A randomized trial comparing uncovered and partially covered self-expandable metal stents in the palliation of distal malignant biliary obstruction

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Background: The most common complication of uncovered biliary self-expandable metal stents (SEMSs) is tumor ingrowth. The addition of an impenetrable covering may prolong stent patency.

Objective: To compare stent patency between uncovered and partially covered SEMSs in malignant biliary obstruction.

Design: Multicenter randomized trial.

Setting: Four teaching hospitals.

Patients: Adults with inoperable distal malignant biliary obstruction.

Interventions: Uncovered or partially covered SEMS insertion.

Main Outcome Measures: Time to recurrent biliary obstruction, patient survival, serious adverse events, and mechanism of recurrent biliary obstruction.

Results: From October 2002 to May 2008, 129 patients were randomized. Recurrent biliary obstruction was observed in 11 of 61 uncovered SEMSs (18%) and 20 of 68 partially covered SEMSs (29%). The median times to recurrent biliary obstruction were 711 days and 357 days for the uncovered and partially covered SEMS groups, respectively ($P = .530$). Median patient survival was 239 days for the uncovered SEMS and 227 days for the partially covered SEMS groups ($P = .997$). Serious adverse events occurred in 27 (44%) and 42 (62%) patients in the uncovered and partially covered SEMS groups, respectively ($P = .046$). None of the uncovered and 8 (12%) of the partially covered SEMSs migrated ($P = .0061$).

Limitations: Intended sample size was not reached. Allocation to treatment groups was unequal.

Conclusions: There was no significant difference in time to recurrent biliary obstruction or patient survival between the partially covered and uncovered SEMS groups. Partially covered SEMSs were associated with more serious adverse events, particularly migration. (Clinical trial registration number: NCT01047332.) (Gastrointest Endosc 2010;72:907-14.)

Abbreviations: CI, confidence interval; IQR, interquartile range; SD, standard deviation; SEMS, self-expandable metal stent.

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Malignant biliary obstruction is a common sequela of pancreatic cancer, and its development can hinder the use of chemotherapy, decrease patient quality of life, and decrease survival. Palliation of malignant biliary obstruction is usually achieved by endoscopic stent placement. Self-expandable metal stents (SEMSs) have a larger diameter, resulting in a longer patency compared with large-bore plastic stents.[1-4] Tumor ingrowth is the most common mechanism of stent obstruction with the uncovered SEMS. Covered SEMSs were developed to prevent tumor ingrowth and prolong stent patency. However, there are insufficient data demonstrating clear superiority of commercially available covered SEMSs over uncovered SEMSs in the palliation of malignant biliary obstruction.

A previously published randomized trial demonstrated improved stent patency and an absence of tumor ingrowth with a covered SEMS compared with an uncovered SEMS.[5] The covered SEMS used in that study was handcrafted and is not commercially available. A subsequent retrospective cohort study[6] and a prospective cohort with a retrospective comparison group[7] did not demonstrate a difference in stent patency between uncovered and partially covered SEMSs. In addition, covered SEMSs may increase the frequency of pancreatitis and cholecystitis due to pancreatic duct and cystic duct occlusion by the stent covering.[5,8,9] Covered SEMSs are also more likely to migrate due to a lack of tissue embedding.[7-10]

Our present objective was to prospectively compare an uncovered and partially covered SEMS in the palliation of distal malignant biliary obstruction. The outcomes of interest were duration of stent patency, patient survivial, mechanism of stent obstruction, and serious adverse events.

Take-home Message

- The addition of a partial covering to the self-expandable metal stent did not prolong the time to recurrent biliary obstruction and was associated with a higher rate of complications compared with the uncovered self-expandable metal stent in the management of malignant distal biliary obstruction.

METHODS

This was a prospective randomized trial conducted at 4 large teaching hospitals (Brigham and Women's Hospital, Massachusetts General Hospital, and Boston Medical Center, Boston, Massachusetts, and Mayo Clinic, Rochester, Minnesota). Inclusion criteria were (1) age ≥18 years; (2) malignant distal (≥1 cm distal to the biliary hilum) biliary obstruction amenable to stent placement; and (3) not a candidate for curative surgical resection due to tumor stage, operative risk, or patient wishes. Exclusion criteria were (1) inability to obtain informed consent, (2) contraindication to ERCP, (3) prior biliary SEMS placement, and (4) prior biliary surgery. Malignancy was determined by pathology. Cancer stage was determined by transabdominal imaging and/or EUS. Written informed consent was obtained from each of the enrolled patients. The study was approved by the Institutional Review Boards at each of the participating centers.

Randomization and blinding

Subjects were randomized at the time of the ERCP after successful placement of a guidewire across the malignant stricture. Subjects received either an uncovered or a Permalume partially covered Wallstent (Boston Scientific Corporation, Natick, Mass, USA). Randomization was conducted in permuted blocks to balance stent assignment over the 4 sites by using a random number generator. Stent assignment was written on a card, sealed in identical opaque envelopes, and distributed to the sites. Stent assignment was concealed until the time of the interim analysis. The patient and the research assistant conducting the follow-up interviews were blinded to stent assignment.

SEMS insertion

All stents were inserted during ERCP in the usual fashion by experienced pancreaticobiliary endoscopists. Performance of sphincterotomy or biliary dilation before stent insertion was at the discretion of the endoscopist. Opacification of the cystic duct during cholangiography and whether the stent traversed the cystic duct orifice were recorded.

Data collection

Baseline data were collected from the patient before ERCP by a research assistant or advanced endoscopy fellow. Data collected included age, gender, Karnofsky performance score, history of a cholecystectomy or presence of cholelithiasis, primary tumor type and stage, and use of adjuvant chemotherapy or radiation therapy. Follow-up data were collected by telephone interview conducted by a research assistant 1 week after stent insertion and then monthly until patient death. The interview questions evaluated for biliary obstruction, adverse events, and adjuvant therapy. In addition to the scheduled interviews, the patient was instructed to call a pager if symptoms of recurrent biliary obstruction developed. The research assistant also obtained reports of any pertinent investigations conducted at outside hospitals.

Patients were considered to be lost to follow-up if they could not be contacted or declined to participate with the telephone interview within 6 months of randomization. Multiple attempts were made to contact a patient before classifying him or her as lost to follow-up. Patients lost to follow-up were analyzed in an intention-to-treat fashion and censored at the time of their last follow-up interview.

Serious adverse events were defined as adverse events requiring an invasive procedure or hospitalization or resulting in death. Recurrent biliary obstruction was counted

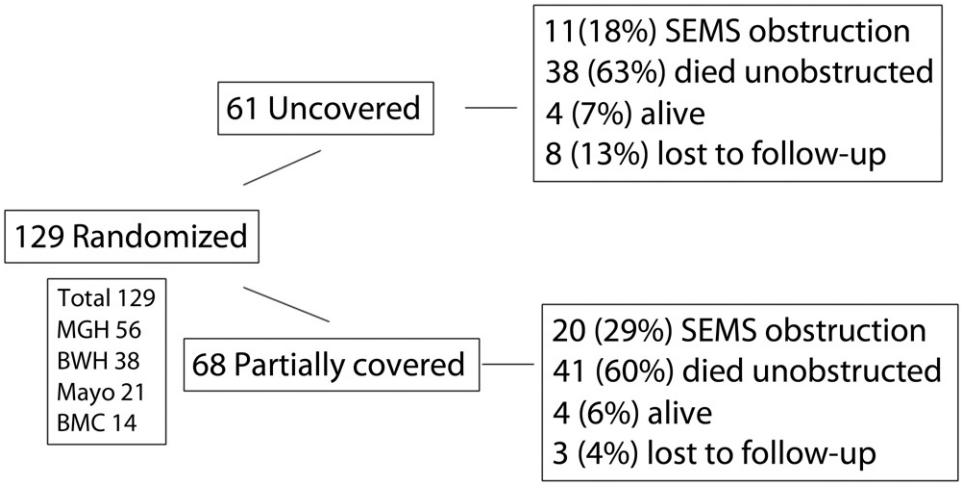

Figure 1. Flow diagram of randomized patients. MGH, Massachusetts General Hospital; BWH, Brigham and Women's Hospital; Mayo, Mayo Clinic Rochester; BMC, Boston Medical Center.

as a serious adverse event, but death because of malignant disease progression was not.

The primary study outcome was time to recurrent biliary obstruction between the two treatment groups. Secondary outcomes of interest were patient survival, serious adverse events, and the mechanism of recurrent biliary obstruction.

Statistical analyses

To demonstrate a 20% difference in the time to recurrent biliary obstruction between the two stents, with a beta error of 0.20 and an alpha error of 0.05, we estimated that 125 patients were required. An interim analysis was planned once 100 patients had been randomized and followed for 6 months. The results of the interim analysis have been presented in abstract form.[11] There was no difference in time to recurrent biliary obstruction, time to death, or total serious adverse events between the two groups. To account for the interim analysis, the total sample size was increased by 10% to 136 patients.

The time to recurrent biliary obstruction was evaluated by using the Kaplan-Meier method and compared by using the log-rank test. Patients not experiencing recurrent biliary obstruction were censored at the date of last follow-up or date of death. Patient survival was evaluated in a similar manner, with patients censored at the date of last follow-up. Differences in baseline characteristics, adverse events, and mechanism of recurrent biliary obstruction between the two groups were analyzed by using the chi-square test or Fisher exact test for categoric data and the Wilcoxon test for continuous data. Factors associated with recurrent biliary obstruction were evaluated by using Cox regression with backward stepwise selection retaining variables with a P value of $\leq .05$. Variables to be analyzed were decided a priori: patient age, gender, Karnofsky performance score, type of primary malignancy, prior plastic stent, and adjuvant chemotherapy or radiation therapy. All data were analyzed in an intention-to-treat fashion. The analysis was conducted by using SAS statistical software, version 4.1 (SAS Institute, Cary, NC, USA).

This was an investigator-initiated study and was funded in part by an American Society for Gastrointestinal Endoscopy Outcomes and Effectiveness Award. Boston Scientific Corporation provided paper case report forms and an electronic database as well as an unrestricted grant that provided partial support for a research assistant once funding from the American Society for Gastrointestinal Endoscopy award was finished.

RESULTS

Baseline patient characteristics

One hundred twenty-nine patients were randomized to receive an uncovered (n = 61) or partially covered (n = 68) SEMS at the 4 sites between October 2002 and May 2008. Patient flow is shown in Figure 1.

The mean patient age was 66 years (standard deviation [SD] 14 years), and 68 (53%) were male. The mean Karnofsky performance score was 75 (SD 17). Pancreatic adenocarcinoma was the primary malignancy in 106 patients (82%). Ninety-one patients (71%) had not undergone a cholecystectomy in the past and 19 of 91 (21%) had known cholelithiasis. Fifty-two patients (40%) were receiving adjuvant therapy at the time of randomization. The baseline characteristics for the treatment groups were equivalent except that significantly more patients with uncovered SEMSs had received prior adjuvant therapy (Table 1). After randomization, however, 44 of 59 patients (75%) in the uncovered SEMS group and 52 of 67 patients (78%) in the covered SEMS group were receiving adjuvant therapy.

TABLE 1. Baseline patient data

	Uncovered SEMS (n = 61)	Partially covered SEMS (n = 68)	*P* value*
Mean age (y), SD	65[13]	66[14]	—
Male gender, no. (%)	31 (49)	30 (56)	—
Mean Karnofsky performance score (SD)	74 (17)	77 (18)	—
Pancreatic cancer, no. (%)	47 (77)	59 (86)	.098
Metastatic disease, no. (%)	30 (61)	31 (59)	—
Gallbladder in situ, no. (%)	45 (76)	46 (70)	—
Prior plastic stent, no. (%)	42 (69)	40 (59)	.237
Adjuvant therapy, no. (%)	20 (33)	35 (52)	.037
Chemotherapy, no. (%)	14 (23)	26 (38)	—
Radiation therapy, no. (%)	0	4 (6)	—
Both, no. (%)	6 (10)	5 (7)	—

**P* values are presented for all analyses performed. If the groups appeared similar on inspection, formal statistical analysis was not performed.

Stent placement

Stent placement was initially successful in 128 patients. In one patient, the ERCP was aborted when the patient aspirated; the stent was successfully inserted 3 days later. One patient required two stents to bridge the stricture, and 128 patients required one stent to bridge the stricture. All stents were transpapillary. A sphincterotomy was performed at the time of SEMS insertion or had been performed previously in 31 patients (51%) in the uncovered SEMS group and 30 patients (44%) in the covered SEMS group.

Patient follow-up

Patient outcomes after randomization are shown in Table 2. The median patient follow-up was 125 days (range, 0-793 days) in the uncovered SEMS group and 201 days (range, 0-1302 days) in the partially covered SEMS group.The mean patient follow-up was 217 days (SD 208 days) in the uncovered SEMS group and 244 days (SD 231 days) in the partially covered SEMS group ($P = .50$).

Eleven patients (9%) were lost to follow-up within 6 months of randomization: 8 in the uncovered SEMS group and 3 in the partially covered SEMS group. The median follow-up of these 11 patients was 76 days (range, 0-125 days) in the uncovered SEMS group and 28 days (range, 0-28 days) in the partially covered SEMS group. Three of these patients declined to participate further in the follow-up telephone interviews, and 8 could not be contacted. In two cases, one in each treatment group, the date of last follow-up was the date of stent insertion.

In total, 26 patients were not followed until their time of death. Six patients declined to participate further, 19 patients could not be contacted, including 6 patients who had already experienced recurrent biliary obstruction (the primary outcome measure), and 1 patient was followed for 786 days. Of these 26 patients, 11 were in the uncovered SEMS group and 15 in the partially covered SEMS group.

Duration of stent patency and patient survival

There was no significant difference in the time to recurrent biliary obstruction between the two groups (Fig. 2). Median time to recurrent biliary obstruction was 711 days (interquartile range [IQR], 283 days to unknown [largest value was censored]) in the uncovered SEMS group and 357 days (IQR, 264-1302 days) in the partially covered SEMS group ($P = .530$). The hazard ratio for recurrent biliary obstruction was 1.27 (95% confidence interval [CI], 0.6-2.7) in the partially covered SEMS group as compared to the uncovered SEMS group. The absolute difference in the probability of no recurrent biliary obstruction at 6 months was 3.0% (95% CI, −10.6%-16.6%) and at 12 months was 8.1% (95% CI, −7.7%-23.9%; Table 2). Median time to recurrent biliary obstruction or death was 159 days (IQR, 75-301 days) in the uncovered SEMS group and 205 days (IQR, 82-311 days) in the partially covered SEMS group ($P = .847$). Median time to patient death was 239 days (IQR, 84-401 days) and 227 days (IQR, 99-365 days) in the uncovered and partially covered SEMS groups, respectively ($P = .997$).

The mechanism of recurrent biliary obstruction in the uncovered SEMS group was tumor ingrowth in 7, tumor ingrowth plus sludge in 1, food debris in 1, and unknown in 2. In the partially covered SEMS group, the mechanism of recurrent biliary obstruction was stent migration in 4, tumor ingrowth in 3, tumor overgrowth in 2, sludge in 2, food debris in 2, migration plus ingrowth in 2, migration plus sludge in 1, tumor ingrowth plus sludge in 1, failure to expand in 1, and unknown in 2.

On regression analysis, two variables were associated with recurrent biliary obstruction when controlling for stent type, age, gender, Karnofsky performance score, and adjuvant therapy after randomization. Placement of a prior plastic stent was associated with a lower probability of recurrent biliary obstruction (hazard ratio 0.39; 95% CI, 0.17-0.93), and pancreatic cancer (hazard ratio 4.96; 95% CI, 1.68-14.59) was associated with a higher probability of recurrent biliary obstruction.

Adverse events

Sixty-two serious adverse events were experienced by 27 patients (44%) in the uncovered SEMS group and 80 serious adverse events were experienced by 42 patients (62%) in the partially covered SEMS group ($P = .046$).

TABLE 2. Patient survival, recurrent biliary obstruction, and serious adverse events

	Uncovered SEMS (n = 61)	Partially covered SEMS (n = 68)	*P* value*
Median days of follow-up, no. (range)	125 (0-793)	201 (0-1302)	—
Median days of survival, no. (IQR)	239 (84-401)	227 (99-365)	.997
Median days to recurrent biliary obstruction, no. (IQR)	711 (283-†)	357 (264-1302)	.530
Probability of no biliary obstruction at 6 months, %	90	87	—
Probability of no biliary obstruction at 12 mo, %	55	47	—
Mechanism of recurrent biliary obstruction,‡ no.			
Tumor ingrowth	8	6	—
Tumor overgrowth	0	3	—
Stent migration	0	6	—
Sludge	1	4	—
Other§	1	2	—
Unknown	2	2	—
Serious adverse events, no. (%)	27 (44)	42 (62)	.046
Recurrent biliary obstruction, no. (%)	11 (18)	20 (29)	—
Stent migration, no. (%)	0	8 (12)	.006
Pancreatitis, no. (%)	1 (2)	0	—
Cholecystitis, no. (% patients with gallbladder)	3/45 (7)	3/46 (7)	—
Other‖, no. (%)	12 (20)	17 (25)	—

**P* values are presented for all analyses performed that were decided a priori.
†Unable to calculate upper confidence interval because the largest value in the Kaplan-Meier analysis of time to recurrent biliary obstruction was censored.
‡Stents may be obstructed by more than one mechanism, therefore, the total does not add up to the number of stent obstructions in each group.
§Includes one patient in each group with food debris in the stent and one covered SEMS that failed to expand.
‖Includes hospital admissions for pain, line sepsis, vomiting, dehydration, deep vein thrombosis, gastric outlet obstruction, radiation gastritis, pneumonia, stroke, and Whipple procedure (2).

In the week after stent insertion, 1 patient had a myocardial infarction; 1 patient developed mild pancreatitis; 1 patient developed bleeding at the sphincterotomy site, which was treated endoscopically; and 3 patients developed cholangitis. Of the 3 patients with cholangitis, 2 responded to antibiotic therapy and, in 1 case, drainage of a liver abscess, and the third required a repeat ERCP and stent replacement for inadequate stent expansion.

Cholecystitis developed in 3 patients in each treatment group. The proportion of patients at risk who developed cholecystitis was 3 of 45 (7%) and 3 of 46 (7%) in the uncovered and partially covered SEMS groups, respectively. None of the uncovered SEMSs migrated, whereas 8 partially covered SEMSs (12%) migrated ($P = .0061$). Migration did not appear to be related to prior plastic stent insertion or sphincterotomy. Of the patients in whom a partially covered SEMS migrated, one had a prior plastic stent and one had a sphincterotomy. All of the stents migrated distally. Migration contributed to recurrent biliary obstruction in 6 cases. Migration caused duodenal perforation in two cases and contributed to upper GI hemorrhage in one. In all 3 cases, the stent migrated distally to abut the opposite wall of the duodenum, and the proximal portion of the stent was retained in the bile duct. Of the two patients sustaining a duodenal perforation, one underwent laparoscopic gastrojejunostomy with good results and died from progression of pancreatic cancer 10 months later. The second patient was not an operative candidate and was managed with endoscopic enteral stent placement across the perforation and gastrostomy tube placement, but died 3 weeks later. The patient experiencing duodenal bleeding was managed endoscopically with epinephrine injection and electrocautery. That patient had been anticoagulated for treatment of a deep vein thrombosis.

When serious adverse events due to SEMS migration were excluded from the comparison, there was no significant difference in serious adverse events between the two groups ($P = .25$).

Protocol deviations

The planned sample size, including a 10% increase in the calculated sample size to account for the planned

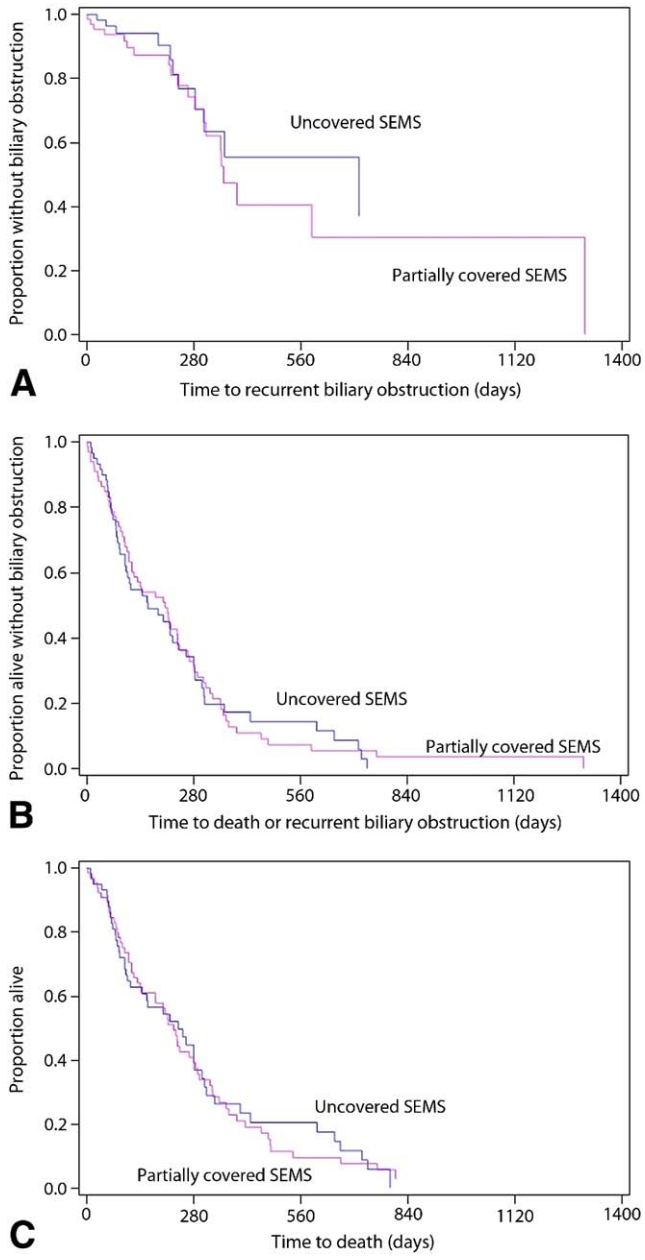

Figure 2. A, Time to recurrent biliary obstruction. Those patients alive and those who died without recurrent biliary obstruction are censored. There is no significant difference between the uncovered and partially covered SEMS groups. **B,** Time to recurrent biliary obstruction or death. Those patients alive without recurrent biliary obstruction at the last follow-up interview are censored. There is no significant difference between the uncovered and partially covered SEMS groups. **C,** Patient survival. Those patients alive at last follow-up interview are censored. There is no significant difference between the uncovered and partially covered SEMS groups.

interim analysis, was 136 patients. We closed the study before reaching this goal because of slow accrual. As a result, the permuted randomization blocks were not completed at any of the 4 sites. In addition, two envelopes were lost at two different sites, both with uncovered stent assignment. The assignment remained random as each site continued to the next envelope. The lost envelopes and incomplete randomization blocks led to more patients assigned to the covered SEMS group than to the uncovered SEMS group.

Two patients, one in each group, were restaged as resectable after their liver lesions were determined not to represent pancreatic cancer metastases as originally thought. Both underwent pancreaticoduodenectomy within 1 month after randomization and were alive at their last follow-up at 7 months and 2 years. One patient underwent a pancreaticoduodenectomy in an out-of-state hospital 9 months after randomization; she died from pancreatic cancer 3 months after surgery. These 3 patients were analyzed in an intention-to-treat fashion.

DISCUSSION

This is the first randomized trial comparing commercially available uncovered and partially covered SEMSs. Our results did not demonstrate a difference in the time to recurrent biliary obstruction or patient death between the two stents, but did demonstrate a higher incidence of serious adverse events in those patients receiving a partially covered SEMS.

The number of serious adverse events we reported was higher than in other studies, owing in part to our inclusion of all adverse events resulting in hospitalization or invasive procedure and our frequent patient follow-up. When considering only serious adverse events that were related to the ERCP or the SEMS, 23% of patients in the uncovered SEMS group and 37% in the partially covered SEMS group were affected. This is in keeping with other publications reporting a 28% to 43% adverse event rate for uncovered and covered SEMS.[5,12] Our results show that serious adverse events occurred more frequently in the partially covered SEMS group. In particular, we noted significantly more stent migration in those patients receiving a partially covered SEMS. The 12% migration rate observed in our study is higher than the 4% to 6% migration seen in other studies[7-10] using the same partially covered SEMS. In two cases, SEMS migration led to duodenal perforation; this was successfully managed by surgery in one patient but the other patient died. To our knowledge, duodenal perforation secondary to biliary SEMS migration has not been reported. Migration did not appear related to prior plastic stent placement or sphincterotomy[13] as previously observed. Isayama et al[14] postulated that SEMS migration may be related to an increased axial force, which is high in Wallstents. The axial force is the straightening force exerted by a stent after it has been bent. Those authors suggested that a high axial force may be associated with stent kinking and biliary wall injury as well as migration. In the present study, migration was noted only with the partially covered SEMS; the combination of the covering and axial force may have led to stent migration in this group.

Cholecystitis after SEMS placement may occur in up to 10% of patients[15] and is associated with tumor invasion of the cystic duct orifice[15,16] and cholelithiasis.[15] There has been

concern that overlap of the cystic duct orifice with a covered SEMS would increase the rate of cholecystitis; however, that was not observed in the present study or in a retrospective multivariable analysis of risk factors for cholecystitis in patients undergoing SEMS placement.[16] Pancreatitis has been reported more frequently in patients receiving a covered SEMS,[5] but this was not seen in the present study.

The mechanism of recurrent biliary obstruction varied between the two groups. Whereas stent migration occurred more frequently in the partially covered SEMS group, tumor ingrowth occurred more commonly in the uncovered SEMS group. However, we also found that the partially covered SEMS was subject to tumor ingrowth, which has been previously reported in some studies[17,18] but not observed in others.[5,12]

The present study had several strengths, including the prospective randomized design to limit bias, strict inclusion and exclusion criteria, and the participation of several endoscopists at 4 medical centers to improve generalizability of our results. Nevertheless, we acknowledge certain limitations. There was an imbalance in assignment between the treatment groups and closure of the study 7 patients short of our intended sample size. Post-hoc analysis, assuming equal allocation of patients and that all additional patients assigned to the uncovered SEMS group experienced recurrent biliary obstruction within 6 months, did not demonstrate a difference between the two groups in time to recurrent biliary obstruction ($P = .79$). Similarly, the observed increase in serious adverse events in the partially covered SEMS group continued even if the additional patients assigned to the uncovered SEMS group were assumed to experience a serious adverse event ($P = .043$).

Despite involving 4 high-volume ERCP centers, we experienced slow patient accrual to this study. Several factors may have contributed and we hope these comments will assist others in designing investigator-initiated trials. We used the same brand of stent for both the uncovered and the partially covered SEMS to distinguish the stent covering as the only difference in design between the two devices. Endoscopists may have chosen other brands of stents to diversify trainee exposure. Insufficient funding limited the availability of the research assistant and led to decreased patient enrollment. Furthermore, the baseline case report form was extensive, and a simpler form may have facilitated patient enrollment by the endoscopist.

We would suggest that future studies use a randomized design but with a simple enrollment scheme and maintain time to recurrent biliary obstruction as the primary end point. Our results and published data indicate that a SEMS covering effective at preventing tumor ingrowth does not directly correlate with the tendency toward migration. Although our migration rate was high, there was no improvement in stent patency with the partially covered SEMS. Similarly, Isayama et al[5] reported a significant reduction in stent obstruction due to decreased ingrowth, but only one instance of stent migration in the covered SEMS group, despite a lack of tissue embedding. Thus, there are other SEMS characteristics that affect migration; identification and modification of these characteristics will be necessary for successful use of SEMSs in malignant strictures. Whether the higher migration with the partially covered SEMSs correlates to its usefulness in managing benign biliary strictures could be a focus of future research.

In conclusion, we found no difference in the time to recurrent biliary obstruction or patient death between the uncovered and the partially covered SEMSs, but there was an increased rate of serious adverse events and stent migration in the partially covered SEMS group. Newer partially covered and fully covered SEMSs are available. Future research should be aimed at evaluating SEMSs that incorporate new coating materials and optimize the covered SEMS design to prevent migration.

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