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Endoscopic Treatment of Pancreatic Calculi

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Chronic pancreatitis is a progressive inflammatory disease that destroys pancreatic parenchyma and alters ductal stricture, leading to ductal destruction and abdominal pain. Pancreatic duct stones (PDSs) are a common complication of chronic pancreatitis that requires treatment to relieve abdominal pain and improve pancreas function. Endoscopic therapy, extracorporeal shock wave lithotripsy (ESWL), and surgery are treatment modalities of PDSs, although lingering controversies have hindered a consensus recommendation. Many comparative studies have reported that surgery is the superior treatment because of reduced duration and frequency of hospitalization, cost, pain relief, and reintervention, while endoscopic therapy is effective and less invasive but cannot be used in all patients. Surgery is the treatment of choice when endoscopic therapy has failed, malignancy is suspected, or duodenal stricture is present. However, in patients with the appropriate indications or at high-risk for surgery, endoscopic therapy in combination with ESWL can be considered a first-line treatment. We expect that the development of advanced endoscopic techniques and equipment will expand the role of endoscopic treatment in PDS removal.

Key Words: Pancreatitis, chronic; Calculi; Endoscopy; Surgery; Lithotripsy

INTRODUCTION

Chronic pancreatitis is a serious inflammatory disease of varying etiology characterized by parenchymal destruction and a change in ductal structure.[1] Pancreatic duct stones (PDSs) develop during the natural course of chronic pancreatitis and are observed in 90% of patients.[2] Ductal obstruction by PDSs causes increased intraductal pressure and ischemia from increased parenchymal pressure causes pain.[3] Therefore, treatment of PDSs is necessary in chronic pancreatitis to alleviate pain and improve pancreatic function by restoring pancreatic duct flow.[4,5]

PDSs can be managed with endoscopic therapy, surgical removal, and extracorporeal shock wave lithotripsy (ESWL).[6] A variety of treatment modalities have been described in clinical research of PDSs, although lingering controversies have hindered a consensus recommendation. This review focuses on endoscopic management of PDSs in chronic pancreatitis.

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HISTORY

Surgery has been the mainstay of PDS treatment, dating to the first reported operation by Haggard and Kirtley[7] in 1883. A hundred years later, advances in medical technology led to the introduction of nonsurgical treatment methods. In 1983, Inui et al.[8] introduced pancreatic sphincterotomy to successfully remove PDSs with a basket and in 1985 Fuji et al.[9] reported that a pancreatic duct stent could be deployed after PDS removal to facilitate pancreatic drainage. In 1987, Sauerbruch et al.[10,11] reported the successful endoscopic removal of PDSs using ESWL, which delivers an extracorporeal shock wave to disintegrate the stones. These modalities have since been studied in various clinical settings.

DIAGNOSIS

Although diffuse pancreatic calcification is a characteristic of chronic pancreatitis, focal calcification can also be ob-

served in islet cell tumors and peripancreatic vascular calcification. Plain abdominal films can identify calcification in only 30% of patients with chronic pancreatitis and cannot be used to easily differentiate between ductal calculi and parenchymal calcification.[12] When pancreatic stones cause duct obstruction, an obstructive hydrostatic effect will dilate the pancreatic duct, which can assist in the diagnosis of the main duct stone. Ultrasonography is useful in detecting the dilated pancreatic duct and PDSs, but the head of pancreas may not be visualized clearly due to overlying bowel gas or body habitus.[13] Computed tomography can better detect pancreatic calcification and is helpful when pseudocyst or pancreatic parenchymal pathology is suspected.[14] Endoscopic retrograde cholangiopancreatography (ERCP) and magnetic resonance cholangiopancreatography (MRCP) can be used to visualize pancreatic duct morphology and identify pseudocysts or duct anomalies. Endoscopic ultrasound is a noninvasive procedure distinct from ERCP, recently adopted widely because it can provide information on the ductal system and the sizes and positions of stones.[15]

INDICATIONS FOR TREATMENT

In patients with chronic pancreatitis, medical treatment is effective for only 31% of patients but long-term, endoscopic treatment is effective for 50% of patients.[16] However, selection of the proper candidate is crucial because endoscopic treatment cannot be used for all patients. Liu et al.[17] reported that the indications for endoscopic treatment were ≤3 noncompacted stones and PDS diameter ≤10 mm located at the pancreatic head or body. If a PDS is situated at the main pancreatic duct and is small, removal is more likely to be successful.[18,19] In contrast, PDSs scattered throughout the pancreatic duct or stones at the side branch duct are difficult to manage with endoscopy.[20,21]

The indications for ESWL are broader than other endoscopic modalities because it can fractionate large and hard PDSs into millimeter sizes. Thus, endoscopic therapy, combined with ESWL, can remove stones in the main duct, as well as those in the accessory pancreatic duct.[22-25] The European Society of Gastrointestinal Endoscopy (ESGE) recommends ESWL as a first step in treating patients with radiopaque PDSs ≥5 mm in the main pancreatic duct, immediately followed by endoscopic extraction of stone fragments, depending on the expertise of the center.[26] ESWL can be performed without pancreatic sphincterotomy or ERCP when the shape of pancreatic duct is confirmed via MRCP. In these cases, even in the absence of pain, it is helpful to preserve pancreatic function if it is not accompanied by parenchymal atrophy. However, ESWL is contraindicated in pregnancy, patients with a tendency to bleed easily, and those with a pacemaker, defibrillator, or abdominal aortic aneurysm.[27] Surgery is indicated for patients who do not meet these indications or for whom nonsurgical treatment has failed.

TECHNIQUES FOR STONE REMOVAL

Endoscopic techniques for stone removal include pancreatic sphincterotomy; stone retrieval using balloons, baskets, or rat tooth forceps; stent placement; mechanical lithotripsy; and endoscopic balloon dilation of the pancreatic orifice after sphincterotomy.[28] Approximately 50% of PDSs can be removed by endoscopic sphincterotomy and stone retrieval,[29] while ESWL can fragment large stones to lessen the burden; therefore, the addition of ESWL can increase the success rate to 60% to 90%.

DIFFICULTY TREATING PANCREATIC CALCULI

Endoscopic removal of PDSs can be difficult due to there being many stones, their hardness and the impacting nature underlying duct stricture.[18,29] Moreover, the complication rate of pancreatic mechanical lithotripsy is 3-fold higher than biliary mechanical lithotripsy.[30] Most complications result from trapped or broken baskets due to hard stones, although acute pancreatitis or pancreatic duct disruption can occur.[30] A tight stricture is found in most patients and there is a risk of possible damage to the surrounding pancreatic parenchyma during treatment.

ENDOSCOPIC PANCREATIC SPHINCTEROTOMY AND BALLOON SPHINCTEROPLASTY

To remove symptomatic, but not spontaneously passing PDSs, pancreatic sphincterotomy can be performed on major or minor papilla. Pancreatic sphincterotomy can be performed with a pull-type sphincter tome over a guide wire or with a needle-knife incision. The risks of pancreatic sphincterotomy are similar to that of biliary sphincterotomy and include acute pancreatitis (2% to 7%), bleeding (0% to 2%), and perforations (<1%) as early complications and sphincter stenosis (up to 10%) as a late complication.[31-33] Moreover, a case report in a tropical area reported the application of endoscopic balloon dilation after pancreatic sphincterotomy for the removal of a large radiolucent stone without stricture in the main pancreatic duct.[28]

EXTRACTION BALLOONS, BASKETS, AND FORCEPS

Baskets, balloons, and forceps are used to remove stones by capturing or sweeping them from the pancreatic duct through the small intestinal lumen. The basket is opened within the duct, to capture the stone and pull it into the small intestinal lumen or the stone may be fragmented by mechanical lithotripsy (Fig. 1). When the PDS diameter is ≤5 mm, standard biliary baskets are less effective than pancreatic stone baskets. Furthermore, it is difficult to capture a ≤6 mm stone within the duct and the complication rate is higher than that of a balloon.[30] Although rare, if the downstream duct is smaller than the stone, an extraction basket may become trapped within the pancreatic duct.[34] In contrast, extraction balloons can be deflated within the duct to minimize the risk of trapping. Thus, PDS removal using an extraction balloon during ERCP is safer with a comparatively low complication rate.[35] However, the balloon can be punctured by the edge of stone. Rat tooth forceps can be used to capture stones 1 to 2 cm distal of the main duct and are relatively safer to use than a basket, although inserting forceps into the pancreatic duct is technically difficult and pancreatic duct trauma is of concern.[36]

STONE FRAGMENTATION USING ESWL

ESWL can fragment PDSs, which consist of calcium carbonate over a protein matrix.[37] The size, an obstacle of endoscopic therapy, can be overcome with stone fragmentation by ESWL (Fig. 2).[12,17,38] ESWL is safe, effective, and noninvasive because broken pieces can be removed spontaneously out of the pancreatic duct once they are reduced in size. Therefore, ESWL can be used as a primary treatment, in addition to its compensatory role in endoscopic therapy.[25,38-40] In a meta-analysis of ESWL, a 37% to 100% clearance rate was noted in 491 patients, and effective pain control occurred spontaneously,[41] while in another review involving 1,100 patients, 89% demonstrated successful fragmentation.[42] In patients who underwent ESWL, long-term follow-up revealed that 85% of patients felt less pain, 50% became completely pain-free without the use of narcotics and 84% avoided surgical intervention.[43] Differences in complete removal rates could be explained by selection criteria, method of preprocedural assessment, ESWL technique and device, ERCP technique and timing, and lack of uniform criteria to determine final outcome.

In a randomized study that compared ESWL alone (*n*=26) to ESWL with endoscopic therapy (*n*=29), ESWL alone was

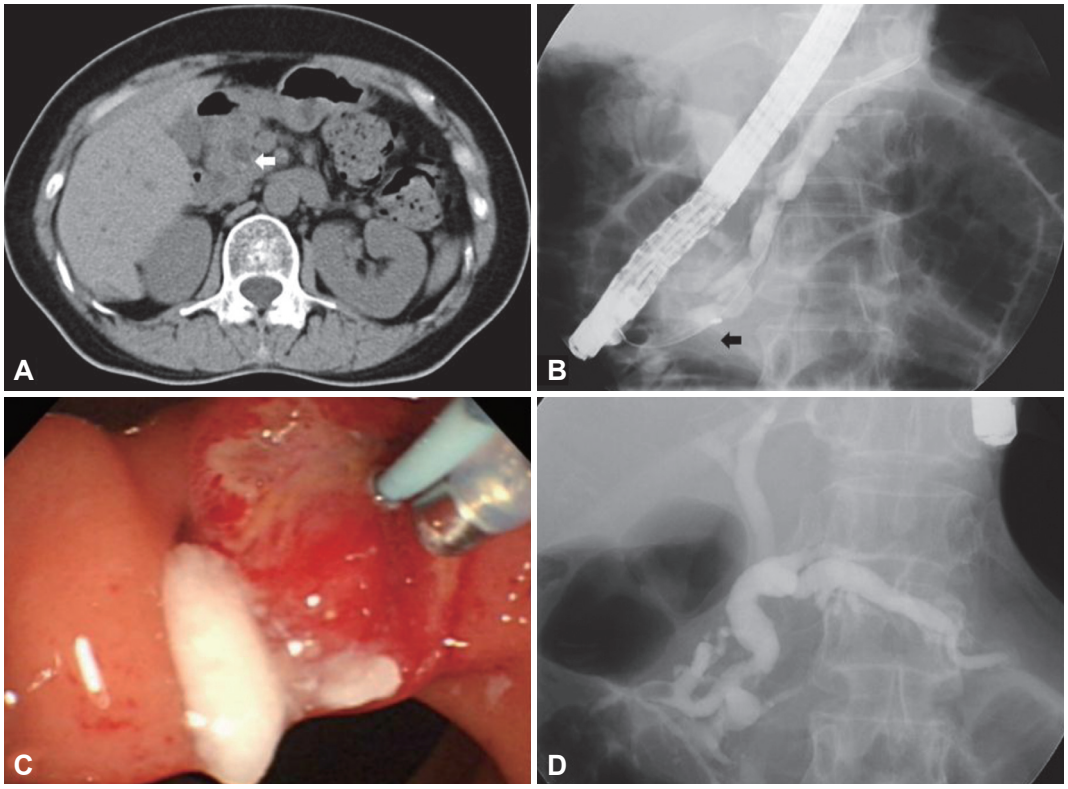

Fig. 1. Endoscopic intervention for pancreatic duct stones (PDSs). (A) Abdominal computed tomographic scan shows a 4 mm sized calcified stone (white arrow) in pancreatic head within dilated pancreatic duct. (B) Small size of the PDSs let basket removal possible (black arrow). (C) PDS was visualized intraluminally. (D) No filling defect was observed in the main pancreatic duct after complete stone removal.

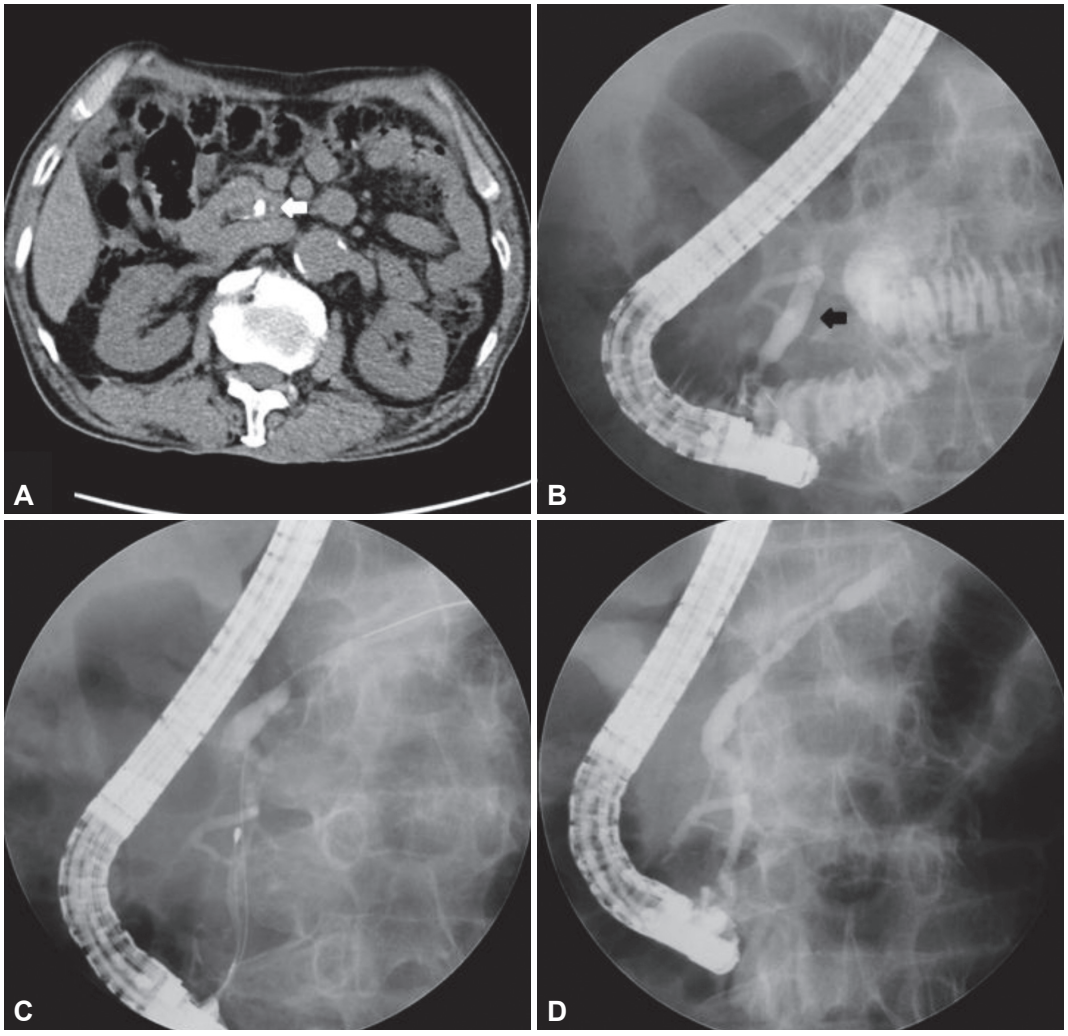

Fig. 2. Endoscopic intervention after extracorporeal shock wave lithotripsy (ESWL) for fragmentation of large stone. (A) Abdominal computed tomographic scan shows 10 mm sized calcified stones (white arrow) in pancreatic head within markedly dilated pancreatic duct. (B) Large pancreatic duct stones in the pancreas head (black arrow) rendered the catheter impassable. (C) After two sessions of ESWL, stones were fragmented to the degree that can be removed with basket. (D) No filling defect was observed in the main pancreatic duct after complete stone removal.

safer and more effective.[40] Long-term follow-up of patients with ESWL with endoscopic therapy determined that pain was alleviated and surgery was avoided in two-thirds of the cases.[14] Thus, ESWL can assist in long-term pain relief, when it is combined with endoscopic therapy to treat PDSs under the proper indications. Complications of ESWL include contusions on the skin or duodenum, mild abdominal discomfort, exacerbation of pancreatitis, and asymptomatic hyperamylasemia. The rate of acute pancreatitis is 6.3% to 12.5%[24,44] and severe complications, such as death, occur in <1% of patients[45] when PDSs in chronic pancreatitis are treated with ESWL alone. It is generally recommended that a pancreatic stent be temporarily inserted during ERCP as a bridge treatment to facilitate drainage and lower the risk of post-ERCP pancreatitis.[46] When performing ESWL, epidural anesthesia is effective[45] and in cases with a radiolucent stone, which can be difficult to target under fluoroscopy, contrast can be injected using an endoscopic nasopancreatic drainage catheter or ultrasound-guided shock wave lithotripsy.

INTRADUCTAL MECHANICAL LITHOTRIPSY AND ELECTRO HYDRAULIC LITHOTRIPSY

Large stones can be removed through papilla with ease when ground into small pieces by mechanical lithotripsy, ESWL, or intraductal electrohydraulic lithotripsy (EHL). Mechanical lithotripsy is accompanied by higher risk of failure and complication; hence, it is performed less frequently than biliary stone lithotripsy.[47] There are a limited number of studies on intraductal EHL for PDS fragmentation.[48] EHL is performed under direct vision via a mother-daughter scope

system using a pancreatoscope or spyscope and can deliver high energy to the stone. The process can directly injure the ductal wall and has limitations when a small endoscope-obstructing stricture is present.[49] In addition, the technique is technically demanding and requires expensive equipment. Therefore, it is considered a second-line treatment after ESWL has failed due to its technically demanding nature and the equipment required.[26]

SHORT-TERM AND LONG-TERM OUTCOMES

The symptom relief rate of endoscopic therapy in PDSs is 77% to 100% in the short term and 54% to 86% in the long term.[14,36,50] Similarly, that of ESWL is 70%.[51] In a previous study,[52] patients with stones >5 mm who did not receive standard endoscopic therapy were followed up after ESWL. Intermediate-term (24 to 60 months) and long-term (>60 months) follow-up demonstrated that pain was well controlled with a low recurrence rate. Long-term outcomes after endoscopic treatment are summarized in Table 1.[38,43,50,52-56]

BENEFIT TO PANCREAS FUNCTION

There is a controversy over whether PDS removal by ESWL and endoscopic treatment can preserve exocrine function. A study by Adamek et al.[19] revealed that endoscopic therapy and ESWL management did not prevent or delay glandular insufficiency, while Inui et al.[53] reported that 38% showed improvement in exocrine function, although this was not significant due to a small sample size. Tandan et al.[52] also reported that exocrine and endocrine dysfunction demonstrated some improvement. In addition, a study using secretin-enhanced MRCP (S-MRCP) demonstrated that pancreatic exocrine function improved after endoscopic intervention. In chronic pancreatitis patients, pancreatic flow output and total excreted volume were measured after endoscopic treatment by S-MRCP. Before the procedure, the values were 3.5 mL/min and 42 mL, respectively. After the procedure, the values were significantly higher, at 5.6 and 72 mL/min, respectively.[52] Therefore, an adequately designed study of exocrine function is necessary.

COMPARISON WITH SURGICAL TREATMENT

In two prospective randomized comparative studies that compared clinical outcomes of endoscopic and surgical treatment for PDSs, surgery was more effective than endoscopic therapy.[57-59] Díte et al.[57] reported that complete or par-

Table 1. Long Term Outcome after Endoscopic Treatment

Year	Authors	Method	No. of patients	Sex (%)/Age, yr	Clinical success rate, %[a]	Follow-up, mo	Conversion to surgery, %	Ongoing endoscopic treatment, %	No further intervention, %
1995	Binmoeller et al.[54]	ERCP	93	M (70)/49	65	58	26	13	61
2002	Rosch et al.[50]	ERCP+ESWL	1,018	M (71)/50	66	58	24	16	60
2004	Delhaye et al.[38]	ERCP+ESWL	56	M (82)/44±12	66	173	21	18	61
2005	Tadenuma et al.[55]	ERCP+ESWL	70	M (72)/48	70	75	1	20	79
2005	Inui et al.[53]	ERCP+ESWL	555	M (84)/52.5	91	44	4	NA	NA
2006	Farnbacher et al.[56]	ERCP	98	M (86)/49±12	66	46	23	18	59
2012	Seven et al.[43]	ERCP+ESWL	120	M (43)/53±15	51	52	16	NA	NA
2013	Tandan et al.[52]	ERCP+ESWL	636	M (65)/<40 yr (59)	65	24–96	9	27	64

Values are presented as mean±SD.
ERCP, endoscopic retrograde cholangiopancreatography; M, male; ESWL, extracorporeal shock wave lithotripsy; NA, not available.
[a]Clinical success rate means complete pain relief after endoscopic treatment.

tial pain relief was achieved in 61% of patients who underwent endoscopic treatment, compared to 86% of patients who underwent surgical treatment (p=0.002). Cahen et al.[58] reported that complete or partial pain relief was achieved in 32% of the endoscopic treatment group compared to 75% of the surgical treatment group (p=0.007) (Table 2). Although the duration and frequency of hospitalizations, and medical costs were similar in the short-term endoscopic treatment and surgery groups, patients in the long-term endoscopic treatment group were hospitalized longer, which resulted in higher medical costs than patients who received short-term endoscopic treatment and surgical treatment.[60] In another study, as modified Puestow procedure was effective for pain relief after 37 months of follow-up and was relatively safe with a 5.7% complication rate.[17] Additional drainage was necessary in 68% of patients who underwent endoscopic intervention, which was higher than the 5% reported in the surgery group. Furthermore, 47% of patients in the endoscopic group received an additional salvage operation that was not effective. Nonetheless, endoscopic treatment was preferred because it is less invasive and surgical treatment could be performed after treatment failure. Thus, endoscopic therapy can delay or obviate the need for an operation.[57,58] Therefore, despite the superiority of surgery for pain management, endoscopic intervention is necessary as a bridging therapy.

NECESSITY OF SURGERY

The aim of surgery is to remove PDSs causing pancreatic duct obstruction and preserve pancreatic function by decompressing the pancreatic duct. The decision to undergo surgery can be made based on many factors, such as the diameter of the main duct, the presence of stricture, an accompanying pseudocyst, the presence of a mass with the possibility of cancer, duodenal or biliary obstruction, the position of the stone, the severity of disease, and one's overall condition (Fig. 3). Thus, surgery is the treatment of choice when endoscopic treatment has failed, malignancy is suspected, and/or duodenal stricture is present. The presence of a main PDS without duct stricture can be successfully managed with endoscopy or ESWL. Instead of performing endoscopic or surgical management, many factors should be considered and surgery should be performed when endoscopy has failed.

CURRENT GUIDELINES

The current American Society for Gastrointestinal Endoscopy (ASGE) and ESGE guidelines for treatment of chronic pancreatitis are useful for the treatment of PDSs.[26,61] Al-

Table 2. Outcomes of Endoscopic Treatment and Surgical Treatment in Randomized Prospective Study

Year	Authors	Method	No. of patients	Sex (%)/Age, yr	Pain relief	Complication	Follow-up, mo	Death	Conversion to surgery
2003	Dite et al.[57]	Endoscopy	36	M (85)/41.7	22 (61)[a]	2 (6)	60	0	0
		Surgery	36		31 (86)	3 (9)	60	0	NA
2007	Cahen et al.[58]	Endoscopy	19	M (58)/52±9	6 (32)[b]	Major 0 (0) Minor 11(58)	24	1 (5)[c]	4 (21)
		Surgery	20	M (75)/46±12	15 (75)	Major 1 (5) Minor 6 (30)	24	0	NA
2011	Cahen et al.[59]	Endoscopy	16	M (58)/52±9	6 (38)[b]	NA	85±14	0	5 (26)
		Surgery	15	M (75)/46±12	12 (80)	NA	92±11	0	NA

Values are presented as number (%) or mean±SD.
M, male; NA, not available.
[a]Pain relief at the end of follow-up was classified as complete (absence of pain or attack) or partial (a reduction in pain of at least three points on the Melzack score); [b]Pain relief at the end of follow-up was classified as complete (Izbicki pain score, ≤10) or partial (Izbicki pain score, >10 after a decrease of >50%); [c]One patient died of a perforated duodenal ulcer 4 days after the last shockwave lithotripsy session.

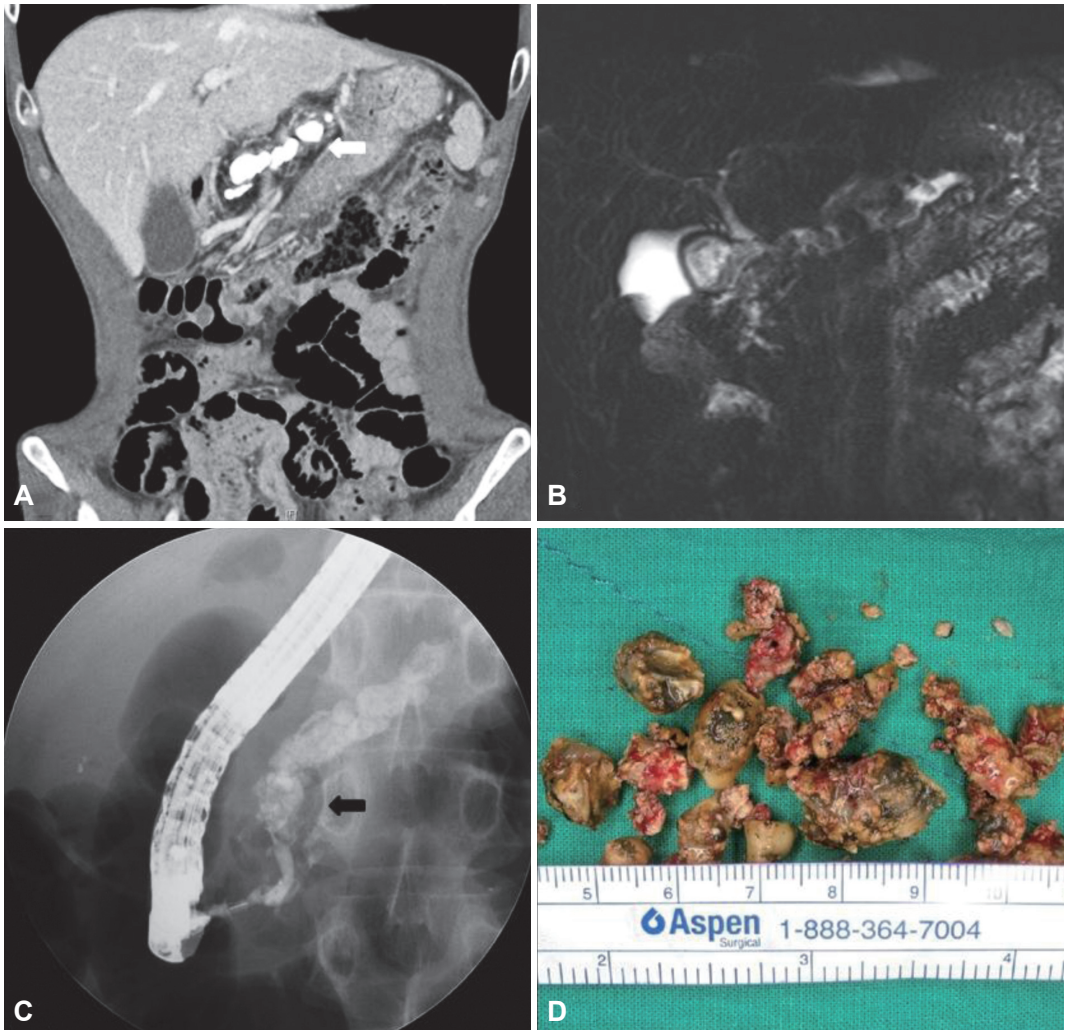

Fig. 3. Surgical treatment for multiple large pancreatic duct stones (PDSs). (A) There are extensive calcified stones in pancreatic duct (white arrow). (B) Magnetic resonance cholangiopancreatography shows markedly dilated pancreatic duct with innumerable internal stones. (C) Pancreatogram via major papilla demonstrates pancreatic duct, full of large PDSs (black arrow), which was an indication for surgical treatment. (D) Multiple PDSs removed by Roux-en Y pancreaticojejunostomy surgery.

though surgical treatment would provide a better outcome, the ASGE suggests endoscopic therapy as the first-line treatment because of its lower degree of invasiveness and recommends several rounds of ESWL for stone fragmentation, as necessary.[61] Unlike the ASGE, the ESGE guideline recommends ESWL as the first treatment step, especially when PDSs are >5 mm. For fewer stones that are <5 mm and located between the pancreatic head and body, the ESGE recommends endoscopy.[26] Both of these guidelines recommend endoscopic treatment as the first-line treatment for such stones, rather than surgery, but the ESGE guideline emphasizes the role of ESWL more than the ASGE guideline.

CONCLUSIONS

For the treatment of pancreatic calculi, a nonsurgical method such as endoscopic therapy in combination with ESWL is as effective as a surgical method. Several comparative studies have reported the superiority of surgery in terms of the duration and frequency of hospitalizations, cost, pain relief, and reintervention. However, in patients with the appropriate indications or who are at high risk for surgery, endoscopic therapy in combination with ESWL can be considered a first-line treatment. We expect that the development of advanced endoscopic techniques and equipment will expand the role of endoscopic treatment in PDS removal.

Conflicts of Interest

The authors have no financial conflicts of interest.

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