapy for Chronic Pancreatitis. Gastrointest Endosc Clin N Am 2015;25(4):765–77.
76. Costamagna G, Bulajic M, Tringali A, et al. Multiple stenting of refractory pancreatic duct strictures in severe chronic pancreatitis: long-term results. Endoscopy 2006;38(3):254–9.
77. Sauer BG, Gurka MJ, Ellen K, et al. Effect of pancreatic duct stent diameter on hospitalization in chronic pancreatitis: does size matter? Pancreas 2009;38(7): 728–31.
78. Tringali A, Costa D, Rota M, et al. Covered self-expandable metal stents for pancreatic duct stricture: a systematic review and meta-analysis. Endosc Int Open 2022;10(9):E1311–21.
79. Sherman S, Kozarek RA, Costamagna G, et al. Soft self-expanding metal stent to treat painful pancreatic duct strictures secondary to chronic pancreatitis: a prospective multicenter trial. Gastrointest Endosc 2022. https://doi.org/10.1016/j.gie.2022.09.021.
80. Francois E, Kahaleh M, Giovannini M, et al. EUS-guided pancreaticogastrostomy. Gastrointestinal endoscopy 2002;56(1):128–33.
81. Dumonceau JM, Delhaye M, Tringali A, et al. Endoscopic treatment of chronic pancreatitis: European Society of Gastrointestinal Endoscopy (ESGE) Guideline - Updated August 2018. Endoscopy 2019;51(2):179–93.
82. Kaufman M, Singh G, Das S, et al. Efficacy of endoscopic ultrasound-guided celiac plexus block and celiac plexus neurolysis for managing abdominal pain associated with chronic pancreatitis and pancreatic cancer. J Clin Gastroenterol 2010;44(2):127–34.
83. Wiersema MJ, Wiersema LM. Endosonography-guided celiac plexus neurolysis. Gastrointestinal endoscopy 1996;44(6):656–62.

84. Puli SR, Reddy JB, Bechtold ML, et al. EUS-guided celiac plexus neurolysis for pain due to chronic pancreatitis or pancreatic cancer pain: a meta-analysis and systematic review. Digestive diseases and sciences 2009;54(11):2330–7.
85. Wyse JM, Chen YI, Sahai AV. Celiac plexus neurolysis in the management of unresectable pancreatic cancer: when and how? World journal of gastroenterology 2014;20(9):2186–92.
86. Pishvaian AC, Collins B, Gagnon G, et al. EUS-guided fiducial placement for CyberKnife radiotherapy of mediastinal and abdominal malignancies. Gastrointestinal endoscopy 2006;64(3):412–7.
87. Mukewar S, Muthusamy VR. Recent Advances in Therapeutic Endosonography for Cancer Treatment. Gastrointest Endosc Clin N Am 2017;27(4):657–80.
88. Bratanic A, Bozic D, Mestrovic A, et al. Role of endoscopic ultrasound in anticancer therapy: Current evidence and future perspectives. World J Gastrointest Oncol 2021;13(12):1863–79.
89. Sun S, Xu H, Xin J, et al. Endoscopic ultrasound-guided interstitial brachytherapy of unresectable pancreatic cancer: results of a pilot trial. Endoscopy 2006;38(4):399–403.
90. Pai M, Habib N, Senturk H, et al. Endoscopic ultrasound guided radiofrequency ablation, for pancreatic cystic neoplasms and neuroendocrine tumors. World J Gastrointest Surg 2015;7(4):52–9.
91. Barthet M, Giovannini M, Lesavre N, et al. Endoscopic ultrasound-guided radiofrequency ablation for pancreatic neuroendocrine tumors and pancreatic cystic neoplasms: a prospective multicenter study. Endoscopy 2019;51(9):836–42.
92. Imperatore N, de Nucci G, Mandelli ED, et al. Endoscopic ultrasound-guided radiofrequency ablation of pancreatic neuroendocrine tumors: a systematic review of the literature. Endosc Int Open 2020;8(12):E1759–64.
93. Dhaliwal A, Kolli S, Dhindsa BS, et al. Efficacy of EUS-RFA in pancreatic tumors: Is it ready for prime time? A systematic review and meta-analysis. Endosc Int Open 2020;8(10):E1243–51.
94. Zhang WY, Li ZS, Jin ZD. Endoscopic ultrasound-guided ethanol ablation therapy for tumors. World J Gastroenterol 2013;19(22):3397–403.
95. Gan SI, Thompson CC, Lauwers GY, et al. Ethanol lavage of pancreatic cystic lesions: initial pilot study. Gastrointest Endosc 2005;61(6):746–52.
96. Du C, Chai NL, Linghu EQ, et al. Endoscopic ultrasound-guided injective ablative treatment of pancreatic cystic neoplasms. World J Gastroenterol 2020; 26(23):3213–24.
97. Qin SY, Lu XP, Jiang HX. EUS-guided ethanol ablation of insulinomas: case series and literature review. Medicine (Baltimore) 2014;93(14):e85.
98. Park DH, Choi JH, Oh D, et al. Endoscopic ultrasonography-guided ethanol ablation for small pancreatic neuroendocrine tumors: results of a pilot study. Clin Endosc 2015;48(2):158–64.
99. Chang KJ, Nguyen PT, Thompson JA, et al. Phase I clinical trial of allogeneic mixed lymphocyte culture (cytoimplant) delivered by endoscopic ultrasound-guided fine-needle injection in patients with advanced pancreatic carcinoma. Cancer 2000;88(6):1325–35.
100. Levy MJ, Alberts SR, Bamlet WR, et al. EUS-guided fine-needle injection of gemcitabine for locally advanced and metastatic pancreatic cancer. Gastrointest Endosc 2017;86(1):161–9.