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Retrospective Study

Angle of covered self-expandable metallic stents after the placement is a risk factor for recurrent biliary obstruction

Angle of covered self-expandable metallic stents after the placement

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Abstract

BACKGROUND

There is a concern that covered self-expandable metallic stents (CSEMS) with low axial forces after the placement cause early recurrent biliary obstruction (RBO) due to precipitating sludge formation.

AIM

To ascertain whether CSEMS's angle after the placement is a risk factor for RBO in unresectable distal malignant biliary obstruction (MBO).

METHODS

Between January 2010 and March 2019, 261 consecutive patients underwent self-expandable metallic stents insertion by endoscopic retrograde cholangiopancreatography in our facility, and 87 patients were included in this study. We evaluated the risk factors for RBO including the angle of CSEMS after the placement as primary outcome. Using SYNAPSE PACS system (FUJIFILM Corporation, Tokyo, Japan), we measured the obtuse angle of CSEMS after the placement on an abdominal radiograph. We also evaluated technical and functional success, adverse events, time to RBO (TRBO), non-RBO rate, survival time, cause of RBO, and procedure of reintervention as secondary outcomes.

RESULTS

We divided the patients into 2 cohorts based on the presence of RBO, RBO group and non-RBO group. The angle of CSEMS after the placement (per 1° and per 10°) was evaluated based on the multivariate Cox proportional hazard analysis, which was an independent risk factor for RBO in unresectable distal MBO [hazard ratio, 0.97 and 0.71; 95% confidence interval (CI) 0.94-0.99, P = 0.01; 0.54-0.92, P = 0.01, respectively]. For early diagnosis of RBO, the cut-off value of the angle of CSEMS after the placement using the receiver operating characteristic curve was 130° [sensitivity 50.0%, specificity

85.5%, area under the curve 0.70 (95%CI, 0.57-0.84)]. TRBO in the < 130° angle group was significantly shorter than that in the 130° ≤ angle group ($P < 0.01$).

CONCLUSION

This study suggests that the angle of CSEMS after the placement for unresectable distal MBO was a risk factor for RBO.

Key Words: Covered self-expandable metallic stents; Recurrent biliary obstruction; Malignant biliary obstruction; Endoscopic retrograde cholangiopancreatography; Angle; Axial force

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Core Tip: We aimed to establish that the angle of covered self-expandable metallic stents (CSEMS) after the placement was a risk factor for recurrent biliary obstruction (RBO) in patients with unresectable malignant distal biliary obstruction. Finally, we included 87 patients in this study and divided them into 2 cohorts. We found that the angle of CSEMS after the placement was an independent risk factor for RBO. Further, we demonstrated that the cut-off value of the angle of CSEMS after the placement was 130°, and that time to RBO in the < 130° group was significantly shorter than that in the 130° ≤ group.

INTRODUCTION

Covered self-expandable metallic stents (CSEMS) have been recommended and widely accepted for managing unresectable distal malignant biliary obstruction (MBO) [1-5].

However, recurrent biliary obstruction (RBO), which is a major problem in patients with MBO, prevents the continuation of treatment and patients experience a poor quality of life. CSEMS have been expected to prolong patency in patients with unresectable distal MBO by preventing tumor ingrowth or epithelial hyperplasia [6, 7]. Additionally, improving the conformability of self-expandable metallic stents (SEMS) in the bile duct has led to reduced risks of migration [7]. In a recent study, sludge formation and food impaction remained as major causes of RBO [8].

Recently, SEMS with low axial forces (AF) to improve compatibility with the bile duct have been used frequently, with increasing concerns that they are likely to cause early RBO as a result of sludge formation and food impaction [9]. AF is the stent-straightening force [10], CSEMS with high AF had a lower frequency of sludge formation and food impaction compared to those with low AF [11].

Therefore, we hypothesized that the time to RBO (TRBO) of CSEMS with low AF was short. This study focused on angle of CSEMS after the placement to investigate the risk factors for RBO of CSEMS with unresectable distal MBO.

MATERIALS AND METHODS

Patients and study design

This retrospective cohort study was conducted in the Department of Gastroenterology, Osaka City University Graduate School of Medicine, Japan. Consecutive patients who underwent SEMS placements by Endoscopic retrograde cholangiopancreatography (ERCP) between January 2010 and March 2019, with follow-up until September 2019 were enrolled. We then included those patients who underwent placement of CSEMS. Exclusion criteria were as follows: (1) postoperative patients (Billroth-II, Roux-en Y reconstruction, *etc.*), (2) patients with hilar biliary stricture, (3) patients with placement of multiple SEMS, (4) patients with benign distal biliary stricture, (5) duplicated patients, (6) patients with absence of abdominal radiograph, (7) patients who had undergone percutaneous transhepatic biliary drainage (PTBD), biliary or duodenal metallic stent, (8) patients with resectable distal MBO, (9) patients with unknown

treatment details, and (10) patients who removed SEMS early due to cholecystitis and pancreatitis. Most cases could be pathologically evaluated, and other cases were diagnosed by radiographic imaging.

Ethical Consideration

The study was conducted in compliance with the principles laid down in the Declaration of Helsinki. The study protocol was approved by the ethics committee of Osaka City University Graduate School of Medicine (No. 2020-022). All patients were given the opportunity to opt out of this study on our website's home page.

Main outcome

The primary outcome is the risk factors for RBO in unresectable distal MBO including assessment of the angle of CSEMS after the placement. The secondary outcomes included the evaluation for technical and functional success, adverse events, TRBO, non-RBO rate, survival time, cause of RBO, and procedure of reintervention.

Endoscopic procedure

All procedures were performed using a side-viewing duodenoscope (JF240, JF260V, TJF240, TJF260V; Olympus Optical Co, Tokyo, Japan) under conscious sedation with intravenous midazolam (3–10 mg) administration, supplemented with pentazocine (15 mg) as needed. These sedative drugs were supplemented as required during the procedure. Prophylactic antibiotics and ulinastatin or nafamostat mesylate were administered to almost all patients to prevent cholangitis and pancreatitis. After selective cannulation of the bile duct using a 0.035- or 0.025-inch guidewire (Hydra Jagwire; Boston Scientific Corporation, Marlborough, USA or VisiGlide 2; TERUMO CORPORATION, Tokyo, Japan), routine cholangiography using a cannula (ERCP catheter; MTW Endoskopie, Wesel, Germany) or sphincterotome (Single Use Sphincterotome V; OLYMPUS MEDICAL SYSTEMS CORP., Tokyo, Japan) was performed. Sphincterotomy was performed at the discretion of the endoscopist with an

electrosurgical generator (ICC 200; ERBE Elektromedizin GmbH, Tübingen, Germany). The endoscopist decided which device would be used during the procedure. All patients were hospitalized for at least 72 h after the procedure. Serum amylase levels were measured at 4 h and 24 h after ERCP. Abdominal computed tomography (CT) was performed if needed.

Covered self-expandable metallic stent

Biliary drainage was performed using partially and fully CSEMS. WallFlex Biliary RX Stent (Boston Scientific Corporation, Marlborough, USA) was the braided-type partially CSEMS used. The braided-type fully CSEMS employed in this study comprised WallFlex Biliary RX Stent (Boston Scientific Corporation, Marlborough, USA), HANAROSTENT Biliary Full Cover Lasso (M.I.Tech Co., Ltd., Seoul, Korea), BONA-SHIMSTENT Covered with Lasso or BONASTENT M-intraductal (Sewoon Medical Inc., Seoul, Korea), Niti-S biliary silicone covered stent (Taewoong Medical, Seoul, Korea), and EGIS Biliary Stent (S&G Biotech Inc., Yongin-si, Korea). The Laser-cut type CSEMS used was X-Suit NIR Covered Biliary Metallic Stent (Medinol Ltd, Jerusalem, Israel).

Follow-up

Review visits based on clinical symptoms, blood tests, abdominal radiographs and/or CT scans were performed every 3 mo, until September 2019 as outpatients. Data were retrospectively collected using the medical records at the latest follow-up. Patients who were lost to follow-up, who underwent any surgery, or who died without RBO were treated as censored cases at the time of last follow-up, operation, or death, respectively.

Definitions

RBO and TRBO

According to the TOKYO criteria [12], we defined RBO as a composite endpoint of either occlusion or migration of CSEMS. We also defined TRBO as the time from the placement of CSEMS to RBO. Stent occlusion was defined as present of elevated liver

enzymes compared with baseline values, accompanied by biliary dilation on imaging studies or endoscopic findings suggesting it. Stent migration was diagnosed when reintervention reveals a completely or partially migrated CSEMS as a cause of RBO.

Technical success and functional success

Furthermore, based on the Tokyo criteria recommendations, technical success was defined as successful deployment of CSEMS in the intended location with sufficient coverage of the stricture, and functional success was defined as a 50% decrease in or normalization of the bilirubin level within 14 days after placement of CSEMS.

Distal MBO

In this study, we defined distal MBO as a malignant biliary stricture situated ≥ 2 cm away from the communication of the bilateral hepatic ducts.

Adverse events

Adverse events were graded according to the American Society of Gastrointestinal Endoscopy (ASGE) lexicon guidelines [13].

Measurement of the angle of CSEMS after the placement

Using a medical imaging and information management system (SYNAPSE PACS SYSTEM; FUJIFILM Corporation, Tokyo, Japan), we retrospectively measured the angle of CSEMS on abdominal radiographs in the standing position. As previously reported [14], we defined the angle as that measured between the lines extending from the proximal and distal points to the narrowest point in the CSEMS (***Figure 1***). We evaluated the obtuse angle of CSEMS after 2 or more days, not immediately after the placement, because CSEMS was not fully expansion and unstable in the position.

Statistical analysis

Medians and interquartile ranges (IQR) were used for continuous variables while percentages and counts were used for categorical variables. Categorical variables were evaluated using the chi-squared or the Fisher exact test, and continuous variables were evaluated using the Mann-Whitney *U* test. Using the Cox proportional hazard model, the risk for RBO of CSEMS was estimated by calculating the hazard ratio (HR) and the 95% confidence interval (CI). TRBO, non-RBO, and survival time were assessed by the Kaplan-Meier method. Using c-statistics, the model was evaluated for reliability utilizing the Hosmer-Lemeshow test for goodness-of-fit and for validity using receiver operating characteristic (ROC) curves. We also used the Pearson correlation test to evaluate the consistency for the angle of CSEMS after the placement by 2 people in the method previously reported [15]. Statistical analyses were performed using IBM® SPSS® software, version 23.0 for Windows (IBM Corporation, NY, USA) and R software version 2.4.3 (R Foundation for Statistical Computing, Vienna, Austria). All statistical tests were two-sided, and a value of $P < 0.05$ was considered statistically significant.

RESULTS

Baseline characteristics of the patients and treatment

We enrolled 261 patients in this study. Forty-four patients (62 sessions) treated with uncovered SEMS were excluded. Among the remaining 217 patients (246 sessions), 12 patients (13 sessions) had previously undergone surgery, 64 patients (79 sessions) underwent the placement of SEMS for hepatic hilar biliary stricture, 22 patients (24 sessions) underwent the placement of multiple SEMS, 3 patients (5 sessions) had benign biliary stricture, 1 patient (10 sessions) was a case of duplication, 12 patients had absent abdominal radiographs, 7 patients had other stents, 3 patients had resectable distal MBO, 3 patients were unknown and in 3 patients CSEMS were removed early due to adverse events. We finally included 87 eligible patients who underwent initial placement of CSEMS for unresectable distal MBO (***Figure* 2**).

The baseline characteristics of the patients and the treatment implemented are shown in ***Table 1***. Pancreatic cancer was the predominant primary disease resulting in distal

MBO (66.7%), and the most common clinical stage was IV (86.2%). Forty-eight patients (55.2%) received chemotherapy, and 11 patients (12.6%) received radiotherapy. Endoscopic sphincterotomy was performed in 60 patients (69.0%). The median of the angle of CSEMS after the placement was 146.0° (IQR: 134.5-156.5).

Short-term results and adverse events

CSEMS were deployed successfully in 87 patients (100.0%), and functional success was observed in 72 patients (82.8%) (***Table 2***). The overall rate of adverse events was 10.3%. The incidence rate of severe acute pancreatitis was 1.1%, and all patients with pancreatitis were managed conservatively. No adverse events associated with cholangitis (including non-occlusion cholangitis), cholecystitis, or other complications (bleeding, perforation, *etc.*) occurred.

Long-term results and reintervention

The median TRBO was 454 [95%CI: 307-not available (NA)] days, during a median follow-up period of 117.0 (IQR: 47.5-220.5) days. The non-RBO rates at 3, 6 and 12 mo after the placement of CSEMS were 88.9%, 78.3%, and 48.7%, respectively (***Figure 3a***). The median overall survival time was 186 (95%CI: 92-394) days (***Figure 3b***). The number of patients with RBO after the placement of CSEMS was 18 cases (20.7%), and the most common cause of RBO was sludge formation and food impaction (11 cases, 61.1%) (***Table 2***). Except for tumor overgrowth, the incidence rate of RBO due to stent occlusion and migration was 72.2%. In 17 out of 18 patients with CSEMS, reintervention for RBO was required and carried out successfully. The procedures during reintervention included additional CSEMS replacement in 9 patients, plastic stent placement in 3 patients, and no additional placement in 5 patients.

Risk factors for the RBO of CSEMS

We divided the patients into 2 cohorts: 18 in the RBO group and 69 in the non-RBO group. The baseline characteristics were similar except for the angle of CSEMS after the

placement which differed significantly between both groups (P = 0.01) (***Table 3***). The angle of CSEMS after the placement (per 1° and per 10°) was a risk factor for RBO based on univariate Cox proportional hazard analysis (HR, 0.96; 95%CI, 0.93-0.99; P < 0.01; HR, 0.67; 95%CI, 0.51-0.87; P < 0.01). In addition to the angle of CSEMS after the placement, we also selected American Society of Anesthesiologists Physical Status and chemotherapy that could potentially be a confounding factor using clinical knowledge [16]. In multivariate Cox proportional hazard analysis, only the angle of CSEMS after the placement (per 1° and per 10°) was significantly associated with shorter duration of RBO (HR, 0.97; 95%CI, 0.94-0.99; P = 0.01; HR, 0.71; 95%CI, 0.54-0.92; P = 0.01) (***Table 4***). The angle of CSEMS after the placement was an independent risk factor for RBO in unresectable distal MBO.

Evaluation of the current study and the obtuse angle of CSEMS after the placement

We evaluated the accuracy of the current study using the ROC curve. For early RBO diagnosis, the angle of 130° had a sensitivity of 50.0% and a specificity of 85.5%, and the ROC analysis showed an area under the curve of 0.70 (95%CI, 0.57-0.84) (***Figure 4***). On comparing the groups based on the angle of CSEMS after the placement: TRBO in the < 130° angle group was significantly shorter than that in the 130° ≤ angle group (P < 0.01) (***Figure 3c***).

Furthermore, we also used the Pearson correlation test to evaluate the consistency of the obtuse angle of CSEMS after the placement. A random number table was created for the 87 patients. Of those, 20 patients were randomly sampled. The angle of CSEMS after the placement was evaluated by 2 board-certified fellows (K.T and H. M) of the Japan Gastroenterological Endoscopy Society. Between them, a significant positive correlation was observed for the angle of CSEMS after the placement (R = 0.92; 95% CI, 0.81-0.97; P < 0.01) (***Figure 5***).

DISCUSSION

We found that the angle of CSEMS after the placement was a risk factor for RBO in unresectable distal MBO. In addition, our study demonstrated that the cut-off value of the angle of CSEMS after the placement for RBO was 130°, and that TRBO in the group with an angle < 130° was significantly shorter than that in the group with an angle 130° ≤. This is the first report demonstrating a new and quantitative risk factor for RBO in CSEMS. We believe that our results are easy for everyone to replicate and provides important information for management of CSEMS.

A CSEMS's angle of < 130° is a risk factor for early RBO. This result suggests that CSEMS with low AF cause sludge formation, food impaction, and stent migration. Several previous studies support these reasons [7] [17-19]. First, the placement of CSEMS with large diameter across the papilla causes loss of sphincter dysfunction, resulting in duodenal-biliary reflux to bile duct because of pressure gradient by food or duodenal contents. These results suggest that disruption of the sphincter mechanism may represent the most important etiologic factor in the development of cholangitis after metallic stent placement for malignant biliary obstruction [18]. In addition, the previous reports were suggested that food debris is an etiologic factor for acute cholangitis and warned that occlusion might be caused by reflux of duodenal contents [19-21]. CSEMS with low AF decrease flow velocity and increase the resistance of bile juice. Therefore, a CSEMS's angle of < 130° easily causes sludge and food impaction and induces early RBO. Additionally, increased outflow pressure of bile juice leads to an elevated risk of stent migration [22]. In our study, the incidence of RBO in the CSEMS's angle < 130° group was inclined to be higher than that in the 130° ≤ group (43.8% vs. 15.5%) (***Table 5***). Isayama *et al* also demonstrated that well-bent SEMS with low AF after the placement led to RBO as a result of sludge formation and food impaction [9], which supports our results. However, unlike this previous report, we proposed for a versatile index, and used the abdominal radiograph. We believe that the measurement of CSEMS's angle is simple in our results.

Our results could change stent management after CSEMS placement. Until now, patients with unfavorable prognosis were not considered for replacement of CSEMS.

However, it is widely accepted that CSEMS are exchanged when stent occlusion and migration occur. There are no definitive guidelines and literature concerning management after CSEMS placement. However, it is now changing. With the advent of effective drugs and radiation therapy, the prognosis of patients has improved [23]. For this reason, stenting has shifted from being used for palliative care to maintaining the overall health status of patients undergoing antitumor therapy as a part of multidisciplinary treatment. Therefore, long-term maintenance without stent dysfunction is strongly recommended. However, recent studies have reported that non-RBO rate at 6 mo were 70-94% for partially CSEMS [24-27] and 63-91% for fully CSEMS [7] [28, 29], and that there was a need for replacement of CSEMS before the patients died.

In our study, among patients who caused RBO of CSEMS in the < 130° angle group, 86% patients had elevated liver enzymes in the latest laboratory data before the occurrence of RBO, compared with previous laboratory data, and all patients were asymptomatic (***Table 5***). Thus, a potentially high risk of RBO might be considered if the CSEMS's angle is < 130° and liver enzymes are elevated. Hence, we suggest the replacement of CSEMS even in asymptomatic patients if the liver enzymes are elevated and the CSEMS's angle is < 130°, while managing such patients. We believe that this information has great significance in the management of patients with CSEMS placement in the clinical practice. Additionally, by deploying a new CSEMS with high AF as needed, it could be possible to expect long-term maintenance without stent dysfunction.

Our study had the following limitations. First, this was a retrospective cohort study in a single center. We acknowledge that patient assignment to different interventions was subject to selection bias. There were differences in the length, diameter, and type of CSEMS used in our study; these factors can influence RBO. However, on multivariate analyses, these factors did not significantly influence RBO. In our results, the angle after placement was a risk factor for RBO, regardless of the CSEMS characteristics selected. A larger prospective multicenter study should be conducted to evaluate the obtuse angle of CSEMS after the placement in unresectable distal MBO. Second, we evaluated the

angle of CSEMS after the placement using 2-dimensional data. Although data from 3-dimension, i.e., CT or magnetic resonance imaging are desirable, we could not evaluate the angle after the placement on unified modality and quantify it using 3-dimensional data. However, there were no previous reports assessing RBO by the angle of CSEMS. Therefore, we considered our method using 2-dimensional data to be simple and highly versatile. Third, the actual results of the censored cases are unknown because the follow-up data were collected only from medical records.

CONCLUSION

The angle of CSEMS after the placement was a risk factor for RBO, and TRBO of CSEMS with low AF was shorter than that of other CSEMS. These results are novel and provide pertinent information for future stent management.

ARTICLE HIGHLIGHTS

Research background

Covered self-expandable metallic stents (CSEMS) cause recurrent biliary obstruction (RBO), which prevents the continuation of treatment and causes a quality of life in patients with unresectable distal malignant biliary obstruction (MBO) to be poor. To date, sludge formation and food impaction have remained to be major causes of RBO. Recently, CSEMS with low Axial force (AF) to improve compatibility with the bile duct have been used frequently, with increasing concerns that they are likely to cause early RBO as a result of sludge formation and food impaction.

Research motivation

Therefore, we hypothesized that the time to RBO (TRBO) of CSEMS with low AF was short. We considered that proving this hypothesis has great significance in the management of patients with CSEMS placement in the clinical practice.

Research objectives

We aimed to evaluate whether the angle of CSEMS after placement was a risk factor for RBO in patients with unresectable distal MBO.

Research methods

Finally, we included 87 patients in this study. We divided the patients into 2 cohorts, RBO group and non-RBO group, and evaluated the risk factors for RBO including the angle of CSEMS after the placement. Using SYNAPSE PACS system (FUJIFILM Corporation, Tokyo, Japan), we measured the obtuse angle of CSEMS after the placement on an abdominal radiograph.

Research results

We found that the angle of CSEMS after placement was an independent risk factor for RBO. Further, we demonstrated that the cut-off value for the angle of CSEMS after placement was 130°, and that time to RBO in the < 130° group was significantly shorter than that in the ≥ 130° group. In our study, among patients who caused RBO of CSEMS in the < 130° angle group, 86% patients had elevated liver enzymes in the latest laboratory data before the occurrence of RBO, compared with previous laboratory data, and all patients were asymptomatic.

Research conclusions

The findings suggest that the angle of CSEMS after placement for unresectable distal MBO, is a risk factor for RBO, and TRBO of CSEMS with low AF is shorter than that of other CSEMS. Hence, while managing such patients, we suggest the replacement of CSEMS even in asymptomatic patients if the liver enzymes are elevated and the CSEMS angle is < 130°. Additionally, by deploying a new CSEMS with high AF as needed, it could be possible to expect long-term maintenance without stent dysfunction.

Research perspectives

These results are novel and provide pertinent information for future stent management. However, further prospective studies with larger cohorts are needed to validate our findings.

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