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*Retrospective Study*

**Biliary metal stents should be placed near the hilar duct in distal malignant biliary stricture patients**

SEMS placement through the upper CBD

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## **Abstract**

### **BACKGROUND**

Endoscopic biliary drainage using a self-expandable metallic stent (SEMS) has been widely performed to treat distal malignant biliary obstruction (DMBO). However, the optimal position of the stent remains unclear.

### **AIM**

To determine the ideal position for SEMS placement.

### **METHODS**

In total, 135 DMBO patients underwent placement of an SEMS (uncovered or covered) over a ten-year period. A total of 127 patients with biliary obstruction between the junction of the cystic duct and Vater's papilla were enrolled. An SEMS was placed through the upper common bile duct (CBD) 2 cm from the biliary hilar duct in 83 patients (Hilar group) or near the top of the biliary obstruction in 44 patients (Lower group). Technical and functional success, adverse events, and risk factors for SEMS dysfunction were evaluated.

### **RESULTS**

The stent patency period was significantly longer in the Hilar group than in the Lower group ( $P$  value < 0.01). In multivariate analysis, the only statistically significant risk factor for SEMS dysfunction was being in the Lower group (hazard ratio: 9.94, 95% confidence interval: 2.25–44.0,  $P$  < 0.01).

### **CONCLUSION**

A longer patency period could be achieved by positioning the SEMS near the biliary hilar duct.

**Key Words:** Endoscopic biliary drainage; Malignant biliary obstruction; Uncovered self-expandable metallic stent; Covered self-expandable metallic stent; biliary hilar duct; Patency period

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**Core Tip:** Endoscopic biliary drainage using a self-expandable metallic stent (SEMS) has been widely performed to treat distal malignant biliary obstruction (DMBO). However, the optimal position of the SEMS remains unclear. This study indicated that the stent patency period was significantly longer when the SEMS was placed near the biliary hilar duct. Furthermore, the placement of a longer SEMS from the biliary hilar duct was thought to overcome the several factors of recurrent biliary obstruction in DMBO patients.

## **INTRODUCTION**

Stricture of the common bile duct (CBD) can occur in several severe diseases (for example, bile duct cancer, pancreatic cancer, or metastasis of other cancers). Since transpapillary biliary stent insertion was first reported by Sohendra and Reynders-Frederix<sup>[1]</sup>, it has become the first choice for biliary drainage in patients with malignant biliary obstruction. At present, uncovered self-expandable metallic stents (USEMSs) and covered SEMSs (CSEMSs) have been reported to be more effective at preventing recurrent biliary obstruction (RBO) than plastic stents (PSs) in distal malignant biliary obstruction (DMBO) patients<sup>[2,3]</sup>.

Whether a USEMS or CSEMS should be used remains a topic of debate. Three reports have asserted that the patency period of CSEMSs was superior to that of USEMSs<sup>[4-6]</sup>. However, others have found that the patency period was similar between

CSEMSs and USEMSs<sup>[7-11]</sup>. Although CSEMS insertion has some disadvantages (such as cholecystitis, pancreatitis, and migration), the stent can be removed<sup>[7-9,12-23]</sup>.

Based on the above findings, SEMS placement may help drain unresectable DMBOs. Determining which stent (USEMS or CSEMS) should be used has gained increasing attention. However, the optimal position of the inserted SEMS has rarely been discussed and remains unclear. Therefore, we aimed to determine the ideal position for SEMS placement.

## **MATERIALS AND METHODS**

### ***Study design and ethics approval***

This is a retrospective study. The patients were not required to provide informed consent because this study used anonymized clinical data obtained after each patient had provided written consent and agreed to undergo medical procedures. Additional details of this study are published on the home page of Fukushima Medical University (approval number 2453).

### ***Patients***

A total of 135 DMBO patients underwent SEMS placement between January 2011 and February 2021 (Figure 1). These patients did not undergo previous surgery of the upper gastrointestinal tract and were undergoing SEMS placement for the first time. Among them, 7 patients whose biliary obstruction was located between the junction of the cystic duct and hilar bile duct were excluded from this study. In addition, one patient who underwent double SEMS placement was excluded. Finally, 127 patients whose biliary obstruction was located between the junction of the cystic duct and Vater's papilla were enrolled. The SEMS was placed through the upper CBD within 2 cm from the junction of the right and left hepatic ducts in 83 patients (Figure 2A and B), and these patients were defined as the Hilar group. In the other 44 patients, who were defined as the Lower group, the SEMS was placed near the top of the biliary obstruction (Figure 2C and D).

### *Endoscopic biliary drainage*

With the patient in a prone position, a duodenoscope was inserted after the patient was sufficiently sedated with midazolam. When the duodenoscope reached Vater's papilla, biliary cannulation was started. After the range of the DMBO was confirmed by cholangiography, an SEMS was inserted from the upper part of the obstruction to Vater's papilla. Endoscopic sphincterotomy (EST) was performed for first-time endoscopic biliary drainage with a PS or before SEMS insertion. The position and type of SEMS (USEMS or CSEMS) were randomly determined by each endoscopist. All procedures were performed by pancreaticobiliary specialists or trainees under the guidance of specialists.

The USEMSs used in this study were as follows: BileRush, 8 mm x 6 cm, 10 mm x 6 or 8 cm (Piolax, Kanagawa, Japan); Bonastent, 10 mm x 8 cm (Standard Sci Tech, Seoul, Korea); HANARO, 10 mm x 7 cm (Boston Scientific, Tokyo, Japan); Niti-S Large cell, 10 mm x 5, 6, 8, or 10 cm (Taewoong Medical, Gyeonggi-do, Korea); WallFlex, 10 mm x 6, 8, or 10 cm (Boston Scientific); X Suit NIR, 10 mm x 8 cm (Olympus Medical, Tokyo, Japan); and Zilver, 10 mm x 6 cm, and Zilver 635, 10 mm x 6, 8, or 10 cm (Cook Medical Japan, Tokyo, Japan). The CSEMSs used in this study were as follows: Bonastent, 10 mm x 7 cm (Standard Sci Tech); HANARO, 10 mm x 5, 6, or 8 cm (Boston Scientific); Niti-S Comvi, partially covered, 10 mm x 6, 7, or 8 cm (Taewoong Medical); WallFlex, fully covered, 10 mm x 6 cm, and partially covered, 10 mm x 6 or 8 cm (Boston Scientific); and X Suit NIR, 10 mm x 4, 6, or 8 cm (Olympus Medical).

### *Outcomes of interest*

The primary outcome was the stent patency period. The secondary outcomes were the technical success rate, functional success rate, adverse events (pancreatitis, post-EST bleeding), severity of adverse events, and stent dysfunction rate. These outcomes were defined according to partially revised version of reported criteria<sup>[24]</sup>. The stent patency period was determined as the time from first SEMS insertion to SEMS dysfunction.

SEMS dysfunction was defined as the recurrence of hepatic dysfunction, jaundice, or dilated bile tract on ultrasonography or computed tomography (CT), which required secondary SEMS placement. Technical success was defined as successful placement of an SEMS that reached from the upper part of the obstruction to Vater's papilla. Functional success was defined as the return of alanine transaminase (ALT) or total bilirubin (TB) to normal values (ALT < 27 U/L, TB < 1.2 mg/dL) or less than half of the pretreatment value. Adverse events and the severity of adverse events were defined according to Cotton's criteria<sup>[25]</sup>. In addition, posttreatment pancreatitis was confirmed by contrast-enhanced CT.

In addition, the patient characteristics (age, sex, serum ALT level, serum TB level, cause of stricture, chemotherapy, duodenal stricture, CBD diameter above the stricture, CBD stricture diameter, CBD stricture length), year of procedure (2011-2015, or 2016-2021), stent diameter, type of SEMS used (USEMS or CSEMS), SEMS shortening, and observational period were compared between the Hilar group and Lower group. The maximum serum ALT and TB values recorded in the previous week up to endoscopic SEMS insertion were used. The cause of stricture was divided into pancreaticobiliary and metastatic according to a past report<sup>[9]</sup>. Duodenal stricture was defined as a stricture that was difficult for the upper gastrointestinal scope to pass through. The diameter and length of the CBD stricture were measured by endoscopic retrograde cholangiography. The year of the procedure was compared between groups because the techniques and devices have advanced over the approximately ten-year study duration. SEMS shortening was determined as more than 1 cm of shortening evident on X-ray or CT imaging after SEMS placement.

### *Statistical analyses*

Student's t test or Welch's t test were used to compare continuous variables. Fisher's exact test was used to compare nominal variables. To analyze the SEMS patency period, the log-rank test was used. To analyze the factors that influenced SEMS dysfunction, a Cox proportional hazard model was used.  $P < 0.05$  was considered statistically



significant. All statistical analyses were performed using EZR (Saitama Medical Centre, Jichi Medical University, Saitama, Japan).

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## RESULTS

The patient characteristics are shown in Table 1. There was no significant difference in age, sex, serum ALT level, serum TB level, stricture cause, chemotherapy, duodenal stricture, CBD diameter above the stricture, CBD stricture diameter, or CBD stricture length between the Hilar group and the Lower group.

The outcomes of SEMS placement are shown in Table 2. There was no difference in the procedure year or rate of technical success, functional success, adverse events, or SEMS shortening between the two groups. The rate of CSEMS use and SEMS diameter were also not significantly different between the two groups. Regarding the type of SEMS used, the covered WallFlex (Boston Scientific) was used significantly more frequently in the Hilar group than in the Lower group (28/83 (33.7%) vs. 7/44 (15.9%),  $P$  value = 0.038), and the X Suit NIR was used significantly more frequently in the Lower group than in the Hilar group (6/44 (13.6%) vs. 0/83 (0%),  $P$  value < 0.01). SEMS dysfunction was observed significantly more often in the Lower group than in the Hilar group (18/44 (41%) vs. 2/83 (2.4%),  $P$  value < 0.01). The causes of SEMS dysfunction were as follows: Hilar group: ingrowth (1) and overgrowth (1); and Lower group: ingrowth (3), overgrowth (2), ingrowth and overgrowth (8), top edge closed by the CBD wall (4), and dislocation (1). In the cases in which the top edge was closed by the CBD wall, the SEMSs used were the Zilver 635 (Cook Medical), WallFlex (Boston Scientific), Niti-S large cell (Taewoong Medical), and HANARO (Boston Scientific) stents. A representative case in which the top edge of the SEMS was closed by the CBD wall is shown in Figure 3. The observational period was longer in the Lower group than in the Hilar group ( $9.12 \pm 12.07$  mo vs.  $4.16 \pm 5.76$  mo,  $P$  value = 0.012).

The results of the stent patency comparison are shown in Figure 4 and Supplementary Figure 1. The stent patency period was significantly longer in the Hilar group than in the Lower group (Figure 4A,  $P$  value < 0.01). The stent patency period



was not significantly different between groups when the patients were divided according to use of a covered WallFlex stent, use of a covered X Suit NIR stent, observational period (Figure 4B and C), age, sex, serum ALT level, serum TB level, metastatic or pancreaticobiliary status, presence or absence of chemotherapy, presence or absence of duodenal stricture, CBD diameter above the stricture, CBD stricture diameter, CBD stricture length, year of procedure, USEMS or CSEMS, presence or absence of SEMS shortening, or observational period (Supplementary Figure 1).

The risk factors for SEMS dysfunction are shown in Table 3. Serum ALT level and lower placement were statistically significant factors in the univariate analysis (ALT: <sup>5</sup>hazard ratio (HR): 1.003, 95% confidence interval (CI): 1.001–1.01, *P* value < 0.01; Lower group: HR: 11.42, 95%CI: 2.61–49.83, *P* value < 0.01). However, the only statistically significant risk factor in the multivariate analysis was lower placement (HR: 9.94, 95%CI: 2.25–44.0, *P* < 0.01).

## **DISCUSSION**

In this study, we investigated the ideal position for SEMS insertion in DMBO patients. The results demonstrated that the SEMS patency period was longer when the stent was placed near the hilar duct.

With regard to why a longer patency period was observed in the Hilar group, it is thought that this position overcomes several causes of SEMS dysfunction. As shown in Table 2, the main causes of SEMS dysfunction were tumor ingrowth and/or overgrowth and a top edge closed by the CBD wall; notably, overgrowth and a top edge closed by the CBD wall could be prevented by using a longer SEMS. Longer SEMSs can delay stent dysfunction due to tumor overgrowth. In the four patients in the Lower group, the top edge of the SEMS was closed by the CBD wall, which may be caused by linearization of the SEMS. The axial force on the stent is thought to be related to the linearization and closing of the top edge by the CBD wall. However, in the four patients with SEMS dysfunction caused by closure of the top edge by the CBD wall, the SEMSs were not necessarily affected by high axial force, except for the WallFlex (Boston

Scientific) stent. When a short SEMS is placed near the top edge of the DMBO, the axial force might be enhanced by the biliary stricture. Using longer SEMSs overcomes this problem because the axial force decreases with increasing distance between the top edge of the SEMS and CBD stricture<sup>[26]</sup>. In fact, a biliary obstruction was relieved by placing a second SEMS near the biliary hilar duct (Figure 3C).

In past reports, time to adequate expansion, degree of CBD stricture<sup>[27]</sup>, duodenal invasion<sup>[28,29]</sup>, duodenal SEMS<sup>[30]</sup>, and anticancer treatment<sup>[29,31]</sup> were reported as risk factors for RBO. The factors related to SEMS expansion and CBD stricture were not an issue in this study because functional success was achieved in almost all patients. Anticancer treatment has been reported to cause RBO as follows. Although anticancer treatment reduces the tumor burden, it can dislocate the CSEMS or induce neutropenia and bacterial overgrowth and, ultimately, cholangitis or sludge formation in the bile duct<sup>[31]</sup>. However, anticancer treatment has not been proposed as a risk factor for RBO in studies that involved patients with a USEMS<sup>[9,32]</sup>. This study involved both USEMSs and CSEMSs. Therefore, anticancer treatment may not be a risk factor for SEMS dysfunction. Duodenal invasion from tumors reduces peristalsis and causes food impaction to the biliary duct, and a duodenal SEMS prevents the outflow of bile juice<sup>[30]</sup>. In this study, any RBO requiring additional SEMS placement was defined as SEMS dysfunction so that SEMS occlusion caused by tumors could be properly evaluated and cases of SEMS occlusion by food impaction could be excluded. Therefore, SEMS placement near the biliary hilar duct was revealed as a new factor related to longer SEMS patency.

3 There were some limitations to this study. First, this was a retrospective observational study performed at a single institution. In the future, it is hoped that a prospective multicenter study will confirm our findings. Second, the type of SEMS was not unified. The axial force or shortening length varied among the SEMSs. Measurement of the axial force was difficult in this study; instead, different kinds of SEMSs were compared. As a result, the type of SEMS did not influence SEMS dysfunction. The WallFlex stent (Boston Scientific), which has a high axial force and a

high shortening rate<sup>[33]</sup>, was used significantly more often in the Hilar group. However, remarkable shortening was rarely observed (the presence or absence of shortening was confirmed in 23 patients 24 h after SEMs placement and in 99 patients more than 48 h after SEMs placement). This was considered to be due to the placement of an SEMs with a longer than established length because the SEMs could not fully expand in the area of the stricture. As described above, the axial force decreases with increasing SEMs length. Because of these factors, the difference in the type of SEMs did not influence the outcomes. Third, SEMs obstruction of sludge or food debris was not considered SEMs dysfunction. In past reports, sludge formation was proposed to be a cause of SEMs dysfunction<sup>[4,5,32,34]</sup>. This factor is surely important for comparisons of patency periods between USEMS and CSEMS. If SEMs obstruction of sludge or food debris was considered stent dysfunction, the patency period was also significantly longer in the Hilar group than in the Lower group (Supplementary Figure 2). Therefore, the obstruction of sludge or food debris did not influence the results of this study. As described above, the SEMs obstruction of sludge or food debris was excluded from SEMs dysfunction to properly evaluate the relationship between the positions of the SEMs and tumor in this study.

## **CONCLUSION**

The results of our study revealed that placement of an SEMs near the biliary hilar duct could delay tumor overgrowth and prevent closure of the top edge of the SEMs by the CBD wall. Thus, in DMBO patients, the SEMs should be placed near the biliary hilar duct to achieve a longer patency period.

## **ARTICLE HIGHLIGHTS**

### ***Research background***

Endoscopic biliary drainage using a self-expanding metallic stent (SEMS) has a longer patency period than endoscopic biliary drainage using a plastic stent. Therefore,

endoscopic SEMS placement is desirable for the treatment of unresectable distant malignant biliary obstruction (DMBO).

### ***Research motivation***

The type of SEMS that should be used for DMBO is a point of active discussion. However, the appropriate position for SEMS insertion is unknown.

### ***Research objectives***

To clarify the appropriate SEMS insertion point for DMBO.

### ***Research methods***

Among 135 DMBO patients who underwent SEMS placement, 127 patients with biliary obstruction between the junction of the cystic duct and Vater papilla were enrolled. In 83 patients (defined as the Hilar group), a SEMS was inserted from the upper common bile duct (CBD), 2 cm within the biliary hilar duct. In the other 44 patients (defined as the Lower group), a SEMS was placed near the top of the biliary obstruction. The patency period was compared between the Hilar group and Lower group. The risk factors for SEMS dysfunction were also investigated.

### ***Research results***

The patency period of SEMS was significantly longer in the Hilar group patients. Multivariate analysis revealed that Lower group classification was the only significant risk factor for SEMS dysfunction.

### ***Research conclusions***

SEMS placement near the biliary hilar duct could extend the patency period in DMBO patients.

### ***Research perspectives***

SEMS placement near the biliary hilar duct might prevent obstructive jaundice and cholangitis and contribute to improved prognosis in DMBO patients.

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