Retrospective evaluation of slim fully covered self-expandable metallic stent for unresectable malignant hilar biliary obstruction.

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【Abstract】(199 words)

Background: There was few reports of covered self-expandable metallic stent (SEMS) placement for malignant hilar-biliary obstruction (MHBO) because of risk of biliary branch obstruction. We studied feasibility and efficacy of 6-mm-diameter slim-fully covered SEMS (SFCSEMS) in relatively large cohort.

Methods: We retrospectively evaluated SFCSEMS in unresectable MHBO from December 2016 to September 2021 in Juntendo University Hospital.

Results: We enrolled consecutive 54 unresectable MHBO (18 bile duct, 11 gallbladder, 8 pancreatic, 2 hepatocellular and 15 metastatic cancer) including Bismuth-type II (n=11), III (n=17), and IV (n=26), and placed two (n=35) or three (n=19) SFCSEMS. The technical and clinical success rate was 100% and 92.5%, respectively, with 76.3 minutes of mean procedure time. Recurrent biliary obstruction (RBO) was observed in 35.2% and the median cumulative time to RBO (TRBO) was 181 days. Other adverse event was 11.1% (4 mild-pancreatitis, 1 segmental-cholangitis, and 1 cholecystitis). There was no failed case of stent exchange and 2nd SFCSEMS (n=6) showed significantly lower RBO (16.7% vs. 81.8%, p=0.0364) and longer TRBO (undefined vs. 86 days; p=0.0617) than plastic stent (n=11).

Conclusions: Endoscopic placement of SFCSEMS for unresectable MHBO was effective and feasible with low incidence of segmental-cholangitis, and exchange strategy of SFCSEMS was promising.

Abbreviations

MHBO, malignant hilar biliary obstruction

AE, adverse event

RBO, recurrent biliary obstruction

TRBO, time to recurrent biliary obstruction

EUS-HGS, endoscopic ultrasound-guided hepaticogastrostomy

PS, plastic stent

SFCSEMS, slim fully covered self-expandable metallic stent

OS, overall survival

SEMS, self-expandable metallic stent

SBS, side-by-side

SIS, stent-in-stent

UCSEMS, Uncovered SEMS

MRCP, magnetic resonance cholangiopancreatography

CT, computed tomography

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【Introduction】

Malignant hilar biliary obstruction (MHBO) is a long-standing clinical problem with no standardized management strategy. [1] In MHBO, it is difficult to determine the Bismuth type and perform multiple stent placements in the divided bile ducts. Re-intervention upon stent occlusion is difficult and maintaining effective drainage in MHBO cases is problematic. The overall survival (OS) of most cancer types has increased because of improvements in chemotherapy. It is necessary to consider the stenting strategy for MHBO with re-intervention after recurrent biliary obstruction (RBO) and conversion surgery at the time of the response to chemotherapy. [2] [3]

Bilateral drainage may be preferred for MHBO because drainage of more than 50% of the liver volume is associated with longer survival.[4] Lee *et al.* demonstrated the superiority of bilateral stenting with an uncovered self-expandable metallic stent (SEMS) for unresectable MHBO in a randomized controlled trial. [5] There are two types of bilateral SEMS placement methods: side-by-side (SBS) and stent-in-stent (SIS). [6] The efficacy and safety of SBS and SIS are reportedly similar. [7] Uncovered SEMS (UCSEMS) is the standard because it has a lower incidence of segmental cholangitis due to biliary branch obstruction. However, UCSEMS is difficult to remove, and re-intervention is problematic. By contrast, a covered SEMS can be removed and is easily

placed, which facilitates re-intervention, but is a contraindication for MHBO. Stent removability and exchangeability were rendered mandatory by the introduction of effective chemotherapy.

Several clinical trials have shown the feasibility of a slim fully covered self-expandable metallic stent (SFCSEMS) 6 mm in diameter for the management of unresectable MHBO. [8] [9] Unexpectedly, the incidence of segmental cholangitis was low, and even Bismuth type IV cases were treatable with an exchange strategy. We have used an SFCSEMS as the standard stent for unresectable MHBO since 2016. We hypothesized that an SFCSEMS 6 mm in diameter, which is thinner than usual, would reduce the risk of adverse events (AEs) and prevent tumor ingrowth, while its removability was expected to facilitate re-intervention. We retrospectively evaluated the safety and effectiveness of SFCSEMS for unresectable MHBO. There have been several clinical trials of SFCSEMS, but the numbers of cases were small; this is the first large case study. [8 , 9]

【Patients and Methods】

Study design

This was a single-center, retrospective, consecutive case series. The patients included in this study received a 6-mm-diameter SFCSEMS in a SBS fashion for unresectable MHBO

from December 2016 to September 2021 in Juntendo University Hospital. The inclusion criteria were as follows: hilar biliary obstruction confirmed by magnetic resonance cholangiopancreatography (MRCP) or computed tomography (CT) above Bismuth II, pathologically confirmed malignancy, and obstructive jaundice or cholangitis requiring stent placement. All patients provided written informed consent. The Ethics Committee of our institution approved the study protocol (E22-0106-H01).

Procedures

Patients underwent endoscopic stent placement under general anesthesia with midazolam and pethidine hydrochloride. Endoscopy was performed using a duodenoscope (TJF-260V; Olympus, Tokyo, Japan; or ED-580T; Fujifilm, Tokyo, Japan). Endoscopic retrograde cholangiopancreatography (ERCP) was performed using an MTW catheter (MTW Endoskopie, Wesel, Germany). Guidewires (0.025-inch VisiGlide 2; Olympus; EndoSelector; Boston Scientific, Marlborough, MA, USA; and 0.035-inch Seekmaster, Revowave Ultrahard; Paiolax, Tokyo, Japan) were used to identify the bile ducts, and for stent insertion. A middle incision for endoscopic sphincterotomy (EST) was performed using the Clevercut3 instrument (Olympus), and stricture dilation was performed using a 4- or 6-mm Hurricane (Boston Scientific) or REN instrument (Kaneka, Tokyo, Japan). In cases of cholangitis, endoscopic nasobiliary drainage (ENBD) was first performed.

Cholangitis was evaluated according to Tokyo Guidelines 2018. [10] Patients who had no definitive pathological diagnosis or who were initially considered to be operable underwent drainage by PS or ENBD, and SFCSEMS placement was performed after a definitive diagnosis of malignancy.

A 6-mm-diameter HANARO SFCSEMS was used in all patients (MI Tech, Seoul, Korea). This braided stent (cross-wired structure) is covered with a silicon membrane on both the inner and outer surfaces and was preloaded into an 8.5 Fr delivery system. In all cases, a 6-mm SFCSEMS was used. The length was selected from among 6, 8, 10, and 12 cm options based on the stricture length. The SFCSEMS was placed across the papilla in a SBS fashion. In cases of insufficient length, the stent was connected. Blood analysis was performed 2 hours after the procedure in all cases to detect AEs, such as post-ERCP pancreatitis and bleeding, as early as possible. [11] During the morning of the next day, the effectiveness of the treatment and occurrence of early AEs were examined. If early AEs were suspected, CT was performed. When AEs (pancreatitis, cholecystitis, segmental cholangitis, and liver abscess) other than RBO requiring stent removal were confirmed, the SFCSEMS was immediately removed and replaced with a PS.

Re-intervention for RBO

In cases of stent occlusion, stent migration with symptoms, and complications requiring

a procedure after SFCSEMS placement, re-intervention was performed. The SFCSEMS was removed through the channel using biopsy forceps (Radial Jaw; Boston Scientific) or a polypectomy snare (SnareMaster; Olympus) and replaced with a PS or SFCSEMS again according to the prognosis and difficulty of re-intervention. If stent replacement was unsuccessful, conversion to endoscopic ultrasound-guided hepaticogastrostomy stent (EUS-HGS) or another uncovered SEMS was performed.

Assessment of outcomes and statistical analysis

Outcome definitions were based on the Tokyo Criteria 2014 for transpapillary biliary stenting. [12] RBO was defined as a composite endpoint of either occlusion or migration, and time to recurrent biliary obstruction (TRBO) refers to the time from SEMS/PS placement to the recurrence of biliary obstruction. The times of occlusion and migration were defined as the times at which symptoms of occlusion and migration were observed, respectively. TRBO was estimated using the Kaplan–Meier method and compared between groups by log-rank test. Categorical variables were analyzed using the chi-squared test or Fisher test. Statistical analysis was performed using SPSS software (version 20.0; SPSS Inc., Chicago, IL, USA). A P-value < 0.05 was considered indicative of statistical significance.

The evaluated outcomes were the technical success rate, clinical success rate,

AE rate, RBO rate, and TRBO for the first and second stent placements after RBO. Technical success was defined as successful stent placement in the intended location with sufficient coverage of the stricture. Clinical success was defined as a 50% decrease in, or normalization, of the bilirubin level, or improvement of cholangitis within 14 days of stent placement. An early complication was defined as any complication that occurred within 30 days, and a late complication as one that occurred after 30 days.

【Results】

Patients

A total of 54 patients received multiple SFCSEMS in a SBS fashion during the study period (Fig. 1). The primary diseases were cholangiocarcinoma in 18 cases, gallbladder cancer in 11 cases, pancreatic cancer in 8 cases, hepatocellular carcinoma in 2 cases, and metastatic cancer in 15 cases (Table 1). The Bismuth classifications were II (n = 11), III (n = 17), and IV (n = 26). Thirty-five patients (64.8%) received three stents and nineteen (35.2%) received two stents (Fig. 2a–c). The 54 cases were observed until death. The median follow-up period was 120 days (interquartile range, 67–230 days).

Outcomes and adverse events (first drainage)

Table 2 shows the outcomes and AEs of the first drainage. The mean procedure time was 76.3 minutes. Thirty-three patients (61.1%) underwent pre-drainage by ENBD or PS

before the first SFCSEMS placement, and direct SFCSEMS placement was performed in 21 patients (38.9%). The number of cases requiring balloon dilatation was 24 patients (44.4%). The technical success rate was 100%, and all 54 patients received a stent in a SBS fashion. The clinical success rate was 92.6% (50/54). Two patients died within 2 weeks due to exacerbation of their present disease, one with segmental cholangitis had a stent removed, and one had prolonged cholangitis that improved after 2 weeks. The median TRBO and OS were 181 and 117 days, respectively, according to the Kaplan-Meier method (Fig. 3a and b).

AEs other than RBO occurred in 11.1% (6/54) of the patients. Early AEs (within 30 days) were seen in four cases of mild pancreatitis, one of segmental cholangitis, and one of cholecystitis. No late AEs were observed. There was no case of liver abscess during any periods. The cholecystitis occurred on day 2 and improved with percutaneous transhepatic gallbladder aspiration, while the two cases of pancreatitis improved with conservative treatment. Three cases (5.6%; one case of segmental cholangitis and two of pancreatitis) required stent removal. In two cases of pancreatitis, stent removal was performed because severe abdominal pain and amylase levels continued to increase until 2 days after ERCP. In all cases, SFCSEMS removal was successful, without AEs. The SFCSEMS in a patient with segmental cholangitis was removed on day 12, while in the

two patients with pancreatitis they were removed on day 2. The latter two patients received a PS and rapidly improved.

Outcome of the second drainage after RBO

Table 3 shows the outcomes of the second drainage. The RBO rate was 35.2% (19/54), and the causes of RBO were sludge in 9 cases (47.3%), overgrowth in 8 cases (42.1%), and migration in 2 cases (10.5%). Among 19 patients who experienced RBO, stent removal was successful in all cases without AEs. Before the second drainage after RBO, 5 patients (23.8%) underwent drainage by ENBD, and 14 patients received direct drainage.

The SFCSEMS were placed in a SBS fashion in 6 of 19 patients for re-intervention (multiple PSs in 11 patients and other uncovered SEMS in 1 patient). In one case, EUS-guided hepaticogastrostomy was performed because a non-drainage area appeared in the left lobe. After re-intervention, the second RBO rate was 16% (1/6) in the SBS group and 81.8% (9/11) in the PS group. The technical success rate in the re-intervention group was 100% (19/19). The RBO rate of second stents was significantly lower in the SFCSEMS group (16.7% *vs*. 81.8%, p = 0.0364), and TRBO tended to be longer in the SFCSEMS group (undefined *vs*. 86 days: p = 0.0617) (Fig. 3c).

【Discussion】

SFCSEMS placement in a SBS fashion is useful for unresectable MHBO. There was

concern about segmental cholangitis caused by obstruction of the bile duct branches, but the incidence of segmental cholangitis was only 1.8% (1/54) in this study, despite the fact that 48.2% (26/54) of the patients were Bismuth IV. Also, the SFCSEMS was successfully removed in all patients. Therefore, use of SFCSEMS will likely increase. Although there have been a few pilot studies of SFCSEMS, this is the first report to include a large number of cases and demonstrate the usefulness of the SFCSEMS as a second stent for re-intervention after RBO. [8, 9]

The optimum stent placement method for unresectable MHBO is under discussion. [1] Bilateral placement of an UCSEMS is preferred for MHBO, [13] and there is reportedly no difference in technical success, clinical success rate, AEs, or TRBO between UCSEMS placement by SBS and SIS. [7 , 14] However, with either method, the uncovered SEMS is difficult to remove due to tumor ingrowth, hampering re-intervention. The OS of cancer has been prolonged by the development of chemotherapy, and it is necessary to consider the stenting strategy for MHBO with re-intervention after RBO and conversion surgery at the time of a response to chemotherapy. [2, 3] The third edition of the Japanese Biliary Tract Cancer Guidelines recommends a PS or UCSEMS for MHBO. Many physicians use a PS because of the ease of re-intervention after RBO, although the results obtained using an UCSEMS were overwhelmingly better in clinical trials.

However, as mentioned above, UCSEMS and partially covered SEMS cannot be removed due to tumor ingrowth, and re-intervention in patients with a UCSEMS placed in a SIS fashion (UCSEMS SIS) is technically difficult because additional drainage must be performed through the stent mesh. [15] For UCSEMS placed in a SBS fashion (UCSEMS SBS), additional stents are added to the lumen of the UCSEMS, but good outcomes have not been reported. Also, some patients require additional stents through the mesh, but the success rate is not high.

In this study, the initial SFCSEMS was removed in all 19 patients who experienced RBO. In one case, the SFCSEMS was successfully removed, but the patient had multiple bile duct obstructions, so the re-intervention was converted to EUS-HGS; the remaining 18 (94.7%) patients underwent successful drainage via the transpapillary approach. Therefore, placement of SFCSEMS may improve the technical success rate of re-intervention. Inoue *et al*. reviewed 67 cases of re-intervention after UCSEMS SBS placement; 79.1% of the cases experienced successful drainage of the intended bile ducts through the mesh of the UCSEMS, while 20.9% underwent a different procedure from that initially planed (such as PTBD or EUS-HGS) because of failure to advance the guidewires into the UCSEMS lumen and failure to advance the device due to interference from the stent mesh .[16] The success rate of UCSEMS SIS was 76.3–80.7% for the same

reason [17, 18]. If a UCSEMS that cannot be removed is placed, it will be difficult to perform conversion surgery at the time of a response to chemotherapy; evaluating the degree of tumor extension in the bile duct will also be problematic, making it difficult to determine resectability. Therefore, SFCSEMS use is likely to increase.

There are two methods of stent placement: above and across the papilla. Cosgrove *et al*. reported that the risk of pancreatitis was significantly lower with above- than across-the papilla method (1.9% *vs*. 11.7%, p = 0.04) due to there being less stress on the papilla, but there was no significant difference in the clinical success, TRBO, or RBO rate. [19] If a stent placed above the papilla needs to be removed, biopsy forceps must be inserted into the bile duct, and the stent must be removed blindly under a fluoroscopic view. Therefore, in terms of ease of removal, the across-the-papilla method, which allows removal under a direct view, is superior.

There are many studies comparing PS and UCSEMS for unresectable MHBO, and there is some evidence that UCSEMS is better in terms of the RBO rate and TRBO. [20] Lee *et al*. reported that the TRBO was 253 days (range: 28–420 days) and 262 days (range: 9–455 days) (p = 0.865) with UCSEMS SIS and SBS, respectively. [14] Therefore, for unresectable MHBO, the UCSEMS is superior to PS in terms of the RBO rate and TRBO, irrespective of placement type. Thus, although the utility of the UCSEMS is clear,

there is insufficient evidence supporting the use of a CSEMS for unresectable MHBO. A meta-analysis showed no significant difference between 6- and 10-mm CSEMS in the distal bile duct in terms of TRBO (142.9 *vs*. 185.8 days, p = 0.057), but the RBO rate was higher in the 6-mm group (39.1% vs 23.9%, p = 0.02). [21] The authors concluded that the RBO rate for CSEMS is related to stent diameter. However, in MHBO cases, a 10-mm CSEMS cannot be placed, so direct comparison by diameter is not possible. If a comparison were to be made, it would be with a 10-mm UCSEMS. Because the main causes of RBO are tumor ingrowth in UCSEMS and sludge in CSEMS, CSEMS may be useful for MHBO because it can be removed and replaced if RBO occurs.

The placement of conventional CSEMS for MHBO was considered a contraindication because of the possibility of obstruction of biliary branches and segmental cholangitis leading to liver abscess. Other concerns include cholecystitis, as well as portal vein obstruction and perforation due to excessive dilatation of the hilar bile duct. We considered that an SFCSEMS 6 mm in diameter, which is thinner than usual, would reduce the risk of the above-mentioned AEs. In two previous studies, an SFCSEMS was placed but the bile duct was excessively dilated; liver abscess and cholecystitis, but not segmental cholangitis, developed. [8, 9] In this study, cholecystitis occurred in one patient (1.8%) and pancreatitis in four patients (7.4%), but segmental cholangitis occurred

in only one patient (1.8%) and liver abscess did not occur. According to a report on ERCP-related adverse events by the European Society of Gastrointestinal Endoscopy, the incidence of post-ERCP pancreatitis varies from 3.5% to 9.7%, similar to our result for multiple SFCSEMS placement. [22] Because stent removal is performed to alleviate AEs, the SFCSEMS was removed in two cases of pancreatitis and one of segmental cholangitis, and immediate improvement was noted. As a result, SFCSEMS placement in a SBS fashion posed a low risk of AEs, and stent removal was sufficient to alleviate symptoms if they did not improve with conservative management.

We also evaluated the utility of the SFCSEMS as a second stent after RBO. The SFCSEMS was replaced in 6 of 19 patients, and multiple PSs were placed in 11 patients as second stents. The RBO rate of second stents was significantly lower in the SFCSEMS group (16.7% *vs*. 81.8%, $p = 0.036$), and TRBO tended to be longer (undefined *vs*. 86 days; $p = 0.061$). There was no significant difference because only a small number of cases were evaluated. In distal bile duct obstruction, CSEMS replacement reportedly prolongs TRBO compared to stent cleaning upon RBO development after CSEMS placement. [23, 24] These results suggest that replacement of the SFCSEMS after RBO increases the RBO rate and TRBO compared to PS, enabling effective drainage. The limitation of this study is that it is a retrospective study, and prospective studies are needed

in the future.

【Conclusion】

Endoscopic placement of the SFCSEMS in a SBS fashion for unresectable MHBO was effective and feasible. The incidence of AEs was low, and they were alleviated by stent removal. When RBO occurred, re-intervention, was easier than for the UCSEMS because of the removability of the SFCSEMS. Exchange of the SFCSEMS may reduce the number of biliary drainage procedures; however, randomized controlled trials are needed to confirm this.

【Conflict of interest】

Author H.I. was supported by research grants from Boston Scientific Japan and FUJIFILM Corporation. The funding source has no role in the design, practice or analysis of this study.

【Figure legends】

Fig. 1 (a) Slim fully covered SEMS 6 mm in diameter (HANARO stent; MI Tech, Seoul, South Korea). Lasso attached to the duodenal side of the stent for removal.

(b) Fluoroscopic view of three SFCSEMSs.

(c) Endoscopic view of three SFCSEMSs.

Fig. 2 Flow chart of patients with unresectable MHBO received a 6-mm-diameter SFCSEMSs in a SBS fashion.

Fig. 3 (a) Kaplan-Meier analysis of the RBO in first SFCSEMS. TRBO was 181 days.

(b) Kaplan-Meier analysis of the OS in first SFCSEMS. OS was 117 days.

(c) TRBO of the second stent tended to be longer in the SFCSEMS group (undefined vs. 86 days: $p = 0.0617$).

Table 1. Patient characteristics.

Table 1. Patients' characteristics	
Number of patients, n	54
Sex: male/female, n	30/24
Age: mean, years	68.4±11.9
Etiology of MHBO, n (%)	
Cholangiocarcinoma	18 (33.3)
Gallbladder carcinoma	12 (20.4)
Pancreatic carcinoma	8 (14.8)
Hepatocellular carcinoma	2 (3.7)
Metastatic cancer	14 (27.8)
Bismuth classification, n (%)	
II	11 (20.4)
III	17 (31.5)
IV	26 (48.2)
Chemotherapy, n(%)	37 (68.5)

MHBO, malignant hilar biliary obstruction

Table 2. Outcomes and adverse events of the first drainage.

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Treatment time, mean, min	76.3±37.3
Number of stents, n (%)	
2 / 3	35(64.8)/19(35.2)
Technical success, n (%)	54(100)
Clinical success, n (%)	50(92.5)
Stricture dilatation, n (%)	24(44.4)
Adverse events other than RBO, n (%)	6(11.1)
Early (< 30 days)/Late (≧ 30 days), n	6/0
Pancreatitis (mild)	4/0
Segmental cholangitis	1/0
Cholecystitis	1/0
Liver abscess	0/0
RBO, n (%)	19(35.2)
2 stents/ 3 stents, n (%)	9(52.6)/10(34.2)
Cause of RBO	
Early (≦ 30 days)/Late (> 30 days), n	3/16
Sludge, n	2/7
Overgrowth, n	1/7
Migration, n	0/2
Cumulative TRBO, Median, days	181
2 stents/ 3 stents, Median, days	204/140
Overall survival, Median, days	117
2 stents/ 3 stents,Median, days	112/181

RBO, recurrent biliary obstruction; TRBO, time to RBO

Table 3. Outcomes of the second drainage.

Table 3. Outcomes of the second drainage	
Re-intervention in case of RBO, n (%)	19(100)
Successful stent removal, n (%)	19 (100)
Method of endscopic re-intervention, n	19
SFCSEMS	6
Plastic stent	11
EUS-HGS	1
Other uncovered SEMS	1
Technical success, n (%)	19 (100)
Clinical success, n (%)	19 (100)
RBO rate, n (%)	
SFCSEMS	1/6 (16.7)
Plastic stent	9/11 (81.8)
p value	0.0364
Cumulative TRBO, Median, days	
SFCSEMS	undefined
Plastic stent	86
p value	0.0617

RBO, recurrent biliary obstruction;SFCSEMS, slim fully covered self-expandable metallic stent; EUS-HGS, endoscopic ultrasound-guided hepaticogastrostomy, TRBO, time to RBO

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Figure 1

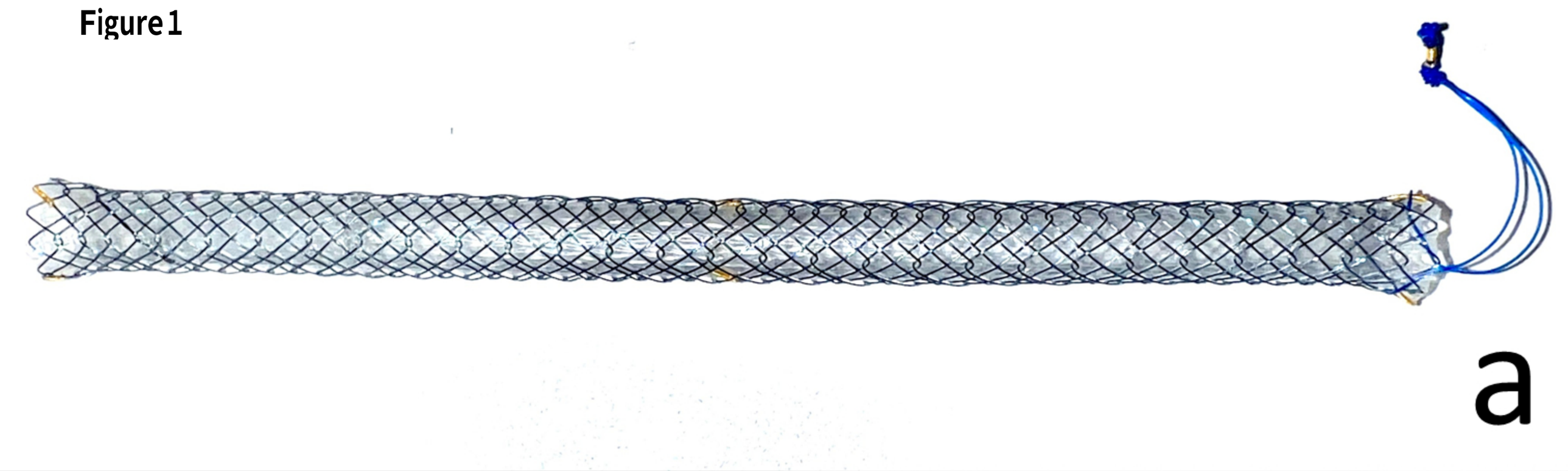


Figure 2

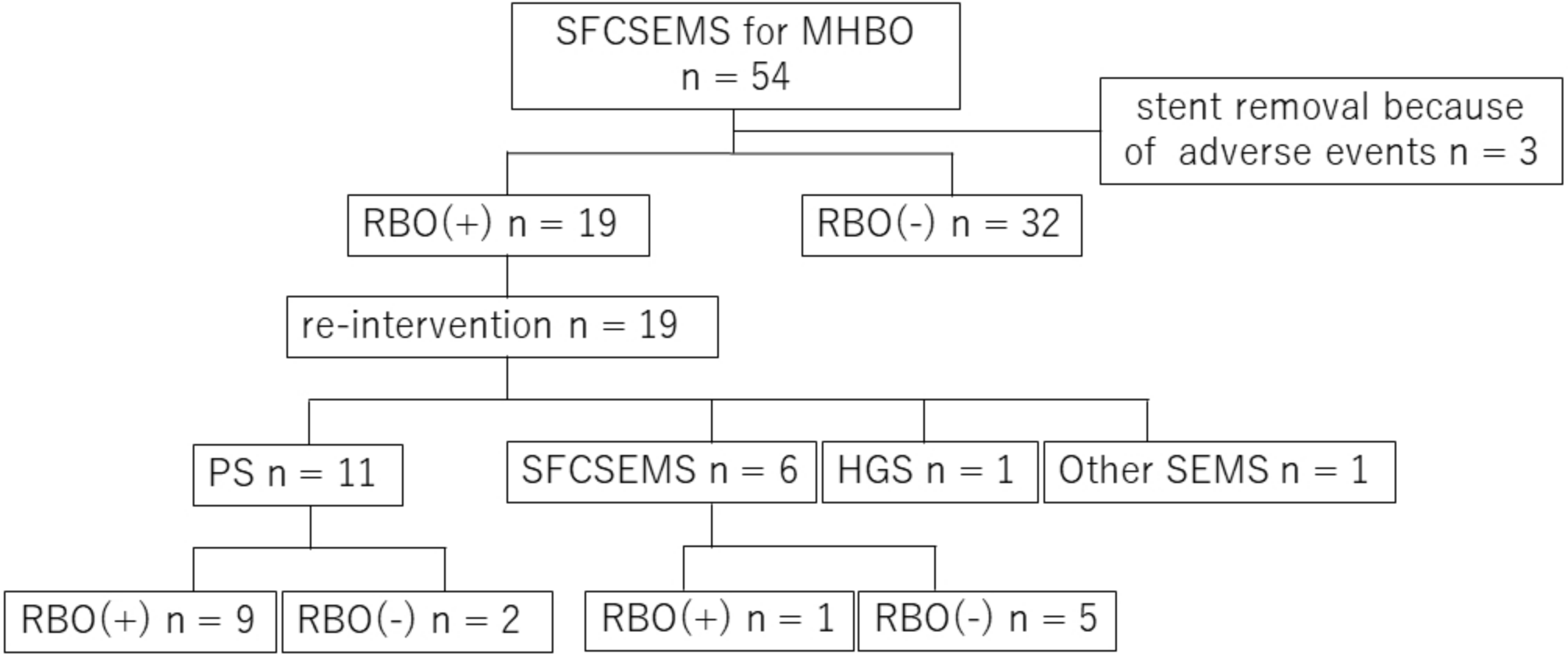
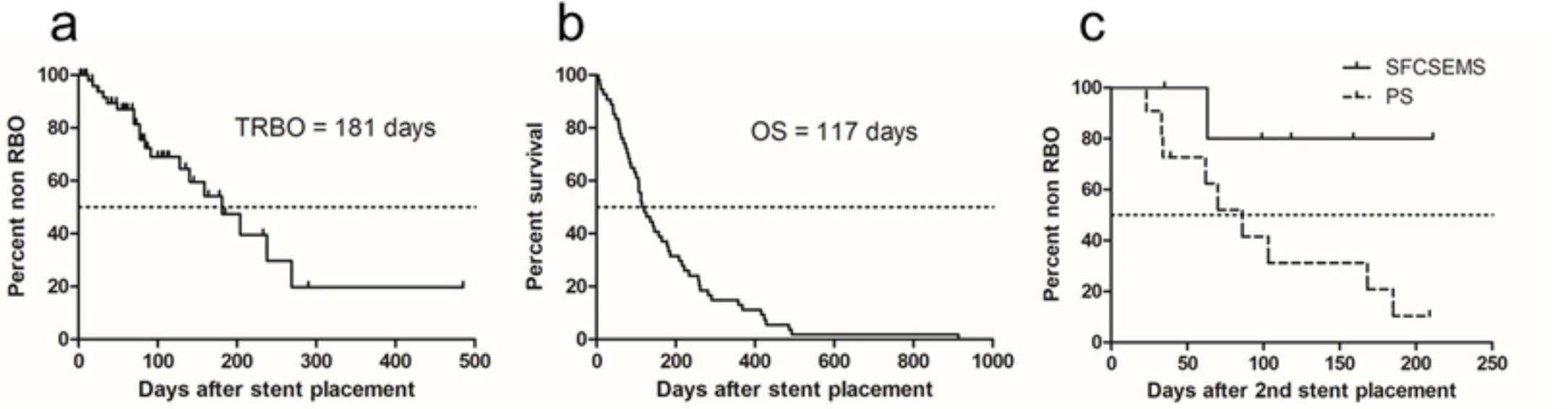

SFCSEMS for MHBO
n = 54
stent removal because of adverse events n = 3
RBO(+) n = 19
RBO(-) n = 32
re-intervention n = 19
PS n = 11
SFCSEMS n = 6
HGS n = 1
Other SEMS n = 1
RBO(+) n = 9
RBO(-) n = 2
RBO(+) n = 1
RBO(-) n = 5

Figure 3



Number at risk, n																	
54	21	5	1	1	1	54	17	6	1	1	SFCSEMS	6	5	3	2	1	0
											PS	11	7	4	3	1	0