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Title: Efficacy of intraductal placement of non-flared fully-covered metal stent for refractory perihilar benign biliary strictures: A multicenter prospective study with long-term observation

Short Title: Intraductal FCSEMS for perihilar BBS

Authors: Kazuyuki Matsumoto[1], Hironari Kato[1], Masakuni Fujii[2], Toru Ueki[3], Yosuke Saragai[4], Hirofumi Tsugeno[5], Tomohiko Mannami[6], and Hiroyuki Okada[1]

[1]Department of Gastroenterology and Hepatology, Okayama University Hospital, Okayama, Japan.

[2]Department of Internal Medicine, Okayama Saiseikai General Hospital, Okayama, Japan

[3]Departments of Internal Medicine, Fukuyama City Hospital, Hiroshima, Japan

[4]Department of Gastroenterology, Iwakuni Medical Center, Hiroshima, Japan.

[5]Department of Gastroenterology, Tsuyama Central Hospital, Okayama, Japan.

[6]Department of Gastroenterology, National Hospital Organization Okayama Medical Center, Okayama, Japan.

Corresponding author: Kazuyuki Matsumoto, M.D., Ph.D.

Address: 2-5-1 Shikata-cho, Okayama 700-8558, Japan.

E-mail: matsumoto. k@okayama-u.ac.jp

Telephone number: +81-86-225-5991

Fax number: +81-86-235-7219

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Conflict of interest

The authors declare no conflicts of interest in association with the present study.

Authors' contributions

KM and HK: conception and design of the research, patient's treatment, and writing the paper. MF, TU, YS, HT, and TM: patient's treatment and collection and interpretation of data. HO: final approval of the article. All authors read and approved the final manuscript.

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Hiroyuki Seki, Department of Internal Medicine, Mitoyo General Hospital, Kagawa, Japan.

Tatsuya Toyokawa, Department of Gastroenterology, National Hospital Organization Fukuyama Medical Center, Hiroshima, Japan.

Key words

benign biliary stricture, fully-covered self-expandable metal stent, intraductal placement, refractory biliary stricture

Abstract

Background: Endoscopic fully-covered self-expandable metal stents (FCSEMSs) are used to treat benign biliary strictures (BBSs), however, treatment for perihilar BBSs is technically challenging. The aim of this study was to evaluate the usefulness of an unflared FCSEMS designed for intraductal placement in patients with refractory perihilar BBS.

Methods: Twenty-two consecutive patients with perihilar BBS unresolved by endoscopic plastic stent placement at 13 tertiary medical centers were prospectively enrolled. The FCSEMS was placed above the papilla and removed after 4 months. The primary outcome was stricture resolution at 4 months, and the secondary outcomes were technical success, stent removal, adverse events, and recurrence.

Results: The technical success rate of intraductal FCSEMS placement was 100%, and plastic stent placement at contralateral or side branch was performed in 86% of patients. The rate of successful stent removal at 4 months was 100%, and stricture resolution was observed in 91% of patients. Stent migration or stent-induced de novo stricture did not occur in any patient. The stricture recurrence rate was 16%, and the median (interquartile range) follow-up duration was 2.8 (1.6–3.3) years.

Conclusions: Intraductal placement of unflared FCSEMS is effective treatment for refractory perihilar BBS.

Introduction

Placement of endoscopic plastic stents (PSs) as treatment for benign biliary strictures (BBSs) is common[1-3]. However, PSs have short maintenance periods and require frequent replacement; thus, fully-covered self-expandable metal stents (FCSEMSs) are currently preferred for the treatment of BBSs[4-6]. FCSEMSs have larger diameters than PSs, they have long patency, and they can be easily removed. A meta-analysis revealed that, in terms of stricture resolution, recurrence, and adverse events, the results of temporary placement of multiple PSs for the treatment of BBSs of various origins are comparable to those of temporary placement of an FCSEMS. Further, placement of an FCSEMS was found to be comparable to placement of multiple PSs in terms of BBS resolution, with fewer endoscopic retrograde cholangiopancreatography (ERCP) sessions, indicating that it is more cost effective to use an FCSEMS than multiple PSs[7].

There are some concerns regarding treating BBSs using FCSEMS placement. First, FCSEMSs can induce de novo strictures via bile duct injury and tissue hyperplasia via the ends of the flare, which is an anchoring system[8,9]. Second, due to difficulty placing the center of the stent in the stricture, stent migration can easily occur and may reduce the stricture resolution rate[6,10]. Finally, there are technical limitations associated with placement of conventional FCSEMSs at the hilar part of BBSs. Due to its placement location, a one-side ductal stent can occlude the contralateral duct, and the length of currently available metal stents is too long for placement at the hilar part of BBSs. Thus,

PSs of long length or the percutaneous approach may be used.

To solve these problems, placement of a newly designed short modified FCSEMS with convex margins inside the common bile duct was proposed[11]. The modified FCSEMS may prevent spontaneous migration and iatrogenic bile duct injury. Although a few studies have reported the treatment of hilar or perihilar BBSs using the modified FCSEMS[11-13], research in this area is limited. Moreover, there are no prospective studies with a uniform stent indwelling period for various diseases. The aim of this prospective study was to evaluate the long-term efficacy and safety of the modified non-flared FCSEMS for patients with refractory perihilar BBS.

Methods

Study design

This study was a multicenter prospective clinical trial conducted at 13 centers. The study was approved by the Institutional Review Board for Human Research of each participating institution (Okayama University Hospital, IRB number: 1705-008) and was registered in the University hospital Medical Information Network database (study identifier: UMIN000027599) in May 2017. Study participation began in May 2017 and ended in April 2021. All the participants provided written informed consent before study participation, and the study was conducted following the guidelines of the Declaration of Helsinki.

Participants

The site investigators screened patients for study eligibility, enrolled participants, and assigned participants to interventions. The inclusion criteria were refractory BBS unresolved by at least one endoscopic treatment that used PSs, absence of malignancy confirmed using histopathological examination and clinical course, complete or incomplete biliary stricture, and stricture more than 15 mm above the ampulla. Complete stricture was defined by absence of contrast medium upstream of the stricture, and incomplete stricture was defined by poor clearance of contrast medium downstream of the stricture. The exclusion criteria were performance status 3 or 4, age below 20 years,

severe complications involving other organs, severe coagulation dysfunction, history of hepaticojejunostomy, intrahepatic bile duct stricture over the secondary branch, diameter of upstream bile duct less than 8 mm as seen on first endoscopic retrograde cholangiography (ERC), and exclusion at investigator's discretion.

FCSEMS-deployment techniques

The short non-flared modified FCSEMS (Bonastent M-Intraductal; Standard Sci Tech Inc., Seoul, South Korea) is made of nitinol wire and is fully covered with a silicone membrane (Figure 1)[11]. The convex margin of the distal ends was designed to minimize tissue hyperplasia, and the diameter of the X-marked cross-wired central 1–2 cm of the stent was designed to be smaller to prevent early migration. A 10-cm retrieval lasso with a metal tip is attached to the distal end of the stent to facilitate stent removal. Stents 8 mm or 10 mm in diameter (center waist diameter: 6–8 mm) and 3–6 cm in length (center waist length: 1–2 cm) with an 8F introduction system were used.

All the patients underwent ERCP using a standard duodenoscope (TJF or JF 260V; Olympus Optical Co. Ltd., Tokyo, Japan). The procedure was performed following an overnight fast, with the patient in prone position and sedated with intravenous anesthesia. Prophylactic antibiotics were administered immediately after the procedure, and 2–3 days after the ERCP procedure.

After insertion of the guidewire through the stricture, dilatation was basically

performed using a balloon 8 mm in diameter (REN biliary dilation catheter; Kaneka Co. or ZARA EPBD balloon; Century Medical). The FCSEMS was then inserted, and the central X-marked portion of the stent was positioned in the center of the stricture. The entire stent was above the level of the papilla. The length of the stent was chosen by adding 1–2 cm to the proximal and distal portions of the stricture. The diameter of the stent to be used was determined based on the diameter of the non-stricture region of the bile duct. For each stricture within 1 cm of the bile duct bifurcation, an additional 7-Fr PS was inserted into the contralateral or side branch of the intrahepatic duct to prevent obstruction by the FCSEMS. A metal stent was inserted after the placement of a contralateral PS (Figures 2A to 2D).

Four months after the initial FCSEMS placement, the stent was removed through the working channel of the scope by grasping the lasso with forceps. After stent removal, balloon sweeping was performed to clean up debris. Thereafter, a balloon-occluded cholangiogram was obtained to evaluate clearance of contrast medium proximal side of the stricture[3]. If there was no flow or poor clearance of contrast medium from proximal side of the stricture, FCSEMS replacement was performed, and the stent was removed after 4 months.

Follow-up and study completion

Laboratory tests were performed to assess liver function six and 12 months after

hospital discharge or whenever patients reported recurrence symptoms. Each patient was followed up for at least 1 year after stent removal. The end time of observation was 1 year after FCSEMS removal from the last enrolled patient.

Outcomes

The primary endpoint was stricture resolution 4 months after FCSEMS placement. The secondary endpoints were technical success, successful stent removal at 4 months, procedure-related adverse event, and stricture recurrence. Improvement in the waist of the stricture and ERC finding of good clearance of contrast medium from proximal side of the stricture within 60 seconds were used in the determination of stricture resolution after FCSEMS removal[3]. Technical success was defined as accurate positioning of the stent along the entire length of the stricture. Procedure-related adverse events were classified as early (within one week of stent placement) or late (more than one week after stent placement). All adverse events were classified and graded according to the American Society for Gastrointestinal Endoscopy consensus guidelines[14]. Stricture recurrence was defined as the clinically and cholangiogram-documented recurrence of a stricture after initial clinical success.

Statistical analysis

Continuous variables were expressed as medians and interquartile ranges (IQRs).

Continuous and categorical variables were compared using Mann–Whitney U test and Fisher's exact test, respectively. Stricture recurrence was calculated using Kaplan–Meier analysis. Statistical analysis was performed using JMP Pro version 15 (SAS Institute Inc., Cary, NC), with probability values less than 0.05 indicating statistical significance. Sample size calculation was not performed in this study owing to this study's single arm observational nature and the fact that refractory perihilar BBSs is a rare disease.

Results

Patient characteristics

The study flowchart is shown in Figure 3. A total of 22 patients underwent FCSEMS placement for refractory BBS. The clinical characteristics of the patients are summarized in Table 1. The most common etiologies of biliary stricture were surgeries related to liver transplantation (59%), cholecystectomy (17%), and chronic inflammation (17%). The median stricture length was 9 mm (IQR: 5–10 mm), and the median number of previous endoscopic treatments was 4 (IQR: 2–8). Fourteen patients (64%) were treated with multiple PSs, and 17 patients (77%) underwent endoscopic sphincterotomy (EST) before FCSEMS placement.

Treatment outcomes and stricture recurrence after stent removal

There were no patients with cholangitis during the 4 months after FCSEMS placement. Data on treatment outcomes and stricture recurrence after stent removal are shown in Table 2. There was technical success of intraductal FCSEMS placement in all the patients. Seventeen patients (77%) underwent balloon dilatation before FCSEMS placement. Among the 19 patients (86%) who underwent PS placement in the contralateral or side branch, the PS was placed above the papilla in 8 and across the papilla in 11. All the patients had successful FCSEMS removal at 4 months, and stricture resolution was observed in 20 patients (91%). Two patients without stricture resolution underwent

FCSEMS replacement, and after 4 months, the FCSEMS was removed. However, stricture resolution was still not observed in these patients; therefore, both patients underwent PS placement. One patient had severe bile leakage 9 days after FCSEMS placement. The patient had intrahepatic bile duct stricture after trans-arterial chemoembolization for hepatocarcinoma. The bile leakage occurred from B3, which was on the proximal side of the stricture. The cause of the bile leak was thought to be guidewire injury to the peripheral bile duct during ERCP. Although the stricture improved after FCSEMS removal at 4 months, PS was inserted to prevent bile leak recurrence. There was no stent migration or stent-induced de novo stricture.

Over a median follow-up period of 2.8 (IQR: 1.6–3.3) years, stricture recurrence was observed in 3 of the 19 patients (16%) who had stricture resolution (Figure 4). The 1- and 2-year recurrence free rate were 89% and 84%. Stricture recurrence was reported 28, 187, and 492 days after FCSEMS removal from the three patients. The stricture recurrence in these patients was treated with PS placement and replacement. Two patients had bile duct stones without stricture recurrence, and the stones were removed endoscopically. The characteristics of patients with difficulty of treatment using FCSEMS placement are shown in Table 3, and a comparison between patients with and without stricture improvement in terms of each parameter is presented in Supplemental Table 1.

Discussion

This is the first long-term prospective observational study of patients with refractory perihilar BBS treated with placement of modified FCSEMS that involved a uniform stent indwelling period for various diseases. The technical success rate of intraductal FCSEMS placement was 100%, and stricture resolution at 4 months was observed in 20 of the 22 patients (91%). No patient had stent migration or stent-induced de novo stricture. Over a median follow-up period of 2.8 (IQR: 1.6–3.3) years, stricture recurrence was observed in three of 19 patients (16%) who had stricture resolution.

In this study, the optimal FCSEMS indwelling duration was not determined. The European Society of Gastrointestinal Endoscopy recommends an FCSEMS indwelling duration of 6 months[15]. Previous multicenter studies reported a direct relationship between stricture resolution rate and mean duration of stent treatment[16-18]. Saxena et al. reported a predictor of stricture resolution and found six-month stent therapy to be superior to three-month stent therapy[16]. In the study by Kahaleh et al., significantly better stricture resolution was reported with stent indwelling durations greater than 3 months than with stent indwelling durations less than 3 months[17]. Further, Park et al. reported consistently high stricture resolution rates with stent indwelling periods greater than 120 days[18]. In this study, we set 4 months as the FCSEMS indwelling duration, and stricture resolution after FCSEMS removal was observed in 20 out of 22 patients (91%). FCSEMS of same diameter and length was used for replacement in two patients without stricture resolution; the etiology of BBS in these patients was donor liver transplantation and

choledochoduodenostomy. However, 4 months later (i.e., a total FCSEMS indwelling duration of 8 months), stricture resolution after FCSEMS removal was not observed in the two patients. Therefore, these patients were considered resistant to stent therapy, and they may not achieve stricture resolution even if stent therapy is continued. We posit that an FCSEMS indwelling duration of 4 months is sufficient for stricture resolution. Moreover, long stent indwelling durations may increase the risk of stent-related adverse events, such as stent migration, stent-induced stricture, and stent occlusion.

Regarding adverse events, no patient in this study had stent migration or stent-induced stricture. In previous studies that used modified FCSEMSs, the reported stent migration rate was 3%–19%, and no patient had stent-induced stricture[11-13]. In contrast, earlier studies that used conventional FCSEMS reported stent migration rates of 19%–31%[4,5,18]. In other words, placement of modified FCSEMS is associated with a lower stent migration rate than placement of conventional FCSEMS. A new design for the waist of the stent as well as cross-wiring of the central portion of the stent as an anchoring system reduces the risk of stent migration, and the convex margin of the ends of the stent may prevent de novo stent-induced intraductal stricture. Moreover, in this study, 86% of patients underwent PS placement at the contralateral or side branch. The rates of PS placement and FCSEMS placement are higher in this study than in earlier studies; therefore, the rate of stent migration in this study was expected to be low.

The stricture resolution rate and stricture recurrence rate in patients with perihilar BBS

treated with placement of modified FCSEMS were 81%–100% and 5%–12%, respectively[11-13]. The stricture resolution rate of patients with chronic pancreatitis is significantly lower than those of patients with other types of BBS[6,18,19]. Further, a meta-analysis of 22 studies revealed that the stricture resolution rate of patients with chronic pancreatitis and patients who underwent orthotopic liver transplantation was 75% and 85%, respectively[19]. The main etiology of perihilar BBS is liver transplantation; thus, the resolution rate of perihilar BBS is higher than that of BBS distal to the bile duct. In this study, the recurrence rate of perihilar BBS over a median follow-up period of 2.8 years was 16%. The follow-up period of this study is longer than those of previous studies that used modified FCSEMS[11-13]. The follow-up duration of this study was considered sufficient to evaluate long-term stricture resolution. Three patients had stricture recurrence within 2 years of FCSEMS removal, with a median time to recurrence of 187 days (range: 28–492 days). A large cohort study of patients with BBS treated with FCSEMS placement reported a stricture recurrence rate of 25.2% (26/103, 95% confidence interval: 0.17–0.34) after stricture resolution, and only two patients had stricture recurrence within 2 years of stent removal[18]. These results of the cohort study are comparable to those of this study. Therefore, we suggest that clinicians monitor patients with stricture resolution for stricture recurrence for at least 2 years after stent removal. Although we evaluated the predictive factors for difficulty of treatment using FCSEMS placement to compare patients with and those without stricture improvement,

there were no significant factors. However, regarding the number of previous treatment sessions, of the three patients in this study who had stricture recurrence after FCSEMS removal, two had undergone more than 10 sessions of PS placement. The means and standard deviations of the number of previous treatment sessions for patients with and without stricture recurrence in this study are 11 ± 6.4 and 4.0 ± 3.8, respectively. The time between stricture onset and FCSEMS placement was also longer in patients without stricture improvement or recurrence than in patients with stricture improvement and no recurrence (median 10 vs. 42 months). Thus, even with FCSEMS, endoscopic treatment may be challenging for patients who required more than 10 sessions of PS placement and/or require a long time for treatment using a FCSEMS

In a meta-analysis comparing FCSEMS and multiple PS treatment for BBS, there was no significant difference in stricture resolution between the FCSEMS and multiple PS groups[7]. Similarly, the stricture recurrence rates were comparable between the FCSEMS and multiple PS groups. However, there were fewer ERCP sessions in the FCSEMS group than in the multiple PS group. Kaffes et al reported an open-label prospective randomized trial of a FCSEMS versus PSs for anastomotic biliary strictures after liver transplantation[20]. A total of 32 patients consented, and subsequently, 20 were randomized to the FCSEMS arm (n = 10) and PS arm (n = 10). Stricture resolution was achieved in all 10 (100%) patients from the FCSEMS arm and in 8 (80%) patients from the PS arm. The median number of ERCP sessions performed per patient was 2 in the FCSEMS arm

and was 4.5 in the PS arm (P = 0.0001). Cost analysis showed that FCSEMS use was more cost effective than PS use (FCSEMS arm: $10,830 vs. PS arm: $23,580; P = 0.02). Although evidence has not been sufficiently established yet, FCSEMS treatment for perihilar BBS might be effective to achieve stricture resolution with fewer ERCP sessions and a lower cost when compared with PS treatment.

This study has some limitations. First, since perihilar BBS is rare and only refractory cases were considered, the number of patients enrolled into this study was small. Second, patients with bile duct diameter less than 8 mm were excluded from this study. Placement of FCSEMS with diameter greater than the bile duct diameter increases the risk of ischemic cholangitis due to biliary overexpansion and aneurysm formation caused by mechanical stimulation by the FCSEMS. The safety of the modified FCSEMS for perihilar BBS in patients with bile duct diameter less than 8 mm was not evaluated. Third, in this study, there was a risk of duodenobiliary reflux since about 80% of patients had EST for previous PS placement and biliary biopsy or cytology. It is unclear if not performing EST prevents duodenal reflux-induced cholangitis and stent occlusion. Finally, 86% of patients underwent 7-Fr PS placement in a contralateral or side branch. Thus, placement of FCSEMS and combined placement of FCSEMS and PS may each improve BBS. In this study, combined placement of FCSEMS and PS was considered necessary for the safe treatment of patients with perihilar BBS.

In conclusion, placement of a short modified FCSEMS with or without a contralateral

PS is effective for resolution of perihilar BBS in patients for whom primary endoscopic PS placement was not effective. Placement of a short modified FCSEMS is technically and clinically feasible and effective for stricture resolution without serious stent-related adverse events.

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Table 1. Patient characteristics (n = 22)	
Parameter	Number
Age, median (IQR), years	65 (56–77)
Sex, female, *n* (%)	12 (55)
Etiology, *n* (%)	
Postoperative	19 (86)
LDLT/cholecystectomy/DLT/hepatectomy/choledochoduodenostomy[a]	11/4/2/1/1
Chronic inflammation[b]	2 (9)
TACE	1 (5)
Stricture length, median (IQR), mm	9 (5–10)
Diameter of bile duct, median (IQR), mm	
Proximal side of stricture	10 (10–15)
Distal side of stricture	8 (8–10)
Number of previous endoscopic treatment sessions, median (IQR)	4 (2–8)
Number of prior plastic stents, *n* (%)	
One	8 (36)
Two	14 (64)
Prior sphincterotomy, *n* (%)	17 (77)
Time between onset of stricture and SEMS placement, median(IQR), mo	10 (6–42)
IQR: interquartile range, LDLT: living donor liver transplantation, DLT: donor liver transplantation, TACE: transcatheter arterial chemoembolization, SEMS: self-expandable metal stent	
[a] Biliary stricture occurred upstream of choledochoduodenostomy	
[b] Biliary stone-related secondary stricture without malignancy	

Table 2. Treatment outcomes and stricture recurrence after stent removal	
Parameter	Number
Technical success, *n* (%)	22 (100)
Placed SEMS, *n* (%)	
Diameter, 8/10 mm	14/8
Length, 30/40/50/60 mm	9/8/4/1
Balloon dilatation before SEMS placement	17 (77)
Combined use of plastic stent, *n* (%)	19 (86)
Stent removal success, *n* (%)	22 (100)
Stricture resolution at 4 months, *n* (%)	20 (91)
Adverse events	1 (5)
Early/late	0/1
Bile leak[a]	1
Stricture recurrence in the follow-up period[b], *n* (%)	3/19 (16)
Median follow-up duration (IQR)[b], years	2.8 (1.6–3.3)
SEMS: self-expandable metal stent, IQR: interquartile range	
[a] bile leak was due to guidewire injury to peripheral bile duct during endoscopic retrograde cholangiopancreatography	
[b] two patients without stricture resolution and one patient with bile leak were excluded	

Table 3. Characteristics of patients with difficulty of treatment using FCSEMS placement					
Parameter	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age/sex	43/F	55/M	65/M	88/F	77/F
Etiology	choledochoduodenostomy	DLT	hepatectomy	chronic inflammation	LDLT
Stricture length, mm	6	12	10	5	8
Number of previous endoscopic sessions	11	3	16	2	15
Number of prior plastic stents	1	2	2	1	2
Time between onset of stricture and SEMS placement, mo	42	6	48	6	67
Balloon dilatation before SEMS placement	No	Yes	Yes	No	Yes
Diameter of FCSEMS used, mm	10	10	8	10	8
Combined use of plastic stent	Yes	Yes	Yes	No	Yes
Stricture resolution at 4 months	No	No	Yes	Yes	Yes
Time to recurrence after stent removal, days	-	-	28	187	492
DLT: donor liver transplantation, LDLT: living donor liver transplantation, FCSEMS: fully-covered self-expandable metal stent					

Supplemental Table 1. Comparison between patients with and those without stricture improvement (n = 21)

Parameter	Stricture improvement and no recurrence (n = 16)	No stricture improvement or recurrence (n = 5)	P-value
Median age, years	63	65	0.93
Female sex, n	9	3	0.88
Etiology, LDLT or DLT, n	11	2	0.25
Median stricture length, mm	10	8	0.87
Median number of previous endoscopic treatment sessions	3	11	0.15
Prior multiple plastic stent treatment, n	10	3	0.92
Balloon dilatation before SEMS placement, n	13	3	0.33
Use of a 10-mm SEMS, n	5	3	0.25
Combined use of plastic stents, n	14	4	0.68
Time between onset of stricture and SEMS placement, months	10	42	0.3

LDLT: living donar liver transplantation, DLT: donar liver transplantation, SEMS: self-expandable metal stent

*One patient who was ineligible for follow-up was excluded

Figure legends

Figure 1
Design and characteristics of the modified fully-covered self-expandable metal stent (BONASTENT M-Intraductal; Standard Sci Tech Inc., Seoul, South Korea): Convex margin at both ends and smaller diameter on center portion having cross-wired structure with 10 cm of long lasso.

Figure 2
Anastomotic biliary stricture after living donor transplantation.
A: Cholangiography finding of complete biliary stricture that was refractory to plastic stent.
B: The anastomotic biliary stricture was located at left intrahepatic bile duct (arrow).
C: Following insertion of contraductal 7Fr inside plastic stent to the B3 to prevent of intrahepatic duct obstruction, a modified FCSEMS was placed at B2 across the anastomotic stricture.
D: Four months later, cholangiography following removal of the stent showed improvement in the waist of the stricture, and good clearance of contrast medium into the downstream.

Figure 3
The study flow chart.
FCSEMS: fully-covered self-expandable metal stent, PS: plastic stent

Figure 4
Stricture recurrence after stricture resolution. The recurrence rate of was 16% during median 2.8 years follow-up period. 1-year and 2-year recurrence free rate were 89% and 84%.