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NARRATIVE REVIEW

Endoscopic interventions in pancreatic strictures and stones—A structured approach

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Abstract

Chronic pancreatitis (CP) is an irreversible disease of varied etiology characterized by destruction of pancreatic tissue and loss of both exocrine and endocrine function. Pain is the dominant and most common presenting symptom. The common cause for pain in CP is ductal hypertension due to obstruction of the flow of pancreatic juice in the main pancreatic duct either due to stones or stricture or a combination of both. With advances in technology and techniques, endoscopic retrograde cholangiography (ERCP) and stenting should be the first line of therapy for strictures of the main pancreatic duct (MPD). Small calculi in the MPD can be extracted by ERCP and balloon trawl. Extracorporeal shockwave lithotripsy (ESWL) remains the standard of care for large pancreatic calculi and aims to fragment the stones 3 mm or less that can easily be extracted by a subsequent ERCP. Single operator pancreatoscopy with intraductal lithotripsy is a technique in evolution and can be tried when ESWL is not available or is unsuccessful in producing stone fragmentation.

Keywords Chronic pancreatitis · ESWL · ERCP · Pancreatoscopy

Introduction

Chronic pancreatitis (CP) is a disease of diverse etiology resulting in irreversible changes in the pancreas. Progressive fibrosis leads to loss of both exocrine and endocrine pancreatic function.

Pain is the dominant feature of CP, being the presenting symptom in over 70% of patients and is eventually seen in 80% to 90% of cases [1–3]. Ductal hypertension is the commonest cause for pain in CP and is due to the obstruction of flow of pancreatic juice in the main pancreatic duct (MPD), either due to stricture or stone or a combination of both [4]. Both endoscopy and surgical therapy are aimed at reducing this ductal hypertension and providing relief from the often excruciating pain present. Pain in CP is, however, multifactorial and other pathophysiological mechanisms include tissue or neural ischemia, neural entrapment, nociception and visceral or central hypersensitivity [5]. These multiple mechanisms of pain explain the persistence of pain in a few patients despite adequate clearance of the MPD.

In this review, we discuss the endoscopic management of strictures and stones following CP.

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Pancreatic ductal strictures

Strictures of the MPD are a common sequelae of CP and are due to inflammation or fibrosis. Incidence of MPD strictures was 18% and 22% in two of our large studies in patients of CP who underwent extracorporeal shockwave lithotripsy (ESWL) therapy for large pancreatic calculi [6, 7].

MPD strictures are defined as high grade narrowing with one of the following [8–10]:

a. MPD dilatation > 6 mm beyond the stricture.
b. Failure of contrast to flow across the stricture or 6 Fr naso-pancreatic tube (NPT) placed across the narrowed area.
c. Pain abdomen on continuous infusion across an NPT placed beyond the stricture.

Endoscopic therapy is ideally indicated for a symptomatic single dominant stricture in head, genu or proximal body.

Multiple strictures in body (chain of lake appearance) or isolated strictures in the tail are not amenable to endotherapy. Malignancy should always be excluded in any stricture of the MPD due to CP. The incidence of malignancy has been reported to be 1.8% at 10 years and 4% at 20 years [11]. Various Indian studies have reported the increased incidence of pancreatic cancer in "tropical pancreatitis," varying between 4% and 8.3% [12, 13]. Appropriate assessment based on the clinical profile, imaging, tumor markers and histology are required to exclude the possibility of malignancy.

Endoscopic retrograde cholangio pancreatography (ERCP) is the procedure of choice in the management of pancreatic strictures. Following deep cannulation of the MPD, a pancreatic sphincterotomy (PS) is performed. The stricture is then dilated with a Soehendra dilator, balloon dilator or a Teflon bougie up to 6 mm [8, 9]. A prior biliary sphincterotomy is only performed if there is an indication for biliary drainage or very rarely to gain access to the MPD [14]. Single plastic stents between 7 and 10 Fr have been used with less chances of stent blockage being reported with a larger stents [14]. In our experience at Asian Institute of Gastroenterology (AIG), a 7-Fr single pig tail stent (SPTS) is ideal for use at the initial ERCP (Figs. 1 and 2) [10]. Based on the treating endoscopist's judgement, a 10-Fr stent in side holes can also be considered. Stent exchanges have been advocated between three and six months and the European Society of Gastrointestinal Endoscopy (ESGE) guidelines suggests that single plastic stent should be placed continuously for one year with appropriate exchanges during that time [14]. Strictures that do not respond to this protocol are referred to as refractory strictures of the MPD. Refractory strictures are best treated with multiple plastic stenting (MPS), fully covered self-expanding metal stents (FC SEMS) or surgery. Cumulative data from many studies had shown pain relief in 70% to 94% of patents on a follow-up of 14–69 months while using single stents [9]. However, a high recurrence rate of 38% at two years after stent removal has been reported [15]. Costamagna et al. introduced the concept of MPS for strictures of MPD in CP. On failure of resolution after the placement of a single plastic stent, multiple plastic stents were placed varying between 8.5 Fr and 11.5 Fr in diameter [16]. These stents were extracted after 12 months. Stricture resolution was seen in 95% and on a 38-month follow-up pain relief was seen in 84% of patients. An average of three stents were placed per patient. Other studies on longer follow-up of 9.5 years revealed pain relief in 89.5% and 77.1% of patients, respectively [17, 18].

Plastic stents can be associated with complications. Occlusion of the stent was seen in 10% of patients with passage of time [19]. Distal migration and impaction on the opposite duodenal wall can lead to perforation, while proximal migration into the pancreas is a challenge for the endoscopist. Distal migration of 3.6% and proximal migration of 2.7% have been reported [14]. The use of SPTS can avoid internal migration and is the practice followed at our institute. The possibility of stent-induced fibrosis in the

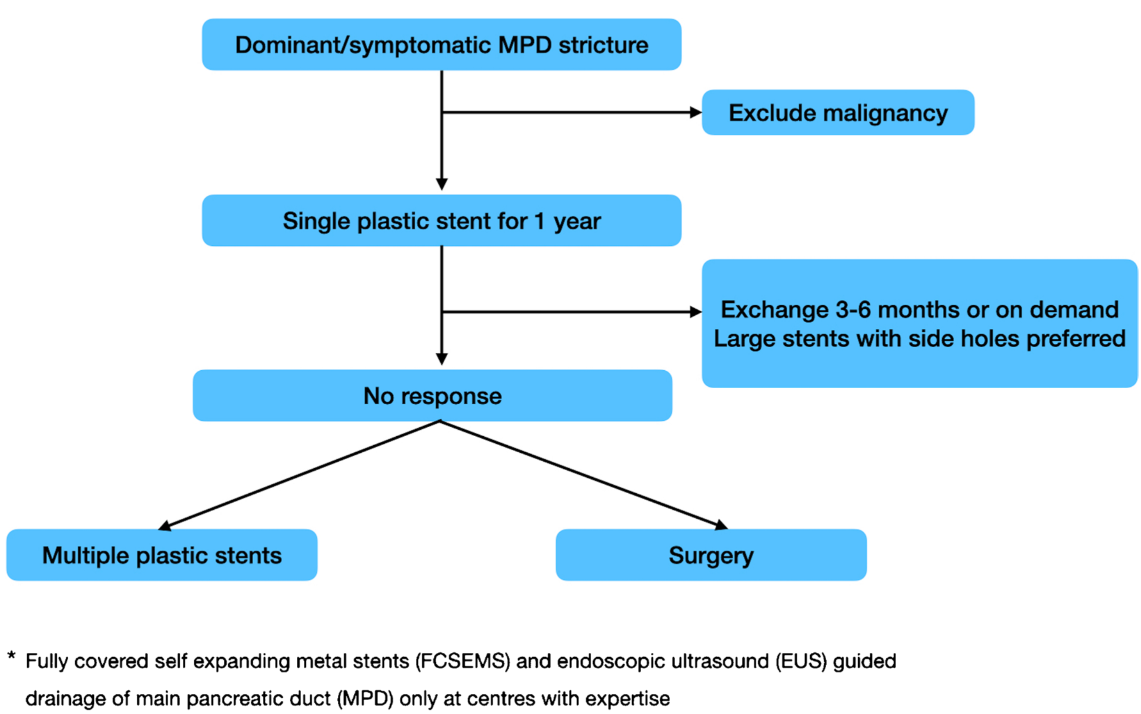

Fig. 1 Structured protocol for main pancreatic duct strictures

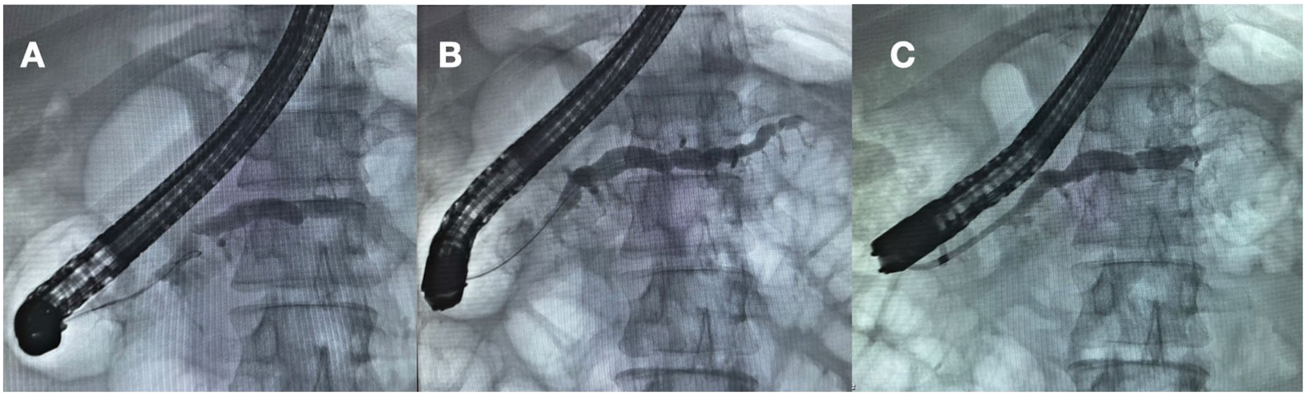

Fig. 2 Endotherapy for pancreatic duct strictures. **A** Stricture in pancreatic duct in head traversed with guidewire, **B** upstream dilated pancreatic duct, **C** single pigtail (7 Fr) pancreatic stent placed

MPD on long-term stenting is also a matter of concern [20]. Other complications include mild pancreatitis (6.2%), sepsis (2.6%), cholangitis (2.3%) and post sphincterotomy bleeding (1.5%) [14]. Severe pancreatitis is rare following stenting in CP [21]. Different types and designs of plastic stents have been deployed to drain the MPD. These include straight stents, SPTS, S-shaped stents, winged stents and stents without side holes [22, 23]. Stents with larger diameter and larger side holes had shown to have less chances of occlusion [24].

FC SEMS have been deployed for refractory MPD strictures. Pain improvement was seen in 85% of patients in four prospective studies which included 61 patients [25]. Three studies of long-term follow-up up to four years revealed pain improvement in 37% to 88% of patients [26–28]. The limitations of FC SEMS included migration (15% to 46%) and development of de novo strictures (16% to 27%) [14]. Many anti-migratory devices have been used to minimize the incidence of migration. A Niti-S Bumpy fully covered SEMS (Taewoong Medical, Gimpo-S, South Korea) is now used, where the contours of the stent adopt to the shape of the MPD and reduce migration. Retrospective analysis of 33 patients with refractory strictures who underwent FC SEMS placement revealed a technical success of 100% and clinical success of 93%. A significant reduction in pain scores and narcotic use was seen in 87% of patients. FC SEMS were removed after 14 months in this study [29]. Long-term follow-up of 33 months median revealed efficacy better than that of plastic stents [30]. Li et al. in a meta-analysis of seven prospective and three retrospective studies including 163 patients analyzed the efficacy of FC SEMS in pancreatic strictures. Stricture resolution was seen in 90% and recurrence in 5% of patients. Duration of stent placement of more than three months did not improve resolution when compared to duration of three months or less. Adverse effect reported were stent migration in 14.1%, acute pancreatitis in 8.6%, severe abdominal pain requiring stent removal in 1.2% and suppurative ductitis from food bolus obstruction of the FC SEMS in 1.2% and de novo strictures in 7.4% [31]. A recent prospective study from India followed up 11 patients with refractory MPD strictures using a Bumpy stent. Median stent indwelling time of seven months (six to 10 months) and a median follow-up of 48 months (40–60 months) were done. FC SEMS can be placed for three to six-month duration in our opinion. Significant decrease in pain score was reported and de novo strictures were seen in one patient (9%). No other adverse effects were observed [32].

Biodegradable non-covered self-expanding stents have not gained much popularity in routine clinical practice. A pilot study was performed in 19 patients who had no stricture resolution six months after placement of plastic stent. Clinical success was seen in 10 of 19 patients (53%) and adverse effects in four of 19 patients (21%) [33].

Endoscopic ultrasonography (EUS) is indicated in those patients with symptomatic strictures of MPD and with failed transpapillary drainage. MPD is punctured through the gastric or duodenal wall and a rendezvous procedure or direct transmural plastic or FC SEMS is deployed [14, 34, 35]. Considerable expertise is required. Rendezvous technique provides physiological pancreatic duct drainage as compared to rendezvous technique, although the technical success can be lower [36]. The procedure is only to be attempted at large volume tertiary care centres.

Pancreatic calculi

Pancreatic calculi (PC) are sequelae of CP and are seen in 50% of patients with the incidence reported to be as high as 100% on follow-up of 14 years [2, 37–39]. Stones were more common in men, heavy alcohol consumers (> 80 gm/day) and heavy smokers (> 20 cigarettes/day) [40]. These calculi contain a central nidus of amorphous trace elements such as nickel, chromium and iron. Calcium carbonate is deposited in layers over this nidus forming a calculi. Calculi along with strictures are the cause for obstruction of the MPD leading to the development of ductal and parenchymal hypertension. These PC may be classified based on density (radio opaque, radiolucent or mixed), number (single, multiple) or location (head, body or tail). They can also be intraductal in the MPD or in the secondary branches and parenchyma.

A recent study has shown that complete ductal clearance by any technique can lead to significant reduction in the diameter of MPD and correlate well with pain reduction [41].

The following techniques have been used for MPD clearance:

1. ERCP and stone extraction
2. ESWL
3. Intraductal lithotripsy using pancreatoscope with electrohydraulic lithotripsy (EHL) or laser lithotripsy (LL)
4. Chemical dissolution
5. Surgery

ERCP and stone extraction

MPD stones < 5-mm diameter and those which are radiolucent and located in the head and proximal body are ideal for extraction by the standard procedure of ERCP, deep cannulation, pancreatic sphincterotomy and balloon trawl or basket extraction. Balloons are liable for rupture because the calculi are spiculated and dense. It is better to use a mini or spiral basket for extraction because of the relatively smaller diameter as well as tortuosity of the MPD. The success rate of extraction at ERCP is, however, not encouraging. Large studies have revealed a complete stone clearance rate between 12% and 48.3% in studies of 680 and 810 patients, respectively, with endoscopy alone [42–44]. Large calculi spiculated edges that cause the calculi to be adherent to the ductal mucosa; smaller diameter of the MPD and its tortuosity as compared to the common bile duct make passage of accessories as well as extraction difficult [7]. A retrospective analysis of over 700 patients using mechanical lithotripsy revealed poor results and unacceptably high complication rates—thrice as high as compared to biliary mechanical lithotripsy [45]. Large stone size (> 10 mm), diffuse stone destruction, proximal stricture and stone impaction in MPD are factors associated with poor success rate [43, 46].

ESGE in its clinical guidelines states that for uncomplicated painful calculi > 5 mm in diameter in MPD, ESWL should be performed followed by subsequent ERCP to extract the fragments [14, 47]. These two guidelines published seven years apart have not changed indicating that ESWL has remained the standard of care for the management of large PC in the MPD [7].

Chemical dissolution

Trimethadone was first used in Japan in the 1980s and the same group has recently published a series of 13 successfully treated patients using this compound [48, 49]. Validation is, however, needed from other large centers prior to the acceptance of chemicals for dissolution in routine clinical practice. Its chief limitation is the long duration of use required to cause dissolution.

Surgery

Prior to advent of advanced endoscopic techniques, surgery was the standard of care for the management of sequelae of CP. Drainage, resection or their combination are the accepted surgical techniques. Surgery and endoscopic modalities are complimentary and not competitive. Proper selection of each patient decides the choice of therapy and ESGE guidelines state early referral for surgery in case of failure of endotherapy [14].

Extracorporeal shock wave lithotripsy

ESWL is presently accepted as the standard of care in the management of large symptomatic calculi in the MPD [6, 7, 14]. It is indicated for single or few calculi in the head, genu or proximal body (> 5 mm or impacted calculus). ESWL is to be avoided in patients with extensive calculi in the head, body and tail; associated tight strictures; presence of suspicious head mass or calcification in side branches and parenchyma. The aim of fragmentation in ESWL is to break the PC to < 3 mm in diameter or reduced the density of the stone mass (Fig. 3) [4, 6, 7, 14].

Third-generation lithotripters that use electromagnetic device to generate shock wave are ideal for fragmenting PC. About 6000 shocks are delivered per session at the rate of 90 shocks per minute and an energy level of 16kv (Fig. 4) [4, 6, 7, 39]. Sessions are performed on successive days till fragmentation is achieved. ERCP and PD clearance as a rule is performed the day after achieving adequate fragmentation. Stents are placed if clearance is not complete or there is an associated stricture. Most of the procedures are performed under epidural anesthesia and IV sedation. Total intravenous anesthesia and general anesthesia have occasionally been used at our institute and as well as other centers [7, 50].

The following criteria are employed to assess stone clearance [4, 6, 7, 51, 52]. This was assessed based on subjective assessment of the fluoroscopy image by the treating endoscopist:

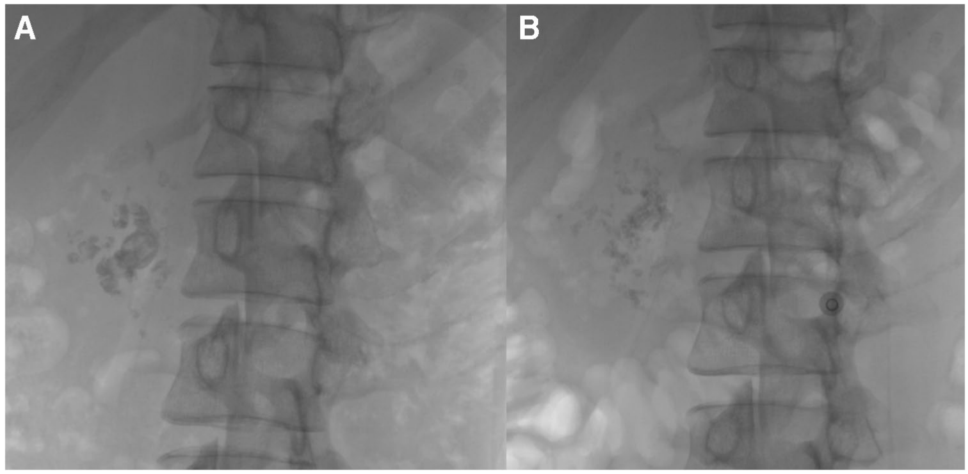

Fig. 3 Large pancreatic head radio-opaque calculi. **A** Pre-extracorporeal shock wave lithotripsy (ESWL), **B** post-ESWL. *ESWL* extracorporeal shock wave lithotripsy, *PC* pancreatic calculi, *US* ultrasound, *EUS* endoscopic ultrasonography, *CT* computed tomography, *MRCP* magnetic resonance cholangiopancreatography, *ERCP* endoscopic retrograde cholangiography, *EPS* extrapyramidal side effects, *PD* pancreatic duct, *NPC* non-pancreatic cyst

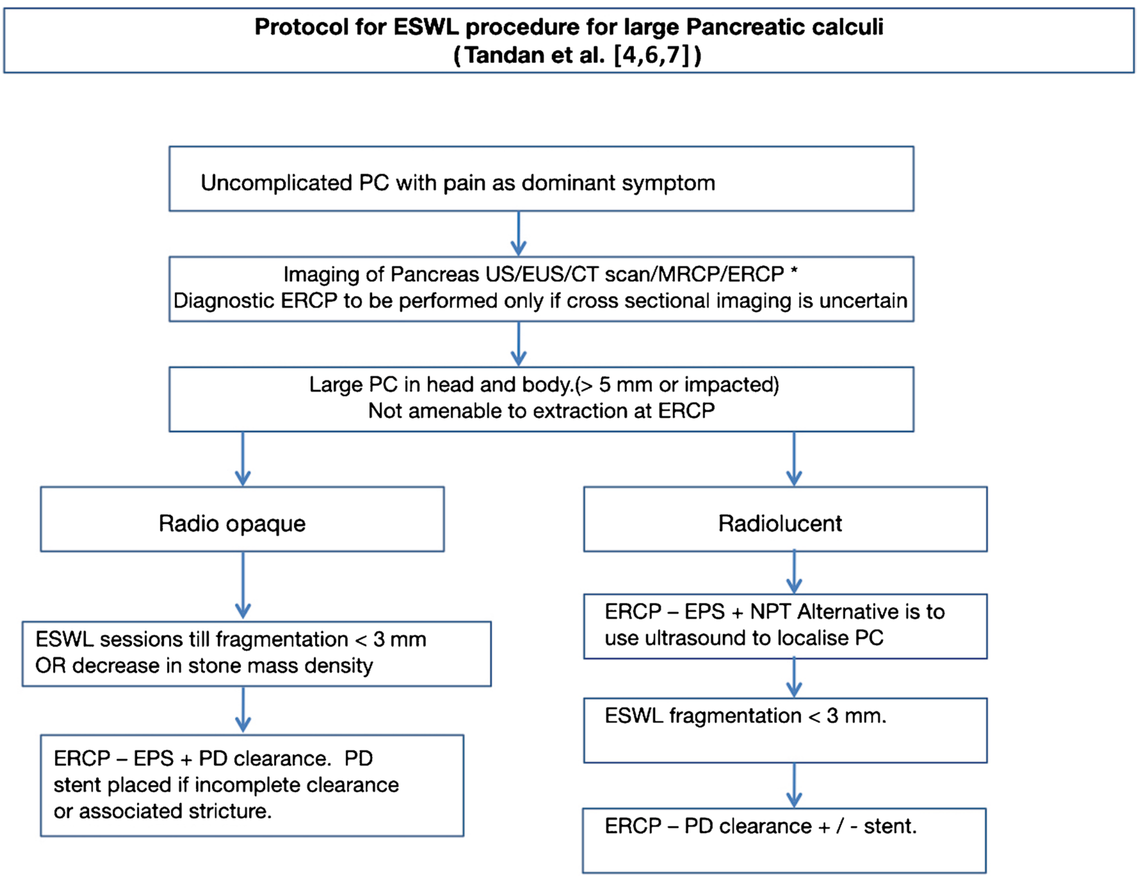

Fig. 4 Standard protocol followed at our institute while performing extracorporeal shock wave lithotripsy (ESWL) for large pancreatic calculi (PC)

a. Complete clearance—clearance of > 90% of stone volume.
b. Partial clearance—clearance between 50% and 90% of stone volume.
c. Unsuccessful clearance—clearance of < 50% of stone volume.

Clinical success is based on pain relief, decrease in use of analgesics, reduction in days of hospitalization and improvement in overall quality of life. In our experience of over 5000 patients, complete stone clearance was seen in 72.6%, partial in 17.3% and unsuccessful in the rest (Table 1). Pain relief was seen in 82.6% of patients on a six-month follow-up [7]. Table 2 shows clearance rate and pain relief seen in large studies from various centers all over the world [7, 42, 53–58].

Table 1 Details the characteristics of pancreatic calculi in our experience of over 5000 patients [7]

Factors	Categories	Number	%
Age	< 20 years	1066	20.8
	21–40	2475	48.3
	41–60	1035	20.1
	> 60	548	10.6
Female		1655	32.3
Etiology	Alcohol and/or smoking	495	9.6
	Idiopathic	4629	90.4
Stone characteristics	Single	3851	75.1
	Multiple	1273	24.8
	Radioopaque	4063	79.2
	Radiolucent	820	16
	Mixed	241	4.7
Stone location	Head	2824	51.1
	Body	1099	21.4
	Tail	384	7.4
	Head/body/tail	817	15.9
Associated stricture		1153	22.5
ESWL sessions	1	614	11.9
	2	1148	22.4
	3	2624	51.2
	4	534	10.4
	> 5 (maximum 8)	204	3.9
Fragmentation	Complete	3722	72.6
	Partial	886	17.3
	Unsuccessful	516	10
Pancreatic sphicterotomy		5022	98
Pancreatic ductal stenting		3536	69
Associated stricture		1153	22.5

ESWL extracorporeal shock wave lithotripsy

Clearance of MPD and subsequent pain relief have reported on a meta-analysis of 27 studies with over 3000 patients. Complete and partial stone clearance was seen in 70.7% and 22%, respectively. Complete pain relief was seen in 52.7% and reduction in intensity of pain in another 33.4%. Quality of life improved in over 88% of patients [52]. Those patients who have complete stone clearance as well as pain relief in the first two years after ESWL are found to have long-term pain relief [59, 60]. As CP especially in India is a disease of the young, long-term pain relief is an important criteria of success. In our experience of 272 patients followed up for eight years, pain relief and avoidance of analgesia were seen in 60% [58]. This follow-up has now extended to two decades and the results are similar. Long-term pain relief has also been reported from other centers [39, 61, 62]. Recurrence of calculi in our experience was seen in 22.8% of patients [7, 39]. However, not all patients with recurrent calculi develop pain. ESWL is also feasible with coexisting pseudocyst with disappearance of pseudocyst in 75% cases at one year with complete pain relief in over 60% [63].

Adverse effects of ESWL

ESWL is a safe procedure with practically negligible serious adverse effects. In our group, over 5000 patients' self-limiting complications were seen in 22% [7, 39]. These included pain at the site of contact of water cushion with abdominal wall in 13.5%, ecchymosis of the skin due to shock waves in 19% and mild pancreatitis in 3.5%. There was no mortality in this group. A report of over 1800 patients including over 1000 from our center revealed a complication rate of 5.8% and a single mortality (0.05%) [47]. Mild adverse effects were reported in 6.7% of 1470 ESWL procedures in another study [64]. Unusual anecdotal complications have been reported but are rarely seen in everyday practice. These

Table 2 Summary of pain relief and stone clearance with duration of follow-up in large studies in extracorporeal shock wave lithotripsy

Author	No of patients	Complete clearance (%)	Pain relief (%)	Follow-up (months)
Delhaye et al. [53]	123	59	85	14
Costamagna et al. [55]	35	74	72	27
Kozarek et al. [57]	40	-	80	30
Farnbacher et al. [42]	125	64	48	29
Dumonaceau et al. [54]	29	-	55	51
Adamek et al. [56]	80	-	76	40
Tandan et al. [58]	272	76	60	96
Tandan et al. [7]	5124	72.9	82	6

include hepatic sub-capsular hematoma, biliary obstruction, splenic abscess and rupture, bowel perforation and necrotizing pancreatitis [65–67].

Limitations of ESWL

Though ESWL is the first-line therapy for managing large PC, it has limitations. Failure to fragment the calculi is seen in about 10% of patients [7]. Identifications of such patients prior to the procedure could help redirect them to alternative therapy such as direct single-operator pancreatoscopy (DSOP) and lithotripsy or for surgery. Calculi of density > 820.5 HU on non-contrast CT have lesser chance of fragmentation [68]. Recurrence of calculi as reported earlier was seen in 22% of patients on follow-up [7, 14]. Trimethadone has been used to dissolve PC [48, 49]. Similar pharmacological agents could help dissolve recurrent calculi thus minimizing repeated interventions. Role of ESWL in reducing exocrine and endocrine functions as well as carcinoma have not been studied. A recent study from our center concluded that early ductal intervention can delay the onset of diabetes [69]. It is possible that disease progression can be modified by early intervention.

Lithotripsy under direct vision

Besides the extracorporeal approach, lithotripsy can also be performed under direct vision using a pancreatoscope. The earliest pancreatoscopy and cholangioscopy were diagnostic in nature and first performed in 1976 [70, 71]. Therapeutic per oral pancreatoscopy was first reported by Howell 1999 [72]. Direct pancreatoscopy gained acceptance and wider use with the development of Spyglass device (Boston Scientific, Mass, USA) and the newer version Spyglass DS which has a wider angle of vision and a large working channel of 1.3 mm.

Lithotripsy using this DSOP can be performed using electro hydraulic lithotripsy (EHL) or laser lithotripsy (LL). EHL is a bipolar probe which generates three different shock wave pulses. The first shock wave produces vapor plasma which causes cavitation in the target calculi. The second and third waves are generated by the rebound of cavitation bubble. These high-frequency hydraulic waves result in fragmentation of calculi [73]. Nd Yag laser is the common laser type used and is double pulsed. It comprises of 532-nm green light and 1064-nm infrared light. Plasma is produced on the stone surface and the infrared rays produce strong shock wave and fragment the stone. Holmium laser has a long wave length of 2100 nm and acts via photo thermal mechanism where energy is directly transmitted via the laser pulse to the stone [74].

Studies using DSOP and EHL or LL are few and with small numbers of patients as it is a technique in evolution. Review and meta-analysis report success rate of 91% and adverse effect in 14% of patients [75–77]. Comparative study of 240 patients who underwent ESWL and 19 who underwent DSOP and lithotripsy concluded that both are similar in efficacy but DSOP requires lesser sessions for complete fragmentation [78]. A study revealed clearance of 70% of 33 patients who underwent EHL and six who underwent LL [79]. Another study revealed that 18 out of 21 patients had complete clearance with one patient reporting mild pancreatitis [80]. Recent reports have reported the use of thulium laser for pancreatoscopy-guided lithotripsy, which has been shown to be highly effective for ureteral stones [81].

DSOP remains an attractive alternate to clear stone in MPD and this technique has been discussed in detail in recent review [82]. It is a technically difficult procedure and should be performed and at expert centers only. Adverse effects as high as 40% have been reported in small series with pancreatitis being the most common [83]. ESGE guidelines recommend that DSOP-guided lithotripsy should be performed where ESWL is not available or the calculi are not fragmented after an adequately performed ESWL [14].

Future research

Future studies should focus on controlled studies comparing extracorporeal approach and pancreatoscopy for pancreatic stones. Moreover, various intra-ductal lithotripsy methods need to be compared such as electrohydraulic lithotripsy, holmium laser lithotripsy and thulium laser lithotripsy.

To conclude, pancreatic strictures and calculi are common sequelae of CP and cause ductal hypertension leading to pain, which is the most distressing symptom of this disease. Proper selection of cases can identify the patient ideal for endotherapy and this should be offered as the first line of therapy in such patients. ERCP and ESWL remain the standard of care in managing this sequelae. EUS-guided drainage of the MPD and use of intra-ductal lithotripsy with the pancreatoscope should be reserved for cases not successfully treated by the earlier mentioned techniques. Further, these should only be performed at high-volume centers with expertise. Surgery is advised in all patients where endoscopy has not been successful in relieving the problem.

Author contribution Concept and design: MT; provision of study material/patients: MT, PP, NJ; acquisition of data: MT; data analysis and interpretation: MT, PP; preparation of initial draft: MT; critical revision of the manuscript: MT, PP, NJ, DNR; important intellectual inputs and revision: MT, PP, NJ, DNR; manuscript writing: all authors; approval of final manuscript: all authors.

Data availability All data associated with the paper is included in the manuscript.

Declarations

Competing interests MT, PP, NJ and DNR declare no competing interests.

Ethical approval Ethical approval exempted as review of existing literature.

Informed consent Informed consent was exempted as it was a review article.

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