Evaluation of a 12-mm diameter covered self-expandable end bare metal stent for malignant biliary obstruction

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ABSTRACT
Background and study aims Biliary metallic stents are used to drain unresectable malignant distal biliary obstructions. This study aimed to evaluate the efficacy of a novel 12-mm-diameter covered, self-expandable end bare metal stent (12-mm CSEEMS).

Patients and methods We evaluated 99 patients with unresectable malignant distal biliary obstructions treated with covered biliary metallic stents. Of the 99 patients, 33 underwent 12-mm CSEEMS placement between June 2015 and April 2017 (12-mm-CSEEMS group) and 66 underwent 10-mm fully-covered self-expandable metal stent (FCSEMS) placement between January 2010 and July 2015 (10-mm-FCSEMS group). The overall survival (OS), the recurrent biliary obstruction (RBO), cause of RBO, time to RBO (TRBO) and adverse events in 12-mm-CSEEMS group and 10-mm-FCSEMS group were evaluated retrospectively.

Results The OS tended to be longer in the 12-mm-CSEEMS group (log rank, \( P = 0.081 \)) and TRBO was significantly longer in the 12-mm-CSEEMS group (log rank, \( P = 0.001 \)) than in the 10-mm-FCSEMS group. Both univariate (HR, 0.449; 95 % CI, 0.279–0.722; \( P = 0.001 \)) and multivariate (HR, 0.458; 95 % CI, 0.283–0.737; \( P = 0.001 \)) Cox hazard analysis found that the risk of RBO was significantly lower in 12-mm CSEEMS than in 10-mm FCSEMS. There were no significant differences between the 12-mm-CSEEMS group and 10-mm-FCSEMS group regarding the cause of RBO and adverse events.

Conclusions The 12-mm CSEEMS showed a low risk of RBO compared with 10-mm FCSEMS and was considered to be effective and safe for draining unresectable malignant distal biliary obstruction.

Introduction
Endoscopic drainage of malignant biliary obstruction using self-expandable metal stents (SEMSs) is a widely used standard procedure to treat obstructive jaundice which enables chemotherapy and improves patients’ symptoms [1–5]. Covered SEMSs (CSEMSs) may prevent tumor ingrowth more effectively than uncovered SEMSs (USEMSs) [6]. In patients with malignant biliary obstruction, Isayama et al. found that the time to recurrent biliary obstruction (RBO) was longer with CSEMS than with USEMS [5]. In patients with biliary obstruction caused by pancreatic carcinoma, Kitano et al. reported that duration of patency was longer with CSEMS than with USEMS [7].

However, several meta-analyses reported that CSEMS has a higher risk of migration than USEMS, despite prevention of ingrowth [1–3,8]. Mukai et al. developed a 12-mm-diameter fully-covered self-expandable metal stent (FCSEMS) to prevent RBO, but it resulted in several cases of migration [9]. Therefore, we evaluated the efficiency of a 12-mm-diameter covered self-expandable-end, bare metal stent (CSEEMS) in patients with malignant distal biliary obstruction for preventing RBO.
Patients and methods

We retrospectively evaluated 99 patients with unresectable malignant distal biliary obstructions treated with covered biliary metallic stents at Fujita Health University Hospital. Of the 99 patients, 33 underwent placement of 12-mm-diameter CSEEMS (Tae Woong Medical, Seoul, Korea) between June 2015 and April 2017 (12-mm-CSEEMS group) (Fig. 1) and 66 underwent 10-mm-diameter FCSEMS (Wallflex biliary RX stent, Boston Scientific, Natick, Massachusetts) placement between January 2010 and July 2015 (10-mm-FCEMS group).

The endpoint of this study was RBO with SEMS, or patients’ death, whichever was earlier. The patients survived during the observation period were considered as censored cases.

Before inserting these metal stents, carcinoma was diagnosed by cytology, biopsy, or endoscopic ultrasound-guided fine-needle aspiration. If diagnosis by tissue biopsy or cytology was not possible, enhanced computed tomography (CT) or magnetic resonance imaging was used. We initially performed drainage using a plastic stent and then switched the plastic stent with a 12-mm CSEEMS or 10-mm FCSEMS after confirming that there was no indication for surgery and that the patients had good life expectancy. Thereafter, the patients were treated with chemotherapy or optimal supportive care.

Eligibility criteria

Patients who were age ≥20 years and those with a life expectancy ≥3 month, an Eastern Cooperative Oncology Group Performance Status (ECOG-PS) < 4 and diagnosed with distal biliary obstruction caused by an unresectable malignancy were included. Patients with ECOG-PS ≥4, massive ascites, an intestinal obstruction distal to the ampulla, and prior biliary SEMS placement and those who were unable to give informed consent for SEMS replacements were excluded.

Ethical affairs

The study protocol was approved by the Institutional Review Board of Fujita Health University Hospital (HM16-059) and was carried out following the ethical principles of the Declaration of Helsinki.

SEMS used in the study

A 12-mm CSEEMS is made of nitinol wire and covered with a silicone membrane, with the proximal 10 mm uncovered and distal 5 mm flared ends designed to prevent migration. The area of 12-mm CSEEMS was 1.44-fold larger than that of 10-mm FCSEMS. A 12-mm CSEEMS is available in lengths of 6, 7, and 8 cm and is equipped with a 9-Fr standard delivery device. For 12-mm CSEEMS, the axial force (AF) at a 20-mm distance from the bending point was 0.65 N, and RF measured at a 4-mm diameter was 4.7 N.

Procedures

SEMS was inserted during endoscopic retrograde cholangiopancreatography (ERCP) by two experienced investigators using a standard duodenoscope (TJF-260V; Olympus, Tokyo, Japan). Sphincterotomy was done before stent insertion in all cases. The length of the SEMS was determined by the primary endoscopist, and the distal end of the SEMS was located in the duodenum.

RBO and adverse events

We followed up all patients at least once a month and examined their clinical findings and biochemical parameters of hepato-biliary functions and inflammation, such as aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, γ-glutamyl transpeptidase, total and direct bilirubin, white blood cell count, and C-reactive protein. CT scanning or abdominal ultrasound was carried out at least once every 2 or 3 months until a patient’s death. RBO and adverse events and their severity were defined according to the Tokyo Criteria 2014 [11]. RBO was defined as an occlusion or migration, and TRBO as the interval between SEMS placement and RBO or patients’ death, whichever was earlier.

Statistical analysis

The Kaplan–Meier method was used to evaluate overall survival (OS), with living patients censored at the last date of follow-up (October 31, 2017). TRBO was also estimated by the Kaplan–Meier method, with patients who had not experienced RBO censored at the end of the study (October 31, 2017). The hazard ratios of prognostic factors for OS and TRBO were estimated by a Cox proportional hazards model, which included age, sex, clinical stage, chemotherapy, prior drainage, and stent types. Continuous variables were compared using the Mann–
Whitney U test and Fisher's exact test for categorical variables. All analyses were done using StatFlex version 6.0 for windows (StatFlex, Osaka, Japan).

Results

Patient characteristics, outcomes, and survival

Clinical characteristics were not significantly different between the 12-mm-CSEEMS group and the 10-mm-FCSEMS group (Table 1). In all 99 patients, placements of 12-mm CSEEMS and 10-mm FCSEMS were technically successful. Median OS of 12-mm-CSEEMS group was 232 days (range, 35–814 days), and 27 patients (81.8%) died and six patients (18.2%) were still alive by the end of the study (Fig. 2). Median OS of the 10-mm-FCSEMS-group was 169.5 days (range, 21–1019 days), and all 66 patients died by the end of the study (Fig. 2). OS was tended to be significantly different between 12-mm-CSEEMS group and 10-mm-FCSEMS group (P = 0.081, Fig. 2). Univariate Cox analysis demonstrated that risk of mortality was lower in patients with chemotherapy (HR, 0.610; 95% CI, 0.4041–0.92560; P = 0.020), and it tended to be lower in patients with clinical stage II or III disease (HR, 0.647; 95% CI, 0.49376–1.03775; P = 0.071) and in the 12-mm-CSEEMS group (HR, 0.667; 95% CI, 0.42377–1.04927; P = 0.080). Multivariate Cox hazard analysis demonstrated that risk of mortality was lower in the females (HR, 1.974; 95% CI, 1.23762–3.14849; P = 0.004), in patients with clinical stage II or III disease (HR, 0.417; 95% CI, 0.24050–0.72313; P = 0.002) and in the 12-mm-CSEEMS group (HR, 0.592; 95% CI, 0.36340–0.96495; P = 0.044) (Table 2).

RBO and TRBO

In the 12-mm-CSEEMS group, RBO occurred in three patients (9.1%) on days 132, 155 and 505 by food impaction in one (3.0%) and tumor ingrowth at the covered part of the stent in two (6.1%) (Table 3). In the 10-mm-FCSEMS group, RBO occurred in 29 patients (43.9%) by food impaction in two (3.0%), sludge formation in...
13 (19.7 %), tumor ingrowth in one (1.5 %), tumor overgrowth in five (7.6 %), kinking in one (1.5 %), distal migration in three (4.5 %) and proximal migration in four (6.1 %) (▶Table 3).

TRBO in the 12-mm-CSEEMS group was significantly longer than that in the 10-mm-FCSEMS group (log rank, \( P = 0.001 \)). Median TRBO in the 12-mm-CSEEMS group was 232 days and median TRBO in the 10-mm-FCSEMS group was 139.5 days (▶Fig. 3).

Univariate Cox analysis (▶Table 4) demonstrated that risk of RBO was significantly lower in the 12-mm-CSEEMS group (HR, 0.449; 95 % CI, 0.27967 – 0.72215; \( P = 0.001 \)) than in the 10-mm-FCSEMS group and chemotherapy also decreased risk of RBO (HR, 0.429; 95% CI, 0.27665 – 0.66392; \( P < 0.001 \)). Multivariate Cox hazard analysis also demonstrated that risk of RBO was significantly lower in the 12-mm-CSEEMS group than in the 10-mm-FCSEMS group (HR, 0.458; 95 % CI, 0.28395 – 0.73744; \( P = 0.001 \)) and chemotherapy decreased risk of RBO (HR, 0.453; 95% CI, 0.27791 – 0.73974; \( P = 0.002 \)).

Early adverse events (≤ 30 days)
In the 12-mm-CSEEMS group, there were no cases of post-endoscopic retrograde cholangiopancreatography pancreatitis (PEP), while one patient (3.0 %) experienced abdominal pain on day 1 and one patient (3.0 %) experienced non-occlusion cholangitis on Day 27 (▶Table 3). In the 10-mm-FCSEMS group, cholecystitis occurred in one patient on Day 7 (1.6 %), PEP occurred in three patients (4.5 %) and hyperamylasemia in one (1.6 %) (▶Table 3). There were no bleeding events in either of the two groups.

▶Table 2 Univariate and multivariate Cox hazard analyses of OS.

| Variables                      | Univariate analysis | Multivariate analysis |
|-------------------------------|---------------------|-----------------------|
|                               | Hazard ratio        | 95 % CI               | \( P \) value | Hazard ratio        | 95 % CI               | \( P \) value |
| Age (years)                   | 1.009               | 0.99109 – 1.02624     | 0.340        | 1.0103               | 0.98964 – 1.0318     | 0.330         |
| Sex, male                     | 1.512               | 0.99728 – 2.29347     | 0.052        | 1.974                | 1.23762 – 3.14849   | 0.004         |
| Primary disease (pancreatic cancer) | 1.092               | 1.09198 – 1.85604     | 0.745        |                     |                       |               |
| Clinical stage (II and III)   | 0.647               | 0.40376 – 103775      | 0.071        | 0.417                | 0.24050 – 0.72313   | 0.002         |
| Chemotherapy                  | 0.610               | 0.4041 – 0.92560      | 0.020        | 0.744                | 0.45211 – 1.22419   | 0.245         |
| 12-mm CSEEMS                  | 0.667               | 0.42377 – 1.04927     | 0.080        | 0.592                | 0.36340 – 0.96495   | 0.044         |

OS, overall survival; CSEEMS, covered, self-expandable end bare metal stent
### Table 3 Recurrent biliary obstruction and adverse events in 12-mm-CSEEMS and 10-mm-FCSEMS groups.

|                        | 12-mm-CSEEMS group (n = 33) | 10-mm-CSEEMS group (n = 66) | P value |
|------------------------|-----------------------------|----------------------------|---------|
| Recurrent biliary obstruction, n (%) | 3 (9.1)                     | 29 (43.9)                   | 0.001   |
| Occlusion, n (%)       | 3 (9.1)                     | 22 (33.3)                   | 0.009   |
| Food impaction         | 1 (3.0)                     | 2 (3.0)                     | 1.000   |
| Sludge                 | 0                           | 13 (19.7)                   | 0.009   |
| Ingrowth               | 2 (6.1)                     | 1 (1.5)                     | 0.549   |
| Overgrowth             | 0                           | 5 (7.6)                     | 0.166   |
| Hemobilia              | 0                           | 0                           | 1.000   |
| Kinking                | 0                           | 1 (1.5)                     | 1.000   |
| Migration, n (%)       | 0                           | 7 (10.6)                    | 0.092   |
| Distal migration       | 0                           | 3 (4.5)                     | 0.549   |
| Proximal migration     | 0                           | 4 (6.1)                     | 0.298   |

#### Adverse events, n (%)

|                        | 12-mm-CSEEMS group (n = 33) | 10-mm-CSEEMS group (n = 66) | P value |
|------------------------|-----------------------------|----------------------------|---------|
| Early adverse events (≤30 days) | 2 (6.1)                   | 5 (7.6)                     | 1.000   |
| Cholecystitis          | 0                           | 1 (1.6)                     | on day 7 | 1.000   |
| Pancreatits            | 0                           | 3 (4.5)                     | on day 1 | 0.298   |
| Hyperamylasemia        | 0                           | 1 (1.6)                     | on day 1 | 1.000   |
| Abdominal pain         | 1 (3.0)                     | 0                           | on day 1 | 0.333   |
| Non-occlusion cholangitis (moderate) | 1 (3.0) | 0 | 0.333   |
| Late adverse events (≥31 days) | 3 (9.1)                   | 8 (12.1)                    | 0.747   |
| Cholecystitis (moderate) | 1 (3.0)                   | 1 (1.6)                     | on day 32 | 1.000   |
| Non-occlusion cholangitis (moderate) | 2 (6.1) | 7 (10.6) | on days 82, 108, 116, 132, 146, 172 and 196 | 0.714   |

CSEEMS, covered, self-expandable end bare metal stent; FCSEEMS, fully-covered self-expandable metal stent

### Table 4 Univariate and multivariate Cox hazard analyses of TRBO.

| Variables                        | Univariate analysis | Multivariate analysis |
|----------------------------------|---------------------|-----------------------|
|                                  | Hazard ratio | 95% CI | P value | Hazard ratio | 95% CI | P value |
| Age (years)                      | 1.012       | 0.99379 – 1.03151 | 0.192 | 1.000       | 0.98209 – 1.01913 | 0.963 |
| Sex, male                        | 1.183       | 0.85001 – 1.93025 | 0.2367 | 1.189       | 0.78224 – 1.80824 | 0.891 |
| Primary disease (pancreatic cancer) | 0.880       | 0.52295 – 1.48068 | 0.6300 |
| Clinical stage (II and III)      | 0.711       | 0.44559 – 1.13394 | 0.1520 |
| Chemotherapy                     | 0.429       | 0.27665 – 0.66392 | 0.0001 | 0.453       | 0.27791 – 0.73974 | 0.002 |
| 12-mm CSEEMS                     | 0.449       | 0.27967 – 0.72215 | 0.0009 | 0.458       | 0.28395 – 0.73744 | 0.001 |

TRBO, time to recurrent biliary obstruction; CSEEMS, covered, self-expandable end bare metal stent
Late adverse events (≥ 31 days)

In the 12-mm-CSEEMS group, acute cholecystitis occurred in one patient on Day 77 (3.0%) and non-obstruction moderate cholangitis occurred in two patients (6.1%) on Days 116 and 151 (Table 3). In the 10-mm-FCSEMS group, acute cholecystitis occurred in one on Day 32 (1.6%) and non-obstruction cholangitis occurred in seven patients (10.6%) (Table 3).

Discussion

Endoscopic drainage of the common bile duct using SEMS is an effective and widely performed treatment for unresectable malignant biliary obstruction. For patients with unresectable tumors, SEMS placement maintains biliary flow, relieves jaundice, improves quality of life, and facilitates delivery of consecutive chemotherapy.

In this study, 12-mm CSEEMS showed a longer TRBO compared with 10-mm FCSEMS. TRBO was significantly longer in the 12-mm-CSEEMS group than in the 10-mm-FCSEMS group (log rank, $P = 0.001$) and both univariate (HR, 0.449; 95% CI, 0.27967–0.72215; $P = 0.001$) and multivariate (HR, 0.458; 95% CI, 0.28395–0.73744; $P = 0.001$) Cox hazard analysis found that 12-mm CSEEMS was associated with a significantly lower risk of RBO. In the 12-mm-CSEEMS group, median TRBO was 232 days and was equal to median OS, on the other hand, median TRBO was 139.5 days, and the median OS was 169.5 days in 10-mm-FCSEMS group.

Because the time of treatment differed between the two groups, patients with pancreatic cancer in the 12-mm-CSEEMS group were treated with newly developed chemotherapy, while those in the 10-mm-FCSEMS received an older chemotherapy regimen [12, 13]. In the 10-mm FCSEMS-group, 30 out of 38 patients (78.9%) undergoing chemotherapy had pancreatic cancer, of whom FOLFILINOX was done in three cases, GnP in one, GEM in 24 and S-1 in two cases. On the other hand, in the 12-mm-CSEEMS group, 18 out of 20 patients (90%) undergoing chemotherapy had pancreatic cancer, of whom FOLFILINOX was done in one case, GnP in 14, GEM in tw and S-1 in one patient. Thus, tumors in the 12-mm-CSEEMS group may have been more effectively controlled than those in the 10-mm-FCSEMS group. The longer TRBO in the 12-mm-CSEEMS group may be affected by the difference in chemotherapy regimen. Thus, a further prospective study is needed to compare TRBO between the two groups.

A meta-analysis of RCT reported better stent patency with CSEMS than with USEMS [6]. It also reported that risk of migration was greater with CSEMS and that there were no differences between CSEMS and USEMS in occurrence of adverse events such as pancreatitis or cholecystitis. Other meta-analyses of CSEMS and USEMS found no benefit for CSEMS [14–16]. In our study, stent patency rate at 6 months was 91.7% with 12-mm CSEEMS, and we did not experience stent migration. With the 10-mm-diameter partially-covering SEMS, stent migration occurred in 7.8% of patients over 1 year in the WATCH study [17]. In that study, 10-mm FCSEMS migrated in seven patients (10.6%) during the observation period of 12 to 410 days. We believe that the 12-mm CSEEMS proximally bare is effective for prevention of migration and the larger-caliber style appears to be effective for preventing occlusion.

Competing interests

None
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