Long-term follow-up after multiple plastic stenting for refractory pancreatic duct strictures in chronic pancreatitis

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ABSTRACT

Background Dominant pancreatic duct strictures in chronic pancreatitis are often managed by endoscopic placement of a single plastic stent. Insertion of multiple plastic stents (MPS) has been proven to be effective in managing refractory strictures, but data are still limited. The aim of this study was to investigate the efficacy and long-term results of MPS to dilate pancreatic duct strictures in chronic pancreatitis.

Methods 48 patients (34 men; mean age 44 years) with chronic pancreatitis and a single pancreatic stent through a refractory stricture in the pancreatic head underwent the following protocol: 1) removal of the single pancreatic stent; 2) balloon dilation of the stricture; 3) insertion of the maximum number of stents; 4) stent removal after 6 – 12 months.

Results The median number of pancreatic plastic stents placed was 3 (diameter 7 – 11.5 Fr, length 3 – 7 cm). Five patients (10.4 %) had persistent strictures after MPS removal. During a mean follow-up of 9.5 years (0.3 – 15.5 years) after stent removal, 74.4 % (32/43) of the patients were asymptomatic, and 25.6 % (11/43) experienced pancreatitis recurrence or pancreatic type pain after a mean time of 26.4 months (8/43, 18.6 % underwent plug extraction without evidence of stricture recurrence; 3/43, 7.0 % had stricture recurrence). No major complications were recorded.

Conclusion Endoscopic multiple plastic stenting of chronic pancreatitis-related pancreatic duct strictures showed satisfactory long-term results, with the option of re-treatment. This procedure can be considered an important therapeutic alternative for painful pancreatic duct strictures located in the head of the pancreas in the setting of chronic pancreatitis.

Introduction

Strictures of the main pancreatic duct (MPD) in the setting of chronic pancreatitis [1, 2] can be due to acute or chronic inflammation with fibrosis [3, 4]. The goal of endotherapy is to bypass MPD strictures to relieve pain related to ductal obstruction, and patients with a single dominant stricture located in the head of the pancreas are the best candidates for endoscopic stenting [5]. Several studies have investigated the short- and long-term results of pancreatic duct stenting in severe chronic pancreatitis and have demonstrated that decompression of the MPD provides relief of pain in most patients [5 – 12].

MPD-dominant strictures are usually managed by the placement of a single plastic stent, which is effective in pain resolution in the short term [1, 13]. However, definitive stent removal is not feasible in a subset of patients owing to suboptimal stricture dilation [5]. In this setting, some other endoscopic therapeutic options have been investigated to avoid the more invasive surgical decompression [1, 3]. Uncovered self-expandable metal stents (SEMS) have been tested, with disappointing re-

sults because tissue ingrowth makes stent removal almost always impossible [14]. Fully covered and removable SEMS showed more promising results, though they were accompanied by a series of complications including recurrence of pancreatitis, stent-induced "de novo" strictures, stent migration, and cholestatic liver dysfunction [15 – 22].

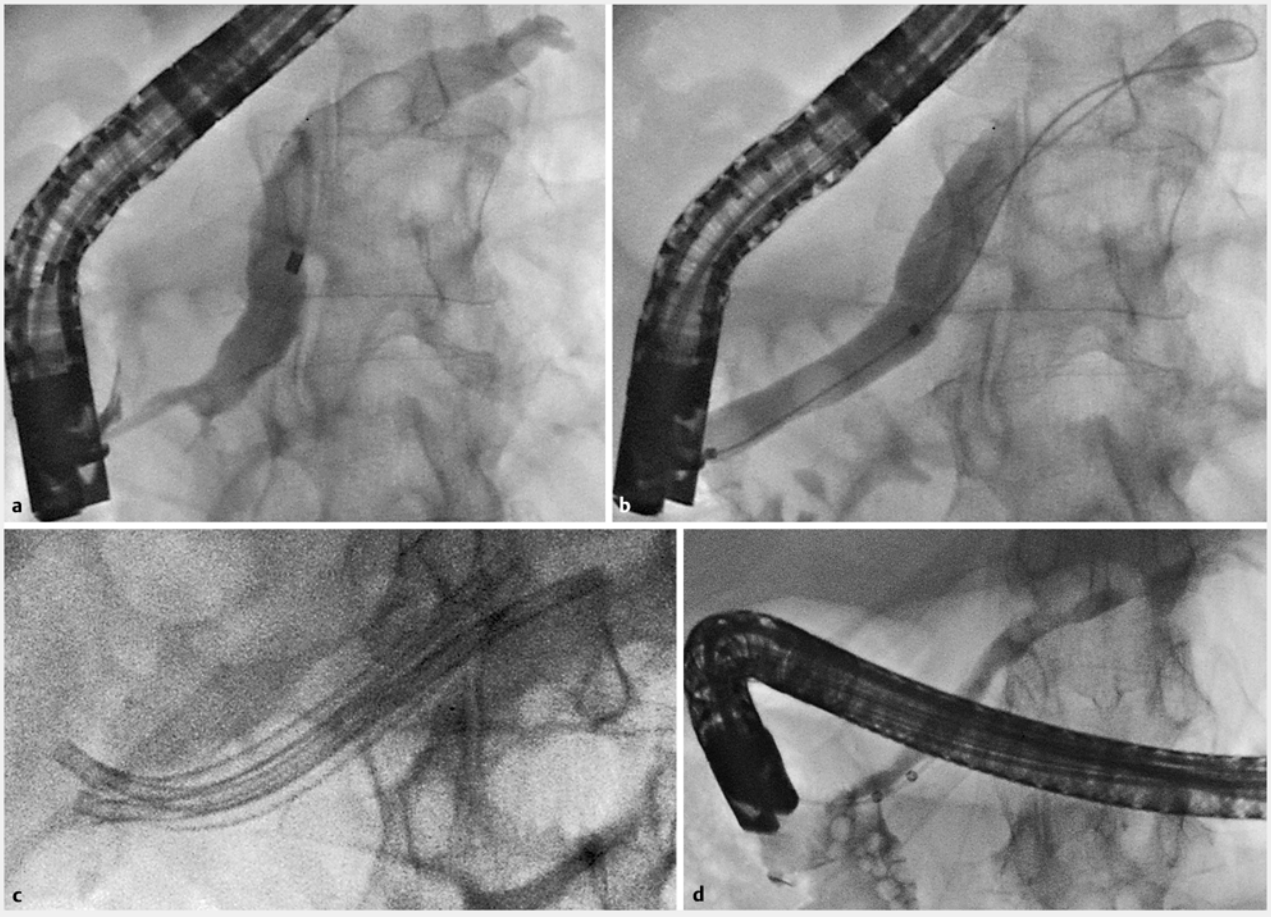
Following our encouraging experience of biliary multiple plastic stents (MPS) to manage benign postoperative biliary strictures [23], in 2006 we used the same therapeutic option to dilate benign pancreatic duct strictures in chronic pancreatitis [24], with promising results. The aim of the current study was to investigate the efficacy of MPS for unrelenting MPD strictures in a larger cohort of patients and with long-term follow-up.

Methods

From December 1999 until May 2018, all patients with chronic pancreatitis who underwent endotherapy at our Endoscopy Unit were retrospectively identified from the prospectively collected endoscopic retrograde cholangiopancreatography (ERCP) database. Patients with symptomatic MPD-dominant strictures refractory to treatment with a single plastic stent were consecutively treated by MPS according to our previously published inclusion criteria [24], as follows: dominant pancreatic duct stricture in the pancreatic head, requiring plastic stenting following pancreatic sphincterotomy at the beginning of endotherapy; recurrent epigastric pain due to pancreatic stent dysfunction; at least two previous placements of a single pancreatic plastic stent (≥ 8.5 Fr in diameter) for 3 months; persistence of the pancreatic head stricture after stent removal; and upstream pancreatic duct dilation > 6 mm.

Refractory dominant stricture in the head of the pancreas was defined as a definite narrowing of the pancreatic duct creating obstruction to pancreatic flow, with persistence of contrast medium in the body and tail for more than 5 minutes after stent removal [24].

The primary study outcome was symptom-free period, defined as no hospitalization for pancreatic pain recurrence or pancreatitis relapse.



▶ **Fig. 1** Endoscopic retrograde cholangiopancreatography images of treatment with multiple pancreatic plastic stents. **a** Main pancreatic duct stricture refractory to a single plastic stent. **b** Balloon dilation (6 mm) of the stricture. **c** Insertion of four pancreatic plastic stents. **d** Stricture resolution after removal of multiple plastic stents.

Endoscopic procedure

ECRP was performed with the patient under propofol sedation or general anesthesia at the discretion of the anesthesiologist. The treatment protocol [24] included four steps:

1. removal of the single pancreatic stent (▶ **Fig. 1a**);
2. balloon dilation of the stricture (6 – 8 – 10 mm according to MPD diameter upsteam) (▶ **Fig. 1b**);
3. insertion of the maximum number of stents allowed by the tightness of the dilated stricture and by the diameter of the MPD (▶ **Fig. 1c**);
4. removal of all stents after 6 – 12 months (▶ **Fig. 1 d**).

To avoid intraductal migration during placement of the stents, the first stent was 2 cm longer than subsequent stents.

Following the procedure patients were given analgesic therapy for 24 hours, with nonsteroidal anti-inflammatory drugs (NSAIDS)/opioids as needed.

After pancreatic stent removal, stricture dilation was assessed according to the following criteria [24]: easy passage of a Fogarty balloon inflated to the same diameter size as that of the pancreatic duct in the body; absence of pain during continuous saline perfusion (1000 mL/24 hours) through a 5 – 7 Fr nasal-pancreatic catheter inserted after stent removal; free flow of contrast medium alongside the nasopancreatic catheter on pancreatogram.

Follow-up

Follow-up was defined as the time from MPS removal until last contact or death, whichever occurred first. The clinical condition of the patients was evaluated every 6 months for the first 2 years, and then annually by a telephone interview focusing on general condition, pain relief/recurrence, and the need for endoscopic re-treatment. If the patient referred to pain during the telephone interview, medical consultation was offered or the general practitioner who followed the patient was contacted. During the last follow-up performed in September 2018, the results of the treatment were assessed by means of a dedicated quality of life questionnaire (Patient's Global Impression of Change [PGIC]): the efficacy of the medical intervention is graded on a 7-point scale, ranging from no perceived benefit of the procedure to very high perceived benefit [25]. Radiological investigations (computed tomography scan, magnetic resonance pancreatography) were not performed systematically but only at the discretion of the physicians based on clinical evaluation.

The ethical committee of the Catholic University of Rome approved data collection and follow-up of patients with chronic pancreatitis treated endoscopically at our Institution (25 May 2017, protocol #0026801/17).

Statistical analysis

The log rank test and chi-squared test were used to compare the length of the symptom-free period after the removal of multiple stents with the symptom-free period achieved by placement of a single stent. A two-tailed *P* value of <0.05 was considered significant. The distribution of symptom-free periods over time was estimated by the Kaplan-Meier curve.

All analyses were performed using MedCalc Statistical Software version 14.8.1 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2014).

Results

Between December 1999 and May 2018, 375 patients underwent ERCP for painful chronic pancreatitis (▶ **Fig. 2**); 48 patients (34 men; mean age 44 years), including those reported previously [24], with a dominant stricture in the head of the pancreas underwent MPS insertion. Patient characteristics are summarized in ▶ **Table 1**. Before MPS treatment, the mean number of ERCPs/patient for single pancreatic stent exchange was 2.7 (range 2 – 5).

Balloon dilation of the cephalic pancreatic duct stricture was successful in all cases through the major or minor papilla, according to anatomy. The most common diameters of stents used were 10 and 11.5 Fr. The length of stents ranged from 3 to 7 cm. Results of the endoscopic treatment are summarized in ▶ **Table 2**.

All patients experienced 24 – 48 hours of post-procedural abdominal pain, which was successfully treated with an NSAID (ketorolac) or opiates (pentazocine). Two patients (4.2 %) ex-

▶ **Fig. 2** Patient enrollment flow chart. ERCP, endoscopic retrograde cholangiopancreatography; FC-SEMS, fully covered self-expandable metal stent; MPD, main pancreatic duct.

▶ **Table 1** Characteristics of 48 patients treated with multiple pancreatic plastic stents (n = 48).

	n	%
Males	34	70.8
History of alcohol abuse*	16	33.3
Cigarette smoker	26	54.2
Pancreas divisum	12	25.0
Dominant dorsal duct	6	12.5
Extracorporeal shock wave lithotripsy	7	14.6

* Alcohol intake averaging more than 80 g/day for over 2 years.

▶ **Table 2** Features of plastic pancreatic stents (n = 48).

	Major papilla	Minor papilla	Major and minor papilla	
Site of multistent insertion, n (%)	31 (64.6)	16 (33.3)	1 (2.1)	
Median number of stents, n	3	3	6 (3 major, 3 minor)	
Stent diameter, n (%)			Major	Minor
▪ 7 Fr	1 (1.0)			
▪ 8.5 Fr	7 (6.7)	13 (24.5)		
▪ 10 Fr	71 (68.3)	31 (58.5)	1	1
▪ 11.5 Fr	25 (24)	9 (17.0)	2	2
Stent length, n (%)			Major	Minor
▪ 3 cm	12 (11.5)	5 (9.4)	1	1
▪ 4 cm	2 (1.9)	2 (3.8)		
▪ 5 cm	65 (62.5)	36 (67.9)	2	2
▪ 6 cm	1 (1.0)	1 (1.9)		
▪ 7 cm	24 (23.1)	9 (17.0)		

perienced mild pancreatitis, which was treated conservatively. All patients were asymptomatic during the indwelling stenting period.

All stents were successfully removed in all cases after a mean time of 6.8 months (range 6 – 18 months). At the time of removal, two stents (1.2 % of all 163 stents placed) had migrated proximally into the pancreatic duct; in both cases this happened in patients with pancreas divisum who received three stents through the minor papilla. Proximally migrated stents were successfully removed using foreign body forceps (FG-44NR-1; Olympus, Tokyo, Japan). Three complete distal migrations (1.8 %) were encountered; in these cases the pancreas had a normal anatomy.

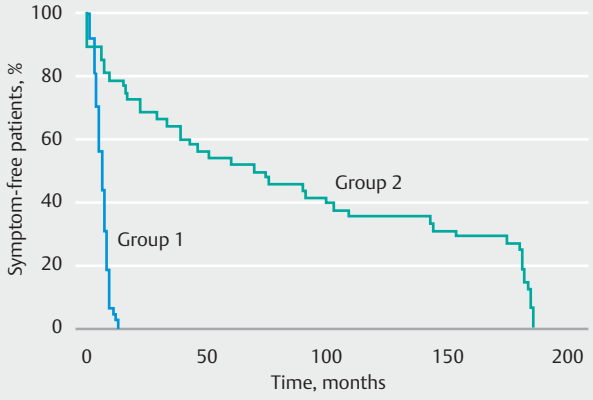
According to the criteria previously described, the dominant stricture was considered resolved upon removal of the MPS in 40 of the 48 patients (83.3 %). Eight patients (16.7 %) had a persistent stricture. A further pancreatic multistenting session with an increased number of stents was proposed, which all eight patients accepted. Three of them showed stricture resolution after the second treatment (overall success 89.6 %). In five patients (10.4 %), the pancreatic stricture was refractory after the second treatment. These patients refused surgery and agreed to an annual [13] or on-demand [26] single plastic stent exchange.

During a mean follow-up of 9.5 years (range 0.3 – 15.5 years), 32/43 patients (74.4 %) with the initial stricture resolution remained asymptomatic, whereas 11/43 (25.6 %) developed recurrence of pancreatitis or pancreatic type pain after a mean time of 26.4 months (range 5 – 108 months) and required a new ERCP to drain the MPD: 8/43 (18.6 %) had no evidence of stricture recurrence and the duct was successfully drained

▶ **Table 3** Results of treatment with multiple pancreatic plastic stents in 48 patients.

	n	%
Pancreatic duct stricture resolution		
▪ After the first treatment	40/48	83.3
▪ After the second treatment	43/48	89.6
Pancreatitis recurrence/pancreatic type pain after stent removal *	11/43	25.6
▪ Plug removal without stricture recurrence	8/43	18.6
▪ Pancreatic duct stricture recurrence	3/43	7.0

* Mean follow-up 9.5 years.



▶ **Fig. 3** Kaplan-Meier survival curve for symptom-free period in patients during single stent treatment (Group 1) and after removal of multiple plastic stents (Group 2) ($P < 0.0001$).

after pancreatic plugs were extracted, whereas 3/43 (7.0 %) had a pancreatic stricture recurrence that required re-stenting (▶ **Table 3**). Three patients died from unrelated causes during follow-up (two heart disease, one metastatic colon cancer).

After MPS removal, 16.3 % (7/43) and 32.6 % (14/43) of the patients continued to drink alcohol and smoke cigarettes, respectively. Symptom recurrence was not related to sustained alcohol intake (6/11) and smoking habits (3/11) ($P > 0.05$).

Kaplan-Meier curves (▶ **Fig. 3**) showed a significantly longer symptom-free period after MPS removal compared with single plastic stent treatment. Most patients (38/43, 88.4 %) reported an improvement in their quality of life after endoscopic treatment, as reflected in a mean PGIC score of 6.1 [25]. A comparison between subgroups of patients with pancreatic head calcification versus no pancreatic calcifications showed stricture resolution in 12/16 (75.0 %) versus 31/32 (96.9 %) patients, respectively ($P = 0.02$).

Considering our historical group of 19 patients [24] who were treated before 2006, 18 were alive after a mean follow-up of 16.7 years (range 15 – 18 years) and one patient had died from metastatic colon cancer without any symptoms related to

chronic pancreatitis. Two of the 16 patients who were asymptomatic at the follow-up published in 2006, had relapse of pancreatitis as a result of stricture recurrence and were re-treated by a single plastic stent.

Discussion

Refractory MPD strictures in chronic pancreatitis could be defined as persistent symptomatic dominant strictures after 1 year of single stent placement [26]. Surgical treatment of chronic pancreatitis is considered to be more effective than endoscopy [26]; however, in daily clinical practice, patients may sometimes refuse surgery because they perceived it to be "aggressive" and "risky", fuelled perhaps by material on social media and the realization that they can undergo less complex treatments [27]. Endotherapy can offer a less invasive approach for refractory MPD strictures by MPS placement and, in recent years, by placement of fully covered SEMS (FC-SEMS). The available evidence for FC-SEMS seems promising, with more than 80 % early stricture resolution and more than 85 % pain improvement [15 – 22]. Limitations of pancreatic FC-SEMS evidence include the short-term follow-up available (≤ 2.5 years) [20] and the reported high rate of various complications (pancreatitis, severe pain, stent-induced duct "de novo" strictures, cholestatic liver dysfunction, and migration) [15 – 21]. Thus, placement of pancreatic FC-SEMS needs further investigation in the setting of clinical trials [13].

The use of a single plastic stent to drain MPD strictures related to chronic pancreatitis is an effective treatment, achieving sustained pain improvement in 62 % – 83 % of the cases after a mean follow-up of 2 – 5.5 years [26]. MPD stricture resolution is not frequent after single plastic stent removal: according to a large study on 100 patients [5], pain control was obtained in only 62 % of cases after stent removal and re-stenting was needed in almost all cases after 2 years.

Placement of multiple pancreatic plastic stents seems a valuable option to obtain both pain relief and sustained stricture resolution according to our previous experience [24]. Following these promising results we continued treating refractory MPD strictures related to chronic pancreatitis according to the same protocol, thus enlarging our cohort of patients. After MPS removal, we observed pain resolution in 89.6 % of patients (43/48) and improvement in quality of life in 88.4 % of these patients (38/43) during a mean follow-up of near 10 years. These satisfactory results on long-term follow-up were assumed to be based on stricture resolution, but in long-standing chronic pancreatitis, pain relief can also be related to the "burn out phenomenon" and the development of pancreatic atrophy. In this clinical scenario, MPS of dominant pancreatic duct strictures in chronic pancreatitis can be considered as a "bridge" to a definitive symptom resolution.

In our series, initial MPD stricture resolution was 83.3 % after stent removal; a second session of multistenting was always feasible as the procedure can be repeated. All of the patients with stricture persistence were re-treated, and 3/8 (37.5 %) were cured without additional morbidity. Adverse events related to the insertion of multiple pancreatic plastic stents were rare in our experience, and plastic stent migration (proximal or distal) was very low (< 2 %) compared with that reported for FC-SEMS [15, 20, 22].

The subgroup analysis of the five patients with MPD stricture persistence showed that pancreatic calcifications were present in four of the patients. Pancreatic head calcifications can be considered a predictive factor for failed MPD stricture dilation even after MPS, similarly to the setting of chronic pancreatitis-related biliary strictures [28]. Patient compliance with the planned and repeated endoscopic procedures was acceptable in our series, with a mean indwelling stenting period of 6.7 months, reflecting the patient acceptance of the treatment.

One-third of the patients received stents through the minor papilla making treatment of chronic pancreatitis more challenging. This is one of the reasons why patients with chronic pancreatitis should be referred to centers with experienced endoscopists and a multidisciplinary team.

During our long-term follow-up, eight cases (18.6 %) required additional ERCP with extraction of pancreatic plugs/stones, which are related to the natural history of chronic pancreatitis. Indeed, after a mean follow-up of 9.5 years, the incidence of MPD stricture recurrence was 7.0 % (3/43), which is similar to the 6.7 % (1/15) observed when analyzing the historical cohort of patients [24], who have now been followed for an average time of 16.7 years.

The main limitations of our study are the absence of a control group and the retrospective design, with possible overestimation of treatment success and underestimation of complications.

Placement of multiple pancreatic plastic stents is considered an effective treatment for refractory chronic pancreatitis-related MPD strictures [13, 26] but it is technically demanding, unpopular, and has not been compared with FC-SEMS [26]. For these reasons, the usual daily practice for MPD strictures related to chronic pancreatitis remains single stent placement and surgery for cases of repeat stenting or stent failure [26]. Our results support the idea of changing the standard of care by positioning MPS in a stricture that persists for over 1 year after single stent placement [26].

In conclusion, in our experience endoscopic multiple stenting of dominant MPD strictures caused by chronic pancreatitis is feasible, safe, and effective in maintaining persistent dilation of the stricture and avoiding recurrent symptoms of chronic pancreatitis, including in long-term follow-up. Further multicenter prospective studies with a larger patient population and a comparison between MPS and FC-SEMS are required to confirm the efficacy of this procedure.

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Competing interests

Andrea Tringali was a consultant for Boston Scientific Corp. Ivo Boškoski is a consultant for Apollo Endosurgery. Dr. Costamagna was supported by grants or donations from Olympus. He is also a member of advisory committees or review panels for Boston Scientific and Cook Endoscopy.

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