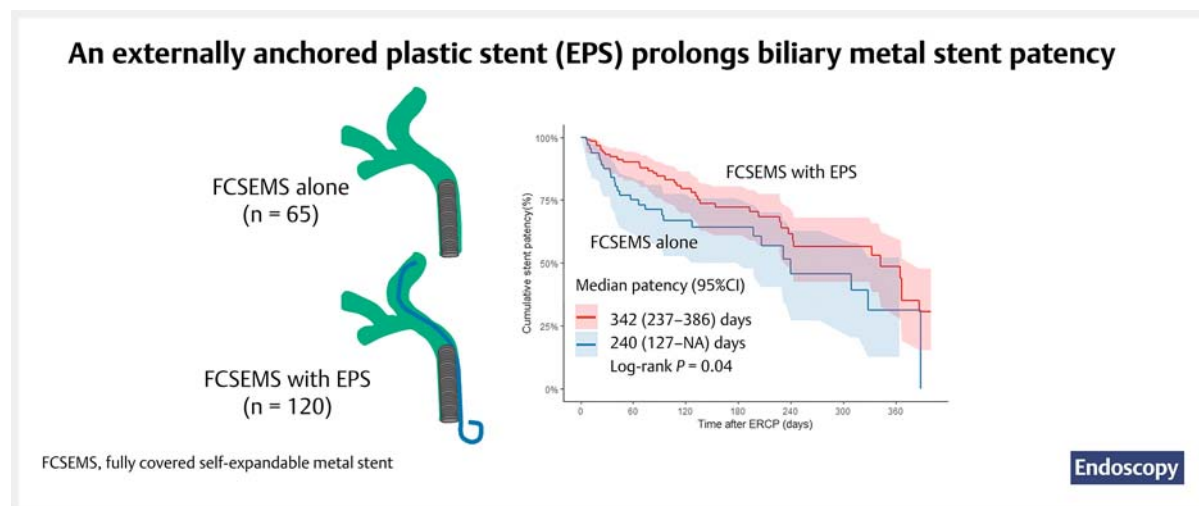


Prolonged patency of fully covered self-expandable metal stents with an externally anchored plastic stent in distal malignant biliary obstruction

GRAPHICAL ABSTRACT



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Tables 1 s, 2 s

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ABSTRACT

Background Fully covered self-expandable metal stents (FCSEMSs) are widely used for endoscopic treatment of distal malignant biliary obstruction (dMBO). We aimed to assess the efficacy of anchoring an external plastic stent to an FCSEMS in dMBO.

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Methods A multicenter retrospective cohort study was performed in patients with dMBO to compare stent patency between FCSEMSs and FCSEMSs with an externally anchored plastic stent (EPS). For external anchoring, a 7-Fr double-pigtail plastic stent (DPPS) was placed first in the bile duct, then an FCSEMS was deployed side-by-side.

Results Among a total of 185 patients, 65 had an FCSEMS alone and 120 had an FCSEMS with an EPS. The median stent patency was significantly longer in the FCSEMS with an EPS group than in the FCSEMS only group (342 vs. 240

days; $P=0.04$). The rate of stent migration was significantly lower in the FCSEMS with an EPS group than in the FCSEMS only group (10.8% vs. 27.7%; $P=0.01$). There were no significant differences in the rates of stent occlusion and adverse events between the two groups.

Conclusions A novel and simple technique of anchoring an external plastic stent may decrease the risk of FCSEMS migration and prolong stent patency, without significantly increasing the adverse events rate in dMBO.

Introduction

Endoscopic biliary stenting is considered the standard treatment for distal malignant biliary obstruction (dMBO) [1]. Because sufficient and prolonged biliary drainage is essential to continue effective palliative chemotherapy, self-expandable metal stents (SEMSs) are recommended because of their durability and reduced needs for reintervention [2, 3]. Fully covered SEMSs (FCSEMSs) have advantages over uncovered SEMSs (USEMSs) in terms of the problem of in-stent restenosis due to tumor ingrowth or epithelial hyperplasia [4, 5]. FCSEMSs can also be easily removed and replaced after stent clogging during chemotherapy [6]. However, the recent drastic improvement in the efficacy of chemotherapy warrants further caution with regard to stent migration, which occurs more frequently with FCSEMSs than with USEMSs.

Recently, we demonstrated the antimigratory efficacy of an internally anchored double-pigtail plastic stent (DPPS) for dMBO in a randomized comparative study [7]. However, we noted some cases where the DPPS was removed along with the migrated FCSEMS, thereby requiring immediate reintervention, which may have occurred because of the shared axis of the two stents in the stricture. To solve the problem caused by the DPPS being coaxial to the FCSEMS, we have devised an alternative antimigration technique. It was assumed that the placement of a 7-Fr DPPS side-by-side with the FCSEMS would not only reduce the stent migration rate but also prolong stent patency with an increased chance of the DPPS remaining in the original position, even after migration of the FCSEMS. In this study, we aimed to evaluate the effect on increasing stent patency of a novel technique of externally anchoring a DPPS to an FCSEMS in dMBOs.

Methods

Subjects and study design

We conducted a multicenter retrospective study to evaluate the efficacy and safety of an externally anchored plastic stent (EPS) with an FCSEMS. Patients who underwent endoscopic retrograde biliary drainage (ERBD) for dMBO at two tertiary care institutions between March 2017 and December 2020 were included. Those patients with previous bile duct surgery, or a stricture of the hilar or intrahepatic ducts were excluded.

The cutoff date for data analysis was 15 November 2021. The final data included 185 dMBO patients, with 65 having an FCSEMS alone and 120 having an FCSEMS with an EPS.

This study was approved by the Institutional Review Boards (H-1911-088-1079, Seoul National University Hospital [SNUH]; NCC 2020-0118, National Cancer Center [NCC], South Korea).

Procedure

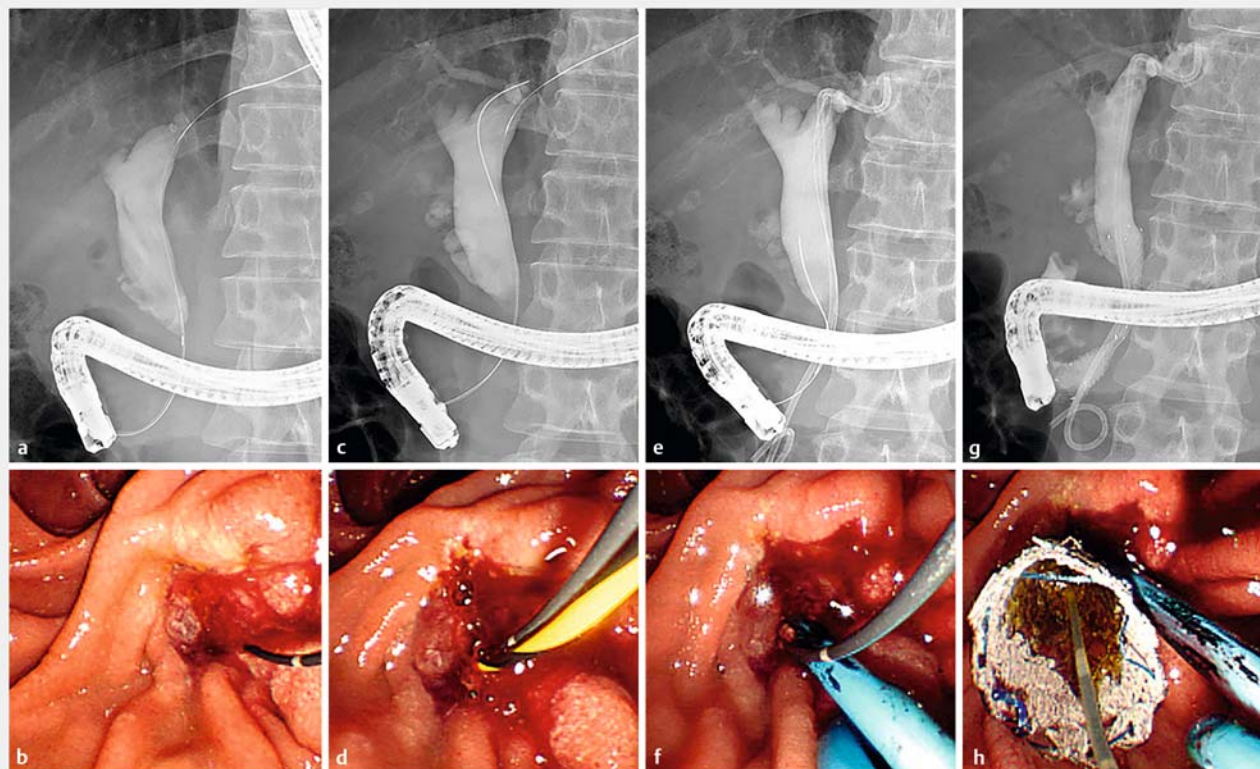
All endoscopies were carried out by qualified endoscopists who had performed more than 1000 endoscopic retrograde cholangiopancreatography (ERCP) procedures. After the site of the suspicious malignant biliary stricture had been visualized on a cholangiogram, an FCSEMS was deployed across the stricture. Two types of FCSEMS design were used, with either a nitinol hook and cross wire structure with a polygonal mesh surface (Bonastent; Standard Sci Tech, Seoul, Korea) or a nitinol wire with a silicone-covered membrane (Aristent; Daewoong, Seoul, Korea).

For the subjects in the EPS group, two guidewires were placed after selective biliary cannulation. A 7-Fr DPPS (Zimmon Biliary Stent; Cook Medical, Bloomington, Indiana, USA) was placed first, then an FCSEMS was deployed side-by-side (► **Fig. 1**). The proximal tip of the DPPS was placed over the FCSEMS, and intrahepatic anchoring of a DPPS longer than 10 cm was preferred, if possible, to ensure that the proximal end was sufficiently anchored in the intrahepatic bile duct to reduce dislodgement of the DPPS from the stricture site [7].

The type and length of the FCSEMS was determined at the discretion of the endoscopist, with consideration of the length of the biliary stricture. The stent deployment time was measured as the time between the initial placement of the guidewire into the intrahepatic bile duct and the deployment of the FCSEMS with/without an EPS.

Outcomes and definitions

The primary outcome was the comparative efficacy of an EPS-anchored FCSEMS to an FCSEMS alone in terms of stent patency. Stent patency was defined as the time between stent placement and stent revision for any stent dysfunction attributable to migration or occlusion, or other causes requiring reintervention [2, 7]. Stent migration and occlusion were investigated



► **Fig. 1** Fluoroscopic (upper row) and endoscopic images (lower row) during the placement of a fully covered self-expandable metal stent (FCSEMS) with external plastic stent anchoring showing: **a–d** two guidewires placed in the bile ducts; **e, f** a double-pigtail plastic stent placed first in the bile duct; **g, h** an FCSEMS deployed side by side.

using laboratory findings, abdominal radiographs, or computed tomography images during clinical follow-up.

Technical success was defined as the successful placement of an FCSEMS, with/without an EPS, in the intended location without disturbing the passage of bile/contrast dye. Clinical success was defined as a decrease in the total bilirubin level to less than half of the pretreatment value within the first month after ERBD. Adverse events followed the American Society for Gastrointestinal Endoscopy (ASGE) lexicon [8].

Statistical analysis

Continuous variables were presented as medians and ranges, and categorical variables were expressed as percentages. To compare the two groups, the Mann–Whitney *U* test was used for continuous variables and the chi-squared test or Fisher's exact test was used for categorical variables. Proportions are presented with exact confidence intervals owing to the uneven sample sizes of the two groups. The probability of stent patency was estimated using the Kaplan–Meier method and compared with a log-rank test. Patients who underwent surgery or died prior to the event were censored.

Univariable analysis was performed to identify the independent risk factors for stent patency. Variables with *P* values < 0.2 were included in the follow-up multivariable Cox proportional hazard regression model. A hazard ratio (HR) and 95% CIs were

calculated. *P* values < 0.05 were considered statistically significant.

Statistical analyses were conducted with SPSS version 25.0 (IBM SPSS Inc., Chicago, Illinois, USA) and R version 4.2.1 (R foundation for Statistical Computing, Vienna, Austria).

Results

Study population

The baseline characteristics of 185 subjects (SNUH 107, NCC 78; median age 66; 76 women) are summarized in ► **Table 1**. The majority of patients had pancreatic cancer, 98 had metastatic disease at the time of the procedure. No significant difference was found between the two study groups, except for cystic duct visualization on cholangiogram. The cystic duct was less frequently visualized in the FCSEMS with an EPS group than in the FCSEMS alone group (*P* < 0.01).

Stent placement

The results of stent placement are summarized in **Table 1 s**. Technical success was achieved in all subjects in both groups. The clinical success rates were 95.8% and 93.8% in the FCSEMS with an EPS and FCSEMS only groups, respectively. The nine patients who did not achieve clinical success showed clinical im-

► Table 1 Baseline characteristics of the 185 patients with distal malignant biliary obstruction who were treated with insertion of a fully covered self-expandable metal stent (FCSEMS) with or without an externally anchored plastic stent (EPS).

Variable	FCSEMS + EPS (n = 120)	FCSEMS alone (n = 65)	P value
Patient-related factors			
Age, median (range), years	66.0 (39–90)	66.0 (33–88)	0.46
Female, n (%)	51 (42.5)	25 (38.5)	0.71
Previous ERBD, n (%)	47 (39.2)	25 (38.5)	>0.99
Previous PTBD, n (%)	9 (7.5)	5 (7.7)	>0.99
Cholecystectomy state, n (%)	116 (96.7)	61 (93.8)	0.46
Total bilirubin, median (range), mg/dL	4.0 (0.2–32)	4.0 (0.3–26)	0.51
Cancer-related factors			
Tumor size, median (range), mm	30.0 (10–67)	28.0 (2–90)	0.12
Cancer type, n (%)			
▪ Pancreatic cancer	87 (72.5)	52 (80.0)	0.31
▪ Biliary tract cancer	16 (13.3)	4 (6.2)	
▪ Metastatic cancer	17 (14.2)	9 (13.8)	
Metastatic disease, n (%)			
▪ Liver metastasis	25 (20.8)	12 (18.5)	0.55
▪ Peritoneal seeding	15 (12.5)	8 (12.3)	
Anticancer treatment, n (%)	106 (88.3)	55 (84.6)	0.63
Subsequent surgery, n (%)	15 (12.5)	12 (18.5)	0.27
Procedure-related factors			
Endoscopic sphincterotomy, n (%)	76 (63.3)	40 (61.5)	0.94
Cystic duct visible on cholangiogram, n (%)	54 (45.0)	45 (69.2)	<0.01
ERBD, endoscopic retrograde biliary drainage; PTBD, percutaneous transhepatic biliary drainage.			

provement after stent revision (n = 7) or percutaneous biliary drainage (n = 2).

The stent deployment time was significantly longer in the FCSEMS with an EPS group than in the FCSEMS only group. The types of FCSEMS used were marginally different between the two groups, while they were markedly different between the institutions. An FCSEMS of 5 or 6 cm in length was used most frequently for dMBO. In the FCSEMS with an EPS group, 6-cm (28.3%) or 12-cm DPPSs (26.7%) were used most frequently.

Study outcomes

Treatment outcomes are presented in ► **Table 2**. The median stent patency was significantly longer in the FCSEMS with an EPS group (342 days, 95%CI 237–386 days) compared with the FCSEMS only group (240 days, 95%CI 127–NA days; $P=0.04$) during a median follow-up of 218 days and 243 days, respectively (► **Fig. 2**).

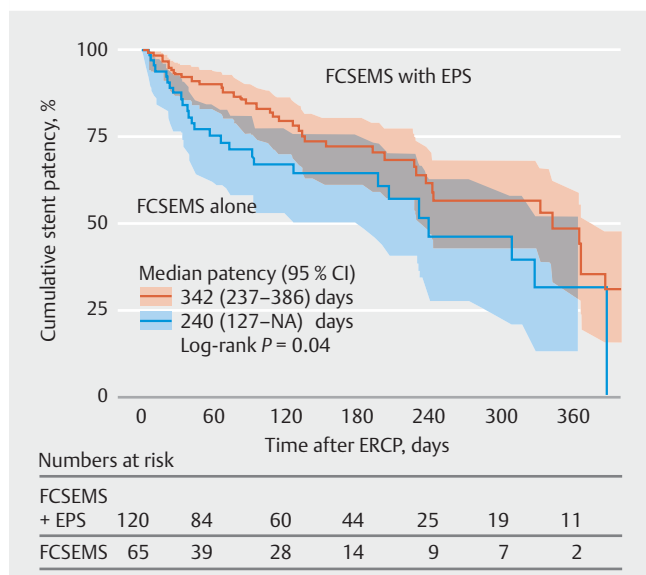
As of the cutoff date, the stent migration rate was significantly lower for the patients with an EPS (10.8%, 95%CI 5.9%–17.8%) than for those with an FCSEMS only (27.7%, 95%CI 17.3%–40.2%; $P=0.01$). Among 13 patients in the FCSEMS with an

EPS group whose stents migrated, 10 patients had the DPPS remaining in the original position. Stent occlusion occurred in 26.7% (95%CI 19.0%–35.5%) in the FCSEMS with an EPS group and 21.5% (95%CI 12.3%–33.5%) in the FCSEMS only group, and the mechanism of occlusion did not differ between the two groups. Stent revision due to migration was performed more frequently in the FCSEMS alone group (17%, 95%CI 8.8%–28.3%) than in the FCSEMS with an EPS group (8%, 95%CI 4.1%–14.8%), but this trend was not statistically significant ($P=0.09$). With regard to adverse events, there were no significant differences between the two groups, and no procedure-related mortality occurred.

The risk factors associated with stent dysfunction were examined using Cox regression models (**Table 2s**). The cystic duct being visible on cholangiogram and the type of FCSEMS, which were significantly different between the two groups, were not associated with stent patency. Sex and placement of an EPS were significantly associated with stent patency in multivariable analyses.

► Table 2 Overall outcomes of endoscopic biliary drainage with a fully covered self-expandable metal stent (FCSEMS) with/without an externally anchored plastic stent (EPS).

Variable	FCSEMS+EPS (n=120)	FCSEMS alone (n=65)	P value
Stent patency, median (95%CI), days	342 (237–386)	240 (127–NA)	0.04
Stent migration, n (%)	13 (10.8)	18 (27.7)	0.01
▪ Proximal	1 (0.8)	4 (6.2)	
▪ Distal	12 (10.0)	14 (21.5)	
Stent occlusion, n (%)	32 (26.7)	14 (21.5)	0.55
▪ Sludge clogging	15 (12.5)	10 (15.4)	
▪ Tumor growth	17 (14.2)	7 (10.8)	
Reason for reintervention, n (%)	43 (35.8)	27 (41.5)	0.55
▪ Migration	10 (8.3)	11 (16.9)	
▪ Occlusion	31 (25.8)	12 (18.5)	
▪ Other	2 (1.7)	4 (6.2)	
Adverse event, n (%)	26 (21.7)	11 (16.9)	0.56
▪ Pancreatitis	8 (6.7)	4 (6.2)	
▪ Cholecystitis	8 (6.7)	4 (6.2)	
▪ Cholangitis	6 (5.0)	2 (3.1)	
▪ Bleeding	5 (4.2)	1 (1.5)	
▪ Perforation	1 (0.8)	0 (0.0)	



► Fig. 2 Cumulative rates of stent patency for the fully covered self-expandable metal stent (FCSEMS) with an externally anchored plastic stent (EPS) group and the FCSEMS alone group. ERCP, endoscopic retrograde cholangiopancreatography.

Discussion

The present study demonstrated that a novel technique of anchoring an EPS to a FCSEMS can significantly prolong stent pa-

tency compared with the stand-alone placement of an FCSEMS. Use of an EPS may be associated with a significantly reduced chance of stent migration and decreased need for reintervention for stent migration.

Although a significantly prolonged patency of FCSEMSs was reported in a meta-analysis, one major concern with FCSEMSs is their higher likelihood of stent migration than USEMSs [9]. Several prior studies have shown the antimigratory properties of an anchoring flap, partially covered design, or novel structure of the stent [10–12]; however, an increased chance of mucosal injury and potential bleeding during removal, or the unique design itself may be important limitations to be considered. On the other hand, the addition of an EPS to an FCSEMS appears to be a simple, safe, and effective method to confer an antimigration effect.

Recently, we reported that anchoring a 7-Fr DPPS inside an FCSEMS prevented stent migration and prolonged stent patency compared with an FCSEMS alone in a randomized controlled study [7]. In the present study, a DPPS was externally anchored first, then an FCSEMS was deployed side-by-side. The antimigration efficacy may not be different between the two techniques, 14% for internally anchoring DPPS and 7% for an EPS [13]. One notable advantage of an EPS is the retention of biliary drainage by a DPPS remaining in the original position even after migration of the FCSEMS. We observed a trend of less reinterventions for stent migration in the FCSEMS with an EPS group than in the FCSEMS only group. The increased time for the anchoring with an EPS may be negligible when considering the to-

tal procedure time. Further studies are warranted to directly compare the cost-effectiveness of the two methods.

The migration rate of FCSEMSs has been reported to be between 5% to 37% [2]. In this study, the migration rate was 27.7% in the FCSEMS only group, which is higher than in previous studies. The high radial force is thought to be an antimigration property of FCSEMSs [6, 14]. The radial force of the FCSEMSs used in the present study is lower than other commercially available FCSEMSs, which may contribute to a higher migration rate [7]. Chemotherapy can also affect stent migration and patency through tumor shrinkage in MBO [6]. Meanwhile, a Japanese multicenter study reported that chemotherapy increased recurrent biliary obstruction caused by biliary sludge formation and cholangitis [15]. In our univariate analysis, the use of chemotherapy was not associated with stent patency. The variety of cancer types and chemotherapy regimens included in the study may have affected the effect of chemotherapy on stent patency. In our study, the placement of an EPS, through its antimigration effect, was the only correctable factor in prolonged stent patency.

Some limitations of our study arise from its retrospective design. The rate of technical success might be overestimated owing to incomplete recording of the detail in the procedure record. The fact that subjects were included at two different centers might be a confounding factor. In real clinical practice, the instrument and techniques used during the endoscopic procedure differed between the institutions. All endoscopists involved in this study were experts in ERCP, with experience of more than 1000 procedures, so technical variations between the institutions would be negligible. Although the type of FCSEMS used at each institution was different in this study, it did not affect the stent patency. Further studies to evaluate the efficacy of an EPS with various types of FCSEMS are warranted for its generalizability in dMBO.

In conclusion, our findings suggest that the external anchoring of a DPPS to an FCSEMS is a simple and effective method to prevent stent migration and prolong stent patency, without increasing the chance of adverse events. We did not include patients who received a USEMS in the present study, which warrants the results from our ongoing clinical trial comparing the use of an FCSEMS with an EPS and a USEMS (NCT05220475).

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Competing interests

The authors declare that they have no conflict of interest.

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