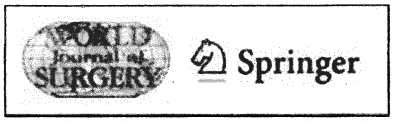

A Comparison between Plastic and Metallic Biliary Stent Placement in Patients Receiving Preoperative Neoadjuvant Chemoradiotherapy for Resectable Pancreatic cancer

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Keywords:	Pancreas, Biliary

Dear Editor:

Please find enclosed the revised version of our manuscript No. WJS-18-07-1284 entitled ***A comparison between plastic and metallic biliary stent placement in patients receiving neoadjuvant chemoradiotherapy for pancreatic cancer***. We sincerely thank the reviewers for their valuable comments and careful consideration of our manuscript. We have revised manuscript as suggested by the reviewers and addressed all the issues raised by the reviewers.

Specific responses to the reviewers are as follows:

Responses to Reviewer #1:

1. Thank you for your kind suggestion. We have included the data of tumor response to neoadjuvant treatment in Table 1, and revised the Methods and Results accordingly. (Page 7 lines 10-11, Page 8 line 17) There were no significant differences in tumor response between two groups. Regarding patient enrollment, we excluded 8 patients who were found to be inoperable at the time of surgery after neoadjuvant chemoradiotherapy (NACRT). We have revised the details in Material and Methods section. (Page 6, lines 4–12)

2. Regarding the relationship between the reintervention rate and bacterial contamination, we have no data in this cohort. However, there was no significant association between reintervention rate and incidence of postoperative infectious complications. Now we have included the data of surgical site infection (SSI) in Table 2.

3. Thank you for your valuable question. Although reintervention occurred more frequently in the PS group than that in MS group, there were no significant differences in the incidence of organ-space SSI and superficial wound infection between the groups. As we described above, we have revised the Materials and Methods and included the actual data in Table 2. (Page 7 line 17)

Responses to Reviewer #2:

1. Thank you for your valuable suggestion. We have added "resectable" to the title and text.

2. We agree. According to the reviewer's suggestion, we have revised the Abstract. (Page 3 lines 2–3)

3. Thank you for valuable comment. According to the reviewer's suggestion, we have revised the Abstract and Introduction. (Page 3 lines 3-5, Page 5 lines 26-28)

4. According to the reviewer's suggestion, we have revised the description throughout the manuscript.

5. We agree. We have revised the Methods in the Abstract. (Page 3 lines 6-10)

6. Thank you very much for the valuable comments. We have revised the conclusion in the Abstract. (Page 3 line 19–Page 4 line 2).

7. To emphasize the novelty of the study, we have revised the last paragraph in the Introduction. (Page 5 lines 19–28)

8. We have revised the Materials and Methods section, indicating that this is a retrospective study. (Page 6 line 1)

9. Thank you again for your comment. We have revised the Methods section to clarify the study design. (Page 6 lines 4–14) In this study, we analyzed only patients who received biliary stent before receiving NACRT. In fact, there was no patient who received biliary stent during NACRT in this study period.

10. As mentioned above, we analyzed only patients who received biliary stent before receiving NACRT. We have described this point in the Materials and Methods section. (Page 6 lines 4–5)

11. Thank you for your comment. According to the reviewer's instruction, we have moved these sentences to the Materials and Methods section. (Page 6 lines 11–14)

12. Thank you again for your valuable suggestion. We have added a new figure showing a representative case in the MS group. Accordingly, we have added the figures and revised the Materials and Methods section and figure legends. (Figure 1, Page 6 lines 14-15, Page 16 lines 2–7)

Responses to Reviewer #3:

1. We agree with the reviewer's criticism. This study was retrospective, and the number of enrolled patients was relatively small. Therefore, it is difficult to reach a definitive conclusion. However, there are few studies focused on stent method for biliary drainage before neoadjuvant chemoradiotherapy for resectable pancreatic cancer. We think that it is one unsolved question in daily clinical practice. Therefore, our data may provide some useful information.

2. We are sincerely sorry for confusion and insufficient explanation about the stent patency and reintervention rates. The stent patency for both groups was demonstrated using the Kaplan–Meier method in original Figure 1. To avoid misunderstanding, we deleted Table 2 and revised the Materials and Methods. (Page 7 line 12) Moreover, we described the details of reintervention in the Results. (Page 8 lines 22–26)

3. Thank you for your question. Our study included the delays in getting to surgery

that were due to both NACRT and stent related complications. Only one patient experienced interstitial pneumonia, and had delays in getting to surgery. The other patients had delays due to stent related complications. We have revised the Results. (Page 9 lines 2-3)

4. We thank the reviewer for raising this important point. The novelty about our study was that MS placement was associated with long patency and did not have an economic disadvantage even during the preoperative 3 months. Accordingly, we revised the Abstract and manuscript. (Page 3 line 19–Page 4 line 1, Page 10 line 22, Page 11 lines 6–9)

5. We also thank for the reviewer's comment. The efficacy was evaluated in terms of stent patency, various perioperative and postoperative outcomes as well as medical cost. The safety was evaluated regarding severe complications. We revised the Introduction and Methods section. (Page 5 lines 26–28)

6. Thank you again for your valuable comment. Although there were no significant differences between MS and PS, MS was superior to PS in stent patency and tended to be better in reintervention rate. Therefore, MS may be recommended for preoperative biliary placement in patients receiving preoperative NACRT for resectable pancreatic cancer. We revised the conclusion in the Abstract and manuscript. (Page 4 lines 1–2, Page 11 lines 9–10)

Thank you very much for your time and consideration. We look forward to your favorable reply.

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Title:

A Comparison between Plastic and Metallic Biliary Stent Placement in Patients Receiving Preoperative Neoadjuvant Chemoradiotherapy for Resectable Pancreatic cancer

Authors:

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Running head:

Biliary plastic stent for pancreatic cancer during NACRT

Keywords; Biliary stent, Neoadjuvant chemoradiotherapy, Pancreatic cancer

Disclosures

Authors Nakamura, Sho, Akahori, Nagai, Nishiwada, Nakagawa, Tanaka, Kichikawa, Tamamoto, Hasegawa, Mitoro, Yoshiji and Ikeda have no conflicts of interest or financial ties to disclose.

Words

Abstract 228 words

Text 2161 words

Abstract

Background: The optimal stent type in patients receiving preoperative neoadjuvant chemoradiotherapy (NACRT) is uncertain. The present study aimed to compare the clinical effectiveness of biliary metallic stent (MS) and plastic stent (PS) in patients undergoing preoperative NACRT for resectable pancreatic cancer.

Methods: This retrospective study included 43 patients who required either biliary MS or PS before initiating NACRT for resectable or borderline resectable pancreatic head cancer. Seventeen patients had MS (MS group), while 23 patients had PS (PS group). All patients received preoperative NACRT, including gemcitabine and concomitant 3-dimensional radiation of 54 Gy, and underwent pancreatectomy. Stent patency, surgery postponement, postoperative outcomes, and cost effectiveness were compared between these groups.

Results: There were no significant differences in baseline demographic or tumor characteristics between the groups. Stent patency was significantly longer in the MS group than in the PS group (P = 0.042). There were no differences in time to surgery, intraoperative characteristics, surgical complications, margin positivity, and pathological response between the groups. Furthermore, the medical cost of maintenance of biliary drainage during NACRT was similar between the groups.

Conclusions: MS placement compared to PS in patients receiving preoperative NACRT provided no significant benefits during the postoperative course of pancreatectomy. However, MS placement was associated with long stent patency while showing no

economic disadvantage. Therefore, MS placement may be recommended in patients receiving preoperative NACRT for resectable pancreatic cancer.

Introduction

Despite improvements in the diagnosis and treatment of pancreatic cancer, its prognosis remains extremely poor. Although surgery is the only option to potentially cure pancreatic cancer, most patients die from local and distant recurrence [1–3]. In recent years, neoadjuvant chemoradiotherapy (NACRT) has drawn attention for application in resectable and borderline resectable pancreatic cancer with a focus on improving prognosis [4–8].

Obstructive jaundice is the most common symptom in patients with pancreatic head cancer, and thus patients often require preoperative biliary drainage before NACRT. A recent report has suggested that routine preoperative biliary drainage might increase the rate of perioperative complications [9]. However, reduction of the serum total bilirubin level and maintenance of biliary drainage during the preoperative period are essential for patient safety during NACRT.

Placement of a metallic stent (MS) or plastic stent (PS) is the most common approach for achieving biliary drainage. The major advantages of a MS over a PS are its long patency and low occlusion rate, whereas the major disadvantage of a MS over a PS is its high cost. Several studies have shown that MS placement for unresectable malignancies is superior to PS placement with regard to both stent patency and avoidance of endoscopic reintervention [10–15] In contrast, studies comparing the safety and usefulness of a biliary MS with those of a biliary PS for preoperative biliary drainage during NACRT are limited [16–19]. A recent study demonstrated that MSs had economic advantages in neoadjuvant settings, which focused on treatments for a period of >5 months. However, PSs may be more advantageous in cost for shorter periods of NACRT. In fact, as far as we know, no study addressed the optimal stent type in patients undergoing preoperative NACRT with an identical protocol for a period of ≤ 3 months. The present study aimed to compare the clinical effectiveness including stent patency, perioperative and postoperative outcomes, and medical cost in patients who underwent preoperative NACRT for resectable pancreatic cancer.

Material and Methods

Patients

Data were identified retrospectively from our institutional database. We reviewed the data of patients who received preoperative NACRT for resectable or borderline resectable pancreatic head cancer between January 2008 and January 2017 at the Nara Medical University Hospital. A total of 54 patients who underwent biliary drainage for obstructive jaundice before NACRT were included in the study. All patients were evaluated for the absence of evidence of distant metastasis using multi-detector computed tomography before NACRT. Patients who were treated with an endoscopic nasobiliary drainage (ENBD) or percutaneous drainage at the beginning of NACRT (n = 3) and who were found to be inoperable at time of surgery with MS (n = 3) and PS (n = 5) were excluded from the study. Of these patients, three with MS and 1 with PS experienced disease progression. Therefore, we enrolled 43 patients in whom complete resection was performed after NACRT. Seventeen patients who received a biliary self-expandable MS before initiating NACRT were classified into a MS group, whereas 26 patients who received a biliary PS were classified into a PS group. The representative case in the MS group was shown in Figure 1. The ethics committee of the Nara Medical University approved the study.

Preoperative biliary drainage

The MSs were covered or uncovered self-expandable stents with a diameter of 8 or 10 mm, and all MSs were placed in our hospital. When primary drainage was performed with ENBD or percutaneous drainage, MS placement was performed using a two-step procedure. MS placement was decided by the clinician. The PSs ranged in diameter from 7 to 8.5 Fr, and were placed endoscopically in a single step.

Preoperative neoadjuvant chemoradiotherapy

The preoperative NACRT regimen included gemcitabine (GEM) and concomitant 3-dimensional radiation at 54 Gy, as previously reported [20, 21]. Systemic GEM (1000 mg/m^2) was administered weekly. Radiotherapy was delivered through four portal fields (anterior, posterior, right, and left) for a single course of 50 Gy in 25 fractions using a 10-megavoltage photon beam (Primus; Toshiba/Siemens, Otawara, Japan), or through 5–9 fields for a single course of 54 Gy in 27 fractions with the intensity-modulated radiation technique using a 6-megavoltage photon beam (Novalis Shaped Beam Surgery

System; BRAINLAB, Heinsteten, Germany). Surgery was performed within 3–5 weeks after the completion of preoperative NACRT.

Evaluation of outcomes

Data on patient demographics, preoperative treatments, surgical treatments, and postoperative outcomes were obtained through a standardized retrospective review of the electronic database of the Nara Medical University. Stage classification and resected specimen evaluation were performed according to the seventh edition of the AJCC/UICC TNM classification [22, 23]. Resectability was classified according to the NCCN guidelines, version 2. 2016. The radiological response was assessed by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1).

The evaluated outcomes in this study were the stent patency during NACRT and the period from the beginning of NACRT to surgery. Furthermore, intraoperative characteristics, postoperative complications, mortality, hospital stay, resection margins, and pathological response were assessed. R0 resection was defined as no microscopic or macroscopic tumor. Postoperative complications included pancreatic fistula formation, delayed gastric emptying, organ-space surgical site infection, superficial wound infection, postoperative hemorrhage, and total postoperative complications, according to the Clavien-Dindo classification (≥ Grade IIIa) [24]. Pancreatic fistula formation was defined according to the guidelines of the International Study Group of Pancreatic Fistula [25]. Postoperative hemorrhage was defined according to the guidelines of the International Study Group of Pancreatic Surgery [26]. Mortality was defined as death within 90 days after surgery. Pathological response was assessed according to Evans classification.

Economic cost of maintaining biliary drainage in preoperative NACRT

Cost analysis was performed to assess the economic impact of maintaining preoperative biliary drainage with a biliary stent. Charges were determined for the biliary stent and delivery system, endoscopic retrograde cholangiopancreatography (ERCP) with stent placement, stent exchange or cleaning, medications for ERCP, and hospital stay. Charges related to emergency admission for reintervention, including charges for ERCP with stent exchange or cleaning, emergency hospital stay, and

additional emergency procedures, were also estimated. These costs were estimated in US dollars (USD) according to data from the Nara Medical University in 2017. The additional cost for each of the stent placements was estimated according to data from the present study and according to the assumption that all MSs were placed endoscopically in a single-step procedure.

Statistical analysis

Continuous variables were compared using the Mann-Whitney *U*-test or the *t*-test, while categorical variables were compared using the chi-square test or Fisher's exact test. All statistical analyses were performed using JMP 13.0 statistical software (SAS Institute Inc., Cary, NC, USA). A P-value <0.05 was considered statistically significant.

Results

Patient characteristics

The patient characteristics are summarized in Table 1. There were no significant differences between the groups with regard to body mass index, prognostic nutrition index (PNI), CA19-9 level, total bilirubin level, tumor status, radiological response or surgical procedure.

Stent patency and reintervention

Stent patency was significantly longer in the MS group than it was in the PS group (P = 0.042; Fig. 2). Regarding the causes of reintervention, stent occlusion occurred in 3 patients in the MS group and 9 patients in the PS group, whereas stent migration occurred in 4 patients in the PS group. In the MS group, two patients experienced reintervention once, and one patient experienced reintervention twice. In contrast, in the PS group, 12 patients experienced reintervention once, and 1 patient experienced reintervention thrice. The number of reinterventions per patient was estimated to be 0.24 in the MS group and 0.57 in the PS group. With respect to the reintervention procedure, stent cleaning was performed in the MS group, while exchange for another PS was performed in the PS group.

Effects of biliary stenting on perioperative outcomes

The time to surgery was 72 days in the MS group and 79 days in the PS group, and there was no significant difference between the groups. Only one patient in the MS group had delayed surgery due to interstitial pneumonia. Additionally, there were no differences in intraoperative characteristics and surgical complications between the two groups (Table 2). There were no significant differences in the occurrence of organ-space SSI and superficial wound infection between the groups. Moreover, there was no difference in mortality between the two groups. The incidences of a margin-negative outcome were 88% in the MS group and 97% in the PS group. There were no significant differences in the resection margins between the groups. Moreover, there were also no differences in the final pathological responses according to Evans classification between the two groups.

Economic impact of maintaining biliary drainage

Table 3 shows the economic impact of main biliary stent placement with ERCP. The cost for planned initial placement of a MS was estimated to be 5,013 USD per patient. On the other hand, the cost for planned placement of a PS was estimated to be 3,308 USD per patient. Furthermore, the additional expense for reintervention and stent cleaning in the MS group was estimated to be 2,667 USD per patient. On the other hand, the additional expense for reintervention and emergency ERCP with stent exchange in the PS group was estimated to be 3,867 USD per patient. The estimated cost of maintenance of biliary drainage during NACRT was similar between the groups (MS group vs. PS group: 5,641 USD per patient vs. 5,539 USD per patient, $P = 0.889$).

Discussion

Although recent studies have shown that MS placement has a better patency duration and a lower incidence of reintervention compared to PS placement in patients with unresectable malignancies [10–15], the usefulness of MS during NACRT has not yet been adequately discussed. Several studies have reported that the reintervention rate for MS placement during NACRT ranges from 7% to 35%, while the rate for PS placement ranges from 45% to 93% [16–19, 27, 28]. All these studies have indicated

that reintervention during NACRT is generally less frequent with MS placement than it is with PS placement. Consistent with these findings of previous studies, our study indicated that patency is longer and reintervention during NACRT is less frequent with MS placement than it is with PS placement. However, in this study, MS placement showed no significant advantages with regard to the time of surgery. Furthermore, there was no difference with regard to the completion of NACRT between MS and PS placement. Thus, the difference in stent patency between MS and PS placement was not associated with postponement of surgery and did not influence the completion of neoadjuvant treatment.

With regard to the controversy of the adverse effects of preoperative biliary stenting on surgical complications, most studies reporting on the use of biliary stents to relieve jaundice included patients who underwent upfront surgery. A previous prospective randomized controlled trial demonstrated more frequent serious complications in patients who underwent preoperative biliary drainage with PSs than in those patients who underwent preoperative biliary drainage with MSs [29]. The increase in the overall complication rate was mainly associated with the high rate of biliary drainage-related complications and not surgery-related complications [29]. Studies on the association between biliary stent use and surgical complications in patients receiving NACRT are limited. We found that postoperative outcomes did not differ significantly between MS placement and PS placement. Our findings are consistent with the findings of a previous study by Kubota et al [18]. Although the rate of preoperative biliary stent-related complications was lower with MS placement than it was with PS placement, MS use during NACRT did not provide any benefits with regard to the postoperative course of pancreatectomy.

In the current study, MS use was not found to have a significant cost disadvantage in the cost effectiveness analysis. Although several studies have compared the cost effectiveness between MS and PS for biliary drainage during NACRT [17–19], the choice of biliary stent remains debatable. Economic issues should be considered in the use of MS, and MS placement should be reserved for patients who may actually benefit from the procedure, as the initial cost is high. Previous studies have shown that a MS has disadvantages with regard to palliation in patients with malignant strictures who survive for 3–6 months or less [30, 31]. Our results suggest that cost effectiveness is

equivalent between placement of MS and PS when patients receiving NACRT have an anticipated therapy duration of about 3 months.

The present study had several limitations. First, this study adopted a nonrandomized, retrospective design, and the number of patients was small. Moreover, this study was conducted at a single institution in Japan. A prospective randomized study should be performed to validate the results of this study. Moreover, further studies are necessary to determine efficient and well-tolerated approaches for biliary drainage during NACRT.

In conclusion, MS placement, compared to PS, in patients receiving preoperative NACRT, provided no significant benefits during the postoperative course of pancreatectomy. However, MS placement was associated with long stent patency while showing no economic disadvantage. Therefore, MS placement may be recommended in patients receiving preoperative NACRT for resectable pancreatic cancer.

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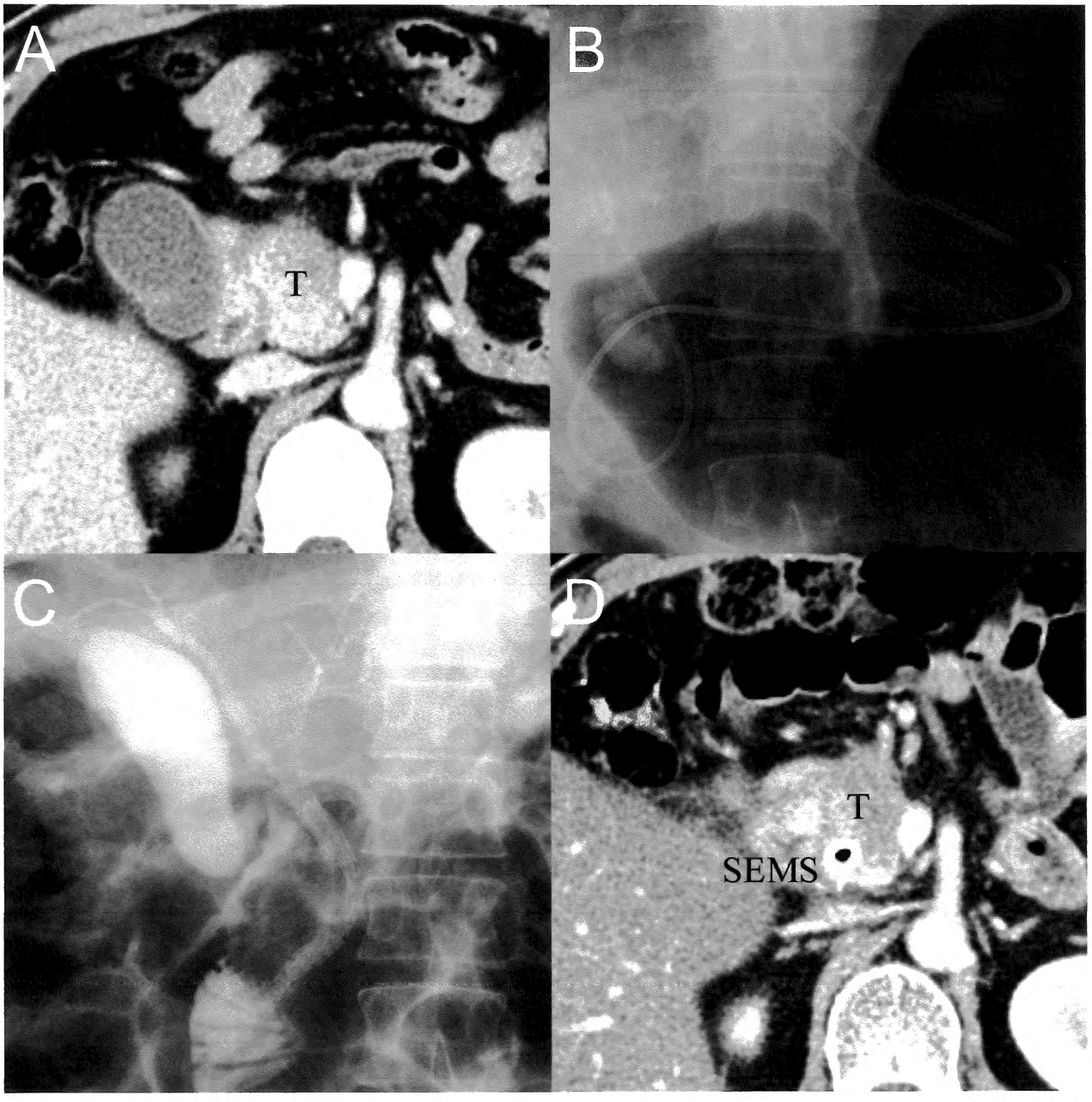
Figure legends

Figure 1. A representative case in the MS group. A; CT image showing a tumor abutting the portal vein. B; primary drainage with ENBD. C; Radiography showing patency and correct position of SEMS. D; CT image showing SEMS positioned across the biliary obstruction.

T tumor, *SEMS* self-expandable metallic stent. *MS* metallic stent. *ENBD* endoscopic nasobiliary drainage. *CT* Computed tomography.

Figure 2. Cumulative stent patency. Metallic stents (MS Group) were patent significantly longer than plastic stents (PS Group) ($P = 0.042$).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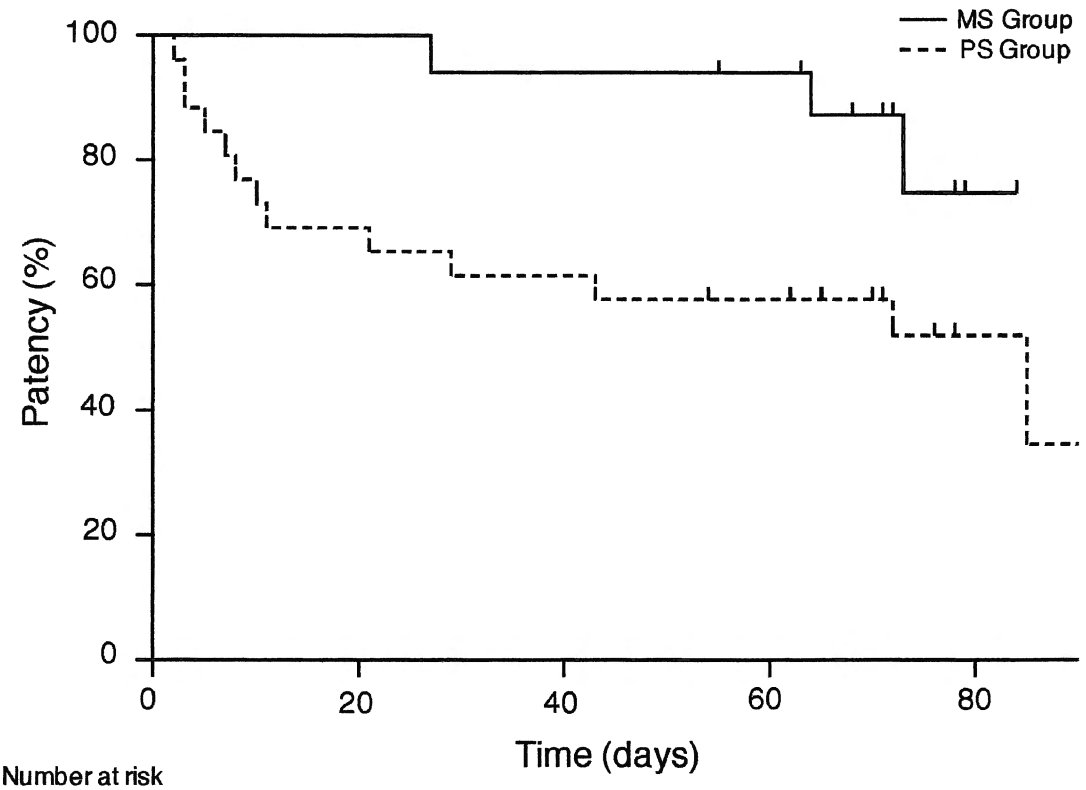

Number at risk					
MS	17	17	17	16	2
PS	26	19	17	14	6

Table 1 Patients characteristics

	MS Group (n=17)	PS group (n=26)	
Age (years, median, range)	70 (52-76)	61 (36-76)	0.106
Gender			
Male	12 (70.6%)	12 (46.2%)	0.133
Female	5 (29.4%)	14 (53.9%)	
BMI (kg/m^2, median, range)	20.4 (14.1-26.0)	21.4 (16.0-28.4)	0.559
PNI	39 (31-54)	41 (32-53)	0.363
CA19-9 (U/mL, median, range)	21 (10-872)	39 (1-789)	0.970
Total bilirubin level (mg/dL)	9.0 (1.4-34.6)	6.1 (1.3-22.0)	0.233
Resectability status			0.344
Resectable	8 (47.1%)	17 (65.4%)	
Borderline resectable	9 (52.9%)	9 (34.6%)	
pT (AGCC/UICC)			0.200
T1	2 (11.8%)	0 (0.0%)	
T2	1 (5.9%)	2 (7.7%)	
T3	14 (82.4%)	24 (92.3%)	
pN (AGCC/UICC)			0.296
N0	11 (64.7%)	21 (80.8%)	
N1	6 (35.3%)	5 (19.2%)	
pStage (AGCC/UICC)			0.354
IA	1 (5.9%)	0 (0.0%)	
IB	1 (5.9%)	2 (7.7%)	
IIA	9 (52.9%)	19 (73.1%)	
IIB	6 (35.3%)	5 (19.2%)	
Radiological response (RECIST 1.1)			0.138
Stable disease	11 (64.7%)	22 (84.6%)	
Partial response	6 (35.3%)	3 (11.5%)	
Complete response	0 (0.0%)	1 (3.9%)	
Procedure			1.000
Pancreatoduodenectomy	16 (94.1%)	25 (96.2%)	
Total pancreatectomy	1 (5.9%)	1 (3.9%)	

MS metallic stent, *PS* plastic stent, *BMI* body mass index, *PNI* prognostic nutrition index, *CA19-9* CAR antigen19-9, *NCCN* National Comprehensive Cancer Network, *AJCC* American Joint Committee on Cancer, *UICC* Union for International Cancer Control, *RECIST* Response Evaluation Criteria in Solid Tumors

Table 2 Perioperative outcomes

	MS Group (n=17)	PS group (n=26)	*P*
Period, NACRT-Surgery (days, median, range)	72 (55-107)	79 (54-115)	0.135
Completion of NACRT	17 (100.0%)	26 (100.0%)	1.000
Intraoperative characteristics			
Blood loss (mL, median, range)	522 (87-1100)	580 (20-6730)	0.260
Operative time (min, median, range)	307 (263-860)	328 (239-642)	0.911
Intraoperative transfusion	8 (47.1%)	11 (42.3%)	1.000
Postoperative complication			
Pancreatic fistula (ISGPF Grade B/C)	1 (5.9%)	2 (7.7%)	1.000
Delayed gastric emptying	0 (0.0%)	1 (3.9%)	1.000
Organ-space surgical site infection	2 (11.8%)	2 (7.7%)	1.000
Superficial wound infection	1 (5.9%)	2 (7.7%)	1.000
Hemorrhage	0 (0.0%)	1 (3.9%)	1.000
Any complication (≥CDIIIa)	4 (23.5%)	5 (19.2%)	1.000
Mortality	1 (5.9%)	0 (0.0%)	0.395
Hospital stay (days, median, range)	16 (9-42)	16 (9-160)	0.470
Resection margin			0.430
Free	15 (88.2%)	25 (96.2%)	
Microscopic residual	1 (5.9%)	1 (3.9%)	
Macroscopic residual	1 (5.9%)	0 (0.0%)	
Pathological response (Evans grade)			0.535
IIA	10 (58.8%)	13 (50.0%)	
IIB	5 (29.4%)	11 (42.3%)	
III	2 (11.8%)	1 (3.9%)	
Unclassifiable	0(0.0%)	1 (3.9%)	

MS metallic stent, *PS* plastic stent, *BMI* body mass index, *PNI* prognostic nutrition index, *CA19-9* CAR antigen19-9, *NCCN* National Comprehensive Cancer Network, *AJCC* American Joint Committee on Cancer, *UICC* Union for International Cancer Control

Table 3 Economic impact of maintaining biliary drainage during neoadjuvant chemoradiotherapy

	MS Group	PS group	
Initial biliary stent placement			
Biliary stent placement (USD)	5,013	3,308	
Number of patients	17	26	
Total (USD)	85,221	86,008	
Stent exchange or cleaning			
Additional expense of reintervention (USD)	2,667	3,867	
Number of reintervention (times)	4	15	
Total (USD)	10,668	58,005	0.889

MS metallic stent, *PS* plastic stent, *NACRT* neoadjuvant chemoradiotherapy