Accepted Manuscript

Submission Date: 2024-08-17
Accepted Date: 2024-11-19
Accepted Manuscript online: 2024-12-16

Endoscopy International Open

Assessment of Safety and Patency of 7-mm Covered Metal Stents for Preoperative Biliary Drainage in Pancreatic Cancer: A Prospective Multicenter Study

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DOI: 10.1055/a-2503-1995

Please cite this article as: Ishiwatari H, Kobayashi Y, Kawaguchi S et al. Assessment of Safety and Patency of 7-mm Covered Metal Stents for Preoperative Biliary Drainage in Pancreatic Cancer: A Prospective Multicenter Study. Endoscopy International Open 2024. doi: 10.1055/a-2503-1995

Conflict of Interest: The authors declare that they have no conflict of interest.

This study was supported by Century Medical Corporation, Clinical Research Support Agreement

Trial registration: jRCTs042200064, Japan Primary Registries Network (http://rctportal.niph.go.jp), Prospective, multicenter, single-arm study

Abstract:
Background and Aim: For preoperative biliary drainage of pancreatic cancer (PC), a 10-mm diameter metal stent (MS) is commonly used; however, the rate of pancreatitis is high. It is hypothesized that smaller-diameter MS may reduce the rate of pancreatitis. Therefore, we conducted a multicenter prospective study to evaluate the efficacy and safety of 7-mm MS.
Methods: Patients requiring initial biliary drainage for obstructive jaundice caused by PC and scheduled for surgery from six facilities were included. After endoscopic retrograde cholangiography, a 7-mm MS was placed at the site of biliary obstruction. The primary endpoint was the rate of pancreatitis, and the secondary endpoints included early and late adverse events (AEs). The pancreatitis rate was assumed to be 18% and 5% with 10- and 7-mm MS, respectively; with a power of 80% and one-sided significance level of 10%, the planned enrollment was 38 patients. If pancreatitis occurred in no more than three patients, this indicates that the 7-mm MS effectively reduced the incidence of pancreatitis.
Results: Overall, 38 patients were enrolled, and 35 patients in whom a 7-mm MS was successfully placed were analyzed. All MS were placed after sphincterotomy. Pancreatitis occurred in four patients (11.4%), and no early AEs were observed. Surgery was performed in 24 patients, and late AEs included stent occlusion in 8 (23%) and cholecystitis in 4 (11%).
Conclusions: The 7-mm MS did not reduce the incidence of pancreatitis among surgical candidates for PC.

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Original article

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INTRODUCTION

Pancreatic cancer (PC) is the most common cause of malignant distal biliary obstruction (MDBO) and can lead to cholangitis and jaundice. PC was the ninth most common cancer diagnosed in 2019, yet ranked fifth in cancer-related mortality, highlighting its poor prognosis [1]. The incidence of PC has increased over the last 30 years [1], with the only curative treatment being surgery. Pancreatic head cancer typically requires pancreaticoduodenectomy. The primary objective of preoperative biliary drainage (PBD) is to enhance perioperative safety. When early surgery is feasible, guidelines do not recommend routine PBD, even in patients with MDBO with jaundice, because it increases the risk of adverse events (AEs) [2,3]. Although the usefulness of neoadjuvant therapy (NAT) remains controversial, its effectiveness has been increasingly demonstrated in several studies, with the Japan Pancreas Society recommending NAT [4–6]. When NAT is implemented, the waiting period for surgery is prolonged, increasing the need for PBD.

The standard method for PBD involves placing a stent across the MDBO following endoscopic retrograde cholangiopancreatography (ERCP) [3,7,8]. Although plastic stents (PS) and metallic stents (MS) are available, MS is recommended because of its low rate of AEs [4,9]. In contrast, higher rates of recurrent biliary obstruction (RBO) and re-intervention impair PS [10]. Another major concern is pancreatitis after ERCP, which can be fatal and cause delays in surgery and cancellation of NAT [11]. The majority of studies comparing PS and MS for PBD reported higher incidence rates of

pancreatitis following MS placement, and a significant difference in diameter was observed between the two stents (10-mm MS vs. 10 Fr PS) [10,12,13]. Based on these data, with respect to stent diameter, there exists a potential trade-off between the risk of pancreatitis and stent occlusion. Although a randomized controlled trial (RCT) comparing the diameter of 8- and 10-mm MS did not reveal a reduction in the pancreatitis rate after placement of the 8-mm MS, the study enrolled patients with unresectable MDBO [14]. In PBD, due to the typically smaller tumor size, the pancreatic duct remains intact in numerous patients, and this cohort may differ from those with unresectable PC. Considering the balance between the risk of pancreatitis and stent obstruction, we hypothesized that MS with a 7 mm diameter would be a potential candidate stent that could potentially reduce the incidence of pancreatitis. This prospective study aimed to investigate the efficacy and safety of MS with a diameter of 7 mm for treating PBD in patients with PC.

METHODS

Study design

This prospective multicenter study was conducted at six tertiary referral centers. This study was approved by the institutional review board of each participating center. Written informed consent was obtained from all patients for ERCP and study enrollment. This study was registered in the Japan Registry of Clinical Registry (Registration No. jRCTs042200064) and was conducted in accordance with the principles of the Declaration of Helsinki (as revised in

2013), the Clinical Research Act, the Enforcement Regulations for the Clinical Research Act, and related notices from the Japanese government.

Patient eligibility

Participants were patients with PC who were scheduled to undergo curative surgery and who met the following inclusion criteria: resectable or borderline resectable PC accompanied by MDBO on computed tomography, judged after discussion with gastroenterologists and surgeons at each participating institution [15,16]; Need for PBD due to cholangitis or jaundice; ≥20 years old; and performance status of 0–1. Patients who met any of the following criteria were excluded: distance from the hilar part of the bile duct to the biliary obstruction ≤2 cm; history of endoscopic biliary drainage; duodenal obstruction around or on the anal side of the major duodenal papilla; active pancreatitis; inability to discontinue the use of antithrombotic drugs; surgically altered gastroduodenal and biliary anatomy, except those who underwent Billroth I reconstruction; or refusal to participate in the study.

MS with a diameter of 7 mm

A fully covered Niti-S S-type biliary stent with a 7 mm diameter (Taewoong Corporation, Seoul, South Korea) was used. The stent was made of nitinol and featured a braided structure with a diameter of 7 mm and a length of 60/80 mm. Figure 1 shows a 7-mm stent alongside a 10-mm stent for reference. The cross-sectional area of the 7-mm stent was reduced by 49%

compared to that of the 10-mm stent. The outer diameter of the delivery sheath was 8.5 Fr.

Protocol treatment

ERCP was performed on an inpatient basis by expert endoscopists with experience in performing >400 ERCP procedures. After biliary cannulation, the length of the biliary stricture was confirmed using cholangiography, followed by sphincterotomy. Then, a 7-mm MS was placed across the biliary stricture and the major duodenal papilla. ERCP was terminated after confirmation of bile outflow and air cholangiographic findings. Forceps biopsy and brush cytology for pancreatic strictures were not permitted but were performed for biliary strictures at the endoscopist's discretion. The use of a prophylactic pancreatic stent was allowed if deemed necessary by the endoscopist, but it was not utilized in any of the patients. Diclofenac was administered without any contraindications to prevent pancreatitis. Other drugs, such as ulinastatin and nafamostat mesylate, were used according to the institutional protocol.

Follow-up after ERCP

Assessment of AE after placement of the 7-mm MS was based on the TOKYO Criteria 2014 [17]. Blood tests and examinations were conducted by the participating physicians to evaluate the presence of AEs. The participants started oral feeding if there were no AEs on the day after ERCP. Subsequently, follow-up was continued for 6 months, and examinations and blood tests were performed at 1, 2, 4, and 6 months after ERCP. When surgery was performed within six months, follow-up observation was terminated at the time of surgery. If stent occlusion was

suspected (e.g., fever or jaundice), participants were encouraged to seek medical advice, and clinical evaluation, blood tests, and radiographic imaging were performed. If the liver enzyme levels were elevated and bile duct dilation was observed on imaging, stent occlusion was suspected, and ERCP was performed. When stent occlusion was confirmed on cholangiography, it was defined as RBO, with the date of ERCP being the date of RBO. If stent occlusion was not confirmed on cholangiography, it was classified as non-occlusion cholangitis. RBO treatment was performed at the endoscopist's discretion. Additionally, whether curative surgery or chemotherapy was administered was recorded. Pathological findings of the surgical specimens were documented in the surgical cases.

Statistical analysis

Our hypothesis was that using the 7-mm MS would result in a lower incidence of pancreatitis than using the 10-mm MS; assuming that the incidence of pancreatitis with the 10-mm MS was 18%, this would decrease to 5% with the 7-mm MS [10]. We calculated the minimum number of patients (36) required to achieve a one-sided significance level of 10% and power of >80%, acknowledging that this significance level was chosen for an exploratory study [18]. The planned number of registrations was set at 38 patients within 2 years to account for ineligibility after registration and other unforeseen circumstances. The primary endpoint was the rate of pancreatitis after placement of the 7-mm MS. For patients in whom the protocol treatment was performed, the rate of pancreatitis was calculated by

dividing the number of patients who developed pancreatitis by the total number of patients. If pancreatitis occurred in no more than three of the 38 patients, the incidence of pancreatitis was considered to have decreased [18]. The secondary endpoints included early (within 28 days) and late (after 28 days) AE rates. Furthermore, the factors affecting the occurrence of pancreatitis were investigated. All data were collected using a web-based electronic data capture system and managed by an independent data center. We used R version 4.3.2 for statistical analyses (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patients' characteristics and data related to ERCP

Overall, 38 patients were enrolled in this study between December 2020 and March 2022. Each patient was followed for up to 6 months post-ERCP, with follow-up examinations and blood tests at specified intervals, until the final participant was observed on 2 August 2022. If surgery occurred within this period, follow-up concluded at the time of surgery. Although ERCP was attempted in 38 patients, stent placement was unsuccessful in two patients due to duodenal obstruction and in one patient due to failed biliary cannulation. Patient characteristics are shown in Table 1. The treatment protocol was followed for 35 patients (Figure 2). The median tumor diameter and maximum diameter of the main pancreatic duct were 26 and 5 mm, respectively. Tumor invasion of the duodenum and major duodenal papilla was observed in 31.4% and 5.7% of the patients, respectively (Table 2). After biliary cannulation, sphincterotomy was performed, and a 7-mm MS was placed across the MDBO and duodenal major papilla in all patients. Unintentional injection of contrast medium or insertion of a guidewire into the pancreatic duct occurred in 48.6% of the patients.

Diclofenac was not administered to one patient because of low blood pressure. Except for the drugs in Table 2, other methods were not utilized to prevent pancreatitis.

AEs within 28 days

AEs are summarized in Table 3. Acute pancreatitis occurred in four patients, all of whom were mild. The rate of pancreatitis was 11.4% (4/35) (80% confidence interval: 5.1-21.6, 95% confidence interval: 3.2-26.7). No other AEs were reported.

AEs after 28 days

Surgery was performed in 24 patients, and the median waiting period until surgery was 88 days (Table 4). NAT was administered to 20 patients. Surgery was not performed in 11 patients, and chemotherapy was administered in 4 of these patients. Adenocarcinoma was confirmed in all patients based on the pathological findings from surgical or biopsy specimens. Overall, late AEs occurred in 12 patients (34.2%): RBO in 8 and cholecystitis in 4. Stent dislocation without cholangitis occurred in four patients (11.4%).

Factors related to post-ERCP pancreatitis

We analyzed univariate factors related to pancreatitis (Table 5). The factors included age, sex, tumor size, main pancreatic duct diameter, gallbladder stones, cholangitis, procedural time, tumor invasion into the major duodenal papilla, insertion of a contrast agent or guidewire into the pancreatic duct, and stent length. None of these factors were associated with pancreatitis. Additionally, no difference was observed in the diameter

of the main pancreatic duct between patients with and without pancreatitis (5.5 mm vs. 5 mm, respectively).

DISCUSSION

In this multicenter prospective study, we evaluated the efficacy and safety of 7-mm MS as a PBD for patients with PC. The rate of pancreatitis was 11.4%, and late AEs occurred in 34.2% of the patients (RBO, 22.9%; cholecystitis, 11.4%).

For PBD, pancreatitis rates were reportedly 11.6%–18% and 0%–7% for 10-mm MS and 10-Fr PS, respectively [10,12,13]. Similar rates were demonstrated in previous studies on patients with unresectable cancer, indicating that the pancreatitis rate after MS placement was higher than that after PS placement [19]. Based on these data, a reduction in pancreatitis rates with slimmer MS appears plausible. In our study, the minimum required sample size was 36 patients, according to the sample size calculation. Although the final analysis included 35 patients, we believe that the occurrence of pancreatitis in 4 cases would not have been substantially impacted by a slightly larger sample size. In contrast, a recent prospective study evaluating 6-mm MS for PBD showed a pancreatitis rate of 3.1% [20]. This result supports the possibility of using slimmer MS; however, the results of the present study did not support this. These conflicting results may stem from differences in patient backgrounds and the configuration and characteristics of MS. Surgical candidates for PC are more likely to have an intact main pancreatic duct, which can increase the rate of pancreatitis. Variations in the proportion of

these patients may have contributed to this difference. Regarding the configuration and characteristics of the MS, the 1-mm difference in stent diameter between our study and the previous study might not account for the difference in pancreatitis rates. Furthermore, two forces act on the MS: the radial force, which refers to the power to expand the stent radially, and the axial force (AF), which refers to the power to return to a straight position after bending [21]. A retrospective study showed that a higher AF could increase the pancreatitis rate after MS placement [22]. We did not examine the AF of our stent; however, the differences in AF may have affected our results.

A major concern regarding slimmer MS is that it may increase the incidence of RBO. Previous studies on PBD revealed a higher RBO or re-intervention rate for PS (23.2%–30%) than for 10-mm MS (3.1%–14%) [10,12,13]. As RBO occurs over time, a longer waiting period until surgery becomes disadvantageous for patients with PS. In an RCT by Song et al. with a waiting period of approximately 13 days, no significant difference was observed in the AE rate until surgery [12]. Conversely, in studies with a waiting period of 3–5 weeks, a difference was observed, and the outcome for PS worsened [10,13]. Additionally, studies comparing PS and 10-mm MS for PBD in patients who underwent NAT have demonstrated better outcomes for MS [23,24]. In our study, the median waiting period until surgery was 88 days, and RBO requiring re-intervention occurred in 4 of 24 patients (17%). In a study that evaluated the 6-mm MS, the waiting period was 96 days, and 25% of patients required re-intervention for stent-related AEs [20]. As these results were similar to or slightly better than the outcomes of PS, it is

inevitable that a slimmer MS carries an increased risk of RBO until surgery compared with the 10-mm MS.

What is the ideal stent for PBD in patients undergoing NAT? As discussed above, there remains a tradeoff between the occurrence of pancreatitis and RBO in terms of stent diameter [25]. As re-intervention is more likely with a decreased stent diameter, a 10-mm diameter stent seems more necessary when implementing NAT. Therefore, a 10-mm diameter MS with a weak AF might be optimal. In addition, stent dislocation due to tumor shrinkage caused by NAT should be considered. In our study, stent dislocation occurred in four patients; however, it did not result in cholangitis, and re-intervention was not required. This finding suggests that stent dislocation does not always result in adverse outcomes. However, cholangitis due to stent dislocation and perforation due to dislocated stents are concerning, indicating that a stent configuration that prevents migration is ideal. Considering the risk of stent dislocation, biodegradable stents may be potential candidates, although this remains speculative [26].

This study had several limitations. First, this was a single-arm study. A comparative trial with a 10-mm MS with the same stent characteristics would be desirable. However, this study was designed to calculate the sample size based on a comparison with the pancreatitis rate of historical controls and to determine whether to proceed with a comparative trial. As the 7-mm MS did not show a significant reduction in the pancreatitis rate, there was no basis to proceed with an RCT. Second, we did not evaluate the presence of pancreatic duct obstruction. Obstruction of the pancreatic duct can affect the incidence of pancreatitis after MS placement. However, strict evaluation of pancreatic duct obstruction requires MRCP or ERCP, which is challenging for all participants. Previous prospective studies on PBD have not evaluated this aspect [10,12,13,20,21]. In this study, the maximum pancreatic duct diameter was used as an alternative. There was no difference in pancreatic duct diameter based on the presence of

pancreatitis; however, given that preoperative PC cases are more likely to have intact pancreatic ducts, this could affect the pancreatitis rate. Further studies are needed to verify this hypothesis. Third, this study might have overstated the severity of mild AEs. Mild pancreatitis is unlikely to have a significant effect on clinical outcomes. Therefore, our study may not have properly evaluated the effects of significant AEs. Although this method is commonly used to evaluate AEs after ERCP and has been used in many studies, it may require reconsideration for PBD assessment [10,12,13,23,24]. Fourth, the AF of MS might have influenced the pancreatitis rate, and different results might have been obtained with 7-mm MS with other characteristics. Fifth, we did not evaluate the impact of the 7-mm MS on surgery; this study primarily aimed to evaluate stents. Previous studies on PBD have not reported a significant increase in the incidence of postsurgical AEs. If an RCT using this stent is conducted in the future, its surgical impact should also be evaluated. Sixth, the use of prophylactic drugs, such as diclofenac, may have reduced the incidence of pancreatitis in our study. However, as the use of diclofenac is mandated by guidelines for preventing post-ERCP pancreatitis, we had no option but to include it. This factor should be considered when comparing our results to studies that did not use preventative medication, as it may have impacted the pancreatitis rate. Finally, we analyzed factors related to pancreatitis; however, due to the small number of pancreatitis cases, the results should be interpreted with caution. To address this limitation, we used a non-parametric exact method, suitable for small sample sizes, but the findings remain exploratory in nature.

CONCLUSION

We evaluated the pancreatitis rate of a 7-mm MS for PBD in patients with PC using the performance of a 10-mm MS as a historical control. We concluded that the 7-mm MS did not reduce the pancreatitis rate.

Conflict of interests: None

Data availability statement: The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

Funding statement: This work was funded by Century Medical Corporation.

Ethics approval statement: This study was approved by the institutional review board of each participating center. This study was registered in the Japan Registry of Clinical Registry (Registration No. jRCTs042200064).

Patient consent statement: Written informed consent was obtained from all patients for ERCP and study enrollment.

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Tables

Table 1. Patient characteristics

No. of patients	38
Age, years, median (range)	74.5 (41–82)
Male sex, n (%)	24 (63.1)
PS (ECOG), 0/1, n	25/13
UICC Stage, IA/IB/IIA/IIB/III	2/3/26/6/1
Maximum tumor size, mm (range)	26 (13–40)
Maximum pancreatic duct diameter, mm (range)	5 (1–15)
Gall bladder stone, n (%)	4 (10.5)
History of cholecystectomy, n (%)	2 (5.3)
History of gastrectomy with Billroth I reconstruction, n (%)	0 (0)
Acute cholangitis, n (%)	2 (5.3)
Grade, mild/moderate/severe	1/0/1

PS, performance status; UICC, Union for International Cancer Control

Table 2. Data related to ERCP

No. of patients	35
Cannulation time, sec, median (range)	210 (5–2,340)
Procedure time, sec, median (range)	886 (361–3,540)
Duodenal invasion, n (%)	11 (31.4)
Tumor involvement of the duodenal major papilla, n (%)	2 (5.7)
Biliary cannulation method when difficult cannulation	
Double guidewire method n, n (%)	2 (5.7)
Precut, n (%)	1 (2.9)
Transpancreatic biliary sphincterotomy, n (%)	1 (2.9)
Rendezvous via PTBD, n (%)	0 (0)
Guidewire insertion or contrast injection into the PD, n (%)	17 (48.6)
Sphincterotomy, n (%)	35 (100)
Tumor involvement of the cystic duct, n (%)	2 (5.7)
Successful placement of 7-mm MS, n (%)	35 (100)
Length of stent, 60/80 mm	10/25
Drugs for prevention of post-ERCP pancreatitis	
Diclofenac	34 (97.1)
Ulinastatin	27 (77.1)
Nafamostat Mesilate	4 (11.4)

ERCP, endoscopic retrograde cholangiopancreatography; PTBD, percutaneous transhepatic biliary drainage; PD, pancreatic duct; MS, metallic stent

Table 3. Adverse events

Early (within 1 month), n (%)	4 (11.4)
Acute pancreatitis, n (%), (95%CI)	4 (11.4), (3.2–26.7)
Mild/moderate/severe	4/0/0
Non-occlusion cholangitis	0
Cholecystitis	0
Bleeding	0
Perforation	0
Others	0
Late (after 1 month until surgery or 6 months), n (%)	12 (34.2)
RBO, n (%), (95%CI)	8 (22.9), (10.4–40.1)
Non-occlusion cholangitis	0
Cholecystitis	4
Mild/moderate/severe	2/2/0

RBO, recurrent biliary obstruction

Table 4. Data of patients who underwent surgery

Number of patients who underwent surgery, n (%)	24 (68.6)
Number of days between surgery and ERCP, median (range)	88 (14–190)
Neoadjuvant chemotherapy	
No planned	3
Impossible to start	1
Partially completed	6
Completed in delay	3
Completed as planned	11
Pathological findings of surgical specimen	
Pancreatic ductal adenocarcinoma	24

ERCP, endoscopic retrograde cholangiopancreatography

Table 5 Factors related to post-ERCP pancreatitis (n=35)

	Post-ERCP Pancreatitis		
	Yes	No	*p*
Age, years (range)	73 (69–77)	74 (41–82)	1
Sex, male	75.0 (3/4)	61.3 (19/31)	1
PS, 0	100 (4/4)	61.2 (19/31)	0.28
Maximum tumor size, median, mm	24 (15–40)	26 (13–40)	0.90
Maximum pancreatic duct diameter, median, mm	5.5 (3–7)	5 (1–15)	0.90
Gall bladder stone, yes	0 (0/4)	12.9 (4/27)	1
Acute cholangitis	0 (0/4)	6.45 (2/31)	1
Cannulation time, sec (range)	330 (48–3,540)	210 (5–1,518)	0.70
Procedure time, sec (range)	855 (429–3,540)	886 (361–2,007)	0.94
Tumor involvement of the duodenal major papilla	25 (1/4)	2.29 (1/31)	0.22
GW insertion or contrast injection into the PD	25 (1/4)	51.6 (16/31)	0.60
Length of MS (60 mm)	50 (2/4)	25.8 (8/31)	0.56

ERCP, endoscopic retrograde cholangiopancreatography; PS, performance status; PD, pancreatic duct; GW, guidewire; MS, metallic stent

Figure legends

Figure 1: Comparison of 10- and 7-mm-diameter metal stents.

The diameter of the stent on the right is 7 mm, whereas that on the left side is 10 mm. The cross-sectional area of the 7-mm metal stent was 49% smaller than that of the 10-mm metal stent.

Figure 2: Flow diagram of the study