

Recent advances in the diagnosis and management of chronic pancreatitis

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Chronic pancreatitis is a chronic condition characterized by pancreatic inflammation that causes fibrosis and the destruction of exocrine and endocrine tissues. Chronic pancreatitis is a progressive disease, and no physiological treatment is available to reverse its course. However, with advances in medical technology, the existing diagnostic and treatment methods for chronic pancreatitis are evolving. Managing patients with chronic pancreatitis is challenging and necessitates a multidisciplinary approach. In this review, we discuss the recent advances in the diagnosis and management of chronic pancreatitis and introduce future alternative modalities.

Keywords: Pancreatitis, chronic; Diagnosis; Therapeutics; Endoscopy

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INTRODUCTION

Chronic pancreatitis is defined as progressive inflammatory destruction of the pancreatic parenchyma and replacement with fibrous tissue that eventually leads to irreversible and permanent dysfunction of the endocrine and exocrine pancreatic gland [1,2]. Most cases of acute pancreatitis are self-limited and improve without complications, but a recent meta-analysis reported a 22% chance of recurrence and a 10% chance of developing chronic pancreatitis after an acute pancreatitis attack. In addition, 36% of patients with recurrent acute pancreatitis progress to chronic pancreatitis [3]. As in

patients with chronic pancreatitis, the quality of life of patients with recurrent acute pancreatitis is impaired due to severe pain and related disability [4].

Chronic pancreatitis is an end-stage diagnostic category with multiple etiologies (Table 1). The underlying causes (e.g., alcohol and hypertriglyceridemia) should be treated first for management of the disease, as there are no approved medications that reverse the underlying fibrotic nature of the disease.

Chronic pancreatitis is usually diagnosed based on previously determined clinical information, imaging findings, and/or pancreatic functional test results [2,5]. Although the diagnosis of chronic calcific pancreati-

Table 1. Etiologies of chronic pancreatitis

Alcohol abuse
Ductal obstruction (tumors, stones)
Trauma
Pancreas divisum
Hypertriglyceridemia
Autoimmune pancreatitis
Idiopathic
Tobacco use
Hereditary pancreatitis

tis is usually apparent, early detection of the disease is challenging and often based on a combination of clinical presentation, imaging findings, and pancreatic function test results [2]. Computed tomography (CT), transabdominal ultrasound, endoscopic retrograde cholangiopancreatography (ERCP), endoscopic ultrasonography (EUS), and magnetic resonance imaging (MRI) are used to evaluate morphological changes in the pancreas. Secretin stimulation endoscopic pancreatic function tests (intraductal secretin stimulation test at ERCP and duodenal juice collection at EUS), fecal elastase, serum trypsin or secretin-enhanced magnetic resonance cholangiopancreatography (MRCP) are used to measure the degree of pancreatic exocrine dysfunction. However, due to a lack of effective methods to reverse chronic pancreatitis, an accurate diagnosis is important during the early stages of chronic pancreatitis so that risk factors may be mitigated to decrease the chance of disease progression. Unfortunately, the modalities used to diagnose early-stage chronic pancreatitis show low sensitivity or false-positive outcomes [2,5-7]. Therefore, most patients with early-stage chronic pancreatitis experience a delayed definitive diagnosis and do not receive pancreas-specific management until many years after symptom onset.

In this review, we describe recent advances in the diagnosis and management of chronic pancreatitis, focusing on the results of diagnostic and treatment modalities, and introduce alternative treatments. The problems with managing patients with chronic pancreatitis are difficult to solve, and further efforts using a multidisciplinary approach are warranted.

UPDATE IN THE DIAGNOSIS OF CHRONIC PANCREATITIS

Fecal elastase level

Indirect pancreatic function testing is used in clinical practice to screen for pancreatic disease. However, this method has a low sensitivity for detecting mild pancreatic disease. Among the indirect pancreatic function tests, the fecal elastase test is used most commonly in clinical practice. However, the major limitations of the fecal elastase test are its lower sensitivity and specificity compared with endoscopic direct pancreatic function testing [8].

The accuracy of the fecal elastase test for detecting an insufficiency in the exocrine pancreas depends on the selected cut-off value. Many studies have used a cut-off level of $< 200 \mu\text{g/g}$ stool, but this level represents a high false-positive rate [9]. Lowering the cutoff to $< 100 \mu\text{g/g}$ stool improves the specificity but decreases the sensitivity [10].

Serum amylase and lipase levels

As mentioned previously, most patients with early-stage chronic pancreatitis experience delays in receiving a definitive diagnosis. Diagnosing early-stage chronic pancreatitis remains a challenge in clinical practice. Should we recommend routine and regular follow-up with expensive tests to all patients with suspected symptoms of chronic pancreatitis? No specialist can answer this question with confidence, and no investigative algorithm of screening modalities and follow-up intervals has been recommended worldwide. The American Pancreatic Association recommends that patients should not be classified as having chronic pancreatitis until definitive diagnostic features are evident, and it proposes a diagnostic sequential algorithm that advances from a noninvasive to a more invasive diagnostic approach [11]. For this reason, a simple blood test would remain of high value in the diagnosis of chronic pancreatitis.

Chronic pancreatitis involves irreversible damage to the pancreas by recurring inflammatory processes leading to fibrosis with destruction of the exocrine and endocrine tissues. This damage may affect pancreatic enzyme synthesis and secretion, resulting in low serum enzyme levels. The correlation between severe exocrine insufficiency and low serum pancreatic enzyme levels

is well-known. Previous reports noted lower serum levels of pancreatic enzymes, particularly lipase, in up to 50% of patients with chronic pancreatitis [12-15]. The serum trypsin assay has been suggested as a laboratory test because serum trypsin levels may be low in patients with advanced chronic pancreatitis [16,17]. However, in clinical practice, the serum trypsin assay is not routinely used because it is two to four times more expensive than the serum amylase and lipase tests, and the results are obtained in several days. Although the role of elevated serum amylase and lipase levels as a valid tool for diagnosing acute pancreatitis and acute episodes of chronic pancreatitis is well-established, low serum amylase and lipase levels as a screening test for chronic pancreatitis is worth considering.

Two recent studies reported low serum amylase and lipase levels in patients with advanced chronic calcific pancreatitis or non-calcific chronic pancreatitis compared with healthy controls [18,19]. According to those studies, when serum amylase and lipase levels are lower than the normal range, the specificity to diagnose chronic pancreatitis is 100%, once the patient's status with post-pancreatectomy (partial or complete) are excluded. Therefore, this result should not be overlooked, because the probability of underlying pancreatic disease is high if serum amylase and lipase levels are below the normal range in subjects, warranting further testing for an underlying pancreatic disease.

Magnetic resonance imaging

Although the most sensitive test and diagnostic gold standard for (early) chronic pancreatitis is the endoscopic pancreatic function test, it is invasive and used only in some large referral centers [20]. MRI with MRCP is a useful tool to evaluate the pancreatic parenchyma, pancreatic ductal changes, and surrounding tissues, especially in cases of chronic pancreatitis [21]. It is also an excellent non-invasive test for diagnosing ductal anomalies, such as anomalous union of the pancreatobiliary duct, pancreas divisum, pancreas ductal strictures, and other ductal obstructions [22]. In particular, secretin-enhanced MRCP improves visualization of the pancreatic duct to ensure better detection of congenital anomalies and allows qualitative measurements of exocrine pancreatic function (Fig. 1) [23-25].

Recent studies have reported that the presence of

two or more abnormal features of secretin-enhanced MRCP are associated with high sensitivity (88%) and specificity (78%) for predicting severe fibrosis and that secretin-enhanced MRCP has a potential role in the detection of exocrine dysfunction in patients with early chronic pancreatitis and recurrent acute pancreatitis [26-28]. MRI can also detect signal changes in the parenchyma related to chronic pancreatitis. Changes in the T₁-weighted MRI signal of the pancreas are correlated with pancreatic exocrine function [27]. This observation has been linked to the loss of acinar cells, which contain T₁ hyperintense, protein-rich cytoplasm being replaced by fibrosis. The T₁ mapping technique measures the specific T₁-relaxation time of the tissues; therefore, it should be useful to diagnose chronic pancreatitis with higher accuracy using the same principle and providing pure T₁ information [29]. Extracellular volume imaging dichotomizes the tissues into intra- and extracellular fractions and calculates the extracellular fraction, which increases as a result of repetitive adverse tissue remodeling leading to tissue fibrosis. The extracellular volume is useful for evaluating chronic pancreatitis [29]. All of this information obtained from MRI and secretin-enhanced MRCP is available without radiation or anesthesia. In the future, further advancements in MRI technology are likely to be developed, and prospective studies will be conducted to better understand the merits of secretin-enhanced MRI/MRCP to determine changes that occur in early chronic pancreatitis [30]. At that time, it may be a good non-invasive diagnostic tool to monitor the progression of acute pancreatitis, recurrent acute pancreatitis, and early-stage chronic pancreatitis [8].

Genetic testing and consultations

Hereditary pancreatitis is defined as the development of pancreatitis in more than one person in a family for more than two generations or pancreatitis associated with genetic inheritance of a pathogenic mutation in the cationic trypsinogen protease serine 1 (*PRSS1*) gene [31]. Although most hereditary pancreatitis cases are associated with an autosomal dominant pattern of inheritance, familial pancreatitis is a broader term used to describe families with pancreatitis with an incidence greater than that expected in the general population, which may or may not be due to genetic defects [31].

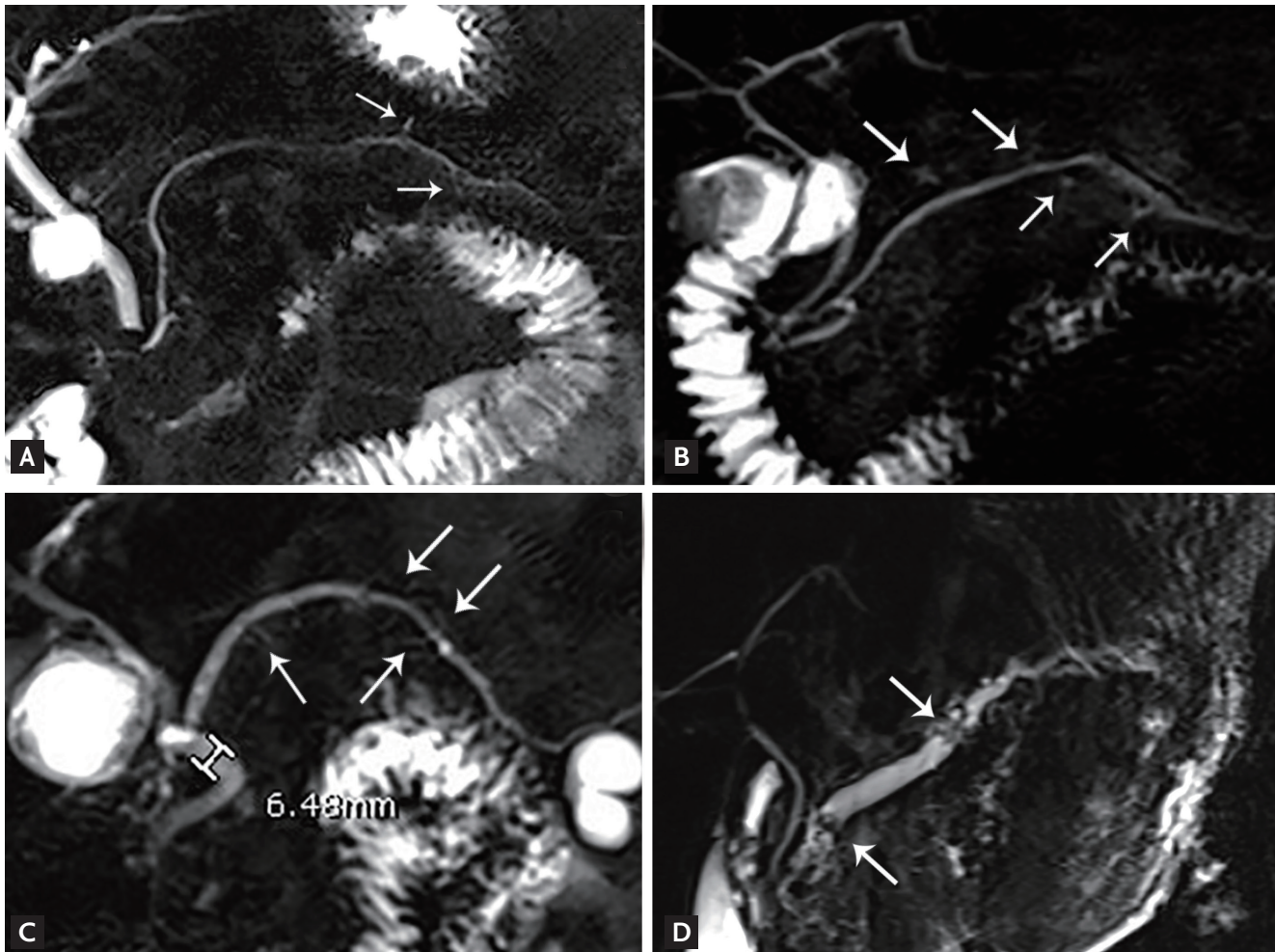


Figure 1. (A) Equivocal chronic pancreatitis (Cambridge grade 1). A 56-year-old male with a history of one documented episode of pancreatitis. Coronal secretin-enhanced magnetic resonance cholangiopancreatography (MRCP) shows two ectatic side branches in the region of the pancreatic body (arrows). The main pancreatic duct is of normal diameter. (B) Mild chronic pancreatitis (Cambridge grade 2). (C) Moderate chronic pancreatitis (Cambridge grade 3). A 51-year-old female patient with recurrent acute pancreatitis. Coronal secretin-enhanced MRCP image shows dilated main pancreatic duct measuring 6.48 mm. In addition, there are more than three ectatic side branches (arrows). (D) Severe chronic pancreatitis (Cambridge grade 4). An 18-year-old patient with a history of chronic hereditary pancreatitis. Coronal secretin-enhanced MRCP image shows multiple intraductal calculi (arrows) causing dilatation of the main and side-branch ducts.

A comprehensive medical history should be recorded to help identify the exact etiology of chronic pancreatitis. In particular, genetic testing should be performed in patients with a family history of the disease or disease onset at a relatively young age (< 20 years) that can be lifelong [32]. Genetic testing should include testing for mutations in *PRSS1*, serine protease inhibitor Kazal type 1 (*SPINK1*), carboxypeptidase A1 (*CPA1*), chymotrypsin C (*CTRC*), and calcium-sensing receptor (*CASR*) and may include screening for variants of the cystic fibrosis

transmembrane conductance regulator (*CFTR*) gene [31].

Genetic testing is important in patients with suspected hereditary pancreatitis because of the high incidence of pancreatic cancer, with a cumulative risk of up to 53 times that of the general population by 70 years of age [33,34]. A recent case-control and cohort study of 402 patients reported that only idiopathic and hereditary pancreatitis, but not alcoholic chronic pancreatitis, are risk factors for pancreatic cancer [35]. Some authorities recommend total pancreatectomy and islet autotransplan-

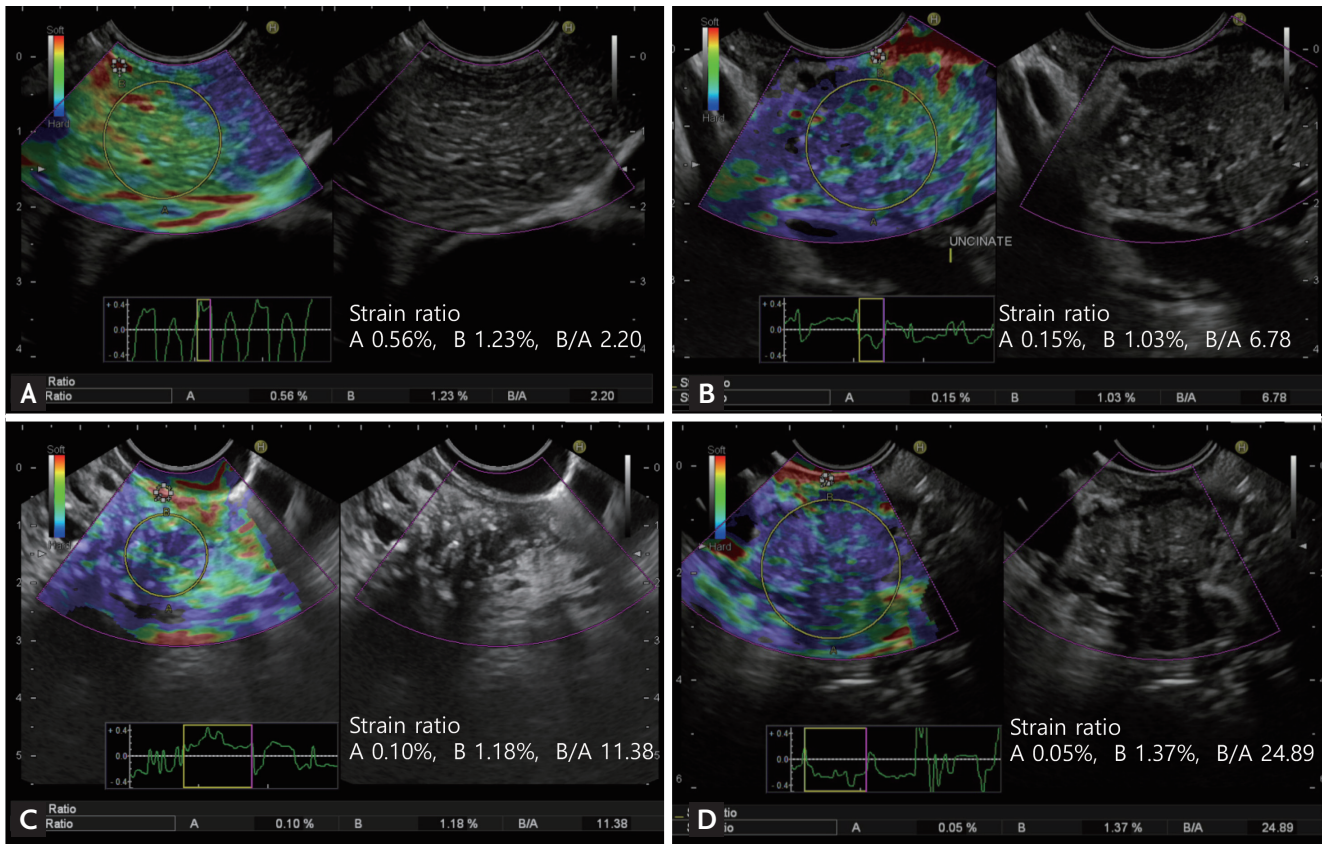


Figure 2. Representative images of quantitative endoscopic ultrasonography elastography. (A) Normal pancreas with a green-colored homogenous pattern (strain ratio, 2.20). (B) Early-stage chronic pancreatitis with a heterogenous pattern (strain ratio, 6.78). (C) Chronic pancreatitis with a heterogenous pattern (strain ratio, 11.38). (D) Pancreatic cancer with a blue-colored homogenous pattern (strain ratio, 24.89).

tation (TP-IAT) as an early treatment in the absence of other better treatments.

Genetic testing should be considered if one or more of the following criteria are met [31]: (1) recurrent acute pancreatitis or chronic pancreatitis of uncertain etiology; (2) early age at onset of idiopathic chronic pancreatitis (< 25 years); (3) unexplained pancreatitis during childhood; (4) family history of idiopathic chronic pancreatitis, recurrent acute pancreatitis, or childhood pancreatitis involving first- or second-degree relatives; (5) family members of individuals with an identified pathogenic gene mutation associated with hereditary pancreatitis.

Confirmed implicated genetic abnormalities serve a role in family planning. Thus, genetic counseling should be offered in tandem with genetic testing. Specific therapy for individual gene abnormalities is largely

not available.

EUS and EUS elastography

EUS is the most sensitive endoscopic test for diagnosing chronic pancreatitis and is recommended for diagnosing early stages of the disease or complications that may accompany disease progression, such as stones, strictures, or concurrent pancreatic malignancy [32]. According to a recent analysis of the Rosemont criteria, which is a scoring system for EUS to diagnose chronic pancreatitis, a “normal” classification is very poorly correlated with histopathology, whereas the classification “suggestive” of chronic pancreatitis is highly associated with histopathology [36]. However, another study of the same cohort reported a very poor correlation between EUS features and the degree of fibrosis determined by histopathology, suggesting that EUS is less accurate

than previously believed [37]. Therefore, EUS alone is not recommended to establish a clinical diagnosis of chronic pancreatitis; the diagnosis should be made in concert with the clinical presentation, laboratory analysis, and cross-sectional imaging [38].

EUS elastography, which may overcome some limitations of EUS, is used to evaluate tissue strain (stiffness) and provides semiquantitative data. The correlation between EUS criteria and the tissue strain ratio has been demonstrated by measuring pancreatic fibrosis to diagnose chronic pancreatitis (Fig. 2) [39-41]. EUS elastography may play a role in the diagnosis of chronic pancreatitis in the future, but further prospective and histopathologically matched studies are required.

UPDATE ON THE TREATMENT OF CHRONIC PANCREATITIS

Therapy for pancreatic exocrine insufficiency and malnutrition

Although chronic uncontrolled pain is the main symptom in most patients with chronic pancreatitis, malnutrition is also a primary problem associated with quality of life and long-term survival. Exocrine and endocrine pancreatic insufficiency and major complications can affect the mortality of patients with chronic pancreatitis [42,43]. It may be difficult to assess nutritional status in patients with chronic pancreatitis; thus, multiple markers should be considered [44]. A thorough nutritional evaluation may include anthropometric parameters (body weight, body mass index, and weight loss), biochemical nutritional markers (plasma proteins [albumin, prealbumin, retinol-binding protein, and transferrin], fat-soluble vitamins, magnesium, zinc, and visceral fat), and imaging (dual-energy X-ray absorptiometry for bone mineral density measurement and CT for muscle mass and visceral fat measurements) [45].

Malnutrition and pancreatic exocrine insufficiency should be monitored as chronic pancreatitis progresses. As pancreatogenic (type 3C) diabetes may occur at a high rate, glucose and glycosylated hemoglobin levels should be measured longitudinally. Undiagnosed diabetes can significantly affect the nutritional status of these patients [44]. Pancreatic exocrine insufficiency appears clinically as steatorrhea, weight loss, malnutrition, metabolic

bone disease, and vitamin and mineral deficiencies. As a result, these patients are at risk of weight loss and malnutrition due to fat maldigestion and malabsorption. Long-term fat malabsorption may also cause deficiencies in calcium, magnesium, zinc, thiamin, folic acid, and fat-soluble vitamins (A, D, E, and K) [10]. The risk of osteoporosis is three times higher in patients with chronic pancreatitis than in the general population, even in patients with adequate excretion function [46].

As the normal pancreas produces at least 90,000 US Pharmacopeia (USP) units (1 USP unit equals 1 European Pharmacological Unit) of lipase per meal, alternative therapies aim to provide a goal of 90,000 USP units per meal. The total dose to reach 90,000 is not always necessary because some patients have some residual pancreatic secretions, and gastric lipase can compensate to some extent. A minimum lipase dose of 40,000 to 50,000 USP units is recommended with full meals, and half that dose is needed with snacks to normalize digestion [10,32]. Enteric-coated oral replacement capsules are generally preferred. Pancreatic enzyme replacement therapy has been proven effective with respect to fat and protein digestion, symptoms, quality of life, and nutritional status [45,47,48]. Acidic pH and bacterial overgrowth in the intestine play a major role in the lack of an appropriate response. Therefore, adding a proton pump inhibitor before meals to protect denaturation by gastric acid, or special antibiotic treatments for small intestinal bacterial overgrowth should be considered in cases of an unsatisfactory clinical response to the standard dose of pancreatic enzyme replacement therapy [45,47,49].

Endoscopic treatment in patients with dominant main pancreatic duct stricture and stones

Main pancreatic duct benign strictures occur in approximately 20% of patients with chronic pancreatitis. In the past, these strictures were managed by resection or bypass drainage surgery. Symptomatic strictures, which can be traversed using a guidewire during ERCP, are now generally managed by serial plastic or metallic pancreatic duct stenting. After 6 to 12 months of an indwelling stent(s), stricture patency is generally established. The long-term durability of this therapy requires further follow-up. Tissue sampling to assure benign stricture is needed.

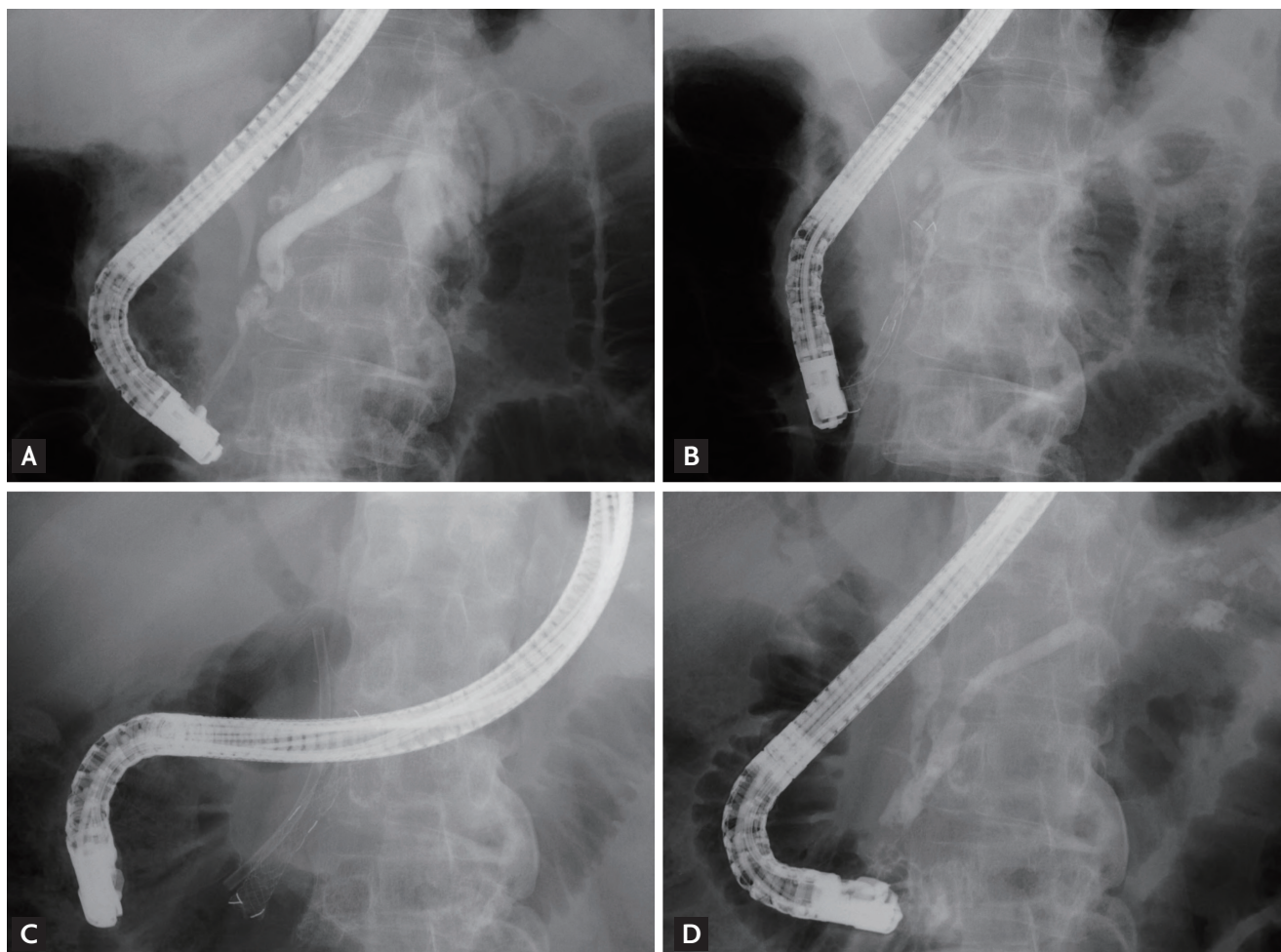


Figure 3. Representative cases of insertion of a fully covered self-expandable metal stent (FC-SEMS) for a main pancreatic duct stricture. (A) Pancreatographic image showing dilation of the main pancreatic duct with a severe stricture at the head of the pancreas. (B) Insertion of a FC-SEMS through the stricture of the main pancreatic duct. (C) Insertion of a plastic stent through the stricture of the distal biliary duct. (D) Follow-up cholangiopancreatography image showing further improvement of the stricture in the main pancreatic duct compared with the stricture in the distal biliary duct.

Main pancreatic duct stones occur in 10% to 20% of chronic pancreatitis patients. Again, in the past, these were treated with surgical resection or decompression. Similar to managing a kidney stone, extracorporeal shock wave lithotripsy has been applied to pancreatic head/body stones. One to three sessions are generally required to fragment the stones. ERCP is then performed to clear the fragments. Patients with the best response to endoscopic treatment are those with obstructing stones located within the pancreatic head. Some studies have used intraductal laser or electrohydraulic lithotripsy with direct peroral pancreatoscopy, with technical success rates of 43% to 100% in clearing pancreatic stones [50,51]. Further comparative studies

are needed.

Endoscopic treatment to remove stones is more difficult if the stones are accompanied by a dominant main pancreatic duct stricture. Approximately 18% of patients with chronic pancreatitis have a main pancreatic duct stricture [51]. Ductal pancreatic stones with an obstruction are accompanied by a main pancreatic duct stricture in 60% to 70% of cases [52,53]. Although there are different stent types, a plastic stent larger than 8.5 Fr should be replaced periodically for at least 1 year to prevent recurrence while resolving the stricture [32]. Complete and successful removal of the stones after resolving the stricture by inserting multiple plastic stents requires much time and effort, and the patient may

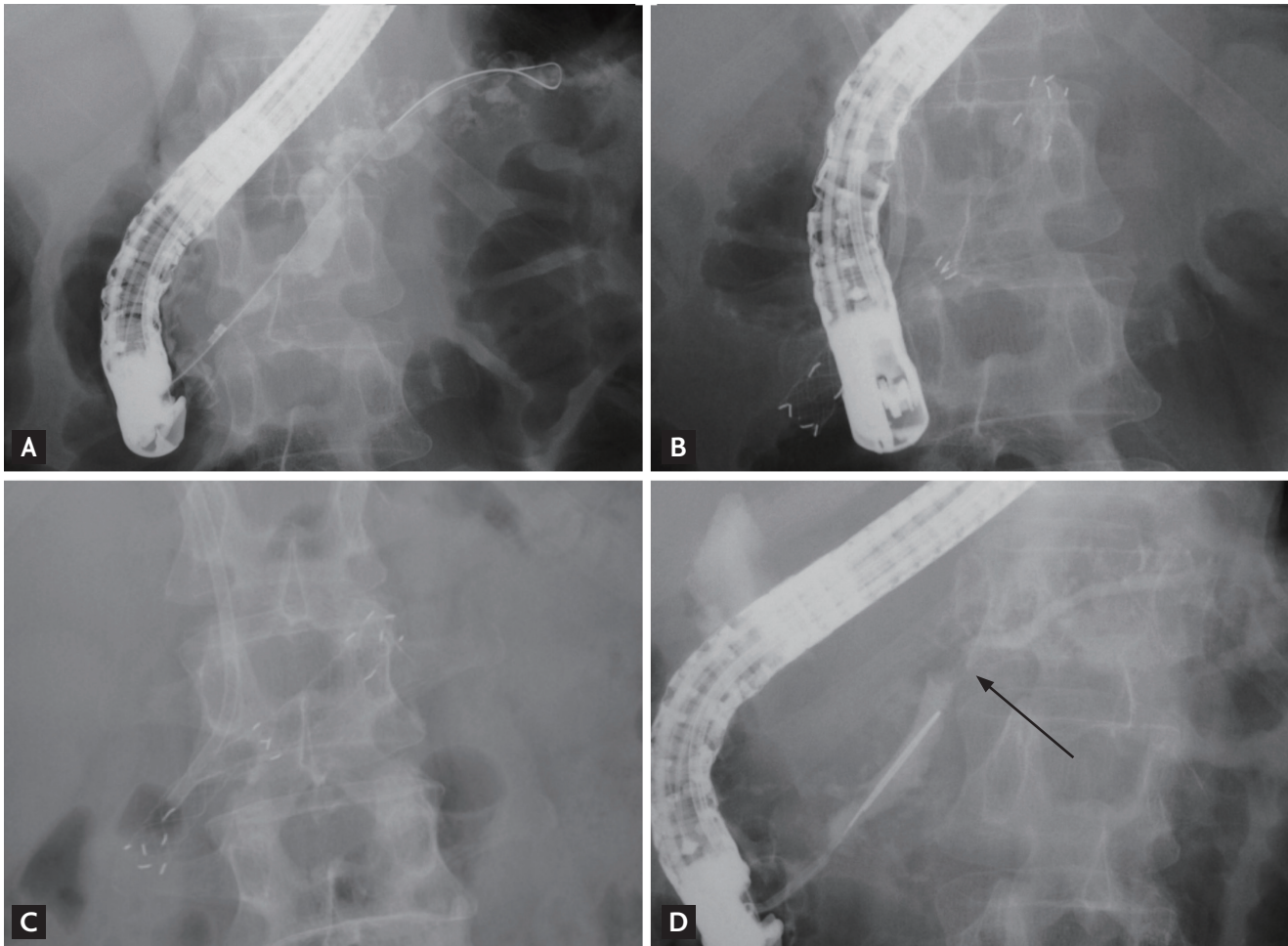


Figure 4. *De novo* stricture at the main pancreatic duct after insertion of a fully covered self-expandable metal stent (FC-SEMS). (A) Pancreatographic image showing dilation of the main pancreatic duct with a stricture in the head of the pancreas. (B) Insertion of a FC-SEMS through the stricture of the main pancreatic duct. (C) Simple abdominal plain X-ray image showing the fully expanded FC-SEMS in the main pancreatic duct. (D) Follow-up pancreatography image showing the *de novo* stricture (arrow) just above the upper end of the previously inserted FC-SEMS.

decide to terminate the treatment midway. To reduce the number of ERCP sessions and treatment duration, resolving a stricture using fully covered self-expandable metal stents (FC-SEMSs) has been attempted; the results showed a very high success rate and long-term efficacy (Fig. 3). However, long-term complications, such as stent migration and *de novo* strictures, should be further evaluated in prospective studies involving larger sample sizes (Fig. 4) [54-57].

Alternative methods are used during ERCP when a guidewire or stone retrieval instrument cannot be passed through the main ductal stricture or beyond an impacted ductal stone in the main pancreatic duct. EUS-guided antegrade FC-SEMS insertion or

EUS-guided rendezvous cannulation can be attempted (Figs. 5 and 6). A retrospective cohort analysis reported a high technical success rate of SEMS insertion for EUS-guided pancreatic duct drainage [58]. However, EUS-guided pancreatic duct intervention has a relatively lower success rate than that of previous reports due to the small diameter of the pancreatic duct, fibrotic pancreatic parenchyma, relatively short guidewire length, and lack of dedicated devices [59,60]. As there are no standard indications or methods for EUS-guided pancreatic duct intervention, more data about this procedure are needed.

Dorsal duct drainage via the minor papilla is another method to treat refractory obstructing chronic calcific

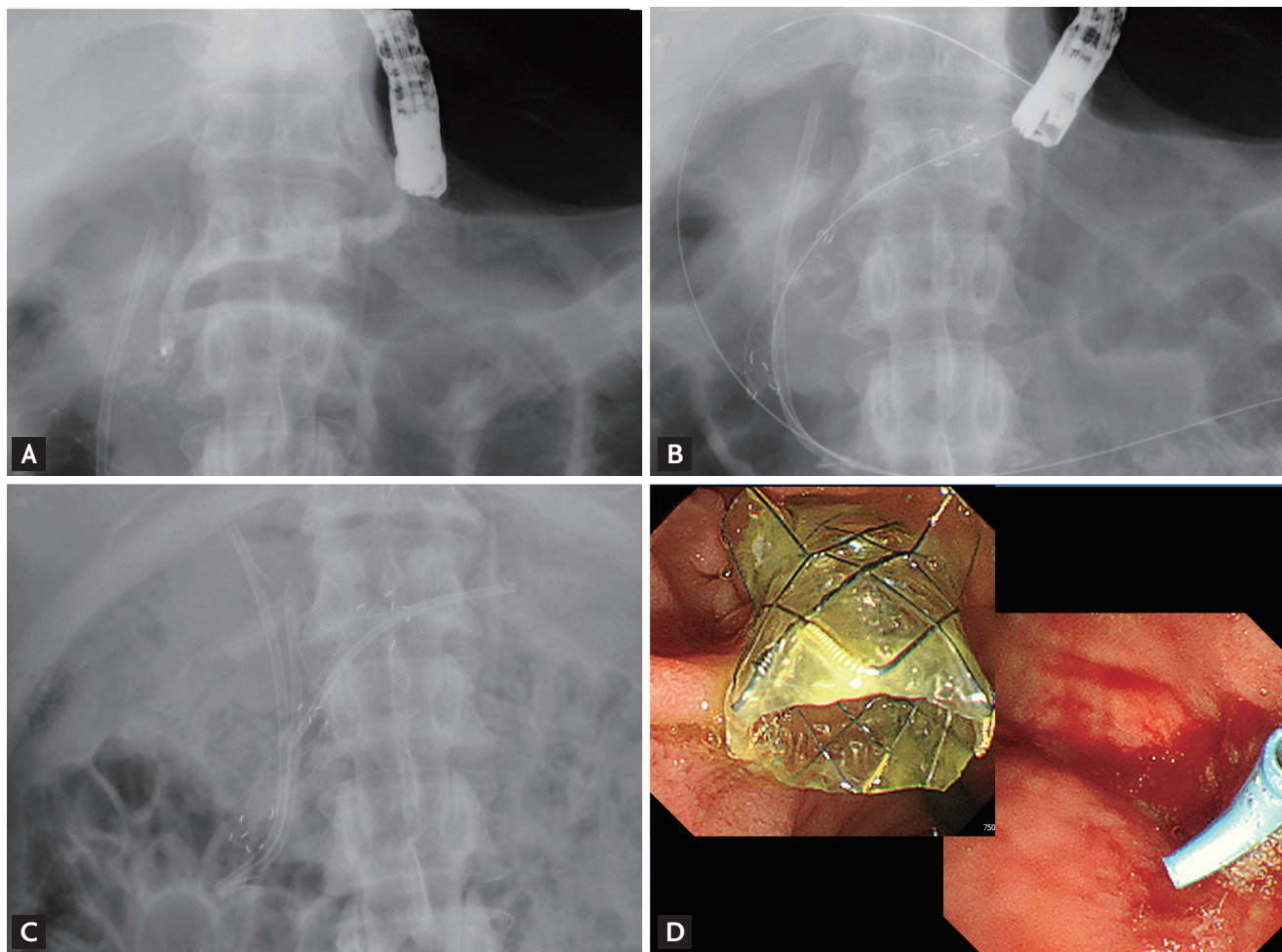


Figure 5. Representative case of endoscopic ultrasonography (EUS)-guided anterograde insertion of a fully covered self-expandable metal stent (FC-SEMS) for a stricture in the main pancreatic duct. (A) EUS-guided anterograde pancreatographic image showing dilation of the main pancreatic duct with a severe stricture at the head of the pancreas. (B) EUS-guided anterograde insertion of a FC-SEMS through the stricture of the main pancreatic duct. (C) Simple abdominal plain X-ray showing the fully expanded FC-SEMS in the main pancreatic duct and two plastic stents in the biliary and pancreatic ducts for internal drainage of pancreatic juice. (D) Endoscopic images showing the status of the end of the FC-SEMS at the ampulla and the end of the plastic stent in the body of the stomach.

pancreatitis (Fig. 7) [61,62]. When the ventral pancreatic duct is obstructed by a stone and/or a high grade stricture, inserting a plastic stent into the dorsal pancreatic duct serves to bypass the refractory stone and main ductal stricture and allows decompression of the main pancreatic duct. These studies have reported high rates of technical success (75% to 91%) and symptomatic pain relief (73% to 83.3%).

Biodegradable self-expandable stents have also been attempted in patients with a benign pancreatic stricture due to chronic pancreatitis [63]. Despite a clinical success rate of only 53%, the stent occlusion rate and

disease flare rate were high. Although there was no mention about the exact mechanism underlying the development of complications in that study, it was assumed that the biodegradable wire was not degraded uniformly, resulting in fracture of the stent. However, biodegradable self-expandable stents may receive great attention as an ideal treatment in the near future.

Endoscopic treatment of a biliary stricture

Conventional treatment for a biliary stricture in patients with chronic pancreatitis involves inserting multiple plastic stents, but recent FC-SEMS insertions

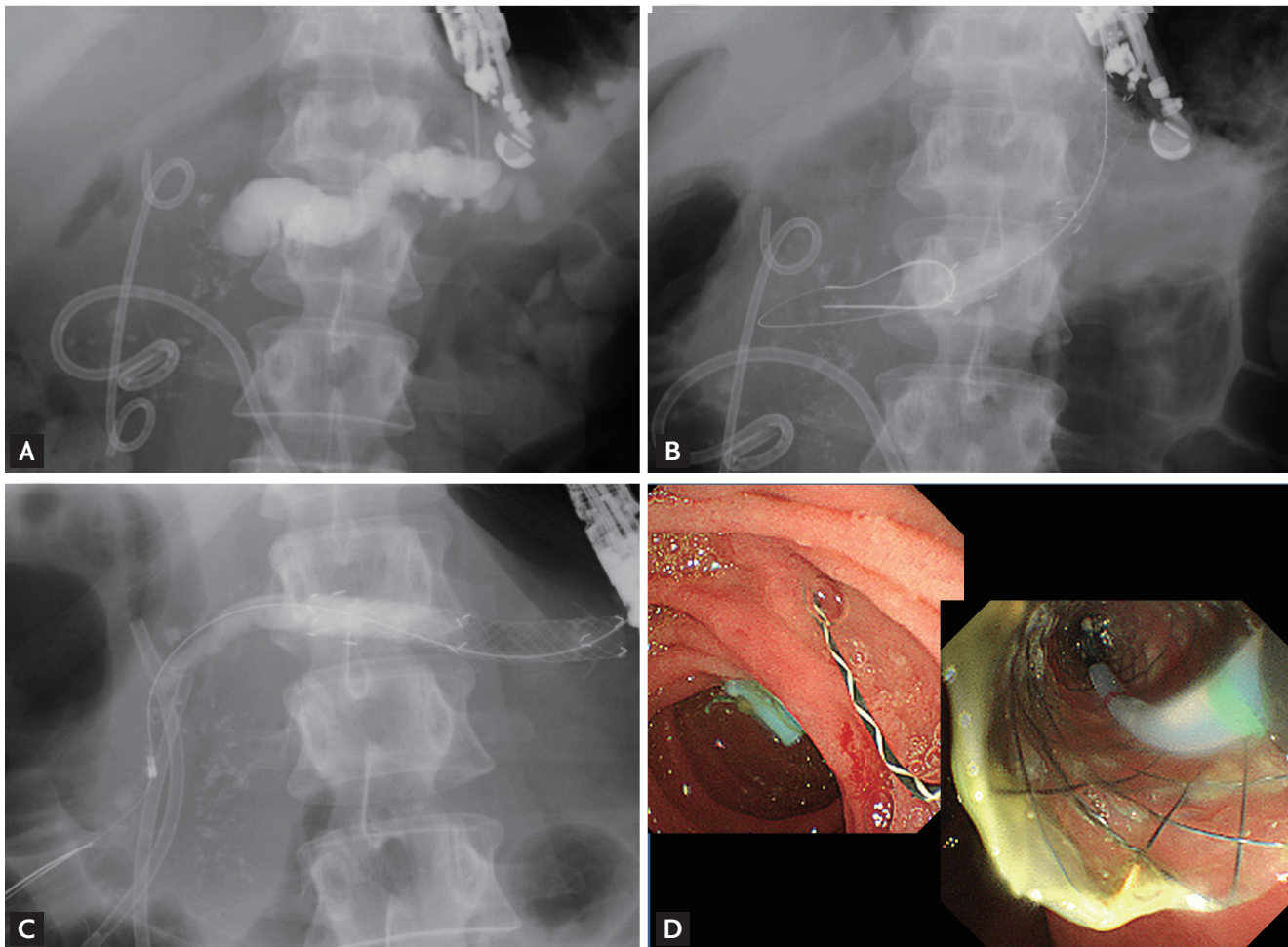


Figure 6. Representative case of endoscopic ultrasonography (EUS)-guided rendezvous cannulation and retrograde insertion of a fully covered self-expandable metal stent (FC-SEMS) for a stricture in the main pancreatic duct. (A) EUS-guided antero-pancreatographic image showing dilation of the main pancreatic duct with a severe stricture at the head of the pancreas. (B) EUS-guided antero-pancreatographic image showing the FC-SEMS inserted for internal drainage of pancreatic juice. (C) EUS-guided antero-pancreatographic image showing a guidewire inserted into the duodenum through the dorsal pancreatic duct. (D) Endoscopic images showing retrograde insertion of a second FC-SEMS into the main pancreatic duct via the minor papilla.

showed very high resolution rates, suggesting that it may be acceptable as an alternative option [64,65]. However, as the stricture recurrence rate is as high as 41%, surgical treatment should be actively considered if the stricture is refractory to endoscopic therapy [66,67]. It is likely that extrinsic compression caused by a fibrotic pancreatic gland in the distal common bile duct is what causes the biliary stricture to be relatively more refractory than other benign causes.

Treatment of pancreatic/peripancreatic fluid collection

Pancreatic fluid collection occurs after pancreatitis, trauma, or surgery. In the revised Atlanta classification, pan-

creatic fluid collection was classified as acute or chronic. Acute pancreatic fluid collection was further classified as acute peripancreatic fluid collection or acute necrotic collection according to the presence or absence of pancreatic necrosis, respectively. Chronic pancreatic fluid collection was further classified as a pseudocyst and walled-off pancreatic necrosis (WOPN) [68].

Transmural drainage using EUS was first described by Grimm et al. [69] in 1992. Since then, it has been recognized as an acceptable treatment for pancreatic fluid collection because of its high success rate, efficacy, and safety. The therapeutic effect of collecting pancreatic fluid drainage depends on its position, shape, and pat-

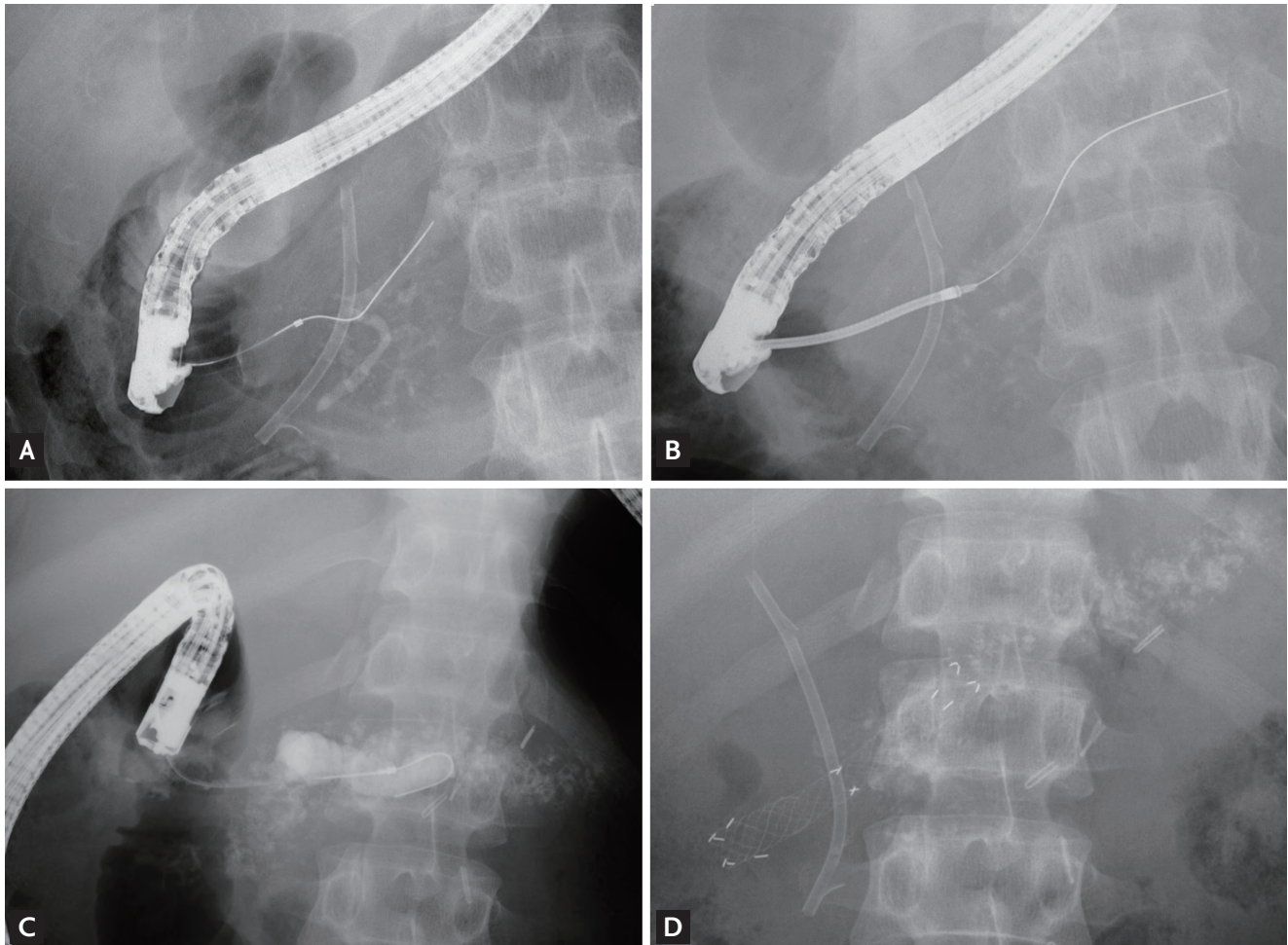


Figure 7. Two representative cases of dorsal pancreatic duct bypass. (A) After failure of conventional cannulation into the pancreatic duct via the major papilla, deep cannulation of the dorsal pancreatic duct was accomplished. (B) The dorsal pancreatic duct was successfully dilated using a Soehendra stent retriever for subsequent insertion of a stent. (C) Image showing multiple complex stones in the head of the pancreas and severe stenosis in the ventral pancreatic duct. A guidewire was successfully advanced into the dorsal pancreatic duct via the minor papilla. (D) Image of a subsequent dorsal pancreatic stent placed in the main pancreatic duct via the minor papilla.

tern. In particular, the drainage effect differs according to the density of the collection contents and the presence or absence of necrotic tissue. A typical pseudocyst heals in more than 90% of cases, whereas pancreatic necrosis is effective in only 50% to 60% of endoscopic treatments [70].

Because metal stents are relatively larger in diameter than plastic stents, it is believed that metal stents have less clogging and a better drainage effect, making them more desirable than plastic stents to treat pancreatic fluid collection. A recent meta-analysis revealed that metal stents show a higher clinical success rate (odds ratio [OR], 3.39; 95% confidence interval [CI], 2.05 to 5.60)

and fewer side effects (OR, 0.37; 95% CI, 0.21 to 0.66). In the sub-analysis, metal stents showed high success rates for pseudocysts (OR, 5.35; 95% CI, 1.35 to 21.19) and pancreatic necrosis (OR, 3.37; 95% CI, 1.89 to 5.99) [71].

A lumen-opposing metal stent (LAMS) was recently developed to expand the indications of SEMS to drain pseudocysts and WOPN. The LAMS is a novel “dumb-bell” design that is easier to deploy than a plastic stent and has the effect of decreasing the risk of perforation or bleeding during the procedure by closely opposing the gastrointestinal wall with the wall of the pseudocyst or WOPN. The characteristic shape of both ends of the LAMS prevents stent migration during intu-

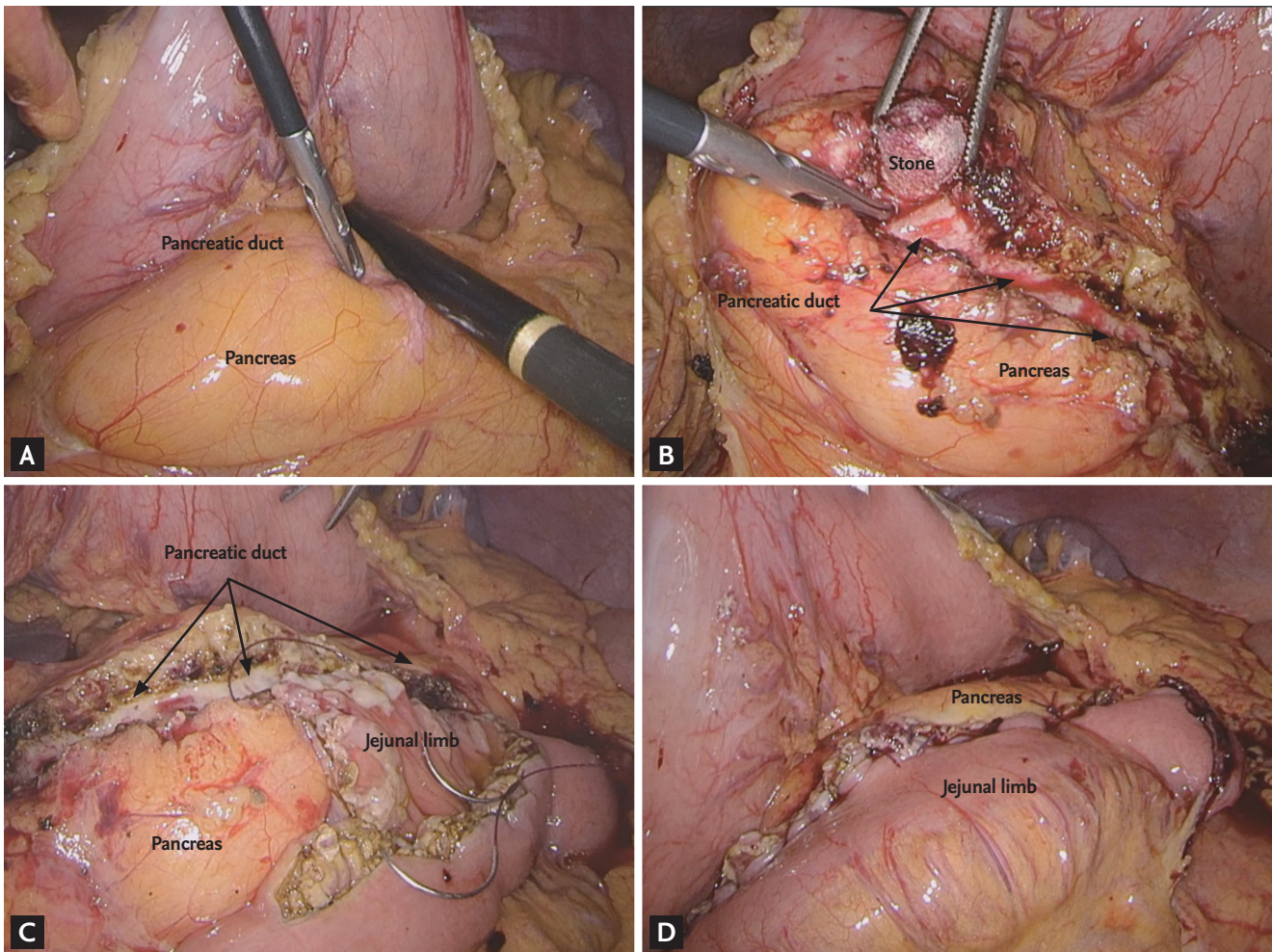


Figure 8. Laparoscopic longitudinal lateral pancreaticojejunostomy. (A) Localization of the pancreatic duct by laparoscopic ultrasonography. (B) The pancreatic duct was opened longitudinally, and the impacted pancreatic stone was extracted. (C) The Roux jejunal limb was placed laterally to the opened pancreatic duct, and the jejunum was also opened longitudinally for anastomosis. (D) Longitudinal lateral pancreaticojejunostomy was completed.

bation for collection in the case of direct endoscopic necrosectomy [72]. However, Bang et al. [73] presented three cases of pseudoaneurysmal bleeding: two cases of mucosal proliferation that covered the tip of the LAMS and one case of bile duct obstruction. Because these complications occurred 3 weeks after the procedure, it was recommended that the LAMS be removed soon after therapy, with recommended short-term follow-up repeat imaging and evaluation (usually 1 to 2 weeks after deployment). According to a recent Cochrane review involving a relatively small number of patients, EUS-guided drainage is a reasonable first-line approach due to its ability to improve short-term quality of life and reduce medical costs compared with

open surgical drainage [74]. Percutaneous, surgical, and combination therapy continue to play clinical roles in WOPN management. It cannot be emphasized enough that the management of WOPN is multidisciplinary, with essential input from surgical and interventional radiologists. We hope to see a large-scale prospective study of long-term patient outcomes after EUS-guided drainage.

There have been conflicting reports regarding the additional effect provided by transpapillary stent insertion for transmural drainage of pancreatic fluid collection (particularly pseudocysts). In a recent meta-analysis, transpapillary pancreatic duct stenting provided no additional clinical benefit for transmural drainage of

pancreatic fluid collection [75,76]. There were a number of limitations to the meta-analysis, such as it included only nine studies and was retrospective. Oftentimes, when MRCP is not clear, ERCP will help definitively diagnose an ongoing leak. For these reasons, the results of that meta-analysis are difficult to generalize.

Celiac plexus block and celiac plexus neurolysis

EUS-guided celiac plexus block (CPB) or celiac plexus neurolysis (CPN) is used to reduce the extremely disabling pain associated with chronic pancreatitis or pancreatic cancer. CPB is a temporizing treatment, most commonly injection of a local anesthetic together with a corticosteroid. In contrast, CPN refers to injection of alcohol or phenol, drugs that generally have a more permanent effect [77]. Although these treatments are particularly helpful in cases of intolerable adverse effects due to opioid therapy, a meta-analysis reported a response rate of 59% in chronic pancreatitis, but did not interrupt analgesic medication, and the duration of pain relief by CPB was approximately 3 months, which was shorter than expected [78]. Thus, patients should be fully informed of the relatively short anticipated duration of benefit [79,80]. A radiofrequency ablation (RFA) probe that passes through a EUS fine needle aspiration needle was developed and applied to pancreatic tumors. A novel study on EUS-guided RFA of the celiac ganglion reported that it provides more pain relief and improves quality of life better compared with the EUS-CPN method [81]. Although a large prospective study and long-term data are needed, EUS-guided RFA may receive attention as a new treatment method in the near future.

Surgical treatment and autologous islet cell transplantation

Although there are no sham-controlled studies on surgery for chronic pancreatitis, a Cochrane review reported greater and higher rates of pain relief in patients with obstructive chronic pancreatitis treated by surgery than by endoscopic treatment [82]. According to that review, current European guidelines indicate that surgery is superior to endoscopic treatment for mid- and long-term pain relief in patients with painful obstructive chronic pancreatitis. Total pancreatectomy may be considered in patients with chronic pancreatitis who do

not have ductal dilation or who complain of severe pain that is not relieved by conventional medical therapy [32].

However, endoscopic and EUS treatments are being updated and reported rapidly. Therefore, existing meta-analyses should be updated. We also believe that it is necessary to treat patients with a continuous multidisciplinary approach as the disease progresses, rather than determine the superiority of any treatment method. If surgical management can be avoided or delayed, endoscopic treatment may be considered an acceptable choice.

A major reason for preferential conservative treatment is based on the “burnout hypothesis” that chronic pancreatitis is a self-limiting disease in which symptoms will diminish spontaneously as the pancreatic parenchyma is progressively destroyed by the disease [13]. However, 50% to 60% of patients have reported sustained pain for more than 10 years after onset of the disease [83,84]. Current European guidelines recommend that early-stage surgery at a less advanced disease stage is favored with respect to optimal long-term pain relief, improved quality of life, and a reduced risk of pancreatic exocrine insufficiency. Although experimental and clinical data on the proper timing for surgery are scarce, a multicenter cohort study suggested that surgical intervention within 3 years of symptom onset was an important determinant of long-term outcomes regarding pain relief and preservation of pancreatic endocrine function [85]. Surgical intervention is generally more effective for patients with refractory pain and a dilated pancreatic duct or refractory obstruction of the duodenum, common bile duct, or main pancreatic duct, symptomatic pseudocysts, or suspected cancer [2].

Persistence of the inflammatory response in patients with chronic pancreatitis leads to various morphological changes and clinical features due to progressive fibrosis and destruction of the parenchyma [86]. Therefore, surgery should be tailored to the patient’s ductal anatomy. The main types are either drainage based (such as pancreatojejunostomy), resection based (including pancreaticoduodenectomy, left-sided pancreatic resection, and total pancreatectomy with or without auto islet transplantation), or a combination of both (such as the Beger and Frey procedures).

Patients with obstructive symptoms and a dilated pancreatic duct are amenable to drainage procedures

avoiding extensive resection. Drainage procedures are less challenging compared with combined type or resection procedures in patients with chronic pancreatitis. The lateral pancreaticojejunostomy (Peustow procedure) is a representative drainage procedure. The dilated portion of the pancreatic duct is opened longitudinally, and a side-to-side anastomosis is created with a Roux-en-Y jejunal limb placed laterally to the opened pancreatic duct (Fig. 8). Due to recent advances in minimally invasive surgery, laparoscopic or robotic surgery has been attempted to maximize the desired goal of relieving pain [87,88].

The Frey procedure involves the addition of coring of the pancreatic head to the lateral pancreaticojejunostomy, so-called duodenum-preserving pancreatic head resection, and has been widely used in patients with a dilated pancreatic duct [2,89]. A meta-analysis of 23 studies comparing the Frey procedure with pancreatoduodenectomy and the Berger procedure showed a shorter surgical time, lower overall morbidity, and more favorable quality of life and pancreatic functional recovery [90]. Long-term follow-up data also demonstrated that the Frey procedure is not inferior in many respects to the Berger procedure [91].

Decompression surgery cannot be performed in patients with chronic pancreatitis but without dilatation of the main pancreatic duct. In these cases, surgical resection should be considered, but adverse effects including endoscopy and exocrine insufficiency can develop [92]. TP-IAT has already been introduced to prevent endocrine function loss, so four decades have already elapsed [93,94]. TP-IAT should be considered based on the presence of intractable pain with impaired quality of life and should be performed when other medical, endoscopic, and/or surgical therapies fail in patients with an established diagnosis of chronic pancreatitis or acute recurrent pancreatitis [95]. Absolute contraindications include prohibitive medical complications, active alcoholism, islet cell failure (poor or no C-peptide on provocative testing), poorly controlled psychiatric disease, steatohepatitis, and portal vein thrombosis [96].

A good therapeutic response for hereditary chronic pancreatitis associated with genetic risk factors accounts for a very small proportion of patients undergoing TP-IAT. TP-IAT has a high probability of achieving

complete pain relief, improved quality of life, discontinued opioid use, and insulin independence. TP-IAT can be actively considered when a drainage procedure is not possible due to the absence of a dilated main duct, because it occurs at a very young age, and the incidence of pancreatic cancer increases with disease duration. The general TP-IAT treatment effect is good compared with total pancreatectomy without IAT. Survival rates are reportedly 97% at 1 year, 90% to 94% at 5 years, and 81% to 84% at 10 years. Opioid independence increases with time and is reportedly 73% at 5 years. Islet cell graft function is seen in at least 80% of cases, while escape from insulin therapy is observed in one-third of patients and has been observed for more than 15 years [97]. However, success rates vary widely among reports depending on various technical factors, injection method, implantation site, and number of cells to be injected [98]. Therefore, it is preferable that a multidisciplinary team performs the procedure at a more specialized center.

CONCLUSIONS

Currently available diagnostic and treatment options for chronic pancreatitis are unsatisfactory in terms of early detection and prevention of its progression. Most novel and experimental therapies aim to limit inflammation and reduce fibrosis and have been tested in animal models [89]. Because chronic pancreatitis is a slowly progressing and incurable disease that continues to afflict patients for life, treatments are relatively limited. Once a patient is diagnosed, we should actively support lifestyle modifications (cessation of alcohol consumption and smoking). As the disease progresses, pain control should be managed carefully to prevent drug addiction, and exocrine insufficiency and diabetes mellitus should be strictly controlled to prevent secondary complications. It is our task to help the patient throughout life using a multidisciplinary approach to maximize outcomes

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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