Chapter

Endoscopic Management of Chronic Pancreatitis

Arda Yavuz

Abstract

Chronic pancreatitis (CP) is a progressive inflammatory disease with several complications. Endoscopic methods make essential contributions to diagnosis and treatment. Endoscopic ultrasound is considered the most sensitive method for diagnosing early CP. Symptoms related to CP, failure of medical therapy, pancreatic changes in imaging (obstructive stones, strictures, and main pancreatic duct [MPD] dilatation), and complications (strictures, pseudocyst, and disruption of MPD) require interventional endoscopic methods. Pancreatic duct stenting could be beneficial when the patient has a dominant stricture in the pancreatic head or a refractory MPD stricture. Before stenting, underlying malignancy should be ruled out by brush cytology. In refractory cases, multiple plastic stents or fully covered self-expanding stents are necessary. Extracorporeal shock wave lithotripsy can also be performed with or without endoscopic retrograde cholangiography for stones in the pancreatic duct. In this case, the stone characteristics, stricture, and exocrine function determine the procedure. Endoscopic ultrasound-guided transmural or transpapillary drainage may be performed for pseudocyst-related CP, which has a success rate similar to surgery. Endosonography-guided celiac plexus block can also be used to treat CP.

Keywords: chronic pancreatitis, pancreatic ductal stones, stricture, pseudocyst, endoscopic ultrasound, celiac plexus block

1. Introduction

Chronic pancreatitis (CP) is a relapsing inflammatory disease characterized by pain, fibrotic strictures in the pancreatic and biliary ducts, calculi in the pancreatic duct, and an increased malignancy risk. Abdominal pain, weight loss, nausea, diarrhea, oily stools, and bloating are the main symptoms of this disease. Exocrine and endocrine insufficiency generally occurs during the late phases of the disease. The annual incidence rate is 5–12/100,000 people [1]. Alcohol consumption is the most common cause, accounting for approximately 65% of all cases [2]. Hereditary factors, congenital anatomical abnormalities, such as pancreas divisum or annulare, and autoimmune inflammation may play a role in the etiology.

Pain, which decreases the quality of life and causes high healthcare costs, is the main indication for endoscopic treatment when lifestyle changes and medical treatment fail. The first treatment step is the cessation of alcohol use and smoking for pain management, followed by the World Health Organization algorithm. Analgesics are

the cornerstone at the beginning; however, when opioids are used, they may cause dependency, opioid-induced constipation, cognitive dysfunction, and opioid-induced hyperalgesia. In such cases, patients should be evaluated by a multidisciplinary team.

As interventional techniques are widely feasible and accepted, they play an important role in managing hepatobiliary diseases. Early diagnosis of CP is possible using endoscopic ultrasound (EUS)-based approaches, and interventional endoscopy can improve the complications of CP. In this chapter, we emphasize the use and importance of endoscopic modalities in the diagnosis and treatment of CP.

2. Endoscopic diagnosis of CP

CP is diagnosed when there is overt endocrine or exocrine dysfunction, atrophy, or calcification observed on imaging. However, these findings are observed in the later stages of the disease. EUS is highly beneficial for diagnosing early CP. Early diagnosis is essential for explaining symptoms, avoiding unnecessary explorations and therapies, investigating etiologies, adequate follow-up, explaining prognostic consequences, genetic evaluation, and appropriate therapy. Moreover, if there is a genetic mutation, total pancreatectomy and islet cell transplantation may be considered for malignancy risk.

EUS provides an opportunity to investigate the pancreatic parenchyma and ductal structures in detail. The parenchymal features of CP on EUS are hyperechoic foci, hyperechoic strands, lobularity, and cysts, and the ductal features are main ductal dilatation, duct irregularity, hyperechoic duct margins, visible side branches, and stones. In traditional EUS systems, the presence of five or more features reliably establishes the diagnosis of CP [3]. An international consensus panel, including 32 internationally recognized endosonographers, developed consensus criteria for EUS features of CP. In this Rosemont classification, the major criteria are hyperechoic foci with shadowing and main pancreatic duct (MPD) calculi and lobularity with honeycombing. Minor criteria are cysts, dilated ducts of ≥3.5 mm, irregular pancreatic duct contour, dilated side branches of ≥1 mm, hyperechoic duct wall, strands, non-shadowing hyperechoic foci, and lobularity with noncontiguous lobules (**Table 1**) [4].

	Parenchymal changes in CP	**Ductal changes in CP**
Major A	Hyperechoic foci with shadowing	MPD calculi
Major B	Lobularity with "honeycombing": ≥3 contiguous lobules measuring minimum 5 mm in length	
Minor	Lobularity without honeycombing	Irregular/ectatic MPD contour
	Hyperechoic foci without shadowing	≥3 dilated side branches
	Cysts	MPD dilatation > 3.5 mm body; >1.5 mm tail
	Hyperechoic stranding	Hyperechoic MPD margin

Consistent with CP: 1 major A and ≥3 minor features, 1 major A and 1 major B features, 2 major A features. Suggestive of CP: 1 major A and ≤3 minor features, 1 major B and ≥3 minor features. Indeterminate for CP: 3–4 minor, 1 major B alone or with <3 minor features. Normal: ≤2 minor without major features.

Table 1.
Rosemont classification.

Recent or active acute pancreatitis can cause overdiagnosis because of parenchymal hyperechoic strands and foci, lobularity, and hyperechoic duct walls. Acute inflammation of the pancreas can also obscure the underlying pancreatic mass. Therefore, EUS should be performed 4 weeks after an acute pancreatitis episode. Moreover, some of these EUS findings can be found normally in individuals as the age and among males, obese individuals, smokers, and alcohol consumers [5–8]. When the diagnosis of CP is debatable, EUS elastography, endoscopic pancreatic function test (ePFT), and distensibility of MPD can be combined with EUS to improve diagnostic success.

EUS elastography has been proposed as a novel and valuable modality for the evaluation of real-time tissue stiffness. It is mainly used in pancreatic tumors but is also highly beneficial in CP. Itoh et al. reported the correlation between parameters in EUS elastography (mean, standard deviation, skewness, and kurtosis) and histological fibrosis in the pancreas [9]. Iglesias-Garcia et al. showed the correlation between the strain ratio and Rosemont classification and exocrine dysfunction, evaluated by the carbon 13 mixed triglyceride breath test [10]. Homogenous stiffness on EUS elastography may also predict autoimmune pancreatitis. Both strain elastography and share wave elastography contributed to the diagnosis of CP using EUS.

The ePFT helped evaluate the exocrine function of the pancreas. In this procedure, gastroscopy was performed, and during the luminal examination, a test dose of secretin was intravenously administered. The gastric fluid was then aspirated as much as possible and discarded, and 3–5 cc post bulbar duodenal secretion was aspirated to rinse the gastric fluid from the suction channel. Furthermore, 3–5 cc duodenal fluid was aspirated as baseline collection; intravenous secretin (0.2 μg/kg) was administered slowly. Every 15 min, the duodenal aspirate was collected for 60 min. If the peak bicarbonate level was <80 mEq/L, then exocrine pancreatic insufficiency was considered. Its sensitivity was 92% and specificity 79% for early CP with normal imaging [11].

Inadequate distension of the MPD after secretin administration is another criterion used for the diagnosis of CP. Pancreatic duct dilatation after secretin stimulation lower than 50% of basal may be considered abnormal. In a study of 41 patients with clinically suspected CP, 77.3% had abnormal ductal compliance [12]. In current reports, additional criteria are suggested for EUS-based multimodal evaluation.

3. Pancreatic ductal stones

Unlike biliary stones, most pancreatic ductal stones are calcified and radiopaque. Stone prevalence increases during CP. In a multicenter study, 62% of 879 patients with CP reported calcified pancreatic stones. Heavy smokers (≥20 cigarettes/day), heavy drinkers (alcohol consumption of >80 g/day), and men have more pancreatic ductal stones than others [13].

Endoscopy, pancreatic sphincterotomy, and basket or balloon dilation allow stone extraction in only 9% of the patients. It is associated with stones of >10 mm, stone impaction, and a diffuse location [14]. Moreover, pancreatic mechanical lithotripsy has a threefold higher complication rate than biliary mechanical lithotripsy. These complications include trapped or broken baskets, traction wire fractures, and pancreatic ductal leak [15]. Furthermore, extracorporeal shock wave lithotripsy (ESWL) allowed successful pancreatic stone clearance in >80% of patients after failed stone extraction with endoscopy [16]. Therefore, primary endoscopy is reserved for selected patients with radiolucent stones or stones of <5 mm in size that are challenging to target with ESWL.

ESWL is a widely accepted treatment modality for radiopaque MPD stones when the MPD stone is larger than 5 mm and located in the head or body of the pancreas. Pancreatic stone clearance is achieved in 90% of the patients with CP; however, this can require multiple sessions [17]. Successful stone fragmentation was defined as stones broken into fragments of ≤2 mm, decreased stone density on radiography, increased stone surface, and heterogeneity of the stone. Ductal clearance could be complete, partial, or unsuccessful if the clearance of stones were <90%, 50–90%, or <50%, respectively. A meta-analysis reported that ESWL provided complete and partial clearance in 70% and 22% of patients, respectively, and pain was absent or mild for 2 years after ESWL in 52.7% and 33.4% of patients, respectively. After the procedure, the quality of life improved in 88.2% of patients [18]. If total stone clearance is achieved, pain relapse within the first 2 years after ESWL is rare. In the present case, half of the patients experienced stone recurrence. Small MPD stones (<5 mm) or radiolucent stones can be treated using endoscopic retrograde cholangiography (ERCP). The use of endoscopic therapy after ESWL is recommended when spontaneous clearance is not achieved. Additional endotherapy and ESWL had no benefit but were associated with longer hospital stays and higher treatment costs [19].

Large or multiple MPD stones or strictures are associated with the need for multiple ESWL sessions. In this case, pancreatic stenting before ESWL can decrease the need for additional ESWL procedures. Solitary stones, MPD stones in the pancreatic head, stones with a density on computed tomography (CT) scans of <820 HU, pancreatic stenting before the procedure, secretin administration before ESWL, and ERCP delayed by 2 days are related to better outcomes [20, 21]. Pancreatic pseudocysts are not related to MPD stone clearance [22]. The most common complication of ESWL is pancreatitis, asymptomatic hyperamylasemia, hematuria, mucosal injury, infection, skin erythema, tenderness, acute stone incarceration in the papilla, bleeding, and perforation could also be seen [23]. Contraindications for ESWL include non-correctable coagulopathy, pregnancy, and the presence of bone, calcified vessels, and lung tissue in the shockwave way [24].

Intracorporeal lithotripsy using electrohydraulic or laser lithotripsy under peroral pancreatoscopy, is recommended when ESWL is unavailable or stones are not fragmented after ESWL. A total of 43–100% of patients had successful MPD clearance in a systematic review. In the most extensive study of 38 patients (280 endoscopic therapy sessions, 88 of them with pancreatoscopy), complete and partial stone clearance was 24% and 10%, respectively [25, 26].

4. MPD strictures

In cases of stenosis in the MPD, possible malignancy should be ruled out using high-quality pancreatic CT or magnetic resonance cholangiopancreatography (MRCP). Brush cytology should be performed, and biopsy should be performed if necessary. A dominant MPD stricture is characterized by upstream MPD dilatation of ≥6 mm, prevention of contrast medium outflow alongside a 6-Fr catheter inserted upstream from the stricture, and abdominal pain during continuous infusion of a nasopancreatic catheter inserted upstream from the stricture with 1 L saline for 12–24 h. Technical success was defined as stent insertion across the dominant MPD stricture. This management aims to decompress the MPD, improves pain, dilates the stricture, and allows stone clearance after ESWL. A prospective non-randomized study on patients with dominant strictures reported less pain in the temporary pancreatic stenting group during a 5-year follow-up (15% vs. 50%) [27]. These strictures

are generally single in >80% of the patients. Temporary single pancreatic stents provide 9–50% resolution and 67.5% pain relief [28, 29].

A refractory stricture was defined as symptomatic persistent dominant strictures or relapse after 1 year of single pancreatic stenting. Refractory strictures can be treated with multiple side-by-side stents, self-expanding metallic stents (SEMSs), or surgery. Temporary insertion of multiple side-by-side stents provided high stricture resolution and pain relief of 89.5% and 77.1%, respectively, during a 9.5-year follow-up [30]. SEMS insertion also achieved high pain improvement in 37–88% of all patients in a follow-up of 3–4 years [31]. Unlike SEMS, uncovered and partially covered stents are not suggested for migration risk.

Pancreatic sphincterotomy is mainly suggested if biliary drainage is necessary to facilitate MPD cannulation. Sphincterotomy is not mandatory for pancreatic stenting. Pancreatic stenting is performed mostly after ESWL if there is a pancreatic stone. The technical success of a single pancreatic stent is approximately 92%. In 18 series of 811 patients, the mean stenting duration was 10.6 months [32].

Multiple side-by-side pancreatic stents are another treatment option for refractory cases. Different stent designs are used: straight, winged, and s-shaped, with side holes. Stents with large side holes are suggested to have a low occlusion risk. The stent diameter is also critical. Patients with CP with ≤8.5-Fr pancreatic stents are 3.2 times more often hospitalized with abdominal pain than patients with CP with a 10-Fr pancreatic stent [33, 34].

The "on-demand" stent exchange strategy is based on clinical and laboratory evaluation at 6-month intervals, such as secretin-enhanced (S)-MRCP, abdominal ultrasound, abdominal radiography, and blood/urinary lipase analysis. However, this policy, in four series of 288 patients, reported a 5.2% rate of pancreatic sepsis [35]. Nevertheless, 12 series of 521 patients in whom the pancreatic stent was changed every 3 months regularly reported no septic complications [36].

Mild pancreatitis and worsening pancreatic pain are the most common short-term complications after plastic stenting, followed by sepsis, cholangitis, and post-sphincterotomy bleeding. During follow-up, proximal and distal stent migration was reported in 2.7% and 3.6% of the cases, respectively. Stent-induced ductal lesions were observed in 18% of the cases, and the mortality rate was 0.4% (7/1620). Complications after SEMS insertion include migration (15–46%), de novo strictures (16–27%), severe pain (7–20%), and stent removal (15%).

EUS-guided access and drainage is another treatment modality for patients with symptomatic MPD obstruction and failed transpapillary drainage. After puncturing the MPD through the gastric or duodenal wall, transpapillary drainage can be facilitated with a guidewire (rendezvous technique), transmural drainage with a plastic stent, or a fully covered SEMS (FCSEMS) can be used to achieve successful pain relief. This is one of the most challenging EUS-guided therapies. Failed EUS-guided access and drainage occur in 10% of cases, and complications such as severe pancreatitis, perforation, bleeding, and hematoma can occur [37]. This procedure is suggested only in tertiary centers after multidisciplinary discussion.

5. Benign biliary strictures

Biliary strictures occur during CP in 3–23% of all patients. Peribiliary fibrosis or pressure of the pancreatic pseudocyst (PPC) may play a role in pathophysiology. They can be asymptomatic or present with jaundice, cholangitis, or choledocholithiasis.

Jaundice could be resolved in 20–50% of patients in 1 month spontaneously [38]. However, secondary biliary cirrhosis is frequent (7.3%), and asymptomatic serum alkaline phosphatase and/or bilirubin for longer than 4 weeks predicts the need for endoscopic management [39]. As in all strictures of the hepatobiliary tract, malignancies should be excluded.

Single plastic stents are ineffective for the long-term management of biliary strictures. Multiple side-by-side plastic stents or FCSEMSs are widely used for endoscopic treatment. These stents have been suggested as the primary treatment for benign biliary strictures in the absence of associated lesions (such as inflammatory masses). Moreover, the success of the treatment was evaluated after 12 months or three endoscopic procedures. A single retrospective study comparing surgery and endoscopy reported that endoscopy had lower morbidity (21%, 83%) and success (15%, 66%) in the second year of treatment, which could be related to accepting incomplete resolution as a failure [40]. Uncovered SEMSs were not considered because of their poor long-term results. Multiple side-by-side plastic stents and FCSEMSs have similar success (88%, 90.9%) and morbidity (23.3%, 28.6%) rates [41]. If the stricture does not respond to endoscopic therapy, hepaticojejunostomy remains a valid treatment option.

6. Pancreatic pseudocysts (PPCs)

One-third of the patients with CP developed PPCs. In the evaluation, potentially malignant mucinous neoplasms should have been excluded. Transmural drainage, transpapillary drainage, or a combination of these techniques can be used in endoscopic treatment. The transpapillary route is only appropriate for half of the PPCs, which are small (<50 mm) and communicate with the MPD in the head or body of the pancreas [42]. Clinical success is defined as resolving the symptoms with complete resolution of PPC or a decrease in PPC to less than 2 cm [43]. Spontaneous regression of chronic PPCs is rare and typically occurs in PPCs of <4 cm. Symptomatic PPCs that cause abdominal pain, gastric outlet obstruction, early satiety, jaundice, weight loss, infection, or bleeding should be treated. Progressive growth of a PPC is an indication for some authors; however, others suggest follow-up for symptoms. If significant vessel compression occurs due to a PPC, the risk-benefit ratio should be checked before intervention.

Endoscopic drainage of PPCs has higher clinical success, shorter hospital stay than percutaneous drainage, and similar morbidity and recurrence rates [44]. Percutaneous drainage seems to be a better option when a PCC is not endoscopically accessible. A meta-analysis of 255 patients reported that surgery had a higher success rate, higher hospital cost, and extended hospital stay with similar morbidity and recurrence rates [45]. Current guidelines suggest endoscopic treatment for an uncomplicated PPC in CP over percutaneous or surgery, if accessible.

S-MRCP is a suggested method for evaluating the PPC and MPD anatomy before the procedure, which has an accuracy of >90% for diagnosing MPD rupture. In the management, transmural drainage is adequate in the absence of MPD rupture. In cases of partial rupture, treatment should include bridging the rupture with a stent. Complete MPD rupture (disconnected pancreatic duct syndrome) is associated with a high recurrence rate. Therefore, long-term indwelling of transmural double pigtail stents should be considered [46]. ERCP is regarded as the gold standard for diagnosing MPD rupture and carries an infection risk for a patient with a sterile PPC [47].

Transmural drainage can be performed using EUS or a conventional approach. EUS-guided transmural drainage has a higher technical success rate; however, there are no differences in the complications or clinical success. This difference occurs because of non-bulging collections, observed in approximately half of all PPCs [48]. Double pigtail plastic stents are generally preferred for PPCs. The number and diameter of these stents were not associated with clinical success [49]. biliary FCSEMSs could also be preferred when disconnected pancreatic duct syndrome is ruled out, and the duration is expected to be lesser than 6 weeks. A double pigtail plastic stent should be inserted through the biliary FCSEMS to prevent migration. Current guidelines suggest retrieval of transmural plastic stents at least 6 weeks after PPC regression; however, long-term indwelling of transmural plastic stents is needed for disconnected pancreatic duct syndrome. Retrospective studies have reported that long-term indwelling stents are highly effective and low PPC recurrence has been reported. PPC recurrence is associated with stent migration within 6 months and MPD disruption at the pancreatic head. Lumen-apposing metal stents can also be used for PPC in CP; however, it is less cost-effective than plastic stents.

Extrahepatic portal hypertension occurs during CP in ≥15% of all patients [50]. In this case, the EUS-guided transmural route was suggested. In two case series with 26 patients, the bleeding rate was 4% [51]. A pseudoaneurysm can occur in 1–10% of the cases during the course of CP [52]. Arterial embolization is suggested before the endoscopic drainage of a PPC.

7. Endosonography-guided celiac plexus block (CPB)

Once medical treatment options fail, persistent severe pancreatic pain can be treated endoscopically or surgically. The CPB can be used in patients with significant abdominal pain who have a poor general condition and have not responded to endoscopic treatment. In this technique, a combination of glucocorticoids and a long-acting local anesthetic (generally bupivacaine) can be administered using CT or EUS. EUS guidance is safer, more effective, and longer-lasting than CT. Bilateral injection (bupivacaine 0.25% [4 ml each side], followed by triamcinolone 80 mg [40 mg each]) and, central or unilateral injection (bupivacaine 0.25% [8 ml], followed by triamcinolone 80 mg) could be used. Bilateral injection seems to be an optimized distribution; however, supporting data are lacking.

It is unclear which patients derive the benefits of CPB. A long duration of pain may negatively affect the outcome because of permanent neuroplastic changes. Narcotic dependence is another factor that makes the treatment challenging. It is difficult to determine whether it is a hyperalgesia-related opioid or ineffective treatment, which also predicts a poor outcome. In a meta-analysis, it has been reported that EUS-guided CPB can relieve pain in 51–59% of patients [53]. However, it is reportedly inferior to surgical management. In a cohort study of 248 patients with CP, CPB was associated with pain relief in 177 patients (76%), with a median duration of 10 weeks [54]. The effect of CPB generally lasts for 3 months, after which the pain may worsen. It could be repeated for 3 or 6 months if it is beneficial in the initial celiac intervention. Nerve destruction may cause an increase in pain, hypotension, hemorrhage, infection, and neurological complications.

Celiac plexus neurolysis and absolute alcohol injection are used in pancreatic malignancies. However, it is not recommended for CP because of its potentially severe side effects. Due to the desmoplastic reaction, the possible future pancreatic surgery

may get complicated. There is no routine recommendation or consensus for CPB or neurolysis for managing CP in the current guidelines.

8. Conclusions

The impact of endoscopy on managing CP is increasing. EUS-based criteria are the gold standard for diagnosing early CP. Early recognition of CP can change patients' futures. ESWL is the primary treatment of choice for patients with pancreatic stones. The strictures should be evaluated for possible malignancies. Plastic stents are feasible and cost-effective for treating benign strictures. Complications such as PPC can be successfully managed with transmural drainage. CPB is an alternative treatment option for opioid-resistant pancreatic pain. Surgery remains a treatment option after repeated procedures and in challenging refractory cases.

Conflict of interest

The author declares no conflict of interest.

Notes/thanks/other declarations

None.

Acronyms and abbreviations

CP	chronic pancreatitis
CPB	celiac plexus block
CT	computed tomography
ePFT	endoscopic pancreatic function test
ERCP	endoscopic retrograde cholangiopancreatography
ESWL	extracorporeal shock wave lithotripsy
EUS	endoscopic ultrasound
FCSEMS	fully covered self-expanding metal stent
MPD	main pancreatic duct
PPC	pancreatic pseudocysts
S-MRCP	secretin-enhanced magnetic resonance cholangiopancreatography

Appendices and nomenclature

None.

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Author details

Arda Yavuz
Department of Gastroenterology, Istanbul Medeniyet University, Istanbul, Turkey

*Address all correspondence to: ardayavuz55@hotmail.com

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