

Novel risk factors for recurrent biliary obstruction and pancreatitis after metallic stent placement in pancreatic cancer



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ABSTRACT

Background and study aims Self-expandable metallic stents (SEMS) are now widely used even for patients with borderline resectable (BR) pancreatic cancer (PC), as

neoadjuvant therapy has become common. Therefore, we conducted this study to evaluate safety of SEMS placement in the population including BR PC and to explore risk factors for recurrent biliary obstruction (RBO), pancreatitis, and cholecystitis.

Patients and methods We retrospectively investigated consecutive patients with PC who received initial SEMS between January 2015 and March 2019. We compared time to RBO (TRBO), causes of RBO, and stent-related adverse events (AEs) according to resectability status. Univariate and multivariate analyses were performed to explore risk factors for TRBO, pancreatitis, and cholecystitis.

Results A total of 135 patients were included (BR 31 and unresectable [UR] 104). Stent-related AEs occurred in 39 patients: pancreatitis 14 (mild/moderate/severe 1/6/7), cholecystitis 12, and non-occluding cholangitis 13. TRBO, causes of RBO, and stent-related AEs were not significantly different according to resectability status. Overall rate of RBO was higher in UR PC due to the longer follow-up period. Sharp common bile duct (CBD) angulation was an independent risk factor for short duration of TRBO. High pancreatic volume index and SEMS of high axial force were independent risk factors for pancreatitis, whereas tumor involvement to orifice of cystic duct was the only risk factor for cholecystitis.

Conclusions We demonstrated that SEMS can be safely deployed even in patients with BR PC. Sharp CBD angulation and high pancreatic volume index were identified as novel risk factors for RBO and pancreatitis, respectively, after SEMS placement.

Introduction

Pancreatic cancer (PC) is the third leading cause of cancer-related death in the United States [1] and the fourth in Japan [2]. Despite recent advances in chemotherapy and surgical techniques, the prognosis for PC remains dismal [3]. Surgical resection with negative margins is the only chance for cure, although approximately 80% of patients who undergo resection experi-

ence local or metastatic recurrence [4, 5]. Neoadjuvant chemoradiotherapy (NACRT) and chemotherapy (NAC) are accepted as new treatment strategies for borderline resectable (BR) PC due to improved margin negative resection rate and median overall survival [6–10]. Recently, neoadjuvant therapy is becoming a new trend even in resectable (R) PC [11, 12].

Malignant biliary obstruction (MBO) is a common clinical manifestation in patients with pancreatic head cancer. Endo-

scopic placement of a self-expandable metallic stent (SEMS) is the standard treatment for distal MBO in patients with unresectable (UR) PC due to the long stent patency compared to plastic stents [13, 14]. Even for patients with BR or R PC who have a prolonged time to surgery, preoperative biliary drainage is considered essential, and several studies have reported the efficacy of SEMS placement in this setting [15–20].

However, data regarding the safety of SEMS placement in BR PC are limited. In addition, there are no studies that have evaluated risk factors for recurrent biliary obstruction (RBO), pancreatitis, and cholecystitis in the population including BR PC. We consider that incidence of RBO and stent-related adverse events (AEs), such as pancreatitis and cholecystitis, differs in accordance with the resectability status of PC. First, we hypothesize that patients with BR PC tend to have a larger pancreas volume and preserved exocrine pancreas function compared to UR PC, and consequently have an increased risk for post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis. Second, we speculate that RBO might be influenced by the resectability status of PC, including factors such as the angulation of the common bile duct (CBD).

Therefore, we conducted this retrospective study to evaluate the safety of SEMS placement according to the resectability status of PC (BR vs UR). We also explored risk factors for RBO, pancreatitis, and cholecystitis after SEMS placement in the population, including both BR and UR PC. Furthermore, we included new parameters such as pancreas volume index and CBD angulation.

Patients and methods

Patients

We retrospectively analyzed consecutive patients with PC who underwent fully-covered SEMS (FCSEMS) placement for distal MBO at our institution between January 2015 and March 2019. Only patients who received initial transpapillary SEMS were included in this study. Excluded patients were as follows: (1) patients who received a SEMS above the papilla; (2) patients who received a duodenal stent across the papilla; (3) patients with surgically altered anatomy; and (4) patients who were lost to follow-up or died within 2 weeks due to cancer itself. Furthermore, patients with R PC were also excluded in this study because we didn't place a SEMS for those who were candidates for upfront surgery. Written informed consent of the procedure was obtained from all patients in accordance with the declaration of Helsinki. This study was approved by the ethics committee of our institution.

Diagnosis, definition and classification

Each patient underwent computed tomography (CT) for tumor staging. Resectability status was defined according to the National Comprehensive Cancer Network (NCCN) guideline [21]. Histological confirmation was obtained from every patient either by bile duct biopsy (or cytology), endoscopic ultrasound fine-needle aspiration, or liver biopsy.

CBD angulation was defined as the first angulation from the ampullary orifice along the course of CBD and was measured on

cholangiogram obtained in the prone position before the deployment of a SEMS [22] (► Fig. 1a). Pancreatic volume index was calculated as the sum of lengths of the normal pancreatic parenchyma measured at three sections as follows: the level of aorta, left adrenal gland, and left kidney (► Fig. 1b). Tumor involvement to orifice of cystic duct (OCD) was evaluated by the results of CT, magnetic resonance cholangiopancreatography, and endoscopic retrograde cholangiography. Tumor involvement to the pancreatic duct (PD) was defined as PD obstruction with upstream PD dilation.

The FCSEMS used in this study were as follows: HANAROS-TENT Biliary (M.I.Tech, Seoul, Korea), Evolution Biliary Controlled-Release Stent–Fully Covered (Cook Medical, Bloomington, USA), Niti-S SUPREMO-10 stent (TaeWoong Medical, Seoul, Korea), Niti-S ComVi Biliary Stent (TaeWoong Medical, Seoul, Korea). Evolution Biliary Controlled-Release Stent–Fully Covered was categorized as high axial force (AF) stent and the other three stents were categorized as low AF stents.

Endoscopic interventions

ERCP was performed using a therapeutic duodenoscope (JF260, TJF260; Olympus Medical Systems, Tokyo, Japan) under moderate sedation with intravenous pethidine and midazolam. We basically performed endoscopic sphincterotomy (EST) with a small to moderate-sized incision and inserted an endoscopic nasobiliary drainage (ENBD) tube in the first session because of reasons such as cholangitis and undetermined biliary stricture. After jaundice or cholangitis subsided, we then deployed a SEMS under fluoroscopic guidance in the second session.

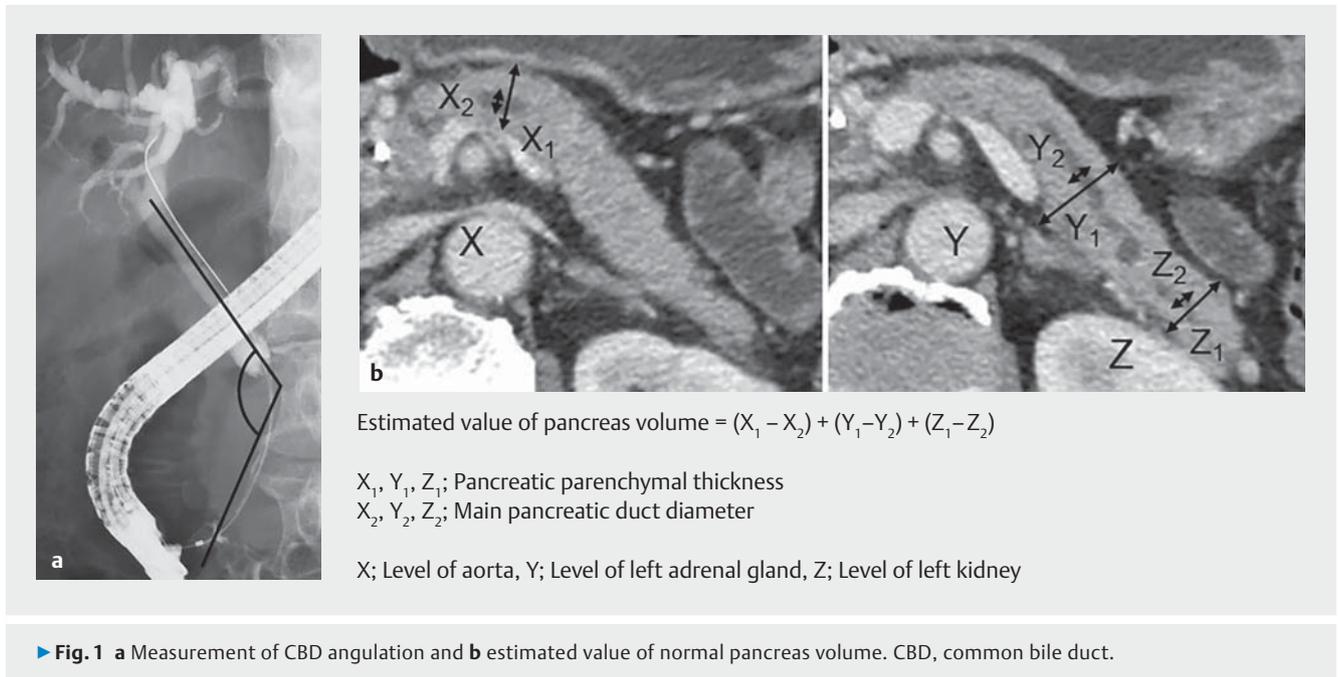
For patients with BR PC, in order to achieve a successful biliary anastomosis during pancreatoduodenectomy, we usually placed a SEMS at least 2 cm below the bifurcation of the hepatic duct. On the other hand, for patients with UR PC, we typically selected a long SEMS because of concern about stent-related AEs such as kinking.

Prophylactic rectal nonsteroidal anti-inflammatory drugs (NSAIDs) were used at the discretion of each endoscopist, and prophylactic pancreatic duct stent placement was not performed in any of the patients.

Chemotherapy

For patients with BR PC, we administered four cycles of gemcitabine plus nab-paclitaxel combination therapy (gemcitabine, 1000 mg/m², nab-paclitaxel, 125 mg/m², on days 1, 8, and 15 every 4 weeks). After four cycles of NAC were completed, a CT was performed for restaging and two experienced radiologists evaluated the degree of vascular involvement and radiologic response. The final decision to perform surgical exploration was determined by an expert panel consisting of medical oncologists, surgeons, and radiologists.

For patients with UR PC, we administered either of the following regimens considering the patient age, Eastern Cooperative Oncology Group performance status, and comorbidities: (1) gemcitabine plus nab-paclitaxel combination therapy; (2) modified FOLFIRINOX (oxaliplatin 85 mg/m², leucovorin, 400 mg/m², irinotecan, 150 mg/m², infusional 5-FU,



2400 mg/m², every 2 weeks); (3) gemcitabine monotherapy; or (4) S-1 monotherapy.

Evaluation

Evaluation of SEMS was defined according to Tokyo Criteria 2014 [23]. RBO was defined as a composite endpoint of either occlusion or migration, and time to RBO (TRBO) was defined as the time from stent placement to RBO. Patients who were lost to follow up, removed the stent, or died without RBO were treated as censored cases at the time of the last follow-up, stent removal, or death. 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 were graded according to the American Society of Gastrointestinal Endoscopy lexicon guidelines [24].

First, we compared TRBO, causes of RBO, and stent-related AEs according to the resectability status of PC. Second, we evaluated factors affecting TRBO using Cox proportional hazards model. Finally, we explored risk factors for pancreatitis and cholecystitis in the population including both BR and UR PC. Patients who had a history of cholecystectomy were excluded in the evaluation of cholecystitis.

Statistical analysis

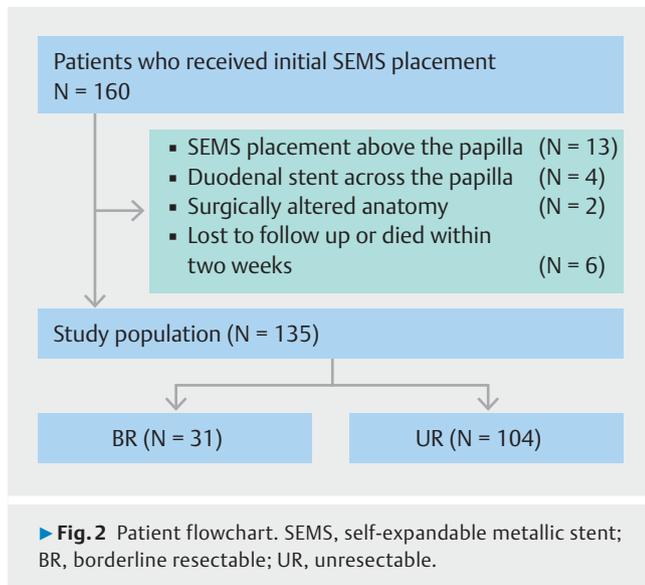
Continuous variables are presented as median (range), and were compared using Mann-Whitney U test or Kruskal-Wallis test as appropriate. Categorical variables are described as absolute numbers (proportions), and were analyzed using χ^2 test or Fisher's exact test as appropriate. TRBO was estimated using the Kaplan-Meier method and Kaplan-Meier curves were compared by the log-rank test. Multivariate analysis was conducted using the cox proportional hazards model to identify risk factors for TRBO. The following eight variables were assessed by

univariate analysis to identify risk factors for pancreatitis: resectability status (BR vs. UR), tumor involvement to PD (yes vs. no), pancreatic volume index (≥ 24 mm vs. < 24 mm), type of SEMS (high AF vs. low AF), length of SEMS (≤ 6 cm vs. > 6 cm), EST before SEMS placement (yes vs. no), contrast injection into PD (yes vs. no), prophylactic rectal NSAIDs use (yes vs. no). The following seven variables were investigated by univariate analysis to identify risk factors for cholecystitis: resectability status (BR vs. UR), tumor involvement to OCD (yes vs. no), CBD angulation (≤ 136 degrees vs. > 136 degrees), gallbladder stone (yes vs. no), type of SEMS (high AF vs. low AF), length of SEMS (≤ 6 cm vs. > 6 cm), OCD occlusion by SEMS (yes vs. no). Cutoff values for pancreatic volume index and CBD angulation were determined by the receiver operating characteristic curve. Factors with $P < 0.10$ were included in the multivariate analysis. Statistical tests were two-sided and $P < 0.05$ was considered statistically significant. Statistical analysis was carried out using the EZR software version 1.40 [25].

Results

Patient characteristics

A total of 160 consecutive patients with PC underwent initial transpapillary fully covered SEMS placement at our institution between January 2015 and March 2019. Twenty-five patients were excluded for reasons written above, and we analyzed the remaining 135 patients (► **Fig. 2**). Forty-four patients (33%) received SEMS in the first session, and the remaining 91 patients (67%) received SEMS in the second session with a median interval of 5 days. Comparison of patient characteristics according to resectability status is summarized in ► **Table 1**. Although patients with BR PC tended to have a smaller primary tumor size (32 mm vs. 37 mm, $P = 0.09$), pancreatic volume index (24 mm vs. 21 mm, $P = 0.39$) was not statistically different between the



two groups. Since the strategy of SEMS deployment was different, patients with BR PC had a higher likelihood of receiving a shorter SEMS ($P=0.02$) and had a lower probability of OCD occlusion by SEMS ($P<0.01$). Furthermore, patients with BR PC tended to have a higher degree of CBD angulation compared to patients with UR PC (140 degrees vs. 136 degrees, $P=0.06$). Rates of tumor involvement to OCD or PD, SEMS stent type, and contrast injection into PD were not statistically different between the two groups.

Comparison of TRBO, causes of RBO and stent related adverse events according to the resectability status

RBO occurred in 35% of the entire cohort. Median TRBO was not statistically different between the two groups (317 days vs. 301 days, $P=0.34$) (► **Fig. 3**). Causes of RBO according to the resectability status are shown in ► **Table 2**. Since BR PC patients without RBO get censored at the time of pancreatic resection (median follow up time from the date of SEMS placement to the date of pancreatic surgery or the date of the last follow up were 140 days for BR PC patients and 239 days for UR PC patients), overall rate of RBO was lower in BR PC patients (19% vs. 39%, $P=0.05$). Complete stent migration occurred in three patients only in UR PC at a median interval of 216 days (range, 175 to 642 days). Stent-related AEs occurred in 39 patients: pancreatitis 14 (mild 1, moderate 6, and severe 7), cholecystitis 12 (moderate 7 and severe 5), and non-occluding cholangitis 13 (► **Table 3**). Stent related adverse events other than RBO were not statistically different between the two groups (26% vs. 30%, $P=0.82$).

Risk factors for TRBO, pancreatitis, and cholecystitis

Univariate and multivariate analyses of risk factors for TRBO are summarized in ► **Table 4**. CBD angulation ≤ 130 degree (hazard ratio [HR], 2.48; 95% confidence interval [CI], 1.38 to 4.49; $P<0.01$) was an independent risk factor for shorter duration of TRBO.

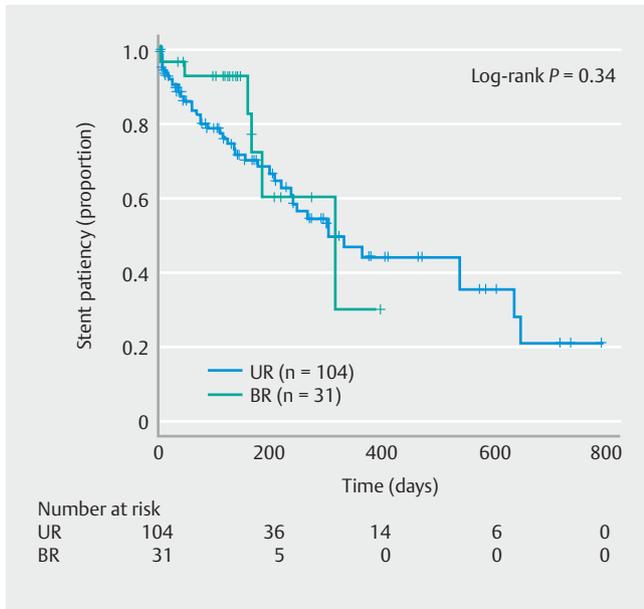
► **Table 1** Comparison of patient characteristics according to the resectability status ($n=135$).

	BR (n=31)	UR (n=104)	P value
Gender, male	14 (45%)	52 (50%)	0.69
Age, years	70 (36–78)	67 (22–87)	0.47
Primary tumor size, mm	32 (19–55)	37 (14–84)	0.09
Post-cholecystectomy	4 (13%)	8 (8%)	0.47
Gallbladder stone	1 (3%)	14 (13%)	0.19
Tumor involvement to OCD	3 (10%)	14 (13%)	0.76
Tumor involvement to PD	29 (94%)	93 (89%)	0.73
CBD angulation, degree	140 (116–158)	136 (104–166)	0.06
Pancreatic volume index, mm	24 (7–56)	21 (0–60)	0.39
SEMS, stent type, high AF	2 (6%)	19 (18%)	0.16
SEMS, stent diameter, 10 mm/8 mm	31/0	103/1	1.00
SEMS, stent length ≤ 6 cm	27 (87%)	68 (65%)	0.02
OCD occlusion by SEMS	17 (55%)	91 (88%)	<0.01
Contrast injection into PD	0 (0%)	2 (2%)	1.00
EST before SEMS placement	31 (100%)	103 (99%)	1.00
Prophylactic rectal NSAIDs	16 (52%)	47 (45%)	0.55
Presence of a duodenal stent	0 (0%)	5 (5%)	0.59
Chemotherapy	30 (97%)	87 (84%)	0.07
Pancreatic resection after chemotherapy	19 (61%)	2 (2%)	<0.01
Median follow up time from SEMS placement to pancreatic resection or the last follow up	140 (44–482)	239 (18–1150)	<0.05

Continuous variables are expressed as median (range) and categorical variables are expressed as absolute numbers (proportions). BR, borderline resectable; UR, unresectable; OCD, orifice of cystic duct; PD, pancreatic duct; CBD, common bile duct; AF, axial force; EST, endoscopic sphincterotomy; NSAIDs, nonsteroidal anti-inflammatory drugs.

Univariate and multivariate analyses of risk factors for pancreatitis are shown in ► **Table 5**. Pancreatic volume index (odds ratio [OR], 5.12; 95% CI, 1.30 to 20.2; $P=0.02$) and SEMS of high AF (OR, 4.50; 95% CI, 1.24 to 16.4; $P=0.02$) were independent risk factors for pancreatitis. Conversely, the resectability status was not an independent risk factor for pancreatitis.

Univariate and multivariate analyses of risk factors for cholecystitis in 123 patients (excluding patients who had a history of cholecystectomy from the whole population) are shown in



► **Fig. 3** Kaplan-Meier curves of time to recurrent biliary obstruction according to resectability status. BR, borderline resectable; UR, unresectable.

► **Table 6.** Only tumor involvement to OCD (OR, 38.6; 95% CI, 8.69 to 172; $P < 0.01$) was an independent risk factor for cholecystitis.

Discussion

This retrospective study evaluated the safety of SEMs placement for PC according to the resectability status of the primary tumor. Our results showed that TRBO, causes of RBO and stent related adverse events were not significantly different depending on the resectability status (BR vs UR). We also clarified risk factors for RBO, pancreatitis, and cholecystitis in the population including both BR and UR PC. We demonstrated that sharp CBD angulation (CBD angulation ≤ 130 degree [HR, 2.48; $P < 0.01$]) was an independent risk factor for shorter duration of TRBO. Moreover, we showed that high pancreatic volume index (pancreatic volume index ≥ 24 mm [OR, 5.12; $P = 0.02$]) and SEMs of high AF (OR, 4.50; $P = 0.02$) were independent risk factors for pancreatitis, whereas tumor involvement to OCD (OR, 38.6; $P < 0.01$) was the only independent risk factor for cholecystitis. The novelty of this study is as follows. First, we investigated the safety of SEMs placement according to the resectability status in the population including both BR and UR PC. Second, we included pancreatic volume index and CBD angulation in the evaluation of risk factors for RBO, pancreatitis, and cholecystitis. To the best of our knowledge, this is the first study to demonstrate that sharp CBD angulation and high pancreatic volume index were independent risk factors for RBO and pancreatitis, respectively, after SEMs placement in PC patients.

RBO occurred in 35% of patients (47/135) after SEMs placement in our study. However, little is known about risk factors for RBO, especially in distal MBO [26]. Our study is important

► **Table 2** Comparison of causes of RBO according to the resectability status (n = 135).

Causes of RBO	BR (n = 31)	UR (n = 104)	P value
Occlusion	3 (10%)	20 (19%)	0.28
▪ Biliary sludge	1 (3%)	9 (9%)	
▪ Food impaction	1 (3%)	9 (9%)	
▪ Tumor ingrowth	0 (0%)	2 (2%)	
▪ Tumor overgrowth	1 (3%)	0 (0%)	
Kinking	1 (3%)	2 (2%)	0.55
Migration	2 (6%)	19 (18%)	0.16
▪ Inward migration	0 (0%)	5 (5%)	
▪ Outward migration	2 (6%)	14 (13%)	
▪ Complete outward migration	0 (0%)	3 (3%)	
Total	6 (19%)	41 (39%)	0.05

RBO, recurrent biliary obstruction; BR, borderline resectable; UR, unresectable

► **Table 3** Comparison of stent related complications according to the resectability status (n = 135).

Complications	BR (n = 31)	UR (n = 104)	P value
Pancreatitis	5 (16%)	9 (9%)	0.31
▪ Time ¹ , early / late	3/2	8/1	
▪ Severity ² , mild/ moderate/severe	0/2/3	1/4/4	
Cholecystitis	3 (10%)	9 (9%)	1.00
▪ Time ¹ , early / late	2/1	6/3	
▪ Severity ² , mild/ moderate/severe	0/3/0	0/4/5	
Non-occluding cholangitis	2 (6%)	11 (11%)	0.73
Liver abscess	1 (3%)	1 (1%)	0.41
Abscess around the bile duct	0 (0%)	1 (1%)	1.00
Total	8 (26%)	31 (30%)	0.82

BR, borderline resectable; UR, unresectable.

¹ Time from SEMs placement to the onset of pancreatitis and cholecystitis was divided into early (≤ 30 days) and late (≥ 31 days) according to Tokyo criteria.

² Severity of pancreatitis and cholecystitis was graded according to the American Society of Gastrointestinal Endoscopy lexicon guidelines.

because we identified sharp CBD angulation as a novel risk factor for shorter duration of TRBO. Based on the fact that sharp CBD angulation is considered as a risk factor for recurrent CBD stones [27, 28], angulated CBD may possibly reflect cholestasis and predispose to RBO. Moreover, we hypothesize that sharp CBD angulation might increase the risk of kinking or migration.

► **Table 4** Univariate and multivariate analyses for time to recurrent biliary obstruction (TRBO) (n = 135).

		Univariate		Multivariate		
		TRBO, day	P value	Hazard ratio	95%CI	P value
Resectability status	BR	317	0.34			
	UR	301				
CBD angulation	≤ 130 degree	185	<0.01	2.48	1.38–4.49	<0.01
	> 130 degree	534				
SEMS type	High AF	185	0.06	1.96	0.96–4.02	0.07
	Low AF	359				
SEMS length	≤ 6 cm	359	0.13			
	> 6 cm	244				
Presence of a duodenal stent	Yes	33	0.40			
	No	317				
Pancreatic surgery after chemotherapy	Yes	NA	0.12			
	No	301				

TRBO, time to recurrent biliary obstruction; CI, confidence interval; BR, borderline resectable; UR, unresectable; CBD, common bile duct; SEMS, self-expandable metallic stent; AF, axial force; NA, not available.

► **Table 5** Univariate and multivariate analyses of risk factors for pancreatitis (n = 135).

		Univariate			Multivariate		
		Odds ratio	95%CI	P value	Odds ratio	95%CI	P value
Resectability status	BR	2.03	0.63–6.58	0.24			
Tumor involvement to PD	Yes	0.33	0.08–1.38	0.13			
Pancreatic volume index	≥ 24 mm	4.40	1.17–16.6	0.03	5.12	1.30–20.2	0.02
SEMS type	high AF	3.65	1.08–12.3	0.04	4.50	1.24–16.4	0.02
SEMS length	≤ 6 cm	0.73	0.23–2.34	0.60			
EST	Yes	672000	0–	0.99			
Contrast injection into PD	Yes	9.23	0.55–156	0.12			
Rectal NSAIDs	Yes	2.23	0.71–7.06	0.17			

CI, confidence interval; BR, borderline resectable; PD, pancreatic duct; SEMS, self-expandable metallic stent; AF, axial force; EST, endoscopic sphincterotomy; NSAIDs, nonsteroidal anti-inflammatory drugs.

Pancreatitis occurred in 10.4% of patients (14/135) after SEMS placement. Nine patients (6.7%, 9/135) developed pancreatitis on the following day, a rate similar to that in previous reports [13, 17]. Interestingly, of the 14 patients, three (21.4%, 3/14) developed late-onset pancreatitis more than 30 days (39 to 118 days) after SEMS placement, which is extremely late compared to previous reports [17, 29]. One patient had UR PC and the other two patients had BR PC. This late onset of pancreatitis might be caused by the preserved pancreas volume (pancreatic volume index: late onset of pancreatitis cases, median 38 mm; early onset of pancreatitis cases, median 26 mm; non-pancreatitis cases, median 21 mm), thus caution should be taken in this group of patients. Several risk factors for pancrea-

titis after SEMS placement have been reported [29–31]. Contrast injection into PD was reported as a significant risk factor for pancreatitis [29], which was inconsistent with our results. Because we typically deployed a SEMS in the second session after drainage by ENBD, incidence of contrast injection into PD was much lower in our study (1%) compared to their study (27%), which may explain the discrepancy. SEMS of high AF was also an independent risk factor for pancreatitis in our study, which is consistent with previous reports [30]. Tumor involvement to PD theoretically causes subsequent distal pancreas atrophy and decreased exocrine function. Therefore, the incidence of pancreatitis in such patients is considered to be low. However, tumor involvement to PD was not an indepen-

► **Table 6** Univariate and multivariate analyses of risk factors for cholecystitis (n = 123).

		Univariate			Multivariate		
		Odds ratio	95%CI	P value	Odds ratio	95%CI	P value
Resectability status	BR	1.21	0.30–4.82	0.79			
Tumor involvement to OCD	Yes	38.6	8.69–172	<0.01	38.6	8.69–172	<0.01
CBD angulation	≤ 136 degrees	2.53	0.72–8.90	0.15			
Gallbladder stone	Yes	1.51	0.30–7.65	0.62			
SEMS type	high AF	1.03	0.21–5.12	0.97			
SEMS length	≤ 6 cm	2.21	0.46–10.6	0.32			
OCD occlusion by SEMS	Yes	43 900 000	0–	0.99			

CI, confidence interval; BR, borderline resectable; OCD, orifice of cystic duct; CBD, common bile duct; SEMS, self-expandable metallic stent; AF, axial force.

dent predictive factor in our study. We suppose that residual pancreas volume better correlates with exocrine function than tumor involvement to PD, resulting as a better predictive factor for pancreatitis. A large pancreatic volume calculated by volumetry was reported to be a risk factor for post-ERCP pancreatitis in the general population [32]. However, it is difficult and cumbersome to calculate the residual pancreas volume by volumetry in pancreatic cancer patients. Importantly, our study demonstrated that pancreatic volume index was an independent risk factor for pancreatitis.

On the other hand, cholecystitis developed in 9.8% of patients (12/123) after SEMS placement. Tumor involvement to OCD, SEMS of high AF, SEMS with short length, and gallbladder stones have been reported to be risk factors for cholecystitis after SEMS placement [29, 33–35]. In our study, tumor involvement to OCD was the only independent risk factor, whereas SEMS of high AF or SEMS with short length were not. It has been speculated that compression at OCD by SEMS of high AF might cause tumor dislocation and deviation from the bile duct axis, resulting in impaired bile efflux and risk for cholecystitis [33]. However, we assume that angulation of CBD and anatomical variations of the cystic duct may also influence incidence of cholecystitis, hence affecting the results of our study. Unfortunately, CBD angulation was not a significant risk factor for cholecystitis in our study, possibly because the number of cholecystitis was relatively low to detect the difference.

As mentioned above, our study identified the following independent risk factors: (1) sharp CBD angulation for short duration of TRBO; (2) high pancreatic volume index and SEMS of high AF for pancreatitis; and (3) tumor involvement to OCD for cholecystitis. Therefore, it might be better to consider different stenting strategy for PC patients who have either of these risk factors. Because patients with BR PC sometimes fail to receive pancreatic resection when severe acute pancreatitis occurs, routine plastic stent exchange may be an option for high-risk patients with BR PC. On the other hand, endoscopic ultrasound-guided transmural SEMS placement such as choledochoduodenostomy might be an option for high-risk patients with UR PC. As for resectable PC, FCSEMS with low axial force would be the best choice for SEMS. However, as mentioned above,

routine plastic stent exchange might also be an option for high risk patients.

Our study has several limitations. First, it was retrospective with a limited sample size. Second, we only evaluated stent-related AEs after SEMS placement, which was usually performed in the second session. However, we suppose that this might also be a strong point because we could evaluate the direct impact of SEMS placement itself by excluding risk factors for post-ERCP pancreatitis, such as difficult cannulation. Furthermore, the incidence of stent-related severe pancreatitis was high in our study, probably because we included patients with BR PC who had a high pancreatic volume index in our analysis. Third, patients with R PC were not included in this study because we did not place a SEMS for those who were candidates for upfront surgery during the study period. Finally, we used the sum of length of the pancreatic parenchyma measured at three sections as a surrogate parameter for residual pancreas volume, which lacks accuracy compared to volumetry. Nonetheless, it is also technically difficult to accurately measure the remnant pancreas volume even by volumetry, because of distal pancreas atrophy and dilated PD. Furthermore, volumetry is very cumbersome and cannot be easily used in daily clinical practice. Therefore, a simple and easily calculated parameter is of critical importance. However, further studies are needed to validate the usefulness of pancreatic volume index.

Conclusion

In conclusion, we demonstrated that SEMS can be safely deployed even in patients with BR PC. Sharp CBD angulation and high pancreatic volume index were identified as novel risk factors for RBO and pancreatitis, respectively, after SEMS placement in patients with PC. Further studies with a larger sample size are warranted to validate our findings.

Competing interests

Dr. Sasahira has received honoraria from Boston Scientific Japan and Cook Medical Japan. Dr. Sasaki has received honoraria from Boston Scientific Japan, Cook Medical Japan, and Century Medical Inc.

References

- [1] Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. *CA Cancer J Clin* 2017; 67: 7–30
- [2] Lucas AL, Malvezzi M, Carioli G et al. Global Trends in pancreatic cancer mortality from 1980 through 2013 and predictions for 2017. *Clin Gastroenterol Hepatol* 2016; 14: 1452–1462.e1454
- [3] Sasaki T, Kanata R, Yamada I et al. Improvement of treatment outcomes for metastatic pancreatic cancer: a real-world data analysis. *In Vivo* 2019; 33: 271–276
- [4] Schnelladorfer T, Ware AL, Sarr MG et al. Long-term survival after pancreatoduodenectomy for pancreatic adenocarcinoma: is cure possible? *Ann Surg* 2008; 247: 456–462
- [5] Cameron JL, He J. Two thousand consecutive pancreaticoduodenectomies. *J Am Coll Surg* 2015; 220: 530–536
- [6] Versteijne E, Vogel JA, Besselink MG et al. Meta-analysis comparing upfront surgery with neoadjuvant treatment in patients with resectable or borderline resectable pancreatic cancer. *Br J Surg* 2018; 105: 946–958
- [7] Shubert CR, Bergquist JR, Groeschl RT et al. Overall survival is increased among stage III pancreatic adenocarcinoma patients receiving neoadjuvant chemotherapy compared to surgery first and adjuvant chemotherapy: An intention to treat analysis of the National Cancer Database. *Surgery* 2016; 160: 1080–1096
- [8] Dhir M, Malhotra GK, Sohal DPS et al. Neoadjuvant treatment of pancreatic adenocarcinoma: a systematic review and meta-analysis of 5520 patients. *World J Surg Oncol* 2017; 15: 183
- [9] Barenboim A, Lahat G, Geva R et al. Neoadjuvant FOLFIRINOX for locally advanced and borderline resectable pancreatic cancer: An intention to treat analysis. *Eur J Surg Oncol* 2018; 44: 1619–1623
- [10] Ielpo B, Duran H, Diaz E et al. Preoperative treatment with gemcitabine plus nab-paclitaxel is a safe and effective chemotherapy for pancreatic adenocarcinoma. *Eur J Surg Oncol* 2016; 42: 1394–1400
- [11] Chawla A, Ferrone CR. Neoadjuvant therapy for resectable pancreatic cancer: an evolving paradigm shift. *Frontiers Oncol* 2019; 9: 1085
- [12] Motoi F, Kosuge T, Ueno H et al. Randomized phase II/III trial of neoadjuvant chemotherapy with gemcitabine and S-1 versus upfront surgery for resectable pancreatic cancer (Prep-02/JSAP05). *Jpn J Clin Oncol* 2019; 49: 190–194
- [13] Isayama H, Yasuda I, Ryozaawa S et al. Results of a Japanese multicenter, randomized trial of endoscopic stenting for non-resectable pancreatic head cancer (JM-test): Covered Wallstent versus DoubleLayer stent. *Dig Endosc* 2011; 23: 310–315
- [14] Almadi MA, Barkun A, Martel M. Plastic vs. self-expandable metal stents for palliation in malignant biliary obstruction: a series of meta-analyses. *Am J Gastroenterol* 2017; 112: 260–273
- [15] Kubota K, Sato T, Watanabe S et al. Covered self-expandable metal stent deployment promises safe neoadjuvant chemoradiation therapy in patients with borderline resectable pancreatic head cancer. *Dig Endosc* 2014; 26: 77–86
- [16] Gardner TB, Spangler CC, Byanova KL et al. Cost-effectiveness and clinical efficacy of biliary stents in patients undergoing neoadjuvant therapy for pancreatic adenocarcinoma in a randomized controlled trial. *Gastrointest Endosc* 2016; 84: 460–466
- [17] Siddiqui AA, Mehendiratta V, Loren D et al. Self-expanding metal stents (SEMS) for preoperative biliary decompression in patients with resectable and borderline-resectable pancreatic cancer: outcomes in 241 patients. *Dig Dis Sci* 2013; 58: 1744–1750
- [18] Tsuboi T, Sasaki T, Serikawa M et al. Preoperative biliary drainage in cases of borderline resectable pancreatic cancer treated with neoadjuvant chemotherapy and surgery. *Gastroenterol Res Pract* 2016; 2016: 7968201
- [19] Wasan SM, Ross WA, Staerkel GA et al. Use of expandable metallic biliary stents in resectable pancreatic cancer. *Am J Gastroenterol* 2005; 100: 2056–2061
- [20] Tol JA, van Hooft JE, Timmer R et al. Metal or plastic stents for preoperative biliary drainage in resectable pancreatic cancer. *Gut* 2016; 65: 1981–1987
- [21] Tempero MA, Malafa MP, Al-Hawary M et al. Pancreatic Adenocarcinoma, Version 2.2017, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* 2017; 15: 1028–1061
- [22] Kim KY, Han J, Kim HG et al. Late Complications and stone recurrence rates after bile duct stone removal by endoscopic sphincterotomy and large balloon dilation are similar to those after endoscopic sphincterotomy alone. *Clin Endosc* 2013; 46: 637–642
- [23] Isayama H, Hamada T, Yasuda I et al. TOKYO criteria 2014 for transpapillary biliary stenting. *Dig Endosc* 2015; 27: 259–264
- [24] Cotton PB, Eisen GM, Aabakken L et al. A lexicon for endoscopic adverse events: report of an ASGE workshop. *Gastrointest Endosc* 2010; 71: 446–454
- [25] Kanda Y. Investigation of the freely available easy-to-use software 'EZ' for medical statistics. *Bone Marrow Transplant* 2013; 48: 452–458
- [26] Miura S, Kanno A, Masamune A et al. Risk factors for recurrent biliary obstruction following placement of self-expandable metallic stents in patients with malignant perihilar biliary stricture. *Endoscopy* 2016; 48: 536–545
- [27] Keizman D, Shalom MI, Konikoff FM. An angulated common bile duct predisposes to recurrent symptomatic bile duct stones after endoscopic stone extraction. *Surg Endosc* 2006; 20: 1594–1599
- [28] Yoo ES, Yoo BM, Kim JH et al. Evaluation of risk factors for recurrent primary common bile duct stone in patients with cholecystectomy. *Scand J Gastroenterol* 2018; 53: 466–470
- [29] Shimizu S, Naitoh I, Nakazawa T et al. Predictive factors for pancreatitis and cholecystitis in endoscopic covered metal stenting for distal malignant biliary obstruction. *J Gastroenterol Hepatol* 2013; 28: 68–72
- [30] Kawakubo K, Isayama H, Nakai Y et al. Risk factors for pancreatitis following transpapillary self-expandable metal stent placement. *Surg Endosc* 2012; 26: 771–776
- [31] Cote GA, Kumar N, Ansstas M et al. Risk of post-ERCP pancreatitis with placement of self-expandable metallic stents. *Gastrointest Endosc* 2010; 72: 748–754
- [32] Maruyama H, Shiba M, Ishikawa-Kakiya Y et al. Positive correlation between pancreatic volume and post-endoscopic retrograde cholangiopancreatography pancreatitis. *J Gastroenterol Hepatol* 2019; doi:10.1111/jgh.14878
- [33] Nakai Y, Isayama H, Kawakubo K et al. Metallic stent with high axial force as a risk factor for cholecystitis in distal malignant biliary obstruction. *J Gastroenterol Hepatol* 2014; 29: 1557–1562
- [34] Suk KT, Kim HS, Kim JW et al. Risk factors for cholecystitis after metal stent placement in malignant biliary obstruction. *Gastrointest Endosc* 2006; 64: 522–529
- [35] Isayama H, Kawabe T, Nakai Y et al. Cholecystitis after metallic stent placement in patients with malignant distal biliary obstruction. *Clin Gastroenterol Hepatol* 2006; 4: 1148–1153