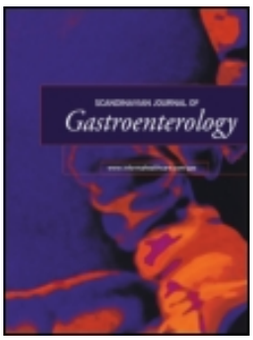

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ORIGINAL ARTICLE

Partially covered versus uncovered self-expandable nitinol stents with anti-migration properties for the palliation of malignant distal biliary obstruction: A randomized controlled trial

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Abstract

Objective. Covered self-expandable metal stents (SEMSs) are increasingly used as alternatives to uncovered SEMSs for the palliation of inoperable malignant distal biliary obstruction to counteract tumor ingrowth. We aimed to compare the outcomes of partially covered and uncovered SEMSs with identical mesh structures and anti-migration properties, such as low axial force and flared ends. ***Materials and methods.*** One hundred and three patients who were diagnosed with inoperable malignant distal biliary obstruction between January 2006 and August 2013 were randomly assigned to either the partially covered ($n = 51$) or uncovered ($n = 52$) SEMS group. ***Results.*** There were no significant differences in the cumulative stent patency, overall patient survival, stent dysfunction-free survival and overall adverse events, including pancreatitis and cholecystitis, between the two groups. Compared to the uncovered group, stent migration (5.9% vs. 0%, $p = 0.118$) and tumor overgrowth (7.8% vs. 1.9%, $p = 0.205$) were non-significantly more frequent in the partially covered group, whereas tumor ingrowth showed a significantly higher incidence in the uncovered group (5.9% vs. 19.2%, $p = 0.041$). Stent migration in the partially covered group occurred only in patients with short stenosis of the utmost distal bile duct (two in ampullary cancer, one in bile duct cancer), and did not occur in any patients with pancreatic cancer. ***Conclusions.*** For the palliation of malignant distal biliary obstruction, endoscopic placement of partially covered SEMSs with anti-migration designs and identical mesh structures to uncovered SEMSs failed to prolong cumulative stent patency or reduce stent migration.

Key Words: *malignant biliary obstruction, self-expandable metal stent, stent migration*

Introduction

Endoscopic retrograde biliary drainage with a self-expandable metal stent (SEMS) is a principle palliative method for inoperable malignant distal biliary obstruction [1,2]. SEMSs are considered superior to plastic stents with large bores in terms of stent patency [3–6], but it remains challenging to determine which type of SEMS is optimal for the palliation of distal biliary obstruction due to stent-related adverse events that cause recurrent biliary obstruction [7–19].

Fully or partially covered SEMSs were designed to overcome the tumor ingrowth occurring with uncovered SEMSs, but in retrospective cohort studies [13,17,18], randomized trials [8–12,15,16,19], and two meta-analyses [7,14], the clinical outcomes of covered SEMSs for stent patency were inconsistent due to the different proportions of stent migration, tumor ingrowth, tumor overgrowth, and bile encrustation in each of these studies. In addition, there have also been conflicting conclusions regarding the incidence of pancreatitis and cholecystitis after placement

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of various types of covered versus uncovered SEMSs [8–13,15–23].

The primary aim of our study was to compare the cumulative stent patency of partially covered and uncovered SEMSs with identical mesh structures and anti-migratory properties, such as relatively low axial force and flared ends. Overall patient survival, stent dysfunction-free patient survival and incidence of adverse events were analyzed as secondary aims.

Methods

This was a prospective, randomized controlled trial performed at a single tertiary referral center (Ajou University Hospital, Suwon, Korea) (Clinical trial registration number: NCT02178618).

Study population

From January 2006 to August 2013, patients with malignant distal biliary obstruction who fulfilled the eligibility criteria were prospectively enrolled. The eligibility criteria were: 1) >20 years of age, 2) malignant biliary obstruction, 2 cm distal to the hilum, 3) unsuitable for curative surgical resection owing to metastasis, locally advanced stage, high operation risk, or patient's wishes and 4) expected survival >4 months based on Karnofsky performance score. Patients were excluded for any of the following medical conditions: 1) history of biliary surgery except cholecystectomy, 2) history of SEMS placement, 3) coagulopathy (International normalized ratio >1.5, platelet count <50,000) and 4) duodenal stricture or surgically altered anatomy (Billroth II or Roux-en-Y). Whenever urgent biliary drainage was needed before completing staging work-up or pathologic confirmation, endoscopic retrograde biliary drainage with a plastic stent or endoscopic naso-biliary drainage was allowed as a temporary bridging method before SEMS placement.

Randomization and stent insertion

Randomization was performed using computer-generated random numbers in sealed opaque envelopes without tumor stage stratification at the time of successful deep cannulation to the bile duct. Patients were assigned to either the partially covered or uncovered SEMS groups (BONASTENT; Standard Sci-Tech Inc, Seoul, South Korea) (Figure 1). Both types of SEMSs had an identical nitinol-based braided hook-cross wire structure with a polygonal mesh surface, both edges flared and looped, and platinum-based radiopaque markers. The partially covered BONASTENT had a silicone membrane

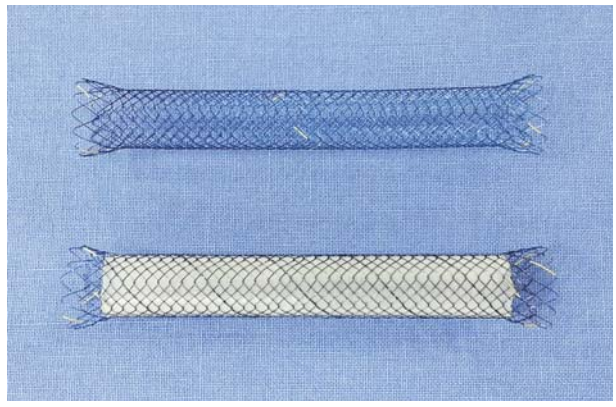

Figure 1. An uncovered BONASTENT (top) and a partially covered BONASTENT (bottom).

with 5-mm uncovered portions at both ends. The axial force 20 mm from the bending point was 0.30 N in the uncovered stent and 0.60 N in the partially covered stent, relatively low compared with most commonly used biliary covered stents (Wallstent 0.95 N, Wallflex stent 0.65 N) [24]. The diameters of the introducers for partially covered and uncovered SEMS were 8Fr and 7Fr, respectively. Both stents could be recaptured for repositioning.

The operator was not blinded to the type of SEMS used. However, patients and research assistants who participated in the patient's follow-up and data analysis were blinded to stent type. All procedures were carried out endoscopically under fluoroscopic guidance, and sphincterotomy was performed at the discretion of the endoscopist. SEMS diameter was 10 mm in all cases, and the length of the SEMS was measured using cannulation devices, considering the longitudinal location of the stricture segment and predicted safety margin.

Follow-up

Periodic surveillance on an out-patient basis was scheduled with liver function tests at one week post-procedurally and monthly thereafter for 1 year. If the patient survived 1 year after SEMS placement, follow-up was performed every 3 months until the patient died. If the patient missed an appointment, the research assistant conducted telephone interviews for information regarding jaundice, adverse events, palliative chemotherapy or radiotherapy, or death. Follow-up data collection was concluded at the date of death or on 30 August 2014 (the date of last 1 year follow-up). Follow-up loss was defined when there was no contact with the patient within 6 months after randomization. This study was

approved by our institutional review board, and informed consent was obtained from each patient.

Measured outcomes

The two types of stents were compared for the following main parameters: 1) cumulative stent patency (from the date of randomization until the date of first documented stent dysfunction), 2) overall patient survival (from the date of randomization until the date of death), 3) stent dysfunction-free patient survival (from the date of randomization until the date of first documented stent dysfunction or death, whichever came first), 4) technical and functional success and 5) procedure-related adverse events, including stent dysfunction, pancreatitis and cholecystitis. Stent dysfunction comprised stent occlusion and stent migration causing recurrent biliary obstruction. Stent dysfunction was suspected based on recurrent jaundice and/or other clinical signs of acute cholangitis and confirmed by subsequent radiologic studies, including computed tomography, percutaneous cholangiography and endoscopic retrograde cholangiopancreatography. Other adverse events and grade of severity were defined according to the consensus criteria [25,26].

Sample size calculation and statistical analyses

We presumed a 24% difference in stent patency between groups (38% vs. 14%) based on the first randomized trial in this field [8]. With a two-sided type I error of 0.05 and a statistical power of 0.8, we calculated a sample size of at least 51 patients for each arm of the study.

We used the Kaplan–Meier method with a log-rank test to evaluate cumulative stent patency, overall patient survival and stent dysfunction-free patient survival between groups. In the calculation of stent dysfunction-free survival, patients who died without stent dysfunction and patients who experienced stent dysfunction before death were regarded as uncensored data, whereas living patients without stent dysfunction were censored at the date of last follow-up because, in previously conducted randomized trials [9,15], median patient survival was shorter than the median cumulative stent patency owing to loss of censored data. Categorical variables were analyzed with either the chi-squared or Fisher's exact test. Quantitative data were analyzed by unpaired Student's t-tests and presented as the mean ± standard deviation. Potential predictive factors for stent dysfunction were examined using the Cox proportional hazard model. A p-value <0.05 was regarded as statistically significant. Statistical analyses were performed in an intention-to-treat fashion, using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics

A total of 103 patients were randomly assigned to either the partially covered SEMS ($n = 51$) or uncovered SEMS ($n = 52$) group. At the last follow-up, 98 patients (95.1%) were confirmed dead (94.1% in the partially covered group, 96.2% in the covered group) (Figure 2).

Baseline demographics and clinical data are presented in Table I. Temporary biliary drainage before SEMS placement was performed in 21 patients (41.2%) in the partially covered and 17 (32.7%) in the uncovered group ($p = 0.372$). The groups were homogenous for history of cholecystectomy, presence of gallbladder (GB) stone (% of GB in situ) and cystic duct involvement by tumor (% of GB in situ). Pancreatic cancer was the primary cause of malignant distal biliary stricture in both groups (56.9% vs. 69.2%). Twenty patients in each group received palliative anticancer treatment (39.2% vs. 38.5%). The technical success rate of SEMS deployment was 100% in both groups. The functional success rate was 98.0% (50/51) and 98.1% (51/52) in the partially covered and uncovered groups, respectively.

Cumulative stent patency

Stent dysfunction was encountered in 17 patients (33.3%) in the partially covered group and 15 (28.8%) in the uncovered group ($p = 0.623$). There were no significant group differences for cumulative stent patency (log-rank test; $p = 0.467$, Figure 3). The median time to stent dysfunction was 395 days (184–428, interquartile range [IQR]) in the partially covered group and 365 days (171-unknown, IQR) in the uncovered group. The 6- and 12-month cumulative stent patency rates were 77.5% and 54.5% in the partially covered group vs. 74.8% and 46.6% in the uncovered group (Table II).

The causes of stent dysfunction are presented in Table III. There was a non-significant trend toward greater stent migration (5.9% vs. 0%) and overgrowth (7.8% vs. 1.9%) in the partially covered vs. uncovered group, whereas tumor ingrowth occurred significantly more frequently in the uncovered group (5.9% vs. 19.2%, $p = 0.041$). Stent migration in the partially covered group occurred only in patients with short stenosis of the utmost distal bile duct (two in ampullary cancer, one in bile duct cancer) but did not occur in any patients with pancreatic cancer. In the

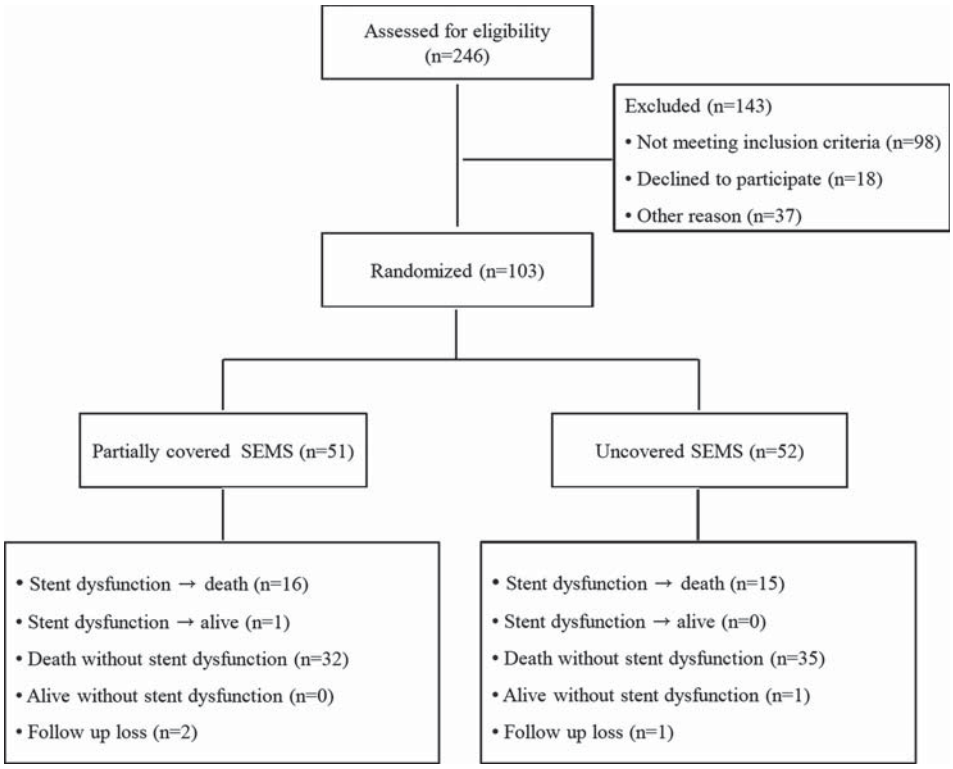

Figure 2. Flow diagram of enrolled study population.

multivariate Cox proportional hazard model, no significant predictors for stent dysfunction were found when age, sex, Karnofsky performance score, prior biliary drainage, stent type, stricture length and anticancer treatment after SEMS placement were included in the analysis.

Subgroup analyses for pancreatic cancer patients are presented in Table IV. There were no significant group differences groups for cumulative stent patency ($p = 0.658$), despite no stent migration and less tumor ingrowth in the partially covered SEMSs group.

Table I. Baseline characteristics of patients.

	Partially covered SEMS ($n = 51$)	Uncovered SEMS ($n = 52$)	p-Value
Age, year	68.7 ± 11.2	68.0 ± 11.3	0.745
Gender (male/female), n	34/17	30/22	0.348
Karnofsky performance score	78.0 ± 9.0	79.4 ± 7.3	0.391
Prior biliary drainage*, n (%)	21 (41.2)	17 (32.7)	0.372
Length of stricture, mm	29.5 ± 15.0	26.3 ± 12.7	0.240
History of cholecystectomy, n (%)	6 (11.8)	2 (3.8)	0.160
Cystic duct involvement by tumor, n (% of GB in situ)	12 (26.7)	9 (18.0)	0.309
GB stone, no (% of GB in situ)	20 (44.4)	18 (36.0)	0.402
Bilirubin level on admission, mg/dl	10.7 ± 8.4	11.4 ± 6.1	0.642
Acute cholangitis on admission, n (%)	15 (29.4)	9 (17.3)	0.146
Diagnosis, n (%)			0.134
Pancreatic cancer	29 (56.9)	36 (69.2)	
Bile duct cancer	17 (33.3)	7 (13.5)	
Gallbladder cancer	2 (3.9)	5 (9.6)	
Ampullary cancer	2 (3.9)	2 (3.8)	
Lymph-node metastasis	1 (2.0)	2 (3.8)	
Liver metastasis, n (%)	16 (31.4)	15 (28.8)	0.683
Palliative CTx and/or RTx, n (%)	20 (39.2)	20 (38.5)	0.937

Continuous variables are expressed as mean ± standard deviation.
*Endoscopic retrograde biliary drainage with a plastic stent or naso-biliary tube.
Abbreviations: CTx: Chemotherapy; GB: Gallbladder; RTx: Radiotherapy; SEMS: Self-expandable metal stent.

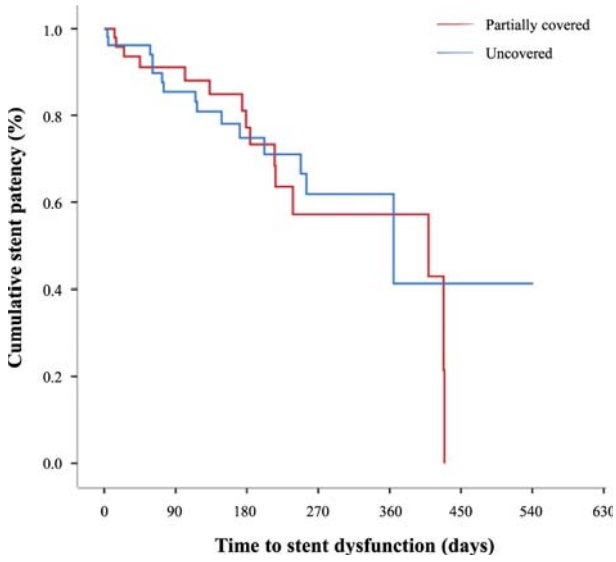

Figure 3. Kaplan–Meier curves of cumulative stent patency: the median stent patency was 395 days in the partially covered group and 365 days in the uncovered group (log-rank $p = 0.467$).

Overall patient survival and stent dysfunction-free patient survival

The log-rank test revealed overall patient survival was not different between groups (median time to death, 219 days [IQR, 76–390] in the partially covered group vs. 245 days [IQR, 133–331] in the uncovered group, $p = 0.276$) (Figure 4, Table II). There were also no group differences in stent dysfunction-free patient survival ($p = 0.453$) (Figure 5, Table II).

Adverse events

Stent dysfunction was a primary adverse event in this study. The rate of overall adverse events following SEMS placement was 47.1% in the partially covered group and 38.5% in the uncovered group ($p = 0.378$) (Table III). Endoscopic sphincterotomy-related bleeding occurred in one patient in the uncovered group, and endoscopic sphincterotomy-related retroperitoneal perforation developed in one patient in each group. These three cases were graded as mild and successfully managed with conservative treatment.

Pancreatitis occurred in three patients (5.9%) in the partially covered group, whereas none developed in the uncovered group ($p = 0.118$). All cases of pancreatitis were classified as mid-pancreatitis, underwent endoscopic sphincterotomy before SEMS deployment, and recovered conservatively. Cholecystitis occurred in 5/45 patients with GB (11.1%) in the partially covered group and 3/50 patients with GB (6.0%) in the uncovered group ($p = 0.470$). No procedure-related mortality was encountered in either group.

Discussion

Biliary decompression is usually recommended for palliation of inoperable malignant distal biliary obstruction because it can prevent biliary infection and liver failure and provide the patient the opportunity to receive anti-cancer chemotherapy and/or radiotherapy [1,2]. Uncovered SEMSs were developed to overcome diameter limitations of plastic stents in order to improve stent patency and extend patient survival. Partially or fully covered SEMSs were introduced to overcome tumor ingrowth, the main cause of stent dysfunction in uncovered SEMSs. Partially covered SEMSs are more frequently used than fully covered SEMSs to prevent stent migration. However, studies comparing uncovered and covered SEMSs have produced conflicting outcomes regarding cumulative stent patency [7–19].

To date, eight prospective randomized trials (summarized in Table V) comparing uncovered and covered SEMSs for inoperable malignant distal biliary obstruction palliation have been published [8–12,15,16,19]. SEMSs were placed exclusively

Table II. Cumulative stent patency, overall patient survival, and stent dysfunction-free survival.

	Partially covered SEMS ($n = 51$)	Uncovered SEMS ($n = 52$)	p-Value
Cumulative stent patency*	395 (184-428)	365 (171-unknown†)	0.467
6-M cumulative patency, %	77.5	74.8	
12-M cumulative patency, %	54.5	46.6	
Patient survival*	219 (76-390)	245 (133-331)	0.276
6 M-survival, %	57.3	58.8	
12 M-survival, %	26.6	15.7	
Stent dysfunction-free survival*	159 (52-218)	155 (111-283)	0.435
6 M-dysfunction-free survival %	43.2	43.2	
12 M-dysfunction-free survival %	10.3	7.9	

*Analyzed using Kaplan–Meier method and log-rank test, expressed as median value (interquartile range) of day.
†Could not be estimated, because of censored data.
Abbreviations: M: Months; SEMS: Self-expandable metal stent.

Table III. Adverse events including stent dysfunction.

	Partially covered SEMS (n = 51)	Uncovered SEMS (n = 52)	p-Value
Pancreatitis, n (%).	3 (5.9)	0 (0.0)	0.118
Cholecystitis, n (% of GB in situ)	5 (11.1)	3 (6.0)	0.470
Cholangitis without stent dysfunction, n (%)	1 (2.0)	2 (3.8)	1.000
Stent dysfunction, n (%)	17 (33.3)	15 (28.8)	0.623
Stent migration	3 (5.9)	0 (0.0)	0.118
Tumor ingrowth	3 (5.9)	10 (19.2)	0.041
Tumor overgrowth	4 (7.8)	1 (1.9)	0.205
Bile encrustation	4 (7.8)	3 (5.8)	0.715
Food impaction	1 (2.0)	1 (1.9)	1.000
Others*	1 (2.0)	0 (0.0)	0.495
Unknown	1 (2.0)	0 (0.0)	0.495
Overall adverse events†, n (%)	24 (47.1)	20 (38.5)	0.378

*One case of hemobilia from pancreas cancer confirmed at angiography.
†Include stent dysfunction, and more than one adverse event in a patient was regarded as one event.
Abbreviations: GB: Gallbladder; SEMS: Self-expandable metal stent.

Table IV. Subgroup analyses in patients with pancreatic cancer.

	Partially covered SEMS (n = 29)	Uncovered SEMS (n = 36)	p-Value
Stent dysfunction, n (%)	9 (31.0)	11 (30.6)	0.967
Stent migration	0 (0.0)	0 (0.0)	1.000
Tumor ingrowth	1 (3.4)	6 (16.7)	0.120
Tumor overgrowth	2 (6.9)	1 (2.8)	0.582
Bile encrustation	3 (10.3)	3 (8.3)	1.000
Food impaction	1 (3.4)	1 (2.8)	1.000
Others*	1 (3.4)	0 (0.0)	0.446
Unknown	1 (3.4)	0 (0.0)	0.446
Cumulative stent patency†	409 (174-428)	365 (148-unknown‡)	0.658

*One case of hemobilia from pancreas cancer confirmed at angiography.
†Analyzed using Kaplan-Meier method and log-rank test, expressed as median value (interquartile range) of day.
‡Could not be estimated, because of censored data.
Abbreviations: M: Months; SEMS: Self-expandable metal stent.

via the endoscopic route in four trials [9,12,15,16] and both endoscopic and percutaneous routes in one [8]. Covered SEMSs with mesh structures identical to uncovered SEMSs were used in these five trials. Exclusively percutaneous SEMS placement was used in the remaining three trials [10,11,19], in which uncovered and covered SEMSs with different mesh structures from different brands were compared. Among the eight trials, one included SEMSs with identical mesh structures and relatively low axial force with both ends flared to prevent stent migration [9].

Two recent meta-analyses [7,14] reached conflicting conclusions due to different methodological approaches and inclusion studies for the analysis of main outcomes. The first meta-analysis [14] of five randomized trials [8,1012,15] reported that covered compared with uncovered SEMSs prolonged cumulative stent patency by 61 days. However, this result was based only on three randomized trials that all showed the superiority of covered SEMS; one used a hand-made covered SEMS not commercially available [8] and two used covered SEMSs with mesh structures different from the uncovered SEMSs, placed exclusively via the percutaneous route [10,11]. The remaining two randomized trials [12,15], which included both types of SEMSs with identical mesh structures and demonstrated no advantages of covered SEMSs for stent patency, were not reflected in conclusion on stent patency because of heterogeneity in definitions and reported variables of stent patency across studies.

The other meta-analysis [7] included the above five randomized trials [8,10–12,15] and four abstracts. Their analysis showed that covered SEMSs have unclear benefits for stent patency at 6 and 12 months, based on the results of four randomized trials [8,11,12,15].

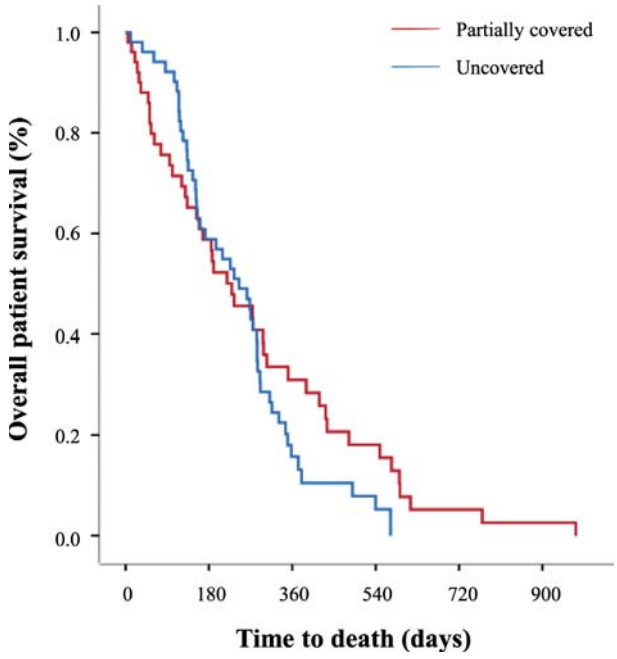

Figure 4. Kaplan–Meier curves of overall patient survival: the median survival time was 219 days in the partially covered group and 245 days in the uncovered group (log-rank $p = 0.276$).

Therefore, further prospective randomized trials are needed using both types of SEMSs with identical mesh structures from the same brand to minimize confounding biases, because SEMS structures and materials determine their mechanical properties, such as radial and axial force, which influence stent dysfunction and adverse events [27–29]. Also covered SEMSs designed to prevent stent migration should be included because stent migration is the main factor counteracting decreased tumor ingrowth in the covered SEMSs. Indeed, four randomized trials with no or negligible stent migration showed significant stent patency prolongation with covered SEMSs [8–11].

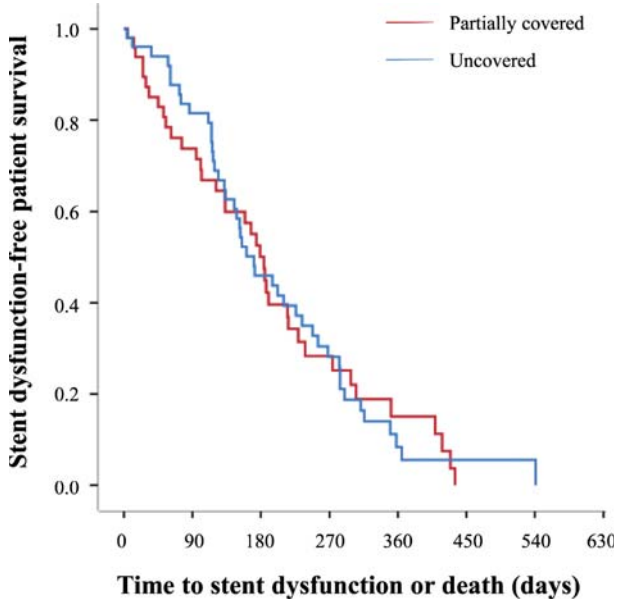

Figure 5. Kaplan–Meier curves of dysfunction-free patient survival: the median dysfunction-free patient survival was 159 days in the partially covered group and 155 days in the uncovered group (log-rank $p = 0.435$).

The multicenter randomized trial by Kitano *et al.* [9]. comparing partially covered and uncovered SEMSs with identical mesh structures and anti-migration system in patients with pancreatic cancer was recently published, and it reported no stent migration and significantly prolonged cumulative stent patency in the partially covered group (median 583 days, partially covered, vs. 314 days, uncovered, log-rank $p = 0.019$). The partially covered SEMSs had relatively low axial force (0.65 N) and 5-mm uncovered flared ends that enabled anti-migration (Wallflex; Boston Scientific, Natick, Mass, USA). However, a recent single-arm prospective study by Sakai *et al.* [30]. with the same partially covered SEMS reported 4.1% stent migration, which was not different from the migration rates of other studies using covered SEMSs with high axial force and non-flared ends (3–11.8%) [12,13,15,17].

Here, we investigated identically structured partially covered and uncovered SEMSs with anti-migration properties, relatively low axial force (0.60 N), and 5-mm uncovered flared portions at both ends. As in Sakai's study [30], we encountered three cases (5.9%) of stent migration in the partially covered SEMSs group and no significant difference in cumulative stent patency between the partially covered and uncovered SEMSs groups ($p = 0.467$). However, stent migration in the partially covered group occurred only in patients with short stenosis of the utmost distal bile duct and not in any patient with pancreatic cancer, consistent with Kitano's study [9] and another randomized trial [11] that exclusively targeted pancreatic cancer.

Risk factors for covered SEMS migration in malignant distal biliary stricture are presumed to include slippery tendencies due to duodenal invasion, low radial SEMS force, and chemotherapy-induced tumor shrinkage [29]. Such migration may also be influenced by the bile duct stricture's length and location, as it occurred only in relatively short strictures in our study. Strictures located in the ampulla and the utmost distal bile duct may act as the only clamping point for the SEMS due to its being located in or near the sphincter of Oddi. Strictures not located in the vicinity of the sphincter of Oddi may act as additional clamping points, reducing the risk of stent migration. However, further study is warranted to support this hypothesis of additional clamping points

Table V. Previous published randomized trials comparing covered and uncovered self-expandable metal stents for the palliation of inoperable malignant distal biliary obstruction.

	Isayama *et al.* (2004) [8]	Telford *et al.* (2010) [15]	Kullman *et al.* (2010) [12]	Krokidis *et al.* (2010) [10]	Krokidis *et al.* (2011) [11]	Kitano *et al.* (2013) [9]	Ung *et al.* (2013) [16]	Lee *et al.* (2014) [19]
No. of patients, U/C	55/57	61/68	200/200	30/30	40/40	60/60	34/34	20/20
Tumor type in covered SEMS group, n (Pancreas/bile duct/GB/ ampullary/LN mets)	34/6/3/2/12	59/NA/NA/ NA/NA	152/12/8/8/16	0/30/0/0/0	40/0/0/0/0	60/0/0/0/0	30/0/2/1/0	12/1/0/0/NA
Chemotherapy in covered group, n (%)	NA	31 (45.6)	NA	NA	NA	47 (78.3)	8 (23.5)	NA
SEMS used	Diamond⋆	Wallstent⋆	Nitinella⋆	U: Wallstent C: Viabil	U: Luminexx C: Viabil	Wallflex⋆	Hanarostent⋆	U: Zilver C: Comvi
Type of cSEMS (patially or fully)	Partially	Partially	Partially	Both	Both	Partially	Fully	Partially
Insertion route	Endoscopic/ percutaneous	Endoscopic	Endoscopic	Percutaneous	Percutaneous	Endoscopic	Endoscopic	Percutaneous
Stent dysfunction rate, U/C (%)	**38.2/14.0**	18.0/29.4	22.5/23.5	**30.0/13.3**	**30.0/10.0**	36.7/23.3	17.0/13.0	20.0/50.0
Stent patency, U/C (log-rank *p* value)	**161/304**† (0.007)	711/357‡ (0.530)	199/154§ (0.326)	**166/227**† (0.046)	**166/234**† (0.007)	**314/583**‡ (0.019)	127/153‡ (0.05<)	**413/207**† (0.041)
Stent migration, U/C (%)	0.0/1.8	**0.0/11.8**	**0.0/3.0**	0.0/0.0	0.0/0.0	0.0/0.0	NA	0.0/10/.
Tumor ingrowth, U/C (%)	**29.1/0.0**	13.1/8.8	**10.5/4.5**	**26.7/0.0**	**27.5/0.0**	**25.0/0.0**	NA	10.0/0.0
Tumor overgrowth, U/C (%)	3.6/7.0	0.0/4.4	5.0/9.0	3.3/6.7	7.5/5.0	3.3/5.0	NA	5.0/20.0
Bile encrustation, U/C (%)	0.0/3.5	1.6/5.9	2.0/6.0	3.3/6.7	2.5/5.0	10.0/18.3	NA	5.0/20.0
Cholecystitis, U/C (%)	0.0/3.5	6.7/6.5	1.0/1.0	0.0/0.0	0.0/0.0	3.3/1.7	0.0/0.0	0.0/5.0
Pancreatitis, U/C (%)	1.8/8.8	1.6/0.0	2.0/1.5	0.0/0.0	0.0/0.0	0.0/1.7	0.0/2.9	0.0/0.0

Numeric values in bold means statistically significant ($p < 0.05$).
⋆Covered and uncovered SEMS with an identical mesh structure.
†Mean.
‡Median.
§First quartile.
Abbreviations: C: Covered; NA: Not available SEMS: Self-expandable metal stent; U: Uncovered.

reducing stent migration. The slippery tendencies of covered SEMS may also be related to tumor consistency, as ampullary cancer is usually soft and friable [31].

In a subgroup analysis of pancreatic cancer in our study, the superiority of the partially covered SEMSs was not noted in terms of cumulative stent patency ($p = 0.658$), despite no stent migration and less tumor ingrowth in the partially covered SEMSs group. This result may be due to a counter-effect of increased tumor overgrowth and bile encrustation, although it could also have been influenced by the relatively small and unbalanced population of pancreatic cancer subjects using both types of SEMSs. The two meta-analyses reported a significantly higher rate of tumor overgrowth in the covered SEMSs groups [7,14], although their reasons were not clearly stated. Therefore, further studies are needed to clarify the mechanisms of tumor overgrowth with covered SEMSs to aid the development of ideal stents.

Six randomized trials [8–12,15] and one large retrospective cohort study [18] reported a higher rate of bile encrustation with covered SEMSs. Sphincter function loss caused by persistent transpapillary SEMS positioning predisposes to ascending infection, leading to bacterial attachment to the covering material and biofilm formation [32]. Thus, the development of a new coating material to minimize bacterial attachment and biofilm formation may contribute to longer covered SEMS stent patency.

Regarding adverse events, our data showed no significant group differences in the incidence of cholecystitis and pancreatitis, although there was a trend toward more cholecystitis and pancreatitis in the partially covered SEMS group. These results are in accordance with the previously described randomized trials [8–12,15,16,19] and meta-analyses [7,14].

The main strength of our study is that it was a prospective randomized trial comparing partially covered and uncovered SEMSs with identical mesh structures and anti-migration systems. Our conclusions are different from those of the first randomized trial with anti-migratory SEMSs [9]. Our data showed that anti-migration systems did not guarantee the

reduction of covered SEMS migration, and in the subgroup with pancreatic cancer, longer stent patency was not guaranteed with covered SEMSs, even though stent migration did not occur.

Nevertheless, our study had several limitations. First, it was conducted in a single tertiary referral center; therefore, the measured outcomes may not be generalized. Second, randomization was performed without stratification by tumor stage. Therefore, a bias resulting from unbalanced stage distribution cannot be excluded. Third, three patients were lost to follow-up within 6 months. However, 98 (95.1%) of 103 patients were confirmed dead by the end of follow-up data collection.

In conclusion, there were no differences in cumulative stent patency, patient survival, stent dysfunction-free survival, or adverse events between partially covered and uncovered SEMSs with identical mesh structures and anti-migration properties. Endoscopic placement of partially covered SEMSs with anti-migration properties for the palliation of malignant distal biliary obstruction failed to show a reduction in stent migration. Further comprehensive studies on the mechanisms of stent dysfunction are needed in order to develop a partially covered SEMS with a longer stent patency.

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References

[1] Farley DR, Weaver AL, Nagorney DM. "Natural history" of unresected cholangiocarcinoma: patient outcome after noncurative intervention. Mayo Clin Proc 1995;70:425–9.

[2] Kim JH. Endoscopic stent placement in the palliation of malignant biliary obstruction. Clin Endosc 2011;44:76–86.

[3] Davids PH, Groen AK, Rauws EA, Tytgat GN, Huibregtse K. Randomised trial of self-expanding metal stents versus polyethylene stents for distal malignant biliary obstruction. Lancet 1992;340:1488–92.

[4] Kaassis M, Boyer J, Dumas R, Ponchon T, Coumaros D, Delcenserie R, et al. Plastic or metal stents for malignant stricture of the common bile duct? Results of a randomized prospective study. Gastrointest Endosc 2003;57:178–82.

[5] Knyrim K, Wagner HJ, Pausch J, Vakil N. A prospective, randomized, controlled trial of metal stents for malignant obstruction of the common bile duct. Endoscopy 1993;25: 207–12.

[6] Soderlund C, Linder S. Covered metal versus plastic stents for malignant common bile duct stenosis: a prospective, randomized, controlled trial. Gastrointest Endosc 2006;63: 986–95.

[7] Almadi MA, Barkun AN, Martel M. No benefit of covered vs uncovered self-expandable metal stents in patients with malignant distal biliary obstruction: a meta-analysis. Clin Gastroenterol Hepatol 2013;11:27–37 e21.

[8] Isayama H, Komatsu Y, Tsujino T, Sasahira N, Hirano K, Toda N, et al. A prospective randomised study of "covered" versus "uncovered" diamond stents for the management of distal malignant biliary obstruction. Gut 2004;53:729–34.

[9] Kitano M, Yamashita Y, Tanaka K, Konishi H, Yazumi S, Nakai Y, et al. Covered self-expandable metal stents with an anti-migration system improve patency duration without increased complications compared with uncovered stents for distal biliary obstruction caused by pancreatic carcinoma: a randomized multicenter trial. Am J Gastroenterol 2013; 108:1713–22.

[10] Krokidis M, Fanelli F, Orgera G, Bezzi M, Passariello R, Hatzidakis A. Percutaneous treatment of malignant jaundice due to extrahepatic cholangiocarcinoma: covered Viabil stent versus uncovered Wallstents. Cardiovasc Intervent Radiol 2010;33:97–106.

[11] Krokidis M, Fanelli F, Orgera G, Tsetis D, Mouzas I, Bezzi M, et al. Percutaneous palliation of pancreatic head cancer: randomized comparison of ePTFE/FEP-covered versus uncovered nitinol biliary stents. Cardiovasc Intervent Radiol 2011;34:352–61.

[12] Kullman E, Frozanpor F, Soderlund C, Linder S, Sandstrom P, Lindhoff-Larsson A, et al. Covered versus uncovered self-expandable nitinol stents in the palliative treatment of malignant distal biliary obstruction: results from a randomized, multicenter study. Gastrointest Endosc 2010;72:915–23.

[13] Park do H, Kim MH, Choi JS, Lee SS, Seo DW, Kim JH, et al. Covered versus uncovered wallstent for malignant extrahepatic biliary obstruction: a cohort comparative analysis. Clin Gastroenterol Hepatol 2006;4:790–6.

[14] Saleem A, Leggett CL, Murad MH, Baron TH. Meta-analysis of randomized trials comparing the patency of covered and uncovered self-expandable metal stents for palliation of distal malignant bile duct obstruction. Gastrointest Endosc 2011;74:321–7.

[15] Telford JJ, Carr-Locke DL, Baron TH, Poneros JM, Bounds BC, Kelsey PB, et al. A randomized trial comparing uncovered and partially covered self-expandable metal stents in the palliation of distal malignant biliary obstruction. Gastrointest Endosc 2010;72:907–14.

[16] Ung KA, Stotzer PO, Nilsson A, Gustavsson ML, Johnsson E. Covered and uncovered self-expandable metallic Hanarostents are equally efficacious in the drainage of extrahepatic malignant strictures. Results of a double-blind randomized study. Scand J Gastroenterol 2013;48:459–65.

[17] Yoon WJ, Lee JK, Lee KH, Lee WJ, Ryu JK, Kim YT, et al. A comparison of covered and uncovered Wallstents for the management of distal malignant biliary obstruction. Gastrointest Endosc 2006;63:996–1000.

[18] Lee JH, Krishna SG, Singh A, Ladha HS, Slack RS, Ramireddy S, et al. Comparison of the utility of covered metal stents versus uncovered metal stents in the management of malignant biliary strictures in 749 patients. Gastrointest Endosc 2013;78:312–24.

[19] Lee SJ, Kim MD, Lee MS, Kim IJ, Park SI, Won JY, et al. Comparison of the efficacy of covered versus uncovered metallic stents in treating inoperable malignant common bile duct obstruction: a randomized trial. J Vasc Interv Radiol 2014;25:1912–20.

[20] Ho H, Mahajan A, Gosain S, Jain A, Brock A, Rehan ME, et al. Management of complications associated with partially covered biliary metal stents. Dig Dis Sci 2010;55:516–22.

[21] Nakai Y, Isayama H, Komatsu Y, Tsujino T, Toda N, Sasahira N, et al. Efficacy and safety of the covered Wallstent in patients with distal malignant biliary obstruction. Gastrointest Endosc 2005;62:742–8.
[22] Suk KT, Kim HS, Kim JW, Baik SK, Kwon SO, Kim HG, et al. Risk factors for cholecystitis after metal stent placement in malignant biliary obstruction. Gastrointest Endosc 2006; 64:522–9.
[23] Willingham FF. All wrapped up: metal biliary stents and the effect of stent coverings. Gastrointest Endosc 2010;72:924–6.
[24] Isayama H, Mukai T, Itoi T, Maetani I, Nakai Y, Kawakami H, et al. Comparison of partially covered nitinol stents with partially covered stainless stents as a historical control in a multicenter study of distal malignant biliary obstruction: the WATCH study. Gastrointest Endosc 2012;76:84–92.
[25] Cotton PB, Lehman G, Vennes J, Geenen JE, Russell RC, Meyers WC, et al. Endoscopic sphincterotomy complications and their management: an attempt at consensus. Gastrointest Endosc 1991;37:383–93.
[26] Kiriyama S, Takada T, Strasberg SM, Solomkin JS, Mayumi T, Pitt HA, et al. TG13 guidelines for diagnosis and severity grading of acute cholangitis (with videos). J Hepatobiliary Pancreat Sci 2013;20:24–34.
[27] Isayama H, Nakai Y, Toyokawa Y, Togawa O, Gon C, Ito Y, et al. Measurement of radial and axial forces of biliary self-expandable metallic stents. Gastrointest Endosc 2009; 70:37–44.
[28] Nakai Y, Isayama H, Kawakubo K, Kogure H, Hamada T, Togawa O, et al. Metallic stent with high axial force as a risk factor for cholecystitis in distal malignant biliary obstruction. J Gastroenterol Hepatol 2014;29:1557–62.
[29] Nakai Y, Isayama H, Kogure H, Hamada T, Togawa O, Ito Y, et al. Risk factors for covered metallic stent migration in patients with distal malignant biliary obstruction due to pancreatic cancer. J Gastroenterol Hepatol 2014;29:1744–9.
[30] Sakai Y, Tsuyuguchi T, Hirata N, Sugiyama H, Shimura K, Nakaji S, et al. Long-term outcome of the WallFlex partially covered stent for unresectable malignant biliary obstruction: a multicenter single-arm prospective study. Hepatogastroenterology 2013;60:1854–60.
[31] Park SB, Kim HW, Kang DH, Choi CW, Ryu JH, Chu CW, et al. Metallic or plastic stent for bile duct obstruction in ampullary cancer? Dig Dis Sci 2012;57:786–90.
[32] Leung JW, Liu YL, Desta T, Libby E, Inciardi JF, Lam K. Is there a synergistic effect between mixed bacterial infection in biofilm formation on biliary stents? Gastrointest Endosc 1998;48:250–7.