Chapter 11
ERCP in Chronic Pancreatitis

Antonio R. Cheesman and Christopher J. DiMaio

Case Presentation

A 65-year-old male with alcohol- and tobacco-related chronic calcific pancreatitis with recurrent acute on chronic pancreatitis flares presented for further evaluation and management of abdominal pain. Initial magnetic resonance cholangiopancreatography (MRCP) revealed a severely atrophic pancreas with diffuse main pancreatic duct (MPD) dilatation up to 11 mm; multiple intraductal stones, including a 17 mm one at the head of pancreas (HOP); and scattered parenchymal calcifications (Figs. 11.1 and 11.2).

Given these findings and the presence of pancreatic-type pain, the decision was made to attempt MPD decompression by ERCP. The first ERCP proved technically challenging requiring multiple combinations of accessories for MPD access, ultimately revealing a severe 3-cm-long MPD stricture at the HOP with upstream dilation and multiple proximal filling defects (6–15 mm). The stricture was dilated, and a single 5 Fr pigtail plastic stent was placed (Fig. 11.3).

A. R. Cheesman · C. J. DiMaio (✉)
Division of Gastroenterology, Icahn School of Medicine at Mount Sinai, New York, NY, USA
e-mail: christopher.dimaio@mountsinai.org

D. K. Mullady (ed.), *Dilemmas in ERCP*,
https://doi.org/10.1007/978-3-030-12741-1_11

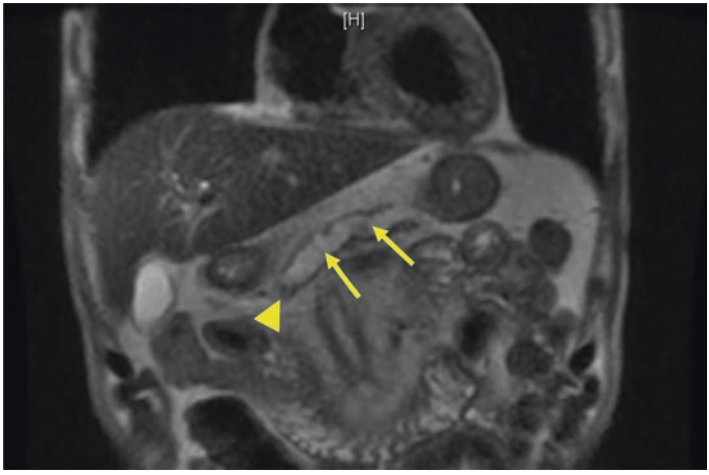

FIGURE 11.1 Coronal MRI/MRCP image demonstrating a markedly dilated main pancreatic duct (arrows) with stricture in the pancreatic duct in the head (arrowhead)

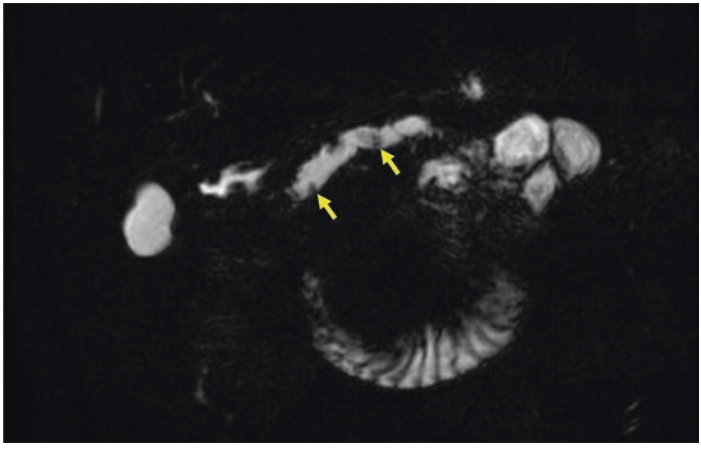

FIGURE 11.2 MRCP image demonstrating dilated main pancreatic duct and scattered intraductal stones (arrows)

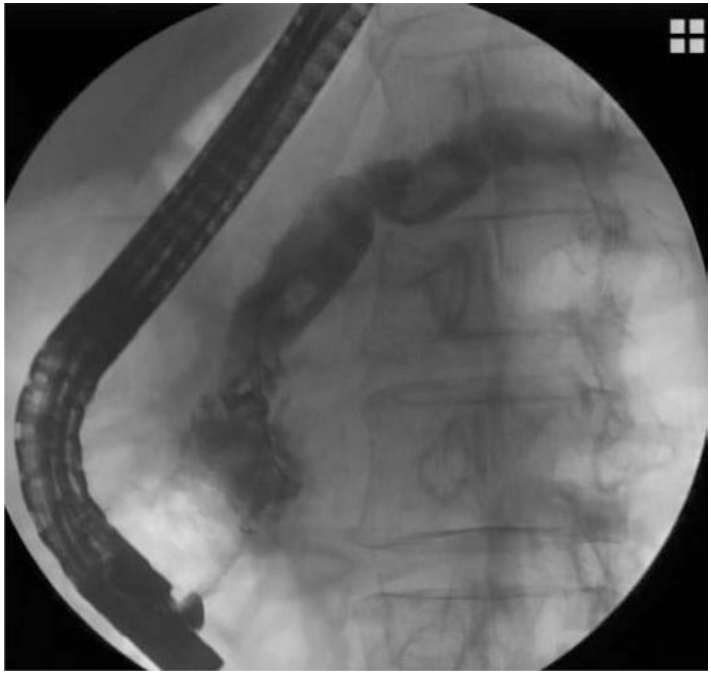

FIGURE 11.3 Pancreatogram demonstrating marked dilation of the pancreatic duct upstream from a severe stricture in the pancreatic head and multiple filling defects consistent with intraductal stones

Repeat ERCP 1 month later was performed. The pancreatic stent was removed and repeat stricture dilation performed; however attempts at stone removal by balloon sweep and basket use were unsuccessful. A new single 7 Fr pigtail plastic stent was placed with limited improvement in pain after 4 weeks. Given high-grade stricture persistence with proximal non-drainable MPD dilation on pancreatography and multiple filling defects, the decision was made to place an 80 × 60 mm fully covered self-expanding metal stent (FC-SEMS) to the MPD (Fig. 11.4).

The patient progressed well with improved pain control. At a follow-up ERCP session, MPD access was performed

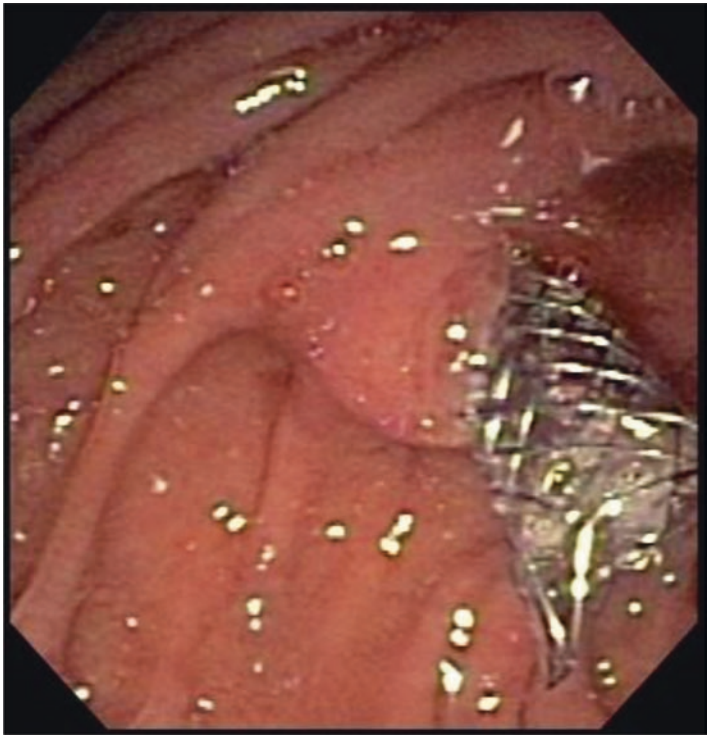

Figure 11.4 Intraduodenal portion of fully covered metallic biliary stent which was placed into the main pancreatic duct due to the persistence and severity of the pancreatic duct stricture despite previous dilation and plastic stenting

through the indwelling metal stent with balloon sweeps for direct stone extraction. Pancreatoscopy confirmed no proximal strictures or residual stones, so the stent was removed revealing now a large 20 mm stone impacted at the ventral pancreatic duct. Through-the-scope electrohydraulic lithotripsy (EHL) proved unsuccessful given the location of the stone, just superior to the ampulla, so a new 10 Fr straight plastic stent was placed (Fig. 11.5).

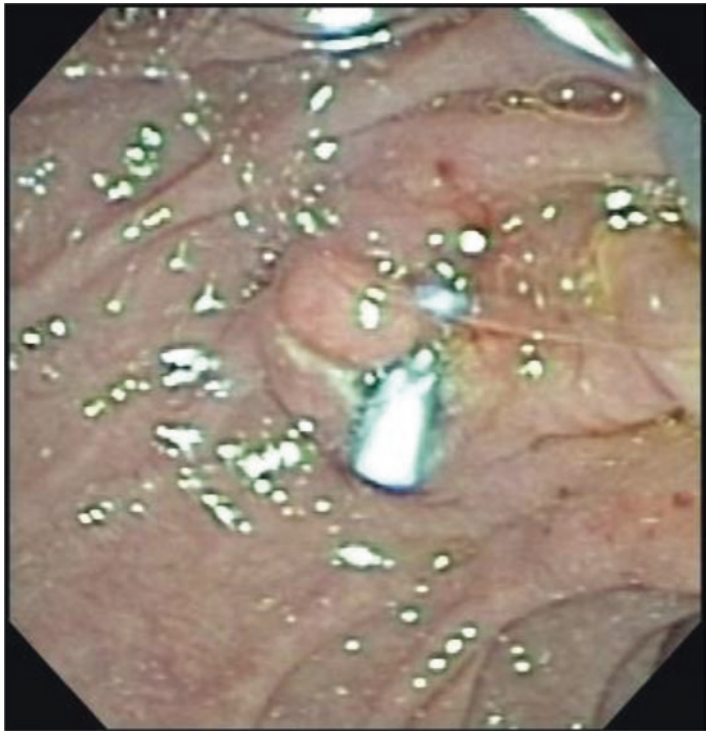

FIGURE 11.5 Following removal of the fully covered metallic stent, the large stone in the pancreatic head could not be fragmented via EHL, so a plastic pancreatic duct stent was placed

Extracorporeal shock wave lithotripsy (ESWL) was then performed successfully. Follow-up ERCP however revealed proximal stent migration into the MPD which failed multiple attempts at removal. Repeat pancreatoscopy showed stent impaction adjacent to a large residual stone (Fig. 11.6). This was successfully treated by EHL, though repeat attempts at stent removal proved unsuccessful. The decision was made to leave the plastic stent in place. The patient continued to prog-

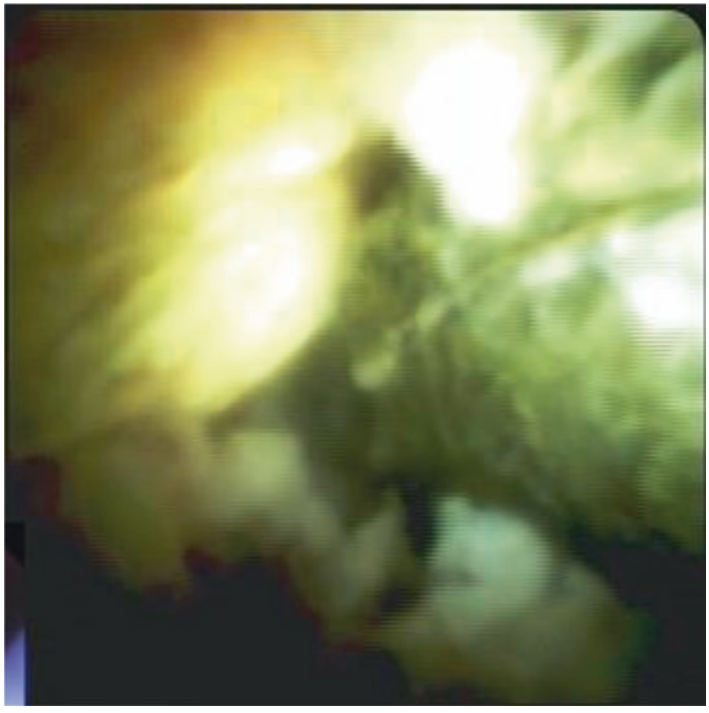

FIGURE 11.6 At follow-up ERCP following the removal of the fully covered metallic stent and a session of ESWL, the previously placed plastic pancreatic duct stent had migrated proximally into the pancreatic duct with persistence of the large pancreatic duct stone, both seen here on pancreatoscopy

ress well with absence of pain and no further interventions after 3 years of follow-up (Fig. 11.7).

Diagnosis/Assessment

The patient previously described presented with recurrent acute pancreatitis exacerbations superimposed on underlying chronic debilitating pain. As such, evaluation for treatable targets and potential new local complications was warranted.

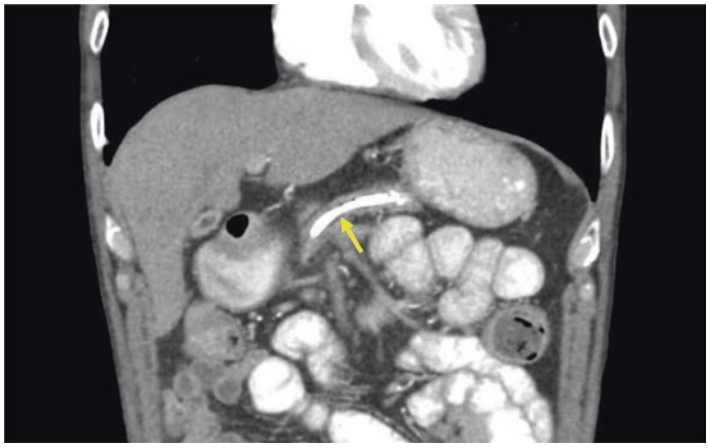

FIGURE 11.7 Coronal CT image with entirely intraductal pancreatic duct stent (arrow)

The importance of complete alcohol and tobacco abstinence was extensively discussed with the patient, and this cannot be emphasized enough, as its impact on disease progression is very well established. In addition, the response to endoscopic therapy and subsequent decisions in management may be more difficult to assess in the absence of alcohol and tobacco cessation.

Despite careful evaluation of MRCP results prior to therapeutic planning, dilation and stenting were performed across a HOP stricture which ultimately proved to be a large impacted stone at the distal MPD; highlighting that strictures, intraductal stones, and parenchymal calcifications may be difficult to differentiate. There should be a low threshold for EUS evaluation, and one must have appropriate understanding of the patient's CP morphology to select appropriate treatment and be prepared for unexpected findings requiring changes in endoscopic management or referral for surgical evaluation.

Finally, it is crucial to set expectations and review potential complications. As discussed later, a significant proportion of patients do not attain long-term benefit from endoscopic

therapy, and selected cases may ultimately require surgery with variable results. Next, we will discuss the existing literature on the assessment of pain, pancreatic stones, and strictures in patients with CP.

Chronic Pancreatitis Pain

Pain is one of the most common and disabling features of CP, presenting in approximately 85% of patients during the disease course [4, 5]. Whether spontaneous resolution of pain occurs ("burnout") is controversial but has been reported in up to 53% of patients after a median of 10 years from diagnosis [6]. Classically two types of pain are described, "Ammann type A," which refers to short-lasting pain episodes separated by long pain-free intervals, and "Ammann type B," which presents with severe continuous non-resolving pain with or without recurrent pain exacerbations, which in turn may represent new local complications of CP.

Pain itself is multifactorial and may result from active inflammation and tissue ischemia, altered nociception (pain threshold, nerve damage, peripheral and central sensitization), local complications (pancreatic duct obstruction, inflammatory masses, pseudocysts, and pancreatic cancer), remote complications (common bile duct obstruction, duodenal obstruction, and small intestinal bacterial overgrowth), and opioid-induced complications (constipation and narcotic bowel syndrome) [4].

When evaluating and managing pain in CP, one must always consider and treat secondary causes of pain. As such, imaging including computed tomography (CT), MRCP, and in selected cases endoscopic ultrasound (EUS) are important to evaluate for strictures, stones, inflammatory masses, and malignancy, which may result in common bile duct (CBD) or MPD obstruction leading to increased intraductal and parenchymal pressure, pancreatic ischemia, and acute inflammation with recurrent acute pancreatitis or chronic pain [2].

Pancreatic Duct Stones

Pancreatic stones result from crystallization and deposition of calcium carbonate due to significant reduction in bicarbonate, citrate, and pancreatic stone protein in the setting of CP. Usually, pancreatic duct stones tend to be hard and sharp; however, occasionally proteins may precipitate forming plugs and stones with softer consistency. MPD strictures reduce flow and lead to stasis, thus facilitating intraductal stone formation [7].

Pancreatic stones can be single or multiple and may be difficult to differentiate from intraparenchymal calcifications on CT particularly when using intravenous (IV) contrast; in addition, as previously noted MPD strictures and stones often coexist. As such, MRCP and/or EUS should always be performed prior to therapeutic attempts. Proximal MPD dilation on MRCP or EUS confirms presence of an obstructive component.

Pancreatic Duct Strictures

Pancreatic strictures can result from acute or chronic pancreatitis, autoimmune pancreatitis, trauma, endoscopic or surgical interventions, and malignancy. Strictures may be single or multiple and are classified as dominant when there is associated ≥6 mm upstream MPD dilatation or contrast outflow obstruction alongside a 6 Fr catheter inserted into the MPD [8]. Refractory strictures are persistent symptomatic dominant strictures despite 1 year of appropriate stent therapy (10 Fr) [9]. In addition, MPD narrowing may result from extrinsic compression by masses or large parenchymal and side-branch stones.

Similar to the evaluation of pancreatic stones, MRCP and/or EUS should be considered. In addition, depending on the level of suspicion, EUS and pancreatoscopy may be required for tissue acquisition to rule out underlying malignancy.

Treatment/Management

The patient previously described presented with multiple challenges for endoscopic management, including difficult MPD access due to a large impacted stone at the HOP initially presumed to be a stricture, and further presence of multiple stones proximally throughout the MPD.

Appropriate identification of the large impacted HOP stone could have led to earlier attempts at ESWL and/or pancreatoscopy-guided intraductal lithotripsy prior to dilation and stenting efforts. While direct balloon-assisted stone extraction failed, and plastic stent placement to the MPD provided limited benefit, placement of a FC-SEMS led to pain relief and facilitated spontaneous passage of upstream MPD stones.

In a recent population-based cohort study of patients with CP and a median follow-up of 10 years, 23% underwent endoscopic therapy, while 11% required surgery [10]. This more closely reflects the general population prevalence, while other studies quoting higher numbers primarily include pancreatic referral centers. For those patients in which invasive procedures are required, however, typically multiple interventions are performed over several years.

Chronic Pancreatitis Pain

In general, nonoperative strategies for managing pain are used before considering more invasive therapies. However, endoscopic therapy, ESWL, and surgery should be considered early in the management of specific structural pathologies, and this should be carefully pursued before patients become opiate dependent [2]. It has been suggested, at least from the surgical literature, that early intervention where the operative indication is pain is associated with improved outcomes including postoperative pain-free status and decreased opiate requirements for patients treated within an optimal cutoff of 26.5 months since CP diagnosis [11].

Endoscopic therapy may restore luminal patency with variable success by removing or bypassing obstructing stones, dilating or stenting strictures, and sealing MPD disruptions. It must be noted however that the amendment of structural abnormalities may not always translate in clinical improvement. Centrally mediated pain and other secondary causes of pain including gastroparesis, small intestinal bacterial overgrowth, and narcotic bowel syndrome can play a role [4].

Pancreatic sphincterotomy is routinely performed in all cases to facilitate therapeutic access to the MPD and stone elimination [12–19]. Biliary sphincterotomy may also be added in selected cases where there is associated cholestasis, CBD obstruction, or cholangitis [8, 20].

As previously mentioned, there is limited to no role for endoscopic management of asymptomatic stones or strictures in CP patients, other than ruling out underlying malignancy in appropriate cases [9]. There is only limited evidence regarding the use of endoscopic therapy in asymptomatic patients to prevent development of exocrine or endocrine pancreatic dysfunction, and a large multicenter study in patients with painful CP in the setting of MPD obstruction due to strictures and/or stones showed no benefit [21].

Pancreatic Duct Stones

Pancreatic stones can be managed by ESWL with or without endoscopic removal, retrograde MPD access and direct removal, or through-the-scope lithotripsy.

Standard endoscopic retrograde pancreatoscopy techniques with sphincterotomy and direct stone removal can be attained by means of extraction balloons, retrieval baskets, and forceps. However in general this is not recommended for stones >5 mm in size, stones impacted proximal to MPD strictures, or those proximal to the pancreatic head given low technical success rates (9–17%) [22, 23] and high risk for complications [8]. In particular there is a risk of basket impaction with the stone behind a stricture.

ESWL achieves successful stone fragmentation in up to 90% of patients [24, 25]. Effective fragmentation has been previously defined as breakdown of stones into fragments of 3 mm or smaller [25, 26]. This in turn leads to spontaneous stone elimination in 70–88% of cases [26, 27]. Similar to outcomes of ERCP-guided stone removal, patients with MPD in the pancreatic head have the best outcomes with ESWL [28]. ESWL alone may provide long-term pain relief in up to 70–96% of patients [26, 27, 29–32]. The use of ESWL however is often limited by local expertise and availability.

In a small randomized controlled trial of ESWL alone vs. ESWL combined with endoscopic removal for management of painful obstructing chronic pancreatitis, there were no differences in post-procedural MPD diameter or pain relapse (ESWL 38% vs. combined therapy 45%) after 2-year follow-up. The cost however was three times higher for those in the combined therapy group [28].

In a large meta-analysis of ESWL with or without adjunct endoscopic stone removal, complete ductal clearance was attained in 70.7%, pain resolution was reported in 52.7%, and pain improvement in another 33.4%, while narcotic use decreased in 79.7% of patients [33].

Based on the available literature, the United European Guidelines recommend ESWL of obstructing stones $\geq$5 mm with immediate endoscopic extraction unless there is considerable local experience with ESWL use for pancreatic stones.

Common contraindications to ESWL include coagulopathy, interposing organ structures, pregnancy, and presence of pacemakers or defibrillators.

Finally, peroral pancreatoscopy with through-the-scope intraductal lithotripsy can be achieved by EHL or laser lithotripsy (LL).

A single center study [23] including 33 patients treated with EHL and 6 patients treated with LL noted complete stone clearance in 70% of patients, with an adverse event rate of 10%. In a multicenter retrospective study [34] of 28 patients with MPD stones who had otherwise failed ERCP (79%), ESWL (32%), and EHL (18%), LL achieved complete ductal

clearance in 79% after a median of 1 session, with only mild adverse events reported (29%). A recent review [35] on the topic also noted a tendency for higher stone clearance rates by use of LL compared to EHL. Subsequently, the largest study to date by Brewer Gutierrez et al. [36] on 103 pts. with CP and MPD stones demonstrated higher success rates for LL (100%) vs. EHL (81%), with similar rates of adverse events (8–9%), in patients that had otherwise failed ESWL in 12% and ERCP extraction in 87% of cases.

One of the potential advantages to take into consideration during therapeutic planning is that direct peroral intraductal lithotripsy may provide an opportunity to address concurrent MPD strictures and complete treatment at index ERCP. There is however limited literature on their relative efficacy and safety compared to ESWL, and for the time being the decision to pursue these techniques as opposed to ESWL should be based on local expertise.

The United European Guidelines recommend ESWL of stones ≥5 mm obstructing the MPD with immediate endoscopic extraction unless there is considerable ESWL experience [9].

Pancreatic Duct Strictures

Pancreatic strictures can be managed by dilation and stenting.

Isolated MPD stricture dilation without stenting has a limited role given its short-lasting effect. The typical initial approach is single plastic stent placement; however MPD stricture resolution in this scenario is still only approximately 60% after the initial procedure [8]. Larger diameter plastic stents (10 vs. ≤8.5 Fr) are typically preferred based on studies showing improved outcomes with lower hospitalization rates [37].

Given limited stricture resolution after a single intervention, repeat procedures are usually required. Both scheduled and "on-demand" stent exchanges have been explored. On-demand exchanges are performed for interval symptom

onset which may relate to stent occlusion that aims to reduce the number of ERCP sessions [38].

Studies looking at scheduled stent exchanges at less than 6-month intervals have shown worse outcomes [39]. On the other hand, a large study of repeated "on-demand" single plastic stent placement with or without ESWL, (median overall stent dwell time of 23 months) showed 62% of patients achieved adequate pain control without need for re-intervention during a median follow-up time of 27 months. For those who relapsed, 80% of cases occurred during the first year after stent removal [17].

The expert recommendation is for scheduled stent exchanges – these are typically performed every 6–12 months – with additional on-demand interventions as needed [8, 9]. Stent removal without replacement can be considered if there is adequate contrast outflow after upstream ductal filling and easy passage of a 6 Fr catheter beyond the stricture [8, 9].

Multiple simultaneous plastic stents may also be employed; this is typically reserved for refractory strictures. In a study of patients that failed single plastic stent placement, resolution was achieved in 84% of cases without additional complications after a median follow-up of 38 months (maximal stents allowed by stricture, median 3, individual size 8.5–11.5 Fr) [40].

Uncovered self-expanding metal stents (UC-SEMS) should not be used. There is limited data for the use of FC-SEMS. Prior reports noted high migration (40%) and stricture recurrence rates [41, 42]. More recently, a small study looking at outcomes of 6 mm diameter FC-SEMS used in benign CP-related MPD strictures, on plastic stent refractory patients, showed pain and radiological improvement in over 80% of cases, with a median post-stent removal follow-up of 47.3 months, after a median stent dwell time of 7.5 months during which there were no migration events [43].

Adverse events from MPD stent placement include acute pancreatitis, duct injury or long-term stent-related duct changes, stent migration and occlusion, bleeding, and infections with abscess formation.

The United European Guidelines recommend the use of single 10 Fr plastic stents with scheduled exchanges – these are typically performed every 6–12 months – with additional on-demand interventions as needed and consideration of multiple simultaneous plastic stents vs. a 3–6-month trial of FC-SEMS for refractory strictures. Surgical drainage procedures should also be considered for refractory and multifocal strictures [9].

Difficult MPD access may result from impassable stones and/or strictures in the proximal MPD or presence of an altered postsurgical anatomy, in which case the trans-papillary approach may not be feasible. In this scenario EUS-guided MPD access can be pursued. Large performance studies on ERCP have shown canalization failure rates of up to 10% [44, 45], while this may be higher in those with CP for the reasons pointed out before.

Indications for EUS-guided MPD access include inaccessible major and minor papilla or pancreaticoenterostomy site by ERCP in patients with ductal disruption/fistula or symptomatic MPD obstruction with associated dilation [46, 47].

Contraindications include non-dilated MPD, multifocal MPD strictures, long distance from gastrointestinal (GI) tract wall or intervening organs/vessel through puncture route, thrombocytopenia, and coagulopathy [46, 47].

EUS-guided MPD access may be achieved by antegrade, with or without rendezvous technique, or by a retrograde approach. In the trans-enteric antegrade technique without rendezvous, MPD stenting is conducted by transluminal stent placement through the GI tract (typically the stomach or duodenum) into the MPD toward and across the papilla, while in the rendezvous variant, a guidewire is advanced in antegrade fashion across the papilla or anastomotic site, followed by retrograde stent insertion into the MPD. The other less commonly used retrograde stenting approach involves transluminal stenting through the GI tract toward the pancreatic tail. In general, the rendezvous approach should be favored whenever the papilla is accessible.

The combined technical success rate on small retrospective series of various forms of EUS-guided MPD access is

79% [47], while a recent large multicenter study of EUS-guided pancreatic duct drainage in 80 patients showed it to be as high as 89% [48]. The overall adverse event rate is 18–21% according to various reports [47, 49]. Most common complications include acute pancreatitis, MPD disruption and leakage, hematomas, bleeding, pancreatic abscess formation, and GI perforation.

Outcomes are closely related to technical expertise; EUS-guided MPD access is technically demanding and should be performed by endoscopists adequately trained in this procedure. The general recommendation is for EUS-guided rendezvous approach to MPD access after failed ERCP whenever the papilla is accessible to endoscopic examination.

Outcomes

The patient previously described progressed well on the long-term follow-up with adequate pain control and no need for further interventions after successful HOP stone fragmentation by consecutive therapy with ESWL and EHL. The plastic stent however was left in place at the MPD after multiple failed attempts at removal in the setting of proximal migration. The relative contribution of the indwelling plastic stent to the patient's indolent clinical course however is difficult to interpret and may be related to "pancreatic burn out." Finally, it must be noted that consideration for surgical MPD drainage would have also been a reasonable option if the patient had remained considerably symptomatic.

Critical appraisal of the outcomes of endoscopic therapy is reviewed, with brief discussion on the indications and comparative outcomes of surgical management in CP.

A large multicenter study [21] with over 1000 patients on endoscopic therapy for painful CP with MPD obstruction due to strictures (47%), stones (18%), or their combination (32%) revealed long-term clinical success rates, defined as improvement or resolution of pain, to be as low as 65% after a median of 4 ERCP sessions with pancreatic sphincterotomy,

stenting, and use of ESWL at the endoscopist's discretion. This was driven largely by adjustments after intention to treat analysis due to the large number of patients requiring surgery (24%) during the mean 4.9 years of follow-up time. There were however no significant differences in outcomes based on index presentation (strictures, stones, or their combination).

Another large meta-analysis [3], including 11 studies and over 1500 patients, on the efficacy of endoscopic therapy for the treatment of painful CP using a similar approach revealed immediate pain relief in up to 88% of patients, but this was reduced to only 67% after the first month and decreased further during a mean of 47 months of follow-up. The adverse event rate was 7.8% after each individual endoscopic intervention. Stents (4–11.5 Fr) were selected according to MPD stricture characteristics, and both on-demand and fixed stent exchange schedules were used at the endoscopist's discretion.

While endotherapy is a viable first-line therapeutic modality for painful obstructing CP, an individualized treatment plan should be developed after detailed pancreatic ductal anatomy evaluation, and early surgical consultation should be sought in cases of complex morphology with pancreatic ductal pathology in the body or tail, multifocal strictures or stones, refractory strictures, and inflammatory masses.

Studies looking at early vs. delayed multimodality surgical intervention for painful CP, where the operative indication was exclusively pain, have shown an optimal cutoff of 26.5 months since the diagnosis of CP for long-term pain control and opioid independence [11].

Otherwise, two small studies comparing endoscopic therapy vs. multimodality surgical intervention for painful obstructive CP have demonstrated superior pain control outcomes on long-term follow-up after surgery (37 vs. 14% and 75 vs. 32%) [50, 51], leading to a Cochrane Review favoring surgical management where applicable [52]. It must be noted however that the endoscopic techniques used in the two studies included may not reflect the current standard of care.

The United European Guidelines recommend that surgical evaluation be considered for the management of inflammatory masses, multifocal strictures and/or stones affecting the pancreatic body or tail, or refractory strictures. However endoscopic therapy may still be attempted initially, with referral for surgical consideration if there is no clinical response after 6–8 weeks [9].

Table 11.1 Endoscopic therapies for chronic pancreatitis

Pancreatic sphincterotomy
Pancreatic duct stone extraction
Direct endoscopic extraction with or without extracorporeal shock wave lithotripsy
Intraductal electrohydraulic or laser lithotripsy
Pancreatic duct stricture dilation and stenting
Pancreatic duct leak stenting
Biliary sphincterotomy
Common bile duct stricture dilation and stenting
Drainage of pancreatic pseudocysts

Pearls and Pitfalls

- When considering endoscopic therapy in patient with chronic pancreatitis (Table 11.1), patient selection is key to successful clinical outcomes. The main indication to pursue ERCP and endoscopic decompression is for the relief of chronic pancreatitis-associated pain or recurrent acute pancreatitis attributed to pancreatic duct obstruction.
- Endocrine insufficiency, exocrine insufficiency, and weight loss are not strong indications to pursue pancreatic decompression as a significant clinical response is not expected to occur in the majority of cases.

- Chronic pancreatitis patients suffering from pain but without evidence of pancreatic duct stone, stricture, or dilation should not be offered endoscopic decompression.
- Patients with obstructing disease (stones and/or strictures) localized to the head/neck/proximal body and those in whom intervention is initiated during early course of pain onset tend to have the best response to endoscopic decompression.
- Tobacco and alcohol cessation should be strongly emphasized to all patients with chronic pancreatitis, as cessation may lead to significant relief of pain, and continued use will result in accelerated disease progression and may reduce the therapeutic response to endoscopic interventions.
- The process of pain development and progression in chronic pancreatitis is complex, typically starting at the local level (i.e., pancreatic inflammation, obstruction, ischemia) and evolving to a more centrally mediated process as the disease course progresses. As such, the inclusion of pain management specialists should be sought out sooner rather than later.
- In patients who are not responsive to therapeutic endoscopy, alternative sources of discomfort should be sought out, including chronic pancreatitis-associated biliary obstruction, luminal obstruction, pancreatic duct disruption/leak, pancreatic exocrine insufficiency, GI dysmotility, small bowel bacterial overgrowth, and occult malignancy.
- Surgical intervention should not be considered a failure on the part of the endoscopist. Surgery has a major role in the management of chronic pancreatitis, and data suggests that it may be the more preferable approach in select patients.
- Patients with chronic pancreatitis are at increased risk for the development of pancreatic adenocarcinoma. Thus, any significant change in pain pattern, weight loss, or clinical course should prompt an evaluation for pancreatic cancer.

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