

Update on Endoscopic Management of Main Pancreatic Duct Stones in Chronic Calcific Pancreatitis

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Pancreatic duct stones are a common complication during the natural course of chronic pancreatitis and often contribute to additional pain and pancreatitis. Abdominal pain, one of the major symptoms of chronic pancreatitis, is believed to be caused in part by obstruction of the pancreatic duct system (by stones or strictures) resulting in increasing intraductal pressure and parenchymal ischemia. Pancreatic stones can be managed by surgery, endoscopy, or extracorporeal shock wave lithotripsy. In this review, updated management of pancreatic duct stones is discussed.

Keywords: Pancreatitis, chronic; Calculi; Endoscopy; Lithotripsy; Surgery

INTRODUCTION

Chronic pancreatitis is a progressive inflammatory disease of varied etiology characterized by destruction of pancreatic parenchyma and subsequent fibrosis [1]. Alcohol is a major etiological factor in most industrialized countries [2]. Pancreatic duct calcifications are common in patients with chronic pancreatitis, and up to 90% of patients with alcoholic chronic pancreatitis have such stones during long-term follow-up [3]. Pancreatic duct calculi can lead to an outflow obstruction of the pancreatic duct, resulting in upstream hypertension, increased parenchymal pressure, and ischemia. Pain is the predominant symptom in most patients with chronic pancreatitis [4]. The etiology of pain is multifactorial, although ductal hypertension caused by stones or strictures is believed to be the major cause of pain in patients with chronic pancreatitis [4-9]. Pancreatic stones can be removed in an attempt to decrease the pain. Additionally, restitution of pancreatic duct flow improves

physiological function of the pancreas [10-12].

A pancreatic duct obstruction due to main pancreatic duct stones can often be relieved by surgical or endoscopic techniques or extracorporeal shock wave lithotripsy (ESWL). Removing pancreatic stones endoscopically is less invasive compared to surgery but is more likely to be successful when the stone burden is small and located only in the main duct [13,14]. In a series with a long-term follow-up, a good clinical outcome was recorded in two-thirds of patients, particularly in those with short duration pain before treatment [15]. Due to the complexity of pancreatic stone management, these patients are best managed in large referral centers.

PATHOPHYSIOLOGY

Pancreatic juice is supersaturated with calcium. Calcium is kept in solution by HCO_3^- , citrate, and pancreatic stone

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protein (PSP), and these factors are lower in patients with chronic pancreatitis [16]. Alcohol and chronic pancreatitis decrease the secretion of PSP, which causes the crystallization and deposition of calcium carbonate and the formation of stones [17]. Pancreatic duct strictures cause stagnation of pancreatic juice and enhance the formation of pancreatic stones. Hypercalcemia may cause a rise in the level of calcium in pancreatic juice, which accelerates the formation of pancreatic stones in patients with hyperparathyroidism. Calcium precipitates as CaCO_3 . Protein intraductal precipitates form soft stones and are relatively easy to sweep out endoscopically. A small portion of the stones have a protein core and calcium rim.

DIAGNOSIS

The finding of diffuse pancreatic calcifications on plain abdominal films is quite specific for chronic pancreatitis. Focal calcifications may be observed in cystic and islet cell tumors of the pancreas and in peripancreatic vascular calcifications. Plain abdominal radiographs or barium studies may reveal pancreatic calcification with or without evidence of a mass. Pancreatic calcification can be seen in up to 30% of patients with chronic pancreatitis on a plain abdominal X-ray [18]. Ultrasonography displays dilated pancreatic ducts and stones but it is limited because the pancreas (particularly pancreatic head) cannot be adequately visualized in some patients due to overlying bowel gas or body habitus [2]. The advent of newer imaging modalities such as computed tomography (CT) has improved the ability to detect pancreatic calcification [19]. Specific imaging of the duct system with endoscopic retrograde cholangiopancreatography (ERCP) or magnetic resonance cholangiopancreatography has the advantage of providing detailed images of the duct system and pancreatic stones. Dilation of the duct system upstream to the stone indicates a hydrostatic obstructive effect. Main duct stones cause a greater upstream hydrostatic effect than that of side branch stones, which often have little upstream parenchyma.

MANAGEMENT

In the past, treatment for painful obstructing main

pancreatic duct stones was a surgical lateral pancreaticojejunostomy and open duct stone removal. Over the last 25 years, endoscopic techniques to remove main pancreatic duct stones have been developed using methods analogous to bile duct stone removal. Simple stones can be extracted using various endoscopic techniques such as balloon or basket sweeping. Larger and impacted stones typically require lithotripsy or surgery [20].

Multiple series have demonstrated that removing obstructing stones from the main pancreatic duct improves symptoms in the majority of patients with chronic pancreatitis [13,21]. In randomized endoscopic and surgical therapy trials, surgery is superior for long-term pain reduction in patients with painful obstructive chronic pancreatitis [22,23]. However, endoscopic therapy may be preferred because of its lower degree of invasiveness, reserving surgery as second-line therapy for patients in whom endoscopic therapy fails. Endoscopic therapy may reduce, delay, or eliminate the need for surgical procedures and can predict the response to surgical therapy [24,25]. Adjuvant endoscopic approaches such as pancreatic sphincterotomy, intraductal lithotripsy, and pancreatic duct stricture dilation may be needed. Pain relief from all treatments in patients with alcoholic pancreatitis is poor if drinking continues.

Medical management

Oral pancreatic enzyme supplements, a low fat diet, and analgesics are standard management for patients with chronic pancreatitis with or without duct stones. These therapies do not affect stone size or stone formation. Such treatments are aimed at decreasing pancreatic juice production and hydrostatic pressure by inhibiting the release of cholecystikinin and thereby inhibiting exocrine parenchymal stimulation [26]. No medicines are readily available to dissolve stones. Trimethadione, an old anticonvulsant, dissolves pancreatic calcium stones in some settings [27,28]. However, due to hepatic toxicity of this medicine, it has not received wide usage. Thus, further studies are needed.

Surgery

Surgical removal of pancreatic duct stones is a management option. The objectives of simpler surgery are to remove obstructing calculi, decompress obstructed ducts, and preserve pancreatic tissue as well as adjacent organs.

The decision to perform surgery for patients with pancreatic stones depends on many factors, including the diameter of the main duct, presence of main duct stricture(s), associated pseudocyst(s), simultaneous cancer concerns, associated duodenal or biliary obstruction, the extent of the main duct vs. side branch duct stones, symptom severity, and operative tolerance. Operations are categorized as follows: resective, decompressive (drainage), denervative, and combination surgery. This brief surgical review will only focus on decompressive or drainage procedures, and the most common is a lateral pancreaticojejunostomy (Puestow procedure). This operation is best suited for patients with stones in a dilated main pancreatic duct (preferred ≥ 8 mm), which permits mucosa to mucosa anastomosis. Main pancreatic duct strictures can be simultaneously treated.

A recent report indicated that the modified Puestow procedure is effective for pain relief (-90%) and is safe (5.7% of complication) during a 37-month follow-up [29]. In two prospective studies, surgery was more effective compared with endoscopy for treating painful chronic pancreatitis (many also had stones) [22,23]. This latest study had several limitations. A very high incidence of strictures (84%) was noted in the endoscopy group, and these patients were probably treated with inadequate short-term stenting (median, 27 weeks). Recently, the same author reported the results of a 79-month follow-up of the same group of patients [30]. In that report, 68% of the patients treated by endoscopy required additional drainage compared with 5% in the surgery group ($p = 0.001$). Moreover, 47% of the patients in the endoscopy group eventually underwent surgery. Additionally, surgery was superior for pain relief (80% vs. 38%; $p = 0.042$) and quality of life and pancreatic function were comparable. Overall, these conclusions can be applied to patients with stones located behind strictures. Patients with stones in the main pancreatic duct without strictures are generally treated successfully with endoscopy and/or ESWL. Surgery is often considered second-line therapy for patients in whom endoscopic therapy fails. Surgical drainage is associated with a mortality rate of up to 5%, and long-term prognosis is not as good because pain may recur in up to 50% of patients within 5 years after surgery [31-33]. Even if the superiority of surgery in terms of pain relief for unselected patients is confirmed, an intermediate step between analgesics and surgery is desirable due to the drawbacks of surgery such as invasive-

ness, cost, and possibility of pain relapse even after major surgical procedures.

Endoscopic management

The attractive feature of endoscopic procedures is that they offer an alternative to surgery. The goal of endoscopic treatment for chronic painful pancreatitis with pancreatic duct stones is clearance of calculi from the duct, thus relieving the obstruction and pain [13,14,21,34]. Nonsurgical removal of obstructing pancreatic stones is challenging. Endoscopic extraction of pancreatic duct calculi is usually more difficult than extracting bile duct stones because pancreatic stones are generally speculated and hard and are impacted behind strictures on many occasions [13,35]. The best candidates for endoscopic removal are main duct stones of the head or body with upstream main pancreatic duct dilation. Approximately 50% of pancreatic stones can be removed effectively by standard techniques, including endoscopic sphincterotomy or stone retrieval with a balloon, basket, and/or forceps alone [13,35,36]. Adding ESWL increases clearance rates to 60-90%. Patients with extensive stones of the whole gland or side branch duct stones without main pancreatic duct dilatation are poor candidates for endoscopic removal of pancreatic duct stones [37,38].

Encouraging short- and long-term follow-up (-5 years) results showing improvements in pain (77-100% and 54-86%, respectively) have been reported [15,37]. In a large series of 1,000 patients with chronic pancreatitis who were treated endoscopically with long-term follow-up, 65% of patients with strictures and/or stones showed pain improvement after endotherapy [39]. Others have reported similar outcomes, with clinical improvement rates of approximately 70% [40]. Although most studies have suggested that endotherapy does not improve pancreatic function, one secretin-enhanced magnetic resonance cholangiopancreatography study suggested that pancreatic exocrine function improves after endoscopic therapy [41].

Endoscopic techniques include pancreatic sphincterotomy, stone retrieval (using balloons, baskets, or rat tooth forceps), stent placement, and mechanical lithotripsy [13,34,35,42]. A case series report (four cases) indicated that endoscopic balloon dilation (12-15 mm) of the pancreatic orifice after sphincterotomy is a safe technique that facilitates the removal of large radiolucent stones from the main pancreatic duct [43]. Further studies are needed

before routine use of such large balloons can be recommended. An alternative method is to break the large stones into small pieces so that they can be more easily extracted through the papilla. This can be done using mechanical lithotripsy, intraductal electrohydraulic lithotripsy (EHL), and ESWL.

Several studies have reported that pain relapse occurs more frequently with incomplete stone removal [44-46]. In contrast, other series have reported no difference in pain relapse rates between complete and incomplete removal groups [14,47]. In one study, all patients whose pain relapsed had intraductal pancreatic stones, suggesting that the main cause of pain relapse is recurrent (or remnant) pancreatic stones [44]. Failure to achieve pain relief despite adequate clearance of the pancreatic duct stones indicates other mechanisms of pain in patients with chronic pancreatitis.

Pancreatic sphincterotomy

In most patients, pancreatic sphincterotomy (with or without a biliary sphincterotomy) via the major or minor papilla is performed to facilitate removal of pancreatic stones. This is necessary, as most symptomatic stones have already failed to pass through the intact papilla spontaneously. A pancreatic sphincterotomy can be performed with a needle-knife incision over a guiding pancreatic stent or with a pull-type sphincterotome passed over a guidewire. The risks of pancreatic sphincterotomy are equivalent to biliary sphincterotomy and include early complications of acute pancreatitis (2-7%), bleeding (0-2%), perforations (< 1%), and late complications of sphincter stenosis (up to 10%) [48-50].

Extraction balloons, baskets, and forceps

These devices are used to sweep or capture pancreatic duct stones to deliver stones, sludge, and debris out of the duct system and into the small-bowel lumen. Extraction balloons are very safe to use during ERCP [51]. Unlike stone removal baskets, extraction balloons have no chance of becoming trapped inside the pancreatic duct because the balloon can simply be deflated [51]. Complication rates from such balloon use are very low. The greatest limiting factor for balloons is their fragility (they break when pulling against sharp edged stone) and inability to remove larger stones.

Stones captured with an open basket can be removed

by withdrawing the basket from the duct and pulling the stone out into the small intestinal lumen. Standard biliary baskets are partially effective. Smaller pancreatic stone baskets are more effective if the duct lumen is < 5 mm. Some baskets can be used to forcefully crush stones, a process known as mechanical lithotripsy [52]. The greatest limitation to basket use is the inability to capture a stone within a < 6-mm-diameter duct. Stone extraction baskets are associated with a greater risk of complications than extraction balloons. Although uncommon, stone extraction baskets can become trapped (impacted) in the pancreatic ducts when grasping a stone that is larger than the downstream duct. A variety of endoscopic, ESWL, interventional radiological, and surgical techniques have been used to remedy this situation [53-56].

Rat tooth forceps can also be used to capture stones in the distal 1-2 cm of the main duct. Use of forceps is relatively safe compared to baskets; however, inserting the forceps into the pancreatic duct can be difficult, resulting in trauma of the pancreatic duct.

Dilation and stenting of pancreatic ductal strictures

Stricture dilation may be required to facilitate stone removal or stent placement (Fig. 1). Benign strictures of the main pancreatic duct are generally due to inflammation and fibrosis around the main pancreatic duct. High-grade strictures require dilation prior to insertion of the endoprosthesis. A guidewire must be maneuvered upstream through the narrowing before stenting or dilation of the stricture with a balloon or dilating catheter. Pancreatic duct strictures due to chronic pancreatitis are often densely fibrotic; thus, simple balloon dilation alone does not generally result in a satisfactory long-term response. Therefore, a benign stricture of the main pancreatic duct is usually managed by placing one or multiple plastic stents. Limited trials have been conducted using metal stents for benign strictures of the pancreatic duct [57,58]. The goal of stenting is to progressively dilate the stricture over 6-12 months with larger stents until the stricture narrowing has disappeared, which requires three to five ERCP sessions. The optimum duration of stent placement, stent number and diameter, and degree of balloon dilation are not well known. Post stenting mild pancreatitis occurs in 5-10% of patients. Late complications are mainly related to stent migration and occlusion, which present with pain, pancreatitis, or infection [12]. Additionally, pancreatic

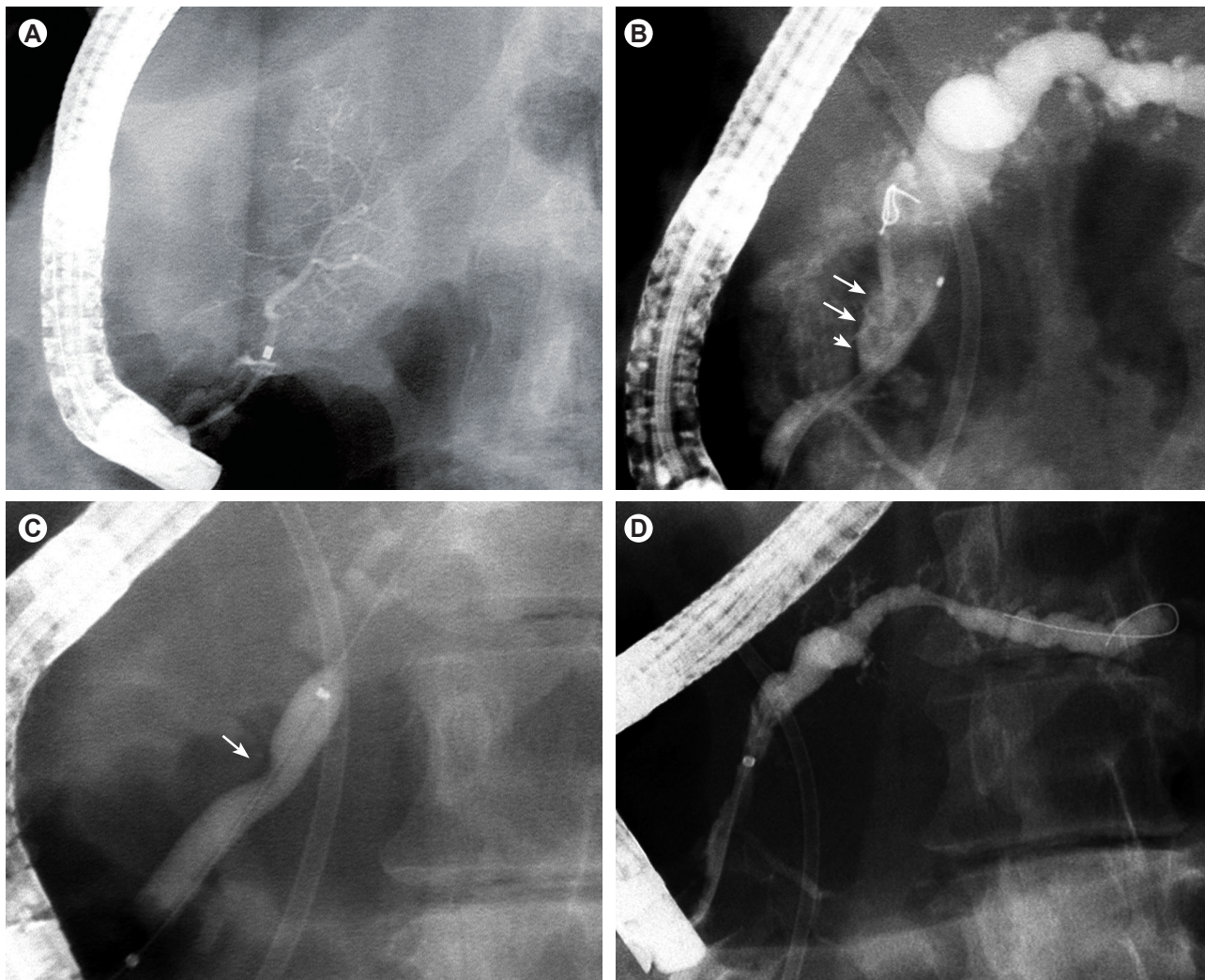


Figure 1. Endoscopic removal of main pancreatic duct stones via the minor papilla. (A) Pancreatogram via major papilla shows blockage of main pancreatic duct suggestive of pancreas divisum. (B) A pancreatic duct stricture (arrowhead) and multiple filling defects (arrows) were observed in the main pancreatic duct. (C) This stricture was dilated using a controlled radial expansion balloon after a pancreatic sphincterotomy. Waist (arrow) of the expanding balloon. (D) No filling defect in the main pancreatic duct was observed after complete stone removal. A pancreatic duct stricture still existed, which was treated with pancreatic stenting.

duct stents may produce ductal changes adjacent to the stricture; however, these changes may improve with time [59,60]. Further research with covered and uncovered metal stents is needed.

Intraductal mechanical lithotripsy

Mechanical lithotripsy using a through-the-scope mechanical lithotripter is technically difficult and has limited success with large pancreatic calculi, particularly when capturing the stones is difficult [61]. Data on mechanical lithotripsy for pancreatic duct stones are limited but suggest that this procedure is performed rarely and carries an increased risk for complications when compared with

lithotripsy for biliary stones [61]. The complication rate of pancreatic mechanical lithotripsy appears to be threefold greater than that for biliary mechanical lithotripsy [52]. The most common complication is a trapped/broken basket (87%) due to hard stones [52]. Acute pancreatitis and pancreatic duct disruption also occur. We use this technique only for a trapped basket during standard extraction.

EHL

Few data are available regarding intraductal EHL for pancreatic duct stone fragmentation [62], which must be done under direct vision with a pancreatoscope via a spe-

cialized mother-daughter scope system. EHL has the advantage of delivering high energy to a tightly focused area of the stone. The high energy delivered carries the risk of duct injury including perforation if directed at the duct wall [63]. We have used the “SpyGlass” pancreatoscope to treat two patients (unpublished data). Further studies are needed.

ESWL

A significant advancement in pancreatic duct stone removal has been achieved with the application of ESWL for fragmentation. Once fragmented, stone pieces may exit spontaneously or with the aid of ERCP techniques. ESWL has been used to facilitate the removal of pancreatic duct

stones during ERCP (Fig. 2). Some studies have reported high stone clearance success rates with ESWL, whereas others have had less impressive results [14,32]. ESWL overcomes the problem of stone size by fragmenting the stones and reducing the stone burden, thus facilitating endoscopic clearance of the duct [24,64,65]. ESWL, which works by concentrating focused shock waves on stones, was first used in the field of gastroenterology by Sauerbruch et al. [66,67] to fragment gall bladder stones and was used later for pancreatic duct stones. Radiopaque stones can be easily targeted by ESWL under fluoroscopy; radiolucent stones can be targeted using ultrasound-guided shock wave lithotripsy or by injection of contrast through a nasopancreatic catheter. ESWL of main pancreatic duct

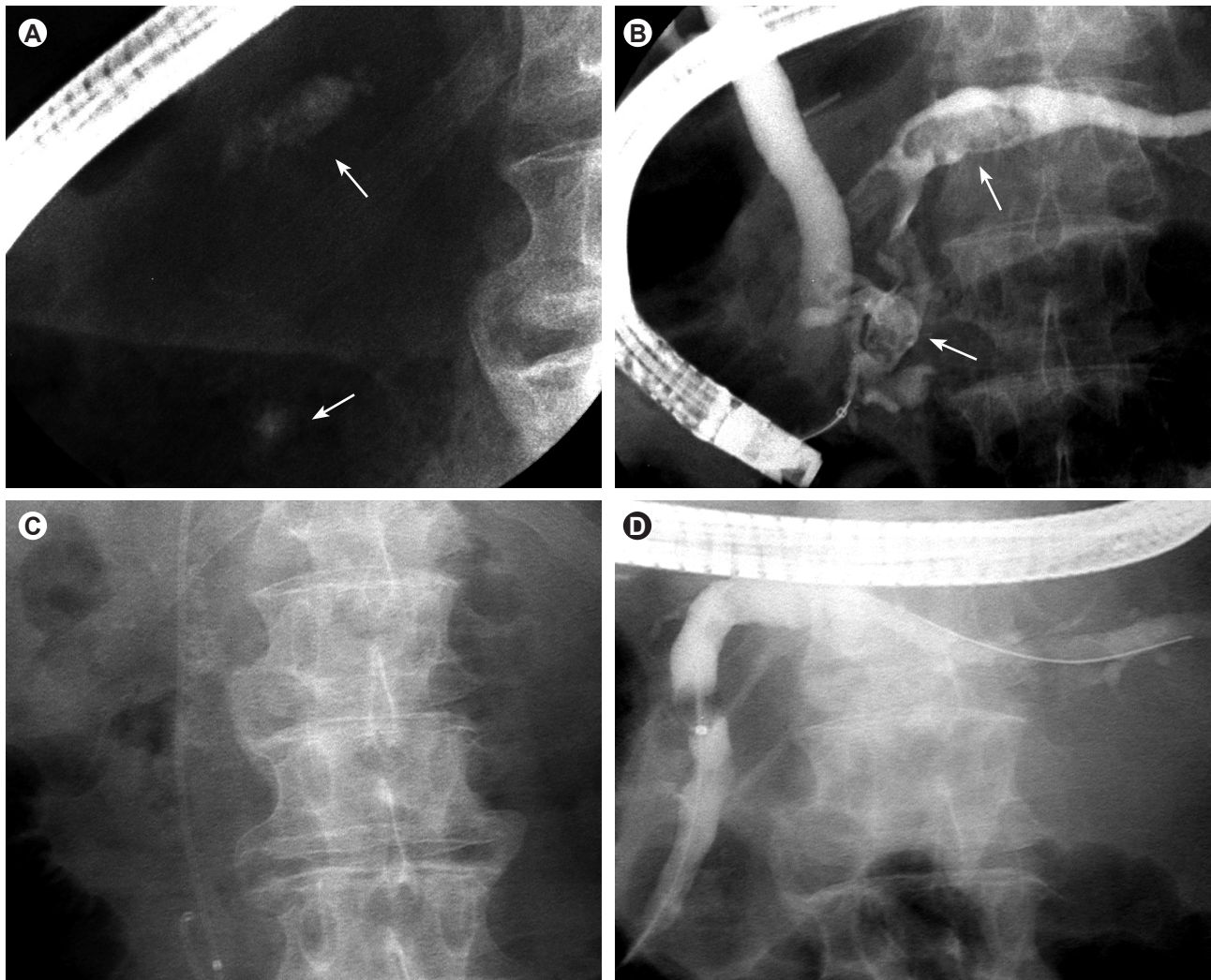


Figure 2. Extracorporeal shock wave lithotripsy (ESWL) to facilitate removal of pancreatic duct stones. (A) Two pancreatic calcifications (arrows) are seen on the plain film. (B) Two filling defects (arrows) were observed in the main pancreatic duct, which were difficult to remove due to their large size. (C) Radiopaque stones seen alongside the pancreatic stent were fragmented successfully after ESWL. (D) Fragmented pancreatic stones are removed by sweeping using a retrieval balloon.

stones is largely considered complementary to endoscopic techniques for stone clearance but has even been proposed as a possible first-line treatment [6,15,68,69].

Early reports of ESWL for obstructing pancreatic duct calculi describe a high degree of technical and clinical efficacy [42,46,47]. A recent large review of the ESWL literature concluded that ESWL results in complete duct clearance in 50% of patients [65]. Complete removal rates differ among institutions. These differences may be due to the type of lithotripter used, the power setting, the number of shocks delivered, the number of treatment sessions, and differences regarding the definition of complete removal of pancreatic stones among institutions. Our group preliminarily reported intravenous secretin-aided fragmentation of main pancreatic duct stones by creating a fluid-filled

space at the circumference of the stones and flushing out the stone fragments during ESWL [70]. In that report, secretin showed a significantly higher rate of complete main pancreatic duct stone clearance. Long-term follow-up studies have shown that ESWL combined with endoscopic drainage of the pancreatic duct relieves pain and may avoid the need for surgery in approximately two-thirds of patients [15,68]. In a randomized study comparing the response of ESWL alone (n = 26) and after ESWL combined with endoscopy (n = 29), the investigators concluded that ESWL alone is a safe, effective, and preferred treatment for select patients [69]. Our suggested general approach for managing patients with pancreatic duct stones is summarized in Fig. 3.

ESWL is a relatively safe technique [69]. The minor

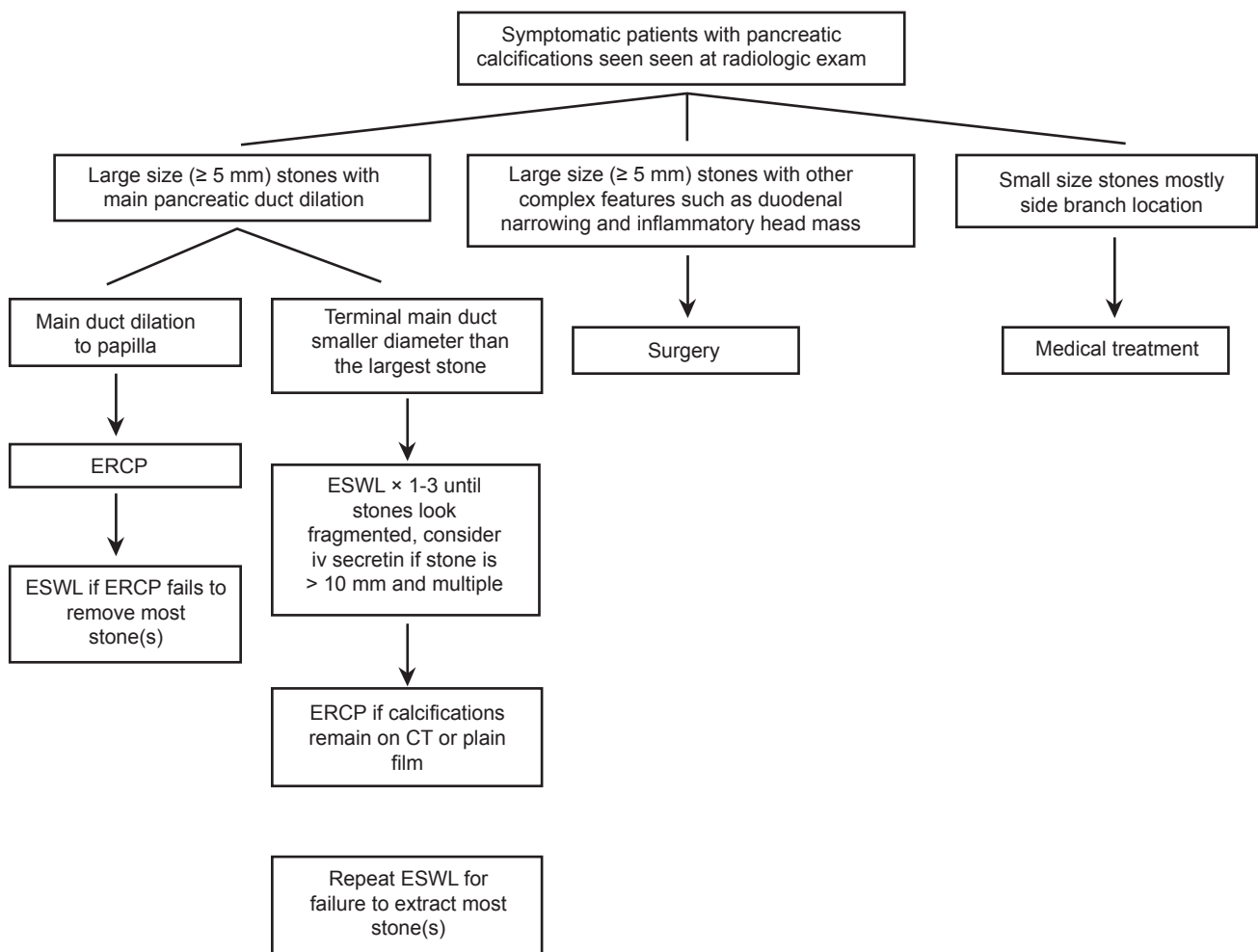


Figure 3. Our suggested algorithm for patients with pancreatic duct stones. ERCP, endoscopic retrograde cholangiopancreatography; ESWL, extracorporeal shock wave lithotripsy; CT, computed tomography.

complications from ESWL include skin or duodenal contusions, exacerbation of pancreatitis, mild abdominal discomfort, and asymptomatic hyperamylasemia. Acute pancreatitis attributed to ESWL has been reported in 6.3-12.5% of patients after ESWL "alone" for treating calcified chronic pancreatitis [6,71]. Serious complications after ESWL have been reported in < 1% of patients [72]. We observed one patient with a right renal subcapsular hematoma. This treatment is often painful and requires general anesthesia or large doses of analgesics. One study has reported that epidural anesthesia produces effective analgesia for these procedures [73].

ESWL for pancreatic duct stones is being performed in South Korea although publications are limited. Cost-effectiveness should be considered in the overall management.

CONCLUSION

Pancreatic duct stones were often considered unimportant or untreatable. However, several effective modalities to treat pancreatic duct stones including ESWL, as well as endoscopic and surgical options, are now available. The patient should help decide whether one surgical session or two or more less-invasive sessions are preferred. Additional prospective randomized studies are needed to further establish the optimal strategy for pancreatic duct stone management.

Conflict of interest

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

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