Original Article

A novel laser-cut fully-covered metal stent with anti-reflux valve in patients with malignant distal biliary obstruction refractory to conventional covered metal stent

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ABSTRACT

Background: Stenting against recurrent biliary obstruction (RBO) after placement of covered metal stent (CMS) for distal malignant biliary obstruction (MBO) is still challenging. This study investigated the feasibility of a novel laser-cut fully-covered metal stent with anti-reflux valve in patients with distal MBO refractory to conventional CMS.

Methods: Patients who underwent Duckbill-type metal stent (DMS) placement between June 2019 and May 2020 were included. Early complications, causes of RBO including non-occlusion cholangitis, and time to RBO (TRBO) were evaluated. TRBO of DMS was also compared with that of previous CMS.

Results: Thirty patients were included: pancreatic cancer/metastatic lymph nodes 29/1; duodenal stenosis 13. Technical and functional success were achieved in all patients. Mild cholangitis and mild pancreatitis developed in each one. Median follow-up period was 167 days (range, 23-527 days). RBO occurred in 9 patients (30%): sludge formation 4, hemobilia 1, symptomatic distal stent migration 3, and non-occlusion cholangitis 1. TRBO of DMS was significantly longer than that of previous CMS (median 224 days vs. median 120 days, p=0.0025). DMS was successfully removed in all of 6 attempted patients when re-intervention was needed.

Conclusions: DMS might be safe and effective in patients with distal MBO refractory to conventional CMS.

INTRODUCTION

Distal malignant biliary obstruction (MBO) is often caused by pancreatic cancer, biliary tract cancer, and lymph node metastasis. Endoscopic placement of a self-expandable metal stent (SEMS) is the standard treatment for unresectable distal MBO due to the long stent patency compared to plastic stents [1-3]. There are two types of SEMS: uncovered SEMS (UMS) and covered SEMS (CMS). Recent meta-analysis demonstrated that migration and sludge rates were higher with CMS, whereas tumor ingrowth was more likely with UMS [4]. Therefore, further stent evolution is desirable to add the benefit of CMS.

Reflux of duodenal contents is unavoidable after placement of SEMS across the papilla [5]. Duodeno-biliary reflux results in stone or sludge formation in the bile duct [6]. Since sludge and food residues easily adhere to the artificial membrane of CMS, biliary sludge or food impaction is one of the major concerns when using CMS compared to UMS. Moreover, duodenal tumor invasion is considered a risk factor for early stent dysfunction [7]. The reduction of intestinal peristalsis may induce duodeno-biliary reflux. Therefore, it is necessary to develop a SEMS that prevents duodeno-biliary reflux, especially in such conditions.

Several types of anti-reflux metal stents (ARMSs) have been introduced to overcome duodeno-biliary reflux: hemispheric-shaped, S-shaped, wineglass-shaped, nipple-shaped, long funnel-shaped, and windsock-shaped ARMS [8-18]. All these previous ARMS are braided type SEMS.

Although ARMS was associated with a lower rate of stent occlusion compared to conventional SEMS in several studies, the results of these studies are inconsistent and the stent patency was not satisfactory enough. Duckbill-type metal stent (DMS) is a fully covered laser-cut type SEMS with a duckbill-shaped anti-reflux valve (ARV) attached to the distal end (Fig. 1). This ARMS has two additional mesh at the distal end to regulate the opening of the long ARV by the outflow of bile and is expected to prevent duodeno-biliary reflux.

Re-intervention after conventional CMS dysfunction is considered a high risk of recurrent stent dysfunction even after exchanging to a new conventional CMS [19]. Moreover, duodeno-biliary reflux is more likely to occur as cancer progresses. Furthermore, the risk of subsequent stent migration is considered to be high since the biliary stricture has already been expanded by the previous SEMS. It can be evaluated effective if this DMS shows longer stent patency compared with previous conventional CMS in this challenging refractory condition. Therefore, we conducted this pilot study to investigate the efficacy and safety of DMS in patients with unresectable distal MBO refractory to conventional CMS.

METHODS

Patients

Consecutive patients with unresectable distal MBO who were complicated with stent dysfunction of

conventional CMS at our institution between June 2019 and May 2020 were identified from our prospectively maintained database. Patients who removed the previous CMS and received the DMS via the papilla were enrolled in this retrospective study. Patients who had previously undergone DMS placement were excluded. All patients provided written informed consent for endoscopic procedures. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of our institution (C-T2020-0111).

The design of ARMS

The DMS is a fully covered laser-cut type SEMS with a 12.5 mm duckbill-shaped ARV attached to the distal end (Duckbill Biliary Stent, Kawasumi Laboratories Inc., Tokyo, Japan) (Fig. 1). The stent is made of nitinol wire and an expanded polytetrafluoroethylene membrane that extends beyond the distal end to create the duckbill-shaped ARV. The stent has two additional mesh at the distal end to regulate the opening of the valve; the valve is usually closed to prevent the reflux of the duodenal content into the bile duct, but opens and allows the bile to flow out when the bile duct pressure increases. Radio-opaque gold markers are located at both the proximal and distal end of the metal part to facilitate the recognition of the stent under fluoroscopy or endoscopic view. The diameter of DMS used in this study was 10 mm and the available lengths were 60 and 80 mm. The diameter of the delivery system was 9 Fr.

Endoscopic procedures

Endoscopic retrograde cholangiopancreatography (ERCP) was performed using a duodenoscope (JF-260V, TJF-260V, TJF-Q290V; Olympus Medical Systems, Tokyo, Japan) under conscious sedation with pethidine and midazolam. We basically removed the occluded SEMS and inserted an endoscopic naso-biliary drainage (ENBD) tube to control cholangitis in the first session. After cholangitis subsided, we placed the DMS after balloon sweeping of the bile duct in the second session. Endoscopic sphincterotomy had already been performed when DMS was deployed in all cases. The length of DMS was decided according to the cholangiogram. The distal end of the metal part of DMS was placed 5–10 mm below the papilla to completely expose the ARV into the duodenum. No cholangiography was performed after DMS placement. When duodenal stent placement was required for duodenal stenosis, duodenal stenting was performed simultaneously.

Data collection and clinical outcomes

The classification reported by Mutignani et al was used in cases with combined malignant duodenal obstruction [20]. The efficacy of DMS was basically evaluated using Tokyo Criteria 2014 [21]. Non-occlusion cholangitis was also considered as recurrent biliary obstruction (RBO) if ENBD placement was necessary to treat cholangitis [22]. Stent occlusion was considered present when elevated liver

enzymes were observed along with biliary dilation on imaging studies or endoscopic findings suggestive of stent occlusion. Stent migration was diagnosed when the SEMS revealed completely or partially migrated.

The primary outcome was time to RBO (TRBO). TRBO was defined as the time from DMS placement to RBO occurrence. The secondary outcomes were technical success, functional success, and complications other than RBO. Technical success was defined as successful deployment of a SEMS in the intended location with sufficient coverage of the stricture. Functional success was defined as a 50% decrease in or normalization of the bilirubin level within 14 days of SEMS placement. In cases without an elevated serum bilirubin level due to prior ENBD placement, functional success was achieved if serum bilirubin level was not exacerbated after SEMS placement. Complications other than RBO were categorized as early (≤30 days after SEMS placement) and late (≥31 days after SEMS placement) according to Tokyo criteria. The severity of adverse events was graded according to the American Society of Gastrointestinal Endoscopy lexicon guidelines [23].

Statistical analysis

Continuous variables are presented as medians (ranges) and were compared using the Mann-Whitney U test. Categorical variables are described as absolute numbers (proportions) and were analyzed using the chi-squared or Fisher's exact test. A $p\ value < 0.05$ was considered statistically significant. Overall

survival (OS) was defined as the time from DMS placement to death or the last follow-up. TRBO was plotted using the Kaplan–Meier method and was compared using the log-rank test. The follow-up data was confirmed until November 30, 2020. All statistical analyses were performed with EZR ver. 1.53 [24].

RESULTS

Patient characteristics

Thirty patients were finally extracted in this study (Fig. 2). Patient characteristics are summarized in Table 1. The median age was 64 years and most patients were metastatic pancreatic cancer. Ascites and peritoneal dissemination were observed in 9 patients (30%) each. Tumor invasion to the duodenum was observed in 13 patients (43%): type I 9, type II 2, and type III 2. Duodenal stent had already been placed in 2 patients. In the two cases of type II, only DMS was placed because solid food could be ingested without indwelling the duodenal stent in spite of duodenal stenosis. Twenty-seven patients (90%) received chemotherapy (first-line 16, second-line 8, and third-line 3) at the time of RBO of previous CMS.

Twenty-one patients (70%) received DMS as a second stent, whereas the remaining 9 patients (30%) received multiple SEMS prior to DMS placement. The types of previous CMS were standard type (10 mm in diameter) (n=28) and large bore type (12 mm in diameter) (n=2). The causes

of RBO were sludge formation in 7, food impaction in 4, symptomatic migration in 11 (proximal 3, distal 8), asymptomatic distal migration in 2, and non-occlusion cholangitis in 6.

ENBD tube was placed prior to DMS deployment in 25 patients (83%). Median duration from ENBD tube insertion to DMS placement was 4 days. Median duration of DMS placement from the diagnosis of primary cancer was 8.8 months.

Clinical outcomes of DMS

Table 2 shows the clinical outcomes of DMS. Eight endoscopists (experienced physician 5, trainee 3) performed the procedure. Two patients (7%) needed to insert the duodenoscope through the duodenal stent placed at the first portion of duodenum. Two patients (7%) received simultaneous placement of a duodenal stent. Technical success was achieved in all patients and the median procedure time was 16 minutes (6-69). Stent length of 6 cm was chosen in 21 cases (70%). Functional success was also achieved in all patients. Mild cholangitis and mild pancreatitis occurred in one patient (3%) each. These two patients recovered with conservative treatment. There were no other procedure-related complications.

The median follow-up period was 167 days (23–527). Chemotherapy was introduced in 21 patients (70%) after DMS placement. The indwelling duodenal stent was occluded in 1 patient, but this patient did not complicate with RBO (Fig 3). RBO occurred in 9 patients (30%). Causes of RBO

were sludge formation in 4, hemobilia in 1, symptomatic distal stent migration in 3, and non-occlusion cholangitis in 1. Of the 9 patients, the ARV was found collapsed in all of the 5 patients (completely 3, partially 2) with RBO due to sludge formation or non-occlusion cholangitis. Median TRBO of these 5 patients was 107 days (87–286). Therefore, DMS could not prevent duodeno-biliary reflux in the long follow up due to ARV damage in these 5 patients. Of the 17 cases in which the previous CMS had RBO due to sludge formation, food impaction, or non-occlusion cholangitis, DMS was able to prevent duodeno-biliary reflux in 11 cases (the remaining 6 cases were sludge formation in 5 and stent migration in 1). Of the remaining 13 cases in which the previous CMS had stent migration, stent migration occurred in only 2 cases. Re-intervention was performed in 9 patients (3 patients experienced complete distal migration) and DMS was successfully removed in all 6 patients using a rat tooth forceps or snare forceps. The median indwelling period of DMS removed was 138 days (range, 62-286 days) and two DMSs were teared during the removal.

Figure 4 shows the Kaplan–Meier curves of TRBO between DMS and previous CMS. TRBO of DMS was significantly longer than that of previous CMS (median 224 days [95% confidence interval (CI), 121–not available (NA)] vs. median 120 days [95%CI, 92–158], p=0.0025). The non-RBO rates at 3 and 6 months of DMS were 85.6% and 66.2%, respectively, whereas those of previous CMS were 70.0% and 23.3%, respectively. During the study period, 16 patients (53%) died due to progression of primary cancer. Median OS was 304 days (95%CI, 97–NA).

The effectiveness of DMS was also compared with or without duodenal stenosis. RBO occurred in 3 cases among 13 patients with duodenal stenosis (23%). While, RBO occurred in 6 cases among 17 patients without duodenal stenosis (35%). Median OS of the patients with duodenal stenosis (n=13) was slightly shorter than that of the patients without duodenal stenosis (n=17) (196 days [95%CI, 46-NA] vs. 357 days [95%CI, 97-NA], p = 0.12). There were no significant difference of median TRBO between these two groups (286 days [95%CI, 59-NA] vs. 224 days [95%CI, 107-NA], p=0.95).

DISCUSSION

DMS demonstrated a significantly longer TRBO than the previous CMS in refractory cases of unresectable distal MBO. Median TRBO was 224 days which was quite long in refractory cases. Even in cases with concomitant duodenal stenosis, the occurrence of RBO was similar to that in cases without duodenal stenosis due to the effect of ARV. The ARV was collapsed in 5 cases and RBO eventually occurred in these cases. On the other hand, DMS was able to prevent duodeno-biliary reflux in almost all the cases without ARV damage in this study (hemobilia 1). Stent migration occurred in 3 cases (10%). Regarding re-intervention, DMS was successfully removed in all 6 cases despite its laser-cut design. Although some improvements are needed, DMS was an effective and safe stent in refractory cases for distal MBO.

Previous reports of ARMS for distal MBO are summarized in Table 3 [8-18]. All the previous ARMS were braided type SEMS and some of them were UMS or partially CMS. The structure of ARV was extremely different in each ARMS. Several comparative studies have been reported. ARMS with a nipple-shaped valve was compared to a conventional UMS as a prospective study [11]. This ARMS successfully provided longer stent patency compared to a conventional UMS (13 months vs. 10 months). Because tumor ingrowth was a major cause of RBO in UMS group, it was not clear how the addition of the ARV contributed to the longer stent patency. ARMS with a long funnel-type ARV was compared with conventional CMS as a prospective study [17]. However, this ARMS was rather worse than the conventional CMS. This ARMS showed a higher rate of stent migration (31%) compared with the conventional CMS. ARMS with a long windsock-type ARV was also compared with a conventional CMS as a prospective study [14]. The ARMS provided 2-fold prolonged stent patency time compared to the CMS (median, 14 months vs. 7 months). In a proof-of concept examination utilizing oral barium after SEMS placement, the suppression of the duodeno-biliary reflux via the ARV was first demonstrated in the human body. Meta-analysis of ARMS compared with conventional CMS concluded that ARMS had a lower risk of stent occlusion, but a higher risk of stent migration [25]. Therefore, improvement of the ARMS including prevention of stent migration is required.

Recently, Kin et al reported the feasibility study of DMS for malignant MBO [18]. They

reported a median TRBO of 261 days, and non-RBO rates at 3 and 6 months were 76% and 55%, respectively. It is difficult to compare the results with our study, because their study included patients who underwent DMS stenting as a first SEMS (47%). In their report, removal of DMS failed in 33% of patients who performed re-intervention for RBO. In our cases, DMS was successfully removed using rat tooth forceps or snare forceps in all patients who performed re-intervention for RBO. Because of the laser-cut design, the DMS cannot be removed through the scope and must be removed with the duodenoscope. RBO owing to the collapse of ARV was observed in some patients in our study too.

DMS is the first laser-cut ARMS. Laser-cut type SEMS is usually considered to have advantages and disadvantages. The advantages of laser-cut type SEMS are that the risk of stent migration is lower than the braided type SEMS. The migration rate of our study was 10% and the previous study of DMS reported by Kin et al was 7%. Considering that all the patients included in our study were pre-dilated the biliary stricture by previous CMS, the stent migration rate was considered to be low in this study. On the other hand, the meta-analysis discussing the previous braided type ARMS summarized that the migration rate was 16.2% [25]. However, it is difficult to compare these data from the previous reports of braided type ARMS because the follow-up period was different and some of the ARMS were UMS or partially CMS. Another advantage of laser-cut type SEMS is that it is easy to place the SEMS precisely due to the low shortening rate during the stent deployment. This point is also important especially when duodenal stricture is present. However, this issue may not be

much different from braided type SEMS because the biliary stricture has already been pre-dilated by the previous CMS. On the other hand, the disadvantage of laser-cut SEMS is that it is sometimes difficult to remove the SEMS when stent dysfunction occur. We successfully removed all the SEMS at re-intervention, but this study only included the refractory cases with poor prognosis. Kin et al previously reported that the success rate of stent removal was only 66%. Therefore, it is necessary to make a decision carefully for stent removal by the skilled endoscopist after fully considering the clinical condition.

DMS has some points to be resolved like other ARMS. In general, biliary cannulation through the ARV is often difficult. However, re-intervention may be possible through a stent mesh in DMS [26]. Damage of ARV is also an issue for ARMS. In this study ARV damage was observed in 5 cases (17%). Previous in vitro study demonstrated that a duodenal pH environment induced a morphological change of ARV leading to stent dysfunction [27]. Therefore, it is better to change the material of ARV to prevent ARV collapse. Stent migration is also one of the big issues for ARMS. In the refractory case, the stenosis is loosened by the previous SEMS placement. Furthermore, it is speculated that the pressure inside the bile duct is higher in ARMS than in conventional CMS. Chemotherapy is also considered as a risk factor for stent migration [28]. Recently, chemotherapy for metastatic pancreatic cancer has been gradually improved and the tumor control rate of first-line and second-line chemotherapy is increasing [29]. It is necessary to lower the migration rate further by

adding the anti-migration system.

Several limitations were involved in our study. First, this was a single-center, small sample-sized retrospective study and the efficacy of DMS was compared with previous conventional CMS. Because this study was a pilot study for refractory cases, further randomized controlled studies or a propensity score matching is needed in the next step. Second, the data of long-term follow-up was lacking. Because the study population was refractory cases of mainly metastatic pancreatic cancer, we set the minimum follow-up period of six months in this study. Third, the efficacy of DMS was evaluated only in patients with refractory cases. Since DMS was a laser-cut type stent, we were afraid that stent removal could be difficult for re-intervention. Therefore, we first conducted this pilot study for the refractory cases. Because stent removal of DMS could be possible for re-intervention in many cases, it is necessary to evaluate this ARMS in a naïve case as the next step.

In conclusion, our study demonstrated that DMS achieved a longer TRBO than previous CMS. DMS was effective in patients with distal MBO refractory to conventional CMS. Further evaluation is needed by conducting a multicenter randomized controlled study with a large number of patients in the situation of both naïve cases and refractory cases. Moreover, double stenting using DMS for combined malignant biliary and duodenal obstruction is also an interesting field to evaluate in the future [30].

Conflict of interest: T.S. received honoraria from Kawasumi Laboratories, Boston Scientific Japan, Century Medical, Cook Japan. N.S. received honoraria from Boston Scientific, Gadelius Medical, Kawasumi Laboratories. All other authors declare no conflicts of interest for this article.

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REFERENCES

1. Nakai Y, Isayama H, Wang HP, Rerknimitr R, Khor C, Yasuda I, et al. International consensus statements for endoscopic management of distal biliary stricture. J Gastroenterol Hepatol. 2020; 35: 967–79.

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

3. Sawas T. Al Halabi S, Parsi MA, Vargo JJ. Self-expandable metal stents versus plastic stents for malignant biliary obstruction: a meta-analysis. Gastrointest Endosc. 2015; 82: 256–67. e7.

4. Tringali A, Hassan C, Rota M, Rossi M, Mutignani M, Aabakken L. Covered vs. uncovered self-expandable metal stents for malignant distal biliary strictures: a systematic review and meta-analysis. Endoscopy. 2018; 50: 631–41.

5. Misra SP, Dwivedi M. Reflux of duodenal contents and cholangitis in patients undergoing self-expandable metal stent placement. Gastrointest Endosc. 2009; 70: 317–21.

6. Zhang R, Luo H, Pan Y, Zhao L, Dong J, Liu Z, et al. Rate of duodenal-biliary reflux increases in patients with recurrent common bile duct stones: evidence from barium meal examination. Gastrointest Endosc. 2015; 82: 660–5.

7. Hamada T, Isayama H, Nakai Y, Togawa O, Kogure H, Kawakubo K, et al. Duodenal invasion is

a risk factor for the early dysfunction of biliary metal stents in unresectable pancreatic cancer. Gastrointest Endosc. 2011; 74: 548–55.

8. Hu B, Wang TT, Shi ZM, Wang SZ, Lu R, Pan YM, et al. A novel antireflux metal stent for the palliation of biliary malignancies: a pilot feasibility study (with video). Gastrointest Endosc. 2011; 73: 143–8.

9. Lee KJ, Chung MJ, Park JY, Lee DH, Jung S, Bang BW, et al. Clinical advantages of a metal stent with an S-shaped anti-reflux valve in malignant biliary obstruction. Dig Endosc. 2013; 25: 308–12.

10. Kim DU, Kwon CI, Kang DH, Ko KH, Hong SP. New antireflux self-expandable metal stent for malignant lower biliary obstruction: in vitro and in vivo preliminary study. Dig Endosc. 2013; 25: 60–6.

11. Hu B, Wang TT, Wu J, Shi ZM, Gao DJ, Pan YM. Antireflux stents to reduce the risk of cholangitis in patients with malignant biliary strictures: a randomized trial. Endoscopy. 2014; 46: 120–6.

12. Hamada T, Isayama H, Nakai Y, Kogure H, Togawa O, Kawakubo K, et al. Novel antireflux covered metal stent for recurrent occlusion of biliary metal stents: a pilot study. Dig Endosc. 2014; 26: 264–9.

13. Hamada T, Isayama H, Nakai Y, Togawa O, Kogure H, Takahara N, et al. Antireflux metal stent

with an antimigration system for distal malignant biliary obstruction: A feasibility pilot study. Surg Laparosc Endosc Percutan Tech. 2015; 25: 212–7.

14. Lee YN, Moon JH, Choi HJ, Choi MH, Lee TH, Cha SW, et al. Effectiveness of a newly designed antireflux valve metal stent to reduce duodenobiliary reflux in patients with unresectable distal malignant biliary obstruction: a randomized, controlled pilot study (with videos). Gastrointest Endosc. 2016; 83: 404–12.

15. Hamada T, Isayama H, Nakai Y, Togawa O, Takahara N, Uchino R, et al. Antireflux metal stent as a first-line metal stent for distal malignant biliary obstruction: A pilot study. Gut Liver. 2017; 11: 142–8.

16. Morita S, Arai Y, Sugawara S, Sone M, Sakamoto Y, Okusaka T, et al. Antireflux metal stent for initial treatment of malignant distal biliary obstruction. Gastroenterol Res Pract. 2018; 2018: 3805173.

17. Hamada T, Isayama H, Nakai Y, Iwashita T, Ito Y, Mukai T, et al. Antireflux covered metal stent for nonresectable distal malignant biliary obstruction: Multicenter randomized controlled trial. Dig Endosc. 2019; 31: 566–74.

18. Kin T, Ishii K, Okabe Y, Itoi T, Katanuma A. Feasibility of biliary stenting to distal malignant biliary obstruction using a novel designed metal stent with duckbill-shaped anti-reflux valve. Dig Endosc 2020 Sep 2. doi: 10.1111/den.13827. Online ahead of print.

19. Togawa O, Isayama H, Tsujino T, Nakai Y, Kogure H, Hamada T, et al. Management of dysfunctional covered self-expandable metallic stents in patients with malignant distal biliary obstruction. J Gastroenterol. 2013; 48: 1300–7.

20. Mutignani M, Tringali A, Shah G, Perri V, Familiari P, Iacopini F, et al. Combined endoscopic stent insertion in malignant biliary and duodenal obstruction. Endoscopy. 2007; 39: 440–7.

21. Isayama H, Hamada T, Yasuda I, Itoi T, Ryozawa S, Nakai Y, et al. Tokyo criteria 2014 for transpapillary biliary stenting. Dig Endosc. 2015; 27: 259–64.

22. Hamada T, Nakai Y, Isayama H. TOKYO criteria: Standardized reporting system for endoscopic biliary stent placement. Gastrointest Interv. 2018; 7: 46–51.

23. Cotton PB, Eisen GM, Aabakken L, Baron TH, Hutter MM, Jacobson BC, et al. A lexicon for endoscopic adverse events: report of an ASGE workshop. Gastrointest Endosc. 2010; 71: 446–54.

24. Kanda Y: Investigation of the freely available easy-to-use software 'ezr' for medical statistics. Bone Marrow Transplant. 2013; 48: 452–8.

25. Renno A, Abdel-Aziz Y, Ahmed T, Alastal Y, Toseef J, Al-Abboodi Y, et al. Antireflux valve metal stent versus conventional self-expandable metal stent in distal malignant biliary obstruction: A systematic review and meta-analysis. Ann Gastroenterol. 2019; 32: 605–13.

26. Mandai K, Nakamura S, Uno K, Yasuda K. Successful re-intervention through stent mesh after

novel antireflux covered metal biliary stent placement. Endoscopy. 2020 Jul 13. doi: 10.1055/a-1201-3045. Online ahead of print.

27. Kwon CI, Moon JP, Yun H, Jeong S, Koh DH, Lee WJ, et al. Evaluation of valve function in antireflux biliary metal stents. BMC Gastroenterol. 2018; 18: 150.

28. Nakai Y, Isayama H, Kogure H, Hamada T, Togawa O, Ito Y, et al. Risk factors for covered metallic stent migration in patients with distal malignant biliary obstruction due to pancreatic cancer. J Gastroenterol Hepatol. 2014; 29: 1744–9.

29. Sohal DPS, Kennedy EB, Cinar P, Conroy T, Copur MS, Crane CH, et al. Mestatatic pancreatic cancer: ASCO guideline update. J Clin Oncol. 2020 Aug 5:JCO2001364. doi: 10.1200/JCO.20.01364. Online ahead of print.

30. Sasaki T, Takeda T, Sasahira N. Double stenting with EUS-CDS using a new anti-reflux metal stent for combined malignant biliary and duodenal obstruction. J Hepatobiliary Pancreat Sci. 2020; 27: e15–6.

Figure legends

Figure 1. Endoscopic view of a Duckbill-type metal stent.

Figure 2. Patient flowchart.

CMS, covered metal stent; MBO, malignant biliary obstruction; MS, metal stent; DMS, duckbill-type metal stent; RBO, recurrent biliary obstruction; EUS-CDS, endoscopic ultrasound-guided choledochoduodenostomy; EBS, endoscopic biliary stenting; PS, plastic stent; RT, radiation therapy; NAC, neo-adjuvant chemotherapy.

Figure 3. Computed tomography of the case with the obstruction of indwelling duodenal stent at the third part of duodenum. The anti-reflux valve maintained pneumobilia in the bile duct and no duodeno-biliary reflux was observed in spite of duodenal stasis.

Figure 4. Kaplan–Meier curves of TRBO between DMS and previous CMS.

RBO, recurrent biliary obstruction; DMS, duckbill-type metal stent; CMS, covered metal stent; TRBO, time-to-recurrent biliary obstruction.

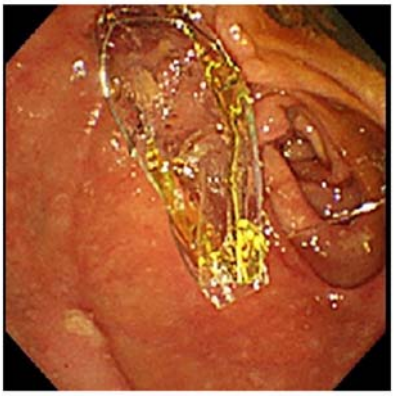

Fig. 1

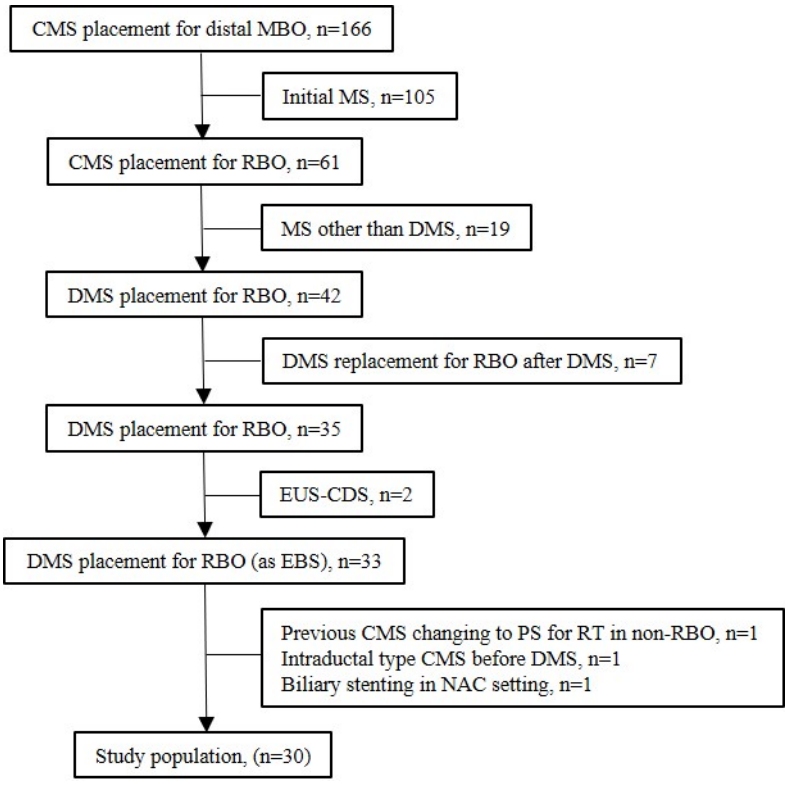
CMS placement for distal MBO, n=166
Initial MS, n=105
CMS placement for RBO, n=61
MS other than DMS, n=19
DMS placement for RBO, n=42
DMS replacement for RBO after DMS, n=7
DMS placement for RBO, n=35
EUS-CDS, n=2
DMS placement for RBO (as EBS), n=33
Previous CMS changing to PS for RT in non-RBO, n=1
Intraductal type CMS before DMS, n=1
Biliary stenting in NAC setting, n=1
Study population, (n=30)

Fig. 2

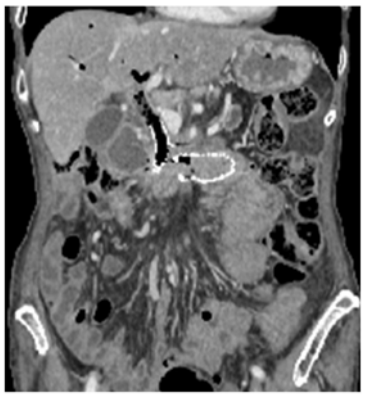

Fig. 3

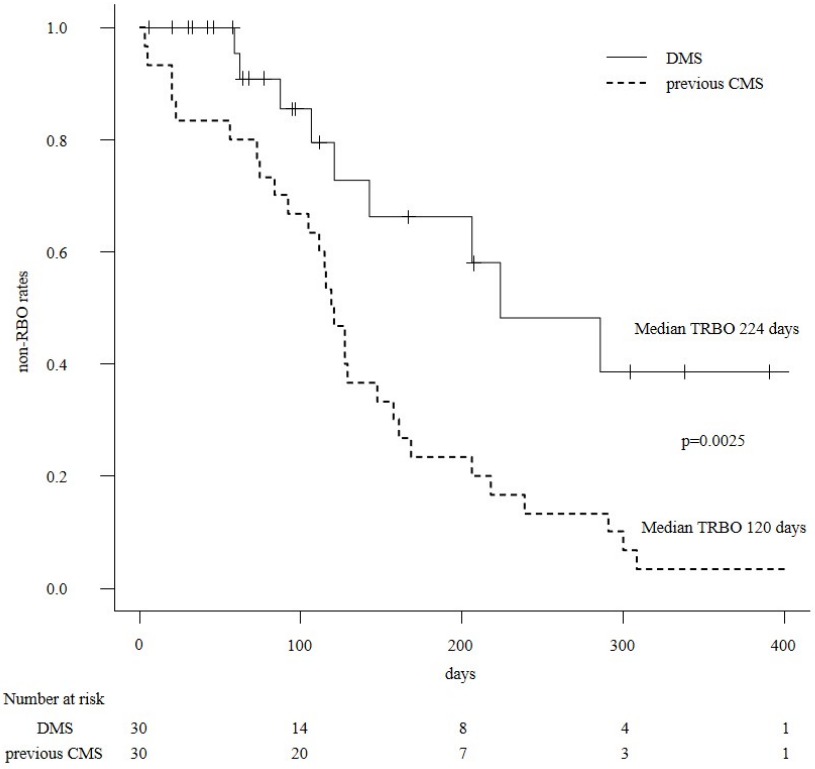
1.0
0.8
0.6
0.4
0.2
0.0
non-RBO rates
DMS
previous CMS
Median TRBO 224 days
p=0.0025
Median TRBO 120 days
0
100
200
300
400
days
Number at risk
DMS 30 14 8 4 1
previous CMS 30 20 7 3 1

Fig. 4

Table 1. Patient characteristics (n=30)

Age, years	64 (46-85)
Sex	
Male	17 (57%)
Female	13 (43%)
Performance status	
0	14 (47%)
1	12 (40%)
2	4 (13%)
Primary disease	
Pancreatic cancer	29 (97%)
Gastric cancer (metastatic lymph node)	1 (3%)
Distant metastasis	22 (73%)
Ascites	9 (30%)
Peritoneal dissemination	9 (30%)
Duodenal stenosis †	13 (43%)
Type I	9 (30%)
Type II	2 (7%)
Type III	2 (7%)
Indwelling duodenal stent	4 (13%)
Anti-cancer treatment before DMS placement	
Chemotherapy	27 (90%)
Best supportive care	3 (10%)
Number of previous CMS	
1	21 (70%)
2	8 (27%)
5	1 (3%)
Causes of previous CMS dysfunction	
Sludge formation	7 (23%)
Food impaction	4 (13%)
Symptomatic stent migration	11 (37%)
Asymptomatic stent migration	2 (7%)
Non-occlusion cholangitis	6 (20%)
Duration of DMS placement from primary cancer diagnosis, months	8.8 (1.2-38.7)

Continuous variables are expressed as median (range) and categorical variables are expressed as absolute numbers (proportions).

DMS, duckbill-type metal stent; CMS, covered metal stent.

† Duodenal stenosis was categorized according to the Mutignani classification.

Table 2. Clinical outcomes of DMS (n=30)

Technical success	30 (100%)
Functional success	30 (100%)
Duodenal stent placement before DMS placement	2 (7%)
Simultaneous placement of duodenal stent	2 (7%)
Stent length, cm	
6 / 8	21 (70%) / 9 (30%)
Procedure time, minutes	16 (6-69)
Early complications other than RBO	2 (7%)
Cholangitis	1 (3%)
Mild / moderate / severe	1 / 0 / 0
Pancreatitis	1 (3%)
Mild / moderate / severe	1 / 0 / 0
Late complications other than RBO	0
Follow-up period, days	167 (23-527)
RBO	9 (30%)
Causes of RBO	
Sludge formation †	4 (13%)
Hemobilia	1 (3%)
Symptomatic stent migration	3 (10%)
Non-occlusion cholangitis †	1 (3%)
Re-intervention for RBO	6 (20%)

Continuous variables are expressed as median (range) and categorical variables are expressed as absolute numbers (proportions).

DMS, duckbill-type metal stent; RBO, recurrent biliary obstruction.

† Anti-reflux valve was found collapsed in these 5 patients (completely 3, partially 2).

Table 3. Summary of previous reports of ARMS

Author	Year	Study design	Shape of valve	N	Rates of naïve case	RBO rates	Median TRBO (months)	Median OS (months)
Hu et al.[8]	2011	Retrospective, single-arm	Hemispheric-shaped	23	100%	26%	14	7.9
Lee et al.[9]	2013	Prospective, single-arm	S-shaped	32	100%	34%	14.4	8.8
Kim et al.[10]	2013	Prospective, single-arm	Wineglass-shaped	5	100%	80%	0.9	NA
Hu et al.[11]	2014	RCT	Nipple-shaped	56	100%	33%	13	8
Hamada et al.[12]	2014	Prospective, single-arm	Long funnel-shaped	13	0%	46%	NR	7.9
Hamada et al.[13]	2015	Prospective, single-arm	Long funnel-shaped	8	0%	50%	2.4	2.3
Lee et al.[14]	2016	RCT	Windsock-shaped	39	100%	18%	13.4	9.5
Hamada et al.[15]	2017	Retrospective, single-arm	Long funnel-shaped	20	100%	35%	8.1	5
Morita et al.[16]	2018	Retrospective, comparative	Long funnel-shaped	32	100%	48%	5.9	NA
Hamada et al.[17]	2019	RCT	Long funnel-shaped	52	100%	47%	8.3	14.1
Kin et al.[18]	2020	Retrospective, single-arm	Duckbill-shaped	30	47%	30%	8.6	4.4
Present study	2021	Retrospective, comparative	Duckbill-shaped	30	0%	30%	7.4	10

ARMS, anti-reflux metal stent; N, number; RBO, recurrent biliary obstruction; TRBO, time to recurrent biliary obstruction; OS, overall survival; RCT, randomized controlled trial; NR, not reached; NA, not available.