

Role of endoscopic retrograde cholangiopancreatography in the management of benign biliary strictures: What's new?

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Abstract

Benign biliary strictures comprise a heterogeneous group of diseases. The most common strictures amenable to endoscopic treatment are post-cholecystectomy, post-liver transplantation, related to primary sclerosing cholangitis and to chronic pancreatitis. Endoscopic treatment of benign biliary strictures is widely used as first line therapy, since it is effective, safe, noninvasive and repeatable. Endoscopic techniques currently used are dilation, multiple plastic stents insertion and fully covered self-expandable metal stents. The main indication for dilation alone is primary sclerosing cholangitis related strictures. In the vast majority of the remaining cases, temporary placement of multiple plastic stents with/without dilation is considered the treatment of choice. Although this approach is effective, it requires multiple endoscopic sessions due to the short duration of stent patency. Fully covered self-expandable metal stents appear as a good alternative to plastic stents, since they have an increased radial diameter, longer stent patency, easier insertion technique and similar efficacy. Recent advances in endoscopic technique and various devices have allowed successful treatment in most cases. The development of novel endoscopic techniques and devices is still ongoing.

Key words: Benign biliary strictures; Bile duct stricture; Endoscopic retrograde cholangiopancreatography; Stents; Cholecystectomy; Liver transplantation; Primary sclerosing cholangitis; Chronic pancreatitis

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Core tip: Endoscopic treatment of benign biliary strictures has been evolved in the last decades and is widely considered as first line therapy. Among endoscopic techniques, multiple plastic stents placement is an

effective method but requires multiple endoscopic sessions. Fully covered self-expandable metal stents appear as a reasonable alternative due to their larger lumen and longer patency. Emergent data proved their efficacy, their low complications rate and cost-effectiveness. We herein discuss the endoscopic management of benign biliary strictures and focus on the outcomes, advantages and disadvantages of each endoscopic technique.

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INTRODUCTION

Endoscopic treatment for benign biliary strictures (BBS) has been evolving in the last decade. The vast majority of BBS are caused by postoperative biliary injuries [mainly post-cholecystectomy and orthotopic liver transplantation (OLT)] or chronic inflammatory disorders [such as chronic pancreatitis and primary sclerosing cholangitis (PSC)]. Less frequent causes of BBS include ischemia, trauma, autoimmune pancreatitis, radiation therapy, as listed in Table 1^[1-7].

Although BBS comprise a heterogeneous group of disorders with variable natural history, its etiology plays an important role in predicting endoscopic treatment success. Post-cholecystectomy BBS, whose incidence has increased 2-3 fold since the increment of laparoscopic cholecystectomy, are very responsive to endoscopic therapy^[8,9]. Bile duct strictures related to OLT can occur in 3% to 6% of patients. Among these, anastomotic strictures are more amenable to endoscopic treatment as compared to nonanastomotic strictures caused by ischemic injury^[5]. Approximately 10%-30% of patients with chronic pancreatitis will develop a symptomatic biliary stricture. However, these BBS are more resistant to endoscopic treatment with an overall lower success rate. On the other hand, BBS related to PSC showed a good response to endoscopic treatment^[5].

The diagnosis of BBS should lead to prompt treatment in order to avoid serious complications such as secondary biliary cirrhosis and end-stage liver failure^[3]. Treatment options for BBS include surgery, percutaneous approach, and endoscopic therapy. Endoscopic treatment is widely accepted as first line treatment option due to its efficacy and less invasiveness. The techniques currently used are dilation; single plastic stent; multiple large-bore plastic stents; and self-expandable metal stent (SEMS)^[1-3,5,6]. Recent advances in these endoscopic techniques and devices have allowed successful treatment of most BBS cases. When endoscopic treat-

ment fails, percutaneous and endoscopic combined approach may be attempted. Surgery is usually reserved for complete transections, prior endoscopic failure and refractory cases. Nevertheless, a consensus regarding the adequate management of BBS has not yet been established.

In this review, the authors will discuss the endoscopic management of BBS and focus on the outcomes, advantages and disadvantages of each endoscopic technique.

DIAGNOSIS

Diagnosis of BBS is usually based on the correlation between clinical, epidemiological, laboratorial data and imaging findings. Patients with biliary strictures can be completely asymptomatic or present with clinical and laboratory evidence of biliary obstruction, such as jaundice, abdominal pain, cholangitis and abnormal liver function tests^[10]. Clinical manifestations can also be related to the underlying cause of obstruction and its location. According to the distance from the stricture to the hepatic hilum, several classification systems for BBS have been proposed; most commonly used are Bismuth classification, which differs from malignant biliary strictures, and Strasberg classification (Table 2)^[11,12].

Abdominal ultrasound is typically the initial method for the evaluation of patients with biliary strictures. Accuracy levels over 90% in the detection of biliary dilation and the level of obstruction have been found. However, its accuracy for detecting the underlying cause is low and the results are operator dependent^[13].

Cross-sectional imaging modalities obtained both by computerized tomography and particularly magnetic resonance cholangiopancreatography (MRCP) can accurately delineate the biliary anatomy, location and length of the stricture. MRCP is therefore very useful before endoscopic retrograde cholangiopancreatography (ERCP) for treatment planning^[14]. Furthermore these imaging methods play a key role in differentiating benign from malignant biliary strictures and, in malignant disease, staging can be performed. Malignancy exclusion is indeed of utmost importance during the diagnostic evaluation of BBS and can be challenging. In a meta-analysis, including 4711 patients with suspected biliary obstruction, MRCP showed a sensitivity and specificity of 98% in determining the level of obstruction and 88% and 95%, respectively, in the detection of malignancy^[15]. Recent advances in magnetic resonance imaging (MRI), such as diffusion weighted MRI, have shown an improvement in the differentiation between benign and malignant lesions^[16].

The diagnostic role of ERCP in biliary obstruction evaluation has decreased with the wider availability of MRCP. However, unlike MRCP, ERCP enables tissue sampling, using biliary brushings or biopsies. A review of 16 studies including 1556 patients with biliary brushings and biopsies obtained during ERCP found an overall

Post-operative injuries	Cholecystectomy Liver transplantation Hepatic resection Biliary anastomosis Biliary reconstruction Biliary enteric anastomosis
Inflammatory	Chronic pancreatitis Primary sclerosing cholangitis Autoimmune pancreatitis Cholelithiasis Immunoglobulin G4 cholangiopathy Infections (recurrent bacterial cholangitis, tuberculosis, histoplasmosis, schistosomiasis, HIV, parasites) Postradiation therapy
Others	Ischemic (hypotension, hepatic artery thrombosis, portal biliopathy) Trauma Mirizzi syndrome Postbiliary sphincterotomy Endoscopic sclerotherapy for duodenal ulcer bleeding

HIV: Human immunodeficiency virus.

Bismuth classification	
I	Low CHD stricture, > 2 cm distal to hilum
II	Proximal CHD stricture, < 2 cm distal do hilum
III	Hilar involvement up to proximal extent of CHD, but confluence preserved
IV	Confluence involved, no communication between left and right ducts
V	Type I, II or III plus stricture of an isolated (aberrant) right duct
Strasberg classification	
A	Small duct injury in continuity with biliary system, with cystic duct leak
B	Injury to sectoral duct with consequent obstruction
C	Injury to sectoral duct with consequent bile leak from a duct not in continuity with biliary system
D	Injury lateral to extrahepatic ducts
E1	Stricture located > 2 cm from bile duct confluence
E2	Stricture located < 2 cm from bile duct confluence
E3	Stricture located at bile duct confluence
E4	Stricture involving right and left bile ducts
E5	Complete occlusion of all bile ducts

CHD: Common hepatic duct.

sensitivity of 41.6% and a negative predictive value of 58%^[17]. One of the reasons for this low sensitivity is the low cellularity of samples obtained; a recent study demonstrated that the identification of drunken honeycomb cells, loosely cohesive clusters of round cells and large atypical cells with foamy cytoplasm may significantly increase sensitivity^[18].

Endoscopic ultrasound (EUS) and intraductal ultrasonography (IDUS) have good accuracy in discriminating benign from malignant strictures in the extra-hepatic bile duct, but some strictures in the common duct and hilar region are difficult to identify. With the introduction of EUS guided fine needle aspiration (FNA) histological diagnosis is also possible. However, the sensitivity of EUS-FNA in distinguishing benign from malignant strictures is widely variable ranging from 43% to 86%^[19-22]. The possibility of peritoneal seeding during EUS-FNA is a limiting factor of this technique^[23].

Intraductal ultrasonography provides high-resolution images of the ductal wall and periductal structures. A review of 397 patients with indeterminate biliary strictures who performed ERCP with IDUS showed a sensitivity, specificity and accuracy of 97.6%, 98% and 92% respectively^[24].

Emerging technologies such as fluorescence *in-situ* hybridization (FISH), confocal laser endomicroscopy and direct cholangioscopy have yielded promising results in the differential diagnosis of biliary strictures. Furthermore measurement of volatile organic compounds in the bile duct fluid can help in the differentiation of benign vs malignant strictures^[25].

Fluorescence *in situ* hybridization uses fluorescently

labeled DNA probes to detect chromosomal abnormalities that can be indicative of tumor. One prospective study compared sensitivity and specificity of cytology with FISH in patients with cholangiocarcinoma and found that sensitivity of cytology was 15% compared to 34% for FISH and specificity was 91% and 98% respectively^[26]. The use of cholangioscopy-directed intraductal biopsies and FISH of brush cytology samples was shown to increase the diagnostic yield^[27,28].

Digital image analysis (DIA) uses Feulgen dye and spectrophotometric principles to quantify abnormalities in nuclear DNA that allow measuring ploidy within the cell. When FISH and DIA are used in combination a malignant diagnosis can be predicted in 67% of the cases compared with 62% and 14% for FISH and DIA when used separately^[29].

Cholangioscopy enables direct visualization and targeted biopsies. However, the sensitivity of its histologic biopsies was only 49% in the diagnosis of malignancy^[30].

Confocal laser endomicroscopy is a new diagnostic tool that uses an intravenous injected contrast agent like fluoresceine. It showed promising results in the diagnosis of biliary stenosis by using a catheter probe, which can be inserted through the working channel of an endoscope, or through a FNA needle. Several studies have shown that this new technique is rather useful in the differentiation between benign and malignant strictures of the bile duct with a high sensitivity of 73%-83%, but a low specificity of 33%-50%^[31-36].

Despite the development of these new diagnostic tools, the majority is still under evaluation in clinical trials.

ENDOSCOPIC THERAPY OF BBS

The objectives of BBS endoscopic treatment include biliary decompression with maintenance of the bile duct patency and prevention of recurrent stricture formation. This can be achieved by using expandable or graduating dilators; inserting single or multiple biliary plastic stents; inserting SEMs or, in some circumstances, by the combination of two modalities. Multiple endoscopic sessions are usually necessary before complete and sustained resolution is achieved. For those patients who may need surgery, endoscopic treatment can be considered as bridging therapy^[7].

During ERCP, there are three main technical decisions that should be made, namely the guide wire choice, the need for dilation and the stent choice. After endoscopic sphincterotomy, the crucial step is to overcome the stricture with a guide wire. The stricture can be negotiated only if there is no common bile duct complete transection. In postoperative stricture this step can be particularly difficult because the stenotic tract, even if short, can be asymmetric, angulated and rich in fibrous tissue. The choice for the adequate guide wire according to the morphology of the stricture is critical. Several types of ERCP guide wires are commercially available with different characteristics and wire tips (straight, tapered, J shaped or looped). Although there is a paucity of comparative studies, hydrophilic guide wires with a straight or J shaped tip are the preferred ones in this clinical setting^[1,37]. In a recent randomized trial involving 197 patients, a novel stiff-shaft flexible guide wire showed higher success rate in stricture cannulation (94% vs 79%, $P = 0.00041$) and lower procedure time (8.1 vs 11.2 min, $P < 0.0001$) when compared to a standard angle-tip hydrophilic wire in combination with a nitinol wire^[38]. Manipulation of guide wires demands patience, skill and optimal fluoroscopic imaging. The direction of the catheter and the wire should also be in the same axis as the stricture. Sometimes straightening the common bile duct by pulling an inflated stone extraction balloon just below the stricture or using the bending capabilities of the papilotome can be helpful. Other devices that can be used to overcome the stricture include tapered tip steerable catheters (3.9-4.9 Fr), a screw drill (7-8.5 Fr Soehendra stent extractor)^[39], angioplasty balloons mounted on 3 Fr catheters^[40], or a 6 Fr wire guided diathermic dilator^[41,42].

After overcoming the stricture with a guide wire, BBS dilation can be considered using either a balloon or bougie system. Although there is no head-to-head comparison between these two techniques, an elevated restenosis rate (up to 47%) has been consistently observed^[43-45]. Balloon dilation alone is therefore considered inappropriate in vast majority of cases. It should be performed only if necessary and during the first endoscopic procedure, because of the forceful disruption of the scar may add further traumatic damage to the tissue with subsequently development of a new

fibrotic reaction. Even so, the underlying cause of BBS should be taken into account in the final decision. According to retrospective studies, balloon dilation alone in BBS in the context of PSC can achieve a clinical and biochemical response in approximately 80% of non-cirrhotic patients^[46-49].

The next step, the choice of the stent, is currently the most contentious decision. Insertion of one plastic stent is easy to perform and cheap, but has short patency and a low rate of long-term success. A widely used alternative is a multiple plastic stent insertion method, where multiple large bore plastic stents (10 to 11.5 Fr) are inserted in the biliary tract at regular time intervals (every 3 to 6 mo) throughout one year^[50-52]. The rationale is that the gradual and continuous dilation of the stricture area may induce tissue remodeling and consolidation. Although it is a very effective technique, it requires multiple endoscopic procedures. SEMs due to its larger lumen and longer patency appear as a reasonable alternative. Bare SEMs, commonly used in malignant biliary obstruction, are not suitable for BBS since stent itself can create irreversible tissue hyperplasia and stent embedment, precluding its removal. With the evolution of stent design, partially covered and fully covered stents have been developed. These stents allow temporary placement and can therefore be used in BBS^[53].

These endoscopic techniques will be individually discussed, focusing on outcomes, advantages, disadvantages and complications.

Dilation

Dilation of BBS is mostly used as a complementary technique before stent placement and rarely as a single method. Actually, PSC is the main indication for dilation alone, when a dominant stricture (defined as a stenosis with < 1.5 mm in the main biliary duct or < 1 mm in the intra-hepatic duct) is present. Even so, the best endoscopic management is not yet defined.

In retrospective studies, dilation alone showed clinical and biochemical response in approximately 80% of non-cirrhotic PSC patients^[46-49]. There is no consensus on the method of dilation to be used, either rigid dilators or balloon dilators. If the stenosis is too tight some authors recommend rigid dilation from 5 Fr to 7 Fr followed by balloon dilators to obtain dilation up to 18 Fr to 24 Fr^[54]. In one prospective uncontrolled study involving 96 patients in which a total of 500 hundred dilations were performed over a 20-year period, the survival free of liver transplantation was 81% at 5 years and 52% after 10 years of follow-up^[55]. The use of stents in BBS related to PSC is still controversial since it was shown to be associated with increased complication rates when compared to balloon dilation. Previous studies with plastic stents showed a high risk of ascending cholangitis (up to 50%)^[56,57]. Although there are no prospective randomized controlled trials comparing dilation with dilation and stenting, a retrospective, single-center study compared endoscopic

Table 3 Studies reporting on the treatment of benign biliary strictures with multiple plastic stent

Ref.	Etiology	Total number (completed treatment) (n)	ERCP number	Balloon dilation	Maximal number of stents	Stenting duration (mo)	Follow-up after stent removal (mo)	Success after end of follow-up (%)
Bourke <i>et al</i> ^[99]	Sphincterotomy	6 (6)	5.2	-	2.2	13	27	100
Costamagna <i>et al</i> ^[51]	Various surgical procedures	45 (42)	4.1	40% of patients	3.2	12	164	89
Draganov <i>et al</i> ^[44]	Surgery (n = 19) Chronic pancreatitis (n = 9) Idiopathic (n = 1)	29 (27)	4	-	2.7	14	48	Surgery 68 Chronic pancreatitis 44
Pozsár <i>et al</i> ^[69]	Chronic pancreatitis	29 (24)	4.2	-	2.4	21	12	62
Catalano <i>et al</i> ^[68]	Chronic pancreatitis	12 (12)	4.7	-	4.3	14	47	92
Kuzela <i>et al</i> ^[100]	Cholecystectomy	43 (43)	6	In some	3.4	12	16	100
Morelli <i>et al</i> ^[101]	OLT	38 (38)	3.5	+	2.5	3.6	12	87
Tabibian <i>et al</i> ^[102]	OLT	83 (69)	4.1	+	NA	15	11	91

ERCP: Endoscopic retrgrade cholangio pancreatograph; NA: Not available; OLT: Orthotopic liver transplantation.

balloon dilation with either percutaneous or endoscopic dilation with stent placement. Stent placement did not achieve any additional benefit and was associated with more infectious complications^[58].

Based on these studies most of authors prefer dilation to stenting in patients with PSC. Stent placement should be reserved for patients with cholangitis and in patients not responding to balloon dilation. Optimal endoscopic intervention is still unclear and results from randomized trials are necessary to answer these questions.

Plastic stents

By keeping the stricture open for a prolonged period of time, plastic stents placement may allow a continuous calibration of the stenosis diameter, with tissue remodeling around the stent and a more sustained stricture resolution.

Various stenting protocols (single stent, two or multiple stents) have been described with different short and long-term results^[1,52].

Single plastic stent placement usually does not achieve good results in terms of BBS resolution or long-term follow-up. Due to their limited stent diameter, single plastic stents have only short-term patency rates, and so multiple endoscopic sessions are required. Furthermore, most of the previous studies are retrospective and heterogeneous with different patient selection criteria, dilation methods, sent diameters, follow-up periods and success definitions. For these reasons, this technique has limited clinical applications^[59].

An aggressive multiple stent strategy described by Costamagna *et al*^[50,51] for the treatment of post-operative biliary strictures is associated with better results than the Amsterdam protocol described by Bergman *et al*^[60] and, thus, is the preferred approach. After the placement of one or two plastic 10 Fr stents at the initial ERCP the maximum number of 10 Fr plastic stents (up to six) are placed at the each subsequent ERCP with stent exchange being performed every 3-4

mo until complete stricture disappearance occurs usually 12-18 mo later^[50,51]. This maximal multiple stenting was also adapted for the treatment of chronic pancreatitis and post-cholecystectomy strictures.

The placement of multiple large bore plastic stents in BBS is achieved in over 90% of patients. However, the long-term patency varies according to BBS etiology. Table 3 summaries clinical trials reported the treatment of BBS with multiple plastic stents.

In post-cholecystectomy BBS, endoscopic treatment can be performed in patients in whom the bile duct has not been transected or ligated. The maximal stent insertion strategy (1 to 6, 10 Fr stents) with 3 monthly exchanges during one year or until complete morphologic disappearance of the stricture has consistently shown good long-term results with success rates over 90% in some series even after prolonged follow-up^[61]. A recurrence rate of 20%-30% within 2 years of stent removal has been reported^[5], but these patients can be successfully retreated endoscopically. The maximal multiple stent strategy is therefore often considered the first line treatment in most cases^[5,52,61,62]. Treatment of peri-hilar stricture are, in turn, more challenging, technically difficult, and with worse success rates than distal strictures (Bismuth III 25% vs 80% in Bismuth I / II)^[5,44,63].

Similarly, in post-OLT strictures multistenting technique is considered the first line treatment. Better results are seen in early anastomotic strictures with resolution achieved within 3 mo whereas those presenting later, usually associated with fibrosis, required longer stenting periods, up to 12 to 24 mo^[64]. Balloon dilation and maximal stent placement every 3 mo seems the most effective strategy with an 80% to 90% success rate. A recently published prospective study by Kaffes *et al*^[65] which compared plastic stents with fully covered self-expandable metal stents (FCSEMS) in anastomotic strictures showed similar stricture resolution between groups after a median follow-up of 23 mo (100% in

FCSEMS group vs 80% in plastic group, $P = ns$). On the other hand, in non-anastomotic strictures endoscopic treatment can be considered either as the first line treatment or as a bridge to retransplantation^[64]. These strictures, vascular in origin, are usually multiple, proximal and its endoscopic treatment associated with low long-term success rate (50%-75%), requiring retransplantation in up to 25%-50% of patients^[5,7,62,64].

Distal common bile duct strictures in chronic pancreatitis are, in turn, more resistant to endoscopic treatment. As many remain symptomless for years its true incidence is unknown. However, 10%-30% of patients with advanced chronic pancreatitis develop a symptomatic biliary stricture^[1]. Treatment is recommended when symptoms occur; in the presence of secondary biliary cirrhosis or bile duct stones; and for persistent (more than 1 mo) asymptomatic elevation of serum alkaline phosphatase (levels greater than twice the upper limit of normal values) and/or serum bilirubin^[66]. The long-term success of single biliary plastic stent strategies has been disappointing specially in the presence of pancreatic head calcifications^[67], whereas multiple stenting for 12 or more mo led to an overall success in 65.2% of patients (60%-92% of cases)^[5,68,69]. Recurrent stricture rates reaching 17% after stent removal have been reported during a mean follow-up period of 42 mo^[5] and can be retreated by ERCP. Recently, Haapamäki *et al*^[70] published a prospective randomized multicenter study comparing the placement of multiple plastic stents with a FCSEMS. During a stenting period of 6 mo, either strategy showed good long-term relief of the stricture, with 2-year stricture-free success of 90% for plastic stent and 92% in the FCSEMS group and no difference in stent related complications. These results need to be followed-up and the results of upcoming trials (NCT01543256) are awaited especially in this population where non-compliance is of serious concern. Due to limited efficacy, need for repeated endoscopic therapy and risk of severe septic complications associated with non-compliance, the choice between endoscopic and surgical options should rely on patient co-morbidities, expected compliance and local expertise^[5,66].

Although some authors suggested that multistenting strategy has a low rate of premature symptomatic stent occlusion and a longer occlusion free survival^[71], these stenting strategies have shown some shortcomings. It is hindered by the need of patient compliance with multiple ERCP sessions over 1-year or more; its inherent costs; and its possible adverse events like cholangitis and other stent related complications. Fully covered SEMs are therefore gaining an increasing role in the treatment of BBS, but there is a lack of published head-to-head comparisons and the results of several on-going randomized trials are awaited.

SEMS

Among endoscopic treatments of BBS, stent placement

has emerged as a less invasive therapeutic option, with lower morbidity and mortality compared to surgery^[72].

In order to overcome major limitations of plastic stents, such as suboptimal stricture resolution and need for frequent ERCPs, SEMs appeared as a good alternative. Besides the initial enthusiasm with the use of partially covered SEMs (PCSEMS), further studies revealed high rates of stent migration (up to 23%), mucosal hyperplasia (up to 36%) and stent occlusion (up to 67%)^[73-80]. Like uncovered SEMs, the clinical use of PCSEMS has been therefore abandoned^[81].

The relative ease removal of FCSEMS triggered the attention of many investigators, leading to an increased use in benign biliary conditions. FCSEMS have, in fact, a covering membrane to prevent ingrowth and hyperplastic reaction, and to improve removability. FCSEMS do not embed into the mucosa, provided that the covering membrane remains intact^[82,83]. Other advantages include an increased radial diameter, longer stent patency, and easy insertion technique^[84-86]. Therefore, FCSEMS have emerged as a promising therapeutic option in the treatment of BBS, and have largely replaced their uncovered, partially covered counterparts, as well as plastic stents. Even so, before its use can be widely recommended the following questions need to be answered. Are FCSEMS-related outcomes significantly better than plastic multistenting procedures? What is the immediate, and long-term clinical success? Can FCSEMS be effectively removed at the end of treatment? Are FCSEMS complications serious enough to preclude their use? Several studies have been published trying to address all these issues.

FCSEMS efficiency in stricture resolution has been demonstrated in several studies that range from relatively small size with less than 10 patients^[83] to more recent and larger ones with over 100 patients^[72,79,87].

In a multicenter, prospective study of 133 patients, Kahaleh *et al*^[72] found a high response rate of stricture resolution, ranging from 61% for anastomotic strictures to 91% for post-surgical strictures, and 81% for chronic pancreatitis related strictures. FCSEMS were removed after a mean time of 95.5 ± 48.7 d. Two predictors for stricture resolution were found, namely longer indwell time (OR = 4.3, 95%CI: 1.24-15.09) and absence of migration (OR = 5.4, 95%CI: 1.001-29.29).

Most recently, Devière *et al*^[87] evaluated the ability to remove FCSEMS after extended indwell and the frequency and durability of stricture resolution. In this prospective, nonrandomized, multinational study of 187 patients stent removal was scheduled at 10-12 mo for patients with chronic pancreatitis or cholecystectomy related strictures, and at 4-6 mo for patients who received liver transplant. Stricture resolution occurred in 76.3% of patients (95%CI: 69.3%-82.3%). Removal success was accomplished in 74.6% (95%CI: 67.5%-80.8%) and it was more frequent in the chronic pancreatitis group (80.5%) than in the liver transplantation (63.4%) or cholecystectomy (61.1%) groups

($P = 0.017$). Endoscopic removal of FCSEMS was accomplished in all patients in whom this procedure was attempted. As such, in some types of BBS, FCSEMS can be left *in situ* for 1-year without compromising removability.

Although FCSEMS feasibility has been well established, comparative studies on the efficacy of multiple plastic stents are still lacking. To the best of our knowledge, only two prospective randomized trials comparing FCSEMS to plastic stents have been published. Kaffes *et al.*^[65], in a study of 32 patients with anastomotic post-liver transplant, showed that FCSEMS reduced the number of ERCPs needed to achieve stricture resolution (median 2 vs 4, $P = 0.0001$) with similar recurrence rates. There was no significant statistical difference between groups neither in stricture resolution (100% in FCSEMS group vs 80% in plastic group, $P = ns$), nor in complication rate (10% in FCSEMS group vs 50% in plastic group, $P = 0.051$). No cases of migration were observed in FCSEMS group. Cost analyses showed that FCSEMS was more cost effective. In the other multicenter, randomized trial, 60 patients with BBS caused by chronic pancreatitis were included. At 6 mo after randomization, all stents were removed and the patients were followed at 6 mo and 2 years after stent removal. The stricture-free success rate after 2 years was 90% (95%CI: 72%-97%) in the plastic group and 92% (95%CI: 70%-98%) in the FCSEMS group ($P = 0.405$). Stent migration was similar in both groups (10% in plastic group vs 7% in FCSEMS group, $P = 1$)^[70]. Recently a systematic review showed a tendency to successful use of FCSEMS in BBS related to chronic pancreatitis [77% (95%CI: 61%-94%) vs 33% (95%CI: 4%-63%), $P = 0.06$] with fewer endoscopic sessions (1.5 vs 3.9, $P = 0.0002$) and subsequently fewer complications. However, these results were not observed in other BBS etiologies other than chronic pancreatitis^[88].

Interestingly, in BBS related to chronic pancreatitis (particularly in calcified pancreatitis) the previous studies with multiple plastic stents showed inferior response to endoscopic therapy. On the contrary, as stated before, there is increasing evidence of a better success rate and lower recurrence rate with FCSEMS. It is thought that both the diameter of the FCSEMS and the duration of indwell may contribute to these findings^[82,87].

Among the available literature, stent duration is not homogeneous or standardized. Even so, it seems that a short stenting period might not be enough to allow for adequate tissue repair. Longer stenting duration should be therefore considered, as it has been independently associated with stricture resolution^[72,87,89].

The drawbacks of FCSEMS include stent migration, duodenal reflux and tissue hyperplasia^[2]. These issues should be addressed in the development of new stents in order to reinforce stent quality. Stent migration is, in fact, the major obstacle of FCSEMS. To minimize stent migration, the concept of flared ends (FE) and anchoring flaps has been introduced. Park *et al.*^[90], compared 2 stents, both with FE at the distal portion and with either

4 anchoring-fins (AF) or FE at the proximal end, in 43 BBS patients. Stents remained *in situ* for a median of 6 mo (interquartile range, 4 to 6) and no migrations were seen in the AF group, whereas a 33% migration was seen in the FE group ($P = 0.004$). Immediate stricture resolution was noted in 91% of patients with AF and 88% of those with FE. Recurrence during the median 4 mo follow-up period after stent removal occurred in 7 patients in total (16%) with no significant difference between the 2 groups. All nonmigrated stents were successfully removed without complications. The authors concluded that the AF design might be superior to the FE regarding antimigration effect for BBS. More recently, Walter *et al.*^[91] conducted a prospective, multicenter cohort study with a novel Niti-S biliary bumpy stent with bilateral FE and a high conformability at the middle part of the stent. In this study, involving 38 patients, the stent was removed after 3 mo. Despite the initial clinical success rate of 80%, the long-term clinical success rate was only 63% and stent migration occurred in 31% of patients. Regarding duodenal reflux issue, some studies using SEMS with antireflux valve have been conducted. However, only cases of malignant biliary obstruction were included^[92-94].

Besides stent migration, acute cholangitis, cholecystitis and pancreatitis have also been reported with FCSEMS placement^[65,70,87,88]. Even so, complications did not preclude its use in the treatment of BBS^[72,82].

After FCSEMS placement, clinical, laboratory and radiological follow-up has not yet been defined. Some authors advocate clinical follow-up for symptom recurrence and liver function tests every 3-6 mo for a minimum of 2 years after stent removal, then yearly with a baseline transabdominal ultrasound or MRCP^[79].

Based on these more recent data, FCSEMS might be recommended as the first line option for BBS, particularly in certain groups of patients, like chronic pancreatitis. Table 4 outlines the main prospective trials regarding FCSEMS use in BBS endoscopic treatment.

NEW AREAS OF RESEARCH

Bioabsorbable self-expandable stent is a growing area of interest in BBS treatment. This type of stent has a larger lumen than plastic stents, which allows better patency rate and reduced biofilm formation. Unlike FCSEMS, it does not require removal of stent and can reduce biliary mucosal hyperplasia. It is a braided structure of filaments made of absorbent polydioxanone or polylactide^[3]. After stent insertion, balloon dilation may be required to promote additional expansion of lumen, because of its radial force is weaker than FCSEMS. In animal models, biostents showed endoscopically deployment with success, expansion to full diameter, and maintenance of patency up to 9 mo^[95-97]. To the best of our knowledge, biodegradable stent have been currently experimented only in animal models^[95-97].

Recently, is has been published some early and

Table 4 Prospective trials reporting placement of self-expandable metal stents in benign biliary strictures

Ref.	No. patients	Etiology	Type of stent	Clinical success (%)	Adverse events (%)	Migration rate (%)	Median follow-up
Park do <i>et al</i> ^[90]	33	CP, BDS, OLT, postsurgical	FCSEMS with 4 AF; FCSEMS with both FE	91 with AF; 88 with FE	3	0 with AF; 33 with FE	6 mo (IQR 4-6)
Wagh <i>et al</i> ^[82]	23	CP, BDS, OLT, idiopathic	Wallflex	96-short term 83-long term	4.3	39	18.8 mo (IQR 14.1-21.3)
Kahaleh <i>et al</i> ^[72]	133	CP, OLT	FCSEMS flared	67	3.1	10.5	95.5 ± 48.7 d
Devière <i>et al</i> ^[87]	187	CP, OLT, CCY	Wallflex	76.3	27.3	29.4	20.3 mo (IQR 12.9-24.3)
Kaffes <i>et al</i> ^[65]	32	OLT	10 FCSEMS; 10 plastic stent	100 in FCSEMS; 80 in plastic stent	1 in FCSEMS, 5 in plastic stent	0 in FCSEMS	24.5 mo (range 4-38) in FCSEMS; 23 (range 1-42) in plastic stent
Haapamäki <i>et al</i> ^[70]	60	CP	30 FCSEMS; 30 plastic stent	92 in FCSEMS; 90 in plastic stent	29	10 in FCSEMS; 7 in plastic stent	40 mo (range-66)

AF: Anchoring fins; BDS: Bile duct stones; CCY: Cholecystectomy; CP: Chronic pancreatitis; FE: Fared ends; FCSEMS: Fully covered self-expandable metal stents; IQR: Interquartile range; OLT: Orthotic liver transplantation.

exciting work looking at intraductal radiofrequency ablation (RFA) in the treatment of BBS. In a pilot study, Hu *et al*^[98] performed intraductal bipolar radiofrequency at power 10W for 90 s/stricture, followed by balloon dilation with/without stent placement, in 9 BBS patients. Seven of them were refractory at endoscopic or percutaneous interventions. The treatment concept is aimed to using ablation power rather than using boogie effect to treat the structure. After RFA, stricture of all patients showed immediate improvement and five patients (55%) achieved stricture resolution during a follow-up of 12.6 mo. Three of the nine patients required no further stenting. Thus, RFA therapy is a new method that appears promising particularly in refractory cases.

CONCLUSION

Over the past 20 years, the progress and development of endoscopic devices and therapeutic options in the management of BBS have been really remarkable. Several prospective randomized trials have been recently published; including the most waited which compare FCSEMS with plastic stents.

Although multiple plastic stent insertion remains a very effective method in the vast majority of patients, there are emergent data suggesting that FCSEMS may be a reasonable alternative treatment option. The most recent studies support its efficacy, its relative low migration rate and low complications rate, and cost-effectiveness. However, data that clearly demonstrate the superiority of FCSEMS over plastic multistenting procedures are lacking. Thus, randomized, controlled trials assessing stent efficacy, complications, and cost-effectiveness are needed before a routine use of FCSEMS can be recommended. Also new functional SEMS are waited; the ideal stent characteristics have not been yet defined. In the near future, not only new techniques, like RFA, but also other therapies involving new devices will be available in clinical practice.

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