Predictors of stent occlusion in patients with unresectable pancreatic cancer after biliary metal stents

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Abstract

Background: Self-expandable metal stents (SEMS) are a widely accepted biliary endoprosthesis for patients with unresectable malignant biliary obstruction. Here, we identified predictors for the occlusion of SEMS in unresectable pancreatic cancer patients with biliary tract obstruction.

Methods: Patients with a distal malignant biliary obstruction caused by unresectable pancreatic cancer who received partially covered SEMS (PC-SEMS) placement for the first time between January 2003 and January 2016 were retrospectively enrolled for analysis. The rates of PC-SEMS occlusion were evaluated. The possible predictors of PC-SEMS occlusion were analyzed using Cox regression analysis.

Results: In total, 120 patients who received PC-SEMS for unresectable pancreatic cancer were identified. The rate of PC-SEMS occlusion was 37%. The median time to occlusion of PC-SEMS was 359 days. The major causes of occlusion included biliary sludge (61%) and tumor ingrowth (30%). Cox multivariate regression analysis revealed that inadequate alkaline phosphatase/gamma-glutamyl transferase decline (defined by a decrease of <50% within 2 wk after PC-SEMS placement) was the only independent predictor of stent occlusion (hazard ratio, 2.86; 95% CI, 1.28-6.25; $p = 0.01$)

Conclusion: Inadequate alkaline phosphatase/gamma-glutamyl transferase decline is a predictor of occlusion of first-time PC-SEMS placement in unresectable pancreatic cancer patients with biliary tract obstruction.

Keywords: Malignant biliary obstruction; Pancreatic cancer; Partially covered self-expandable metal stent; Stent occlusion

1. INTRODUCTION

Pancreatic cancer is the fourth leading cause of cancer deaths in the United States. Moreover, only 4% to 5% of patients survive for 5 years after a diagnosis of pancreatic cancer; this disease is rarely diagnosed in the resectable phase.[1,2] Endoscopic biliary stent placement is a well-established palliative treatment for managing symptomatic malignant biliary obstruction, particularly in cases of unresectable lesion to maintain biliary flow and improve a patient's prognosis and quality of life.[3,4] Some studies have indicated that the patency of self-expandable metal stents (SEMS) is longer than that of plastic stents.[5,6] Therefore, metal stent are frequently substituted for plastic stents in the palliative treatment of malignant biliary obstructions in patients with unresectable pancreatic cancer.

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However, metal stents can occlude after a period of time. This situation can be due to tumor ingrowth and/or overgrowth, mucosal hyperplasia induced by a chronic inflammatory reaction to the stent mesh, biliary sludge, or food impaction in transpapillary stents.[7–9] Covered SEMS were developed to prevent tumor ingrowth, which is a primary cause of recurrent biliary obstruction after uncovered SEMS placement. Nevertheless, the efficacy of partially covered SEMS (PC-SEMS) still remains controversial.[10,11] Moreover, there are insufficient data demonstrating the potential contributing factors or risk factors in the maintenance of PC-SEMS patency in unresectable pancreatic cancer. For these reasons, we aimed to identify the predictors of occlusion of PC-SEMS in unresectable pancreatic cancer patients with biliary tract obstruction. In addition, we evaluated the overall survival in patients with unresectable pancreatic cancer who underwent biliary PC-SEMS placement.

2. METHODS

2.1. Study population

Patients who underwent first-time placement of PC-SEMS for palliative treatment of distal malignant biliary obstruction caused by unresectable pancreatic cancer at Taipei Veterans General Hospital between January 2003 and January 2016 were retrospectively enrolled in this study. The diagnosis of pancreatic cancer was based on pathological and/or typical radiological findings. Patients

who were lost to follow-up within 3 months after PC-SEMS placement were excluded. We collected patient data: demographic data, clinical-laboratory-image data, and endoscopic retrograde cholangiopancreatography and related data. This study complied with the standards of the Declaration of Helsinki and current ethical guidelines; it was also approved by the Institutional Review Board of the Taipei Veterans General Hospital (2017-06-006CC).

2.2. Procedures and parameter recording

All patients underwent endoscopic retrograde cholangiopancreatography in a prone position using a standard duodenoscope (TJF 240 or 260V; Olympus Optical, Tokyo, Japan) after sedation using intravenous midazolam (0.05 mg/kg). Stricture length of the bile duct and stent length was determined using a ruled catheter or guidewire under direct fluoroscopy following contrast injection. Following estimation of the anatomic circumstances and stricture length, PC-SEMS (BONASTENT; Standard Sci-Tech, Seoul, Korea) was deployed according to the experienced endoscopists' decision. The distal end of the PC-SEMS was placed in the duodenal lumen and protruded from the papilla by approximately 1 cm.

Possible factors related to metal stent occlusion were collected according to a search of the previous literature as follows: age (> or < 65 y old),[12] gender,[12–14] prior biliary drainage,[13] serum bilirubin decline (adequate, inadequate, no icterus),[8,13] serum alkaline phosphatase/gamma-glutamyl transferase (ALP/GGT) level, tumor size (> or < 35 mm),[14,15] liver metastasis,[15] ascites,[15] duodenal invasion,[15] stricture length (> or < 25 mm),[8,15] endoscopic sphincterotomy prior to PC-SEMS placement (yes or no)[16], and anticancer therapy (yes or no).[12,15] In our study, an adequate bilirubin decline was defined as a decline in serum bilirubin concentration of more than 50% or a return to the normal range within 2 weeks of stent placement.[13] Moreover, patients who received chemotherapy, radiotherapy, or chemoradiotherapy were enrolled in our anticancer therapy group.

In addition to a serum bilirubin decline, we considered serum ALP and/or GGT decline as one predictor of metal stent occlusion.[14] We defined an "adequate" ALP/GGT decline as a decline in serum ALP and/or GGT concentration of more than 50% or a return to the normal range within 2 weeks of stent placement.[13] Moreover, we also considered antiplatelet drug use as a predictive factor.[17]

2.3. Endpoints

The primary endpoint of the study was the rate and duration of stent occlusion. Stent occlusion and its duration were determined as the time interval between the initial PC-SEMS placement and the recurrence of obstruction or cholangitis requiring re-intervention via an endoscopic approach to identify the cause of the stent occlusion. If there was no evidence of obstruction during a patient's life, the patency period was considered to be equal to the patient's survival duration. Early PC-SEMS occlusion was defined as obstruction occurring within 3 months of PC-SEMS placement. The secondary endpoint of the study was overall survival in patients in whom PC-SEMS placement was carried out. Overall survival was defined as the time between PC-SEMS placement and time of death.

2.4. Statistical analysis

The results are expressed as numbers and percentages of patients or as medians and interquartile ranges. Patients not experiencing stent occlusion were censored at the time of last follow-up or the time of death.

Stent occlusion time and survival time were estimated using the Kaplan-Meier technique. The predictive factors of PC-SEMS occlusion and the prognostic factors of overall survival were both initially assessed using univariate Cox regression analysis. These factors were expressed as hazard ratios (HRs) with 95% CIs. Variables with a p value of less than 0.20 were included in the multivariate Cox regression analysis to estimate an adjusted HR with 95% CIs. The results were considered to be statistically significant when the p value was less than 0.05. All of the analyses were conducted using SPSS version 15 (SPSS, Chicago, IL, USA).

3. RESULTS

3.1. Patient characteristics

A total of 130 consecutive patients who underwent first-time PC-SEMS for distal malignant biliary obstruction caused by unresectable pancreatic cancer were identified. Of this cohort, 10 patients were excluded due to follow-up loss within 3 months of PC-SEMS placement. As a result, 120 patients were analyzed. Patient data and characteristics are listed in Table 1. Liver metastasis, ascites, and duodenal invasion were observed in 49 (41%), 31 (26%), and 35 (29%) patients, respectively. Anticancer therapy was administered in 97 patients (81%).

3.2. Stent occlusion analysis

The causes of early and non-early PC-SEMS occlusion are listed in Table 2. PC-SEMS occlusion was observed in 44 patients (37%), and early occlusion was observed in 16 patients (13%). The median time to occlusion according to the Kaplan-Meier method was 359 days. Major causes of occlusion included the presence of sludge (61%) and tumor ingrowth (30%). The rate of PC-SEMS occlusion by tumor ingrowth was higher in the non-early occlusion group than in the early occlusion group (38% vs 12%).

3.3. Factors related to PC-SEMS occlusion

The results of the univariate and multivariate analyses of the associated predictors for PC-SEMS occlusion are listed in Table 3. Univariate analysis revealed that prior biliary drainage,

Table 1

The Characteristics of the pancreatic cancer patients with PC-SEMS placement

Parameter	
Age, y, median (range)	67 (30-92)
Female gender, n (%)	53 (45)
Prior biliary drainage, n (%)	42 (35)
Total bilirubin, mg/dL, median (range)	5.4 (0.3-27.6)
Bilirubin decline, n (%)	
Adequate, inadequate, no icterus	86 (72)/18 (15)/16 (13)
ALP, mg/dL, median (range)	328 (48-2017)
GGT, mg/dL, median (range)	387 (18-1709)
ALP/GGT decline, n (%)	
Adequate/ inadequate	78 (65)/36 (30)
Antiplatelet drugs use, n (%)	10 (8)
Tumor location, n (%)	
Head/body/tail	105 (88)/12 (10)/3 (2)
Primary tumor size, mm, median (range)	36 (14-80)
Liver metastasis, n (%)	49 (41)
Ascites, n (%)	31 (26)
Duodenal invasion, n (%)	35 (29)
Diameter of PC-SEMS 10 mm/8 mm, n (%)	118 (98)/2 (2)
Stricture length mm, median (range)	20 (7-70)
EST prior to PC-SEMS placement, n (%)	10 (8)
Anticancer therapy, n (%)	97 (81)
Occlusion rate of PC-SEMS, n (%)	44 (37)
The median time to occlusion, d	359

ALP = alkaline phosphatase; EST = endoscopic sphincterotomy; GGT = gamma-glutamyl transferase; PC-SEMS = partially covered self-expandable metal stent.

Table 2

Causes of PC-SEMS occlusion (early and non-early)

PC-SEMS occlusion	Early occlusion, n = 16, n (%)	Non-early occlusion, n = 28, n (%)	Total, n = 44, n (%)
Food impaction	1 (7)	1 (4)	2 (5)
Sludge	11 (67)	16 (58)	27 (61)
Tumor ingrowth	2 (12)	11 (38)	13 (30)
Tumor overgrowth	1 (7)	0 (0)	1 (2)
Unknown	1 (7)	0 (0)	1 (2)

PC-SEMS = partially covered self-expandable metal stent.

inadequate ALP/GGT decline, and duodenal invasion were significantly associated with a higher risk of PC-SEMS occlusion (all $p < 0.05$). Multivariate Cox regression analysis revealed that inadequate ALP/GGT decline was the only independent predictor for stent occlusion (HR, 2.86; 95% CI, 1.28-6.25; $p = 0.01$). The log-rank test and Kaplan-Meier survival analysis for PC-SEMS occlusion showed that patients with inadequate ALP/GGT decline had a significantly higher rate of stent occlusion than patients with adequate ALP/GGT decline ($p < 0.001$) (Fig. 1).

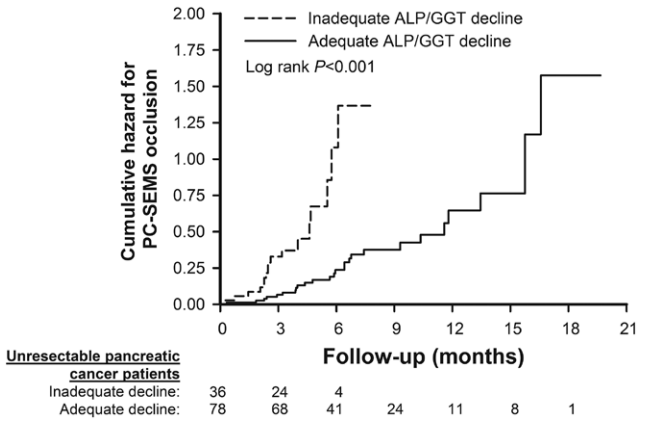

Fig. 1 Kaplan-Meier estimates of cumulative hazard of occlusion of partially covered self-expandable metal stent (PC-SEMS) between unresectable pancreatic cancer patients with adequate and inadequate alkaline phosphatase/gamma-glutamyl transferase (ALP/GGT) decline ($p < 0.001$ between the two groups by the log-rank test).

3.4. Survival analysis

The median survival time according to the Kaplan-Meier method was 233 days, and 88 patients (73%) died during the follow-up period. The results of the univariate and multivariate analyses of the associated prognostic factors on overall survival are listed in Table 4. The univariate analysis revealed that a male gender, prior biliary drainage, inadequate bilirubin decline, inadequate ALP/GGT decline, liver metastasis, duodenal invasion, stricture length >25 mm, no endoscopic sphincterotomy prior to PC-SEMS placement, no anticancer therapy, and early PC-SEMS occlusion were significantly linked to a shorter overall survival period (all $p < 0.05$). Multivariate Cox regression analysis revealed that inadequate ALP/GGT decline was also the only independent predictor for overall survival (HR, 8.02; 95% CI, 2.10-30.60; $p < 0.01$).

4. DISCUSSION

We conducted a single-center retrospective study to analyze the occurrence of PC-SEMS occlusion and further identify possible predictors for the occlusion of PC-SEMS in unresectable pancreatic cancer patients with biliary tract obstruction. In our study, the rate of PC-SEMS occlusion was 37%, which was within the range of biliary obstruction rates of 28%-38% reported in previous studies.[10,11,18,19] Moreover, the median time to dysfunction of PC-SEMS was 359 days, which was also within the range of median time to recurrent biliary obstruction of 357 to 444 days reported in previous studies.[11,18,19] The small differences between our values and those noted in the literature may in part be due to differences in patient characteristics and treatment strategies, which in turn may have influenced the duration of stent patency.

As is well known, the major causes of stent occlusion include tumor ingrowth and/or overgrowth, sludge or stone formation, and food impaction. In our study, biliary sludge was the most common cause of PC-SEMS occlusion. One multicenter, prospective study conducted by Isayama et al[19] also revealed that the major cause of stent occlusion was sludge formation for both partially covered stainless SEMS and partially covered nitinol SEMS. One possible explanation for why sludge was the most common cause of PC-SEMS occlusion is that bacteria play an important role via adherence and subsequent biofilm formation on the membranes of PC-SEMS.[20,21] Therefore, strategies to reduce biofilm formation on the membranes of PC-SEMS are

Table 3

Univariate and multivariate analyses of predictors for PC-SEMS occlusion

Parameter	Univariate analysis HR (95% CI)	p	Multivariate analysis HR (95% CI)	p
Age ≥ 65	0.75 (0.41-1.36)	0.34		
Female	0.68 (0.36-1.27)	0.23		
Prior biliary drainage	1.88 (1.02-3.48)	0.04	1.39 (0.69-2.78)	0.35
Total bilirubin decline	0.42 (0.06-3.25)	0.41		
Inadequate ALP/GGT decline	3.70 (1.75-8.33)	<0.01	2.86 (1.28-6.25)	0.01
Antiplatelet drugs use	0.52 (0.13-2.18)	0.38		
Tumor size >35 mm	1.39 (0.69-2.77)	0.36		
Liver metastasis	1.54 (0.82-2.87)	0.18	1.41 (0.70-2.84)	0.34
Ascites	1.51 (0.70-3.27)	0.30		
Duodenal invasion	1.99 (1.08-3.68)	0.03	1.58 (0.8-3.11)	0.10
Stricture length >25 mm	1.40 (0.50-3.97)	0.52		
EST prior to PC-SEMS placement	0.52 (0.18-1.55)	0.24		
Anticancer therapy	0.63 (0.25-1.61)	0.34		

ALP = alkaline phosphatase; EST = endoscopic sphincterotomy; GGT = gamma-glutamyl transferase; HR = hazard ratio; PC-SEMS = partially covered self-expandable metal stent.

Table 4

Univariate and multivariate analyses of overall survival

Parameter	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Age ≥ 65	0.84 (0.55-1.29)	0.42		
Female	0.58 (0.37-0.91)	0.02	0.25 (0.07-1.11)	0.05
Prior biliary drainage	1.69 (1.10-2.61)	0.02	0.92 (0.41-2.68)	0.92
Total bilirubin decline	0.14 (0.03-0.62)	0.10	0.83 (0.33-2.19)	0.82
Inadequate ALP/GGT decline	2.52 (1.47-4.33)	<0.01	8.02 (2.10-30.60)	<0.01
Antiplatelet drugs use	1.08 (0.49-2.36)	0.85		
Tumor size >35 mm	0.82 (0.49-1.37)	0.44		
Liver metastasis	2.56 (1.63-4.02)	<0.01	0.85 (0.23-3.19)	0.81
Ascites	1.20 (0.75-1.94)	0.45		
Duodenal invasion	1.44 (0.91-2.28)	0.12	1.65 (0.45-6.07)	0.45
Stricture length >25 mm	2.43 (1.27-4.65)	0.01	3.10 (0.99-9.74)	0.05
EST prior to PC-SEMS placement	0.48 (0.21-1.12)	0.09	1.29 (0.24-7.11)	0.77
Anticancer therapy	0.60 (0.36-1.03)	0.06	0.51 (0.14-1.91)	0.32
Early PC-SEMS occlusion	1.78 (0.96-3.31)	0.07	1.85 (0.48-4.07)	0.52

ALP = alkaline phosphatase; EST = endoscopic sphincterotomy; GGT = gamma-glutamyl transferase; HR = hazard ratio; PC-SEMS = partially covered self-expandable metal stent.

necessary to ensure the long-term patency of PC-SEMS in the future.

Interestingly, the proportion of PC-SEMS occlusion due to tumor ingrowth was higher in our study than in previous investigations.[10,19] However, early occlusion due to tumor ingrowth within 3 months occurred in only two cases in our findings. Furthermore, one multicenter randomized trial also found that the PC-SEMS was subject to tumor ingrowth.[18] However, additional comparative studies focused on the characteristic of stents are warranted.

To the best of our knowledge, data pertaining to the predictors of occlusion of the first inserted PC-SEMS in patients with malignant biliary obstruction are scarce. Yokota et al[11] demonstrated that PC-SEMS had longer time to recurrent biliary obstruction than uncovered and fully covered SEMS and that the use of PC-SEMS was the only independent factor linked with a decrease in the risk of recurrent biliary obstruction. To help clinicians identify patients who would most likely need early elective stent exchange or subsequent stent insertion, we found that inadequate ALP/GGT decline was not only the independent predictor for PC-SEMS occlusion. We noted that a poor prognostic factor was linked to overall survival in the multivariate Cox regression analysis. Matsuda et al[13] reported that serum total bilirubin level was an important factor affecting the patency of implanted plastic stent in patients with malignant biliary obstruction. A simple score model that consisted of a high initial bilirubin level was additionally reported to predict early stent occlusion.[16] Brountzos et al[22] also reported that there were no factors affecting the metallic stenting patency of malignant biliary obstruction. However, these authors noted that a serum bilirubin level <4 mg/dL after stenting was the most important independent predictor of survival. In addition to the level of serum bilirubin, Eum et al[12] found that normalized serum bilirubin level was not only associated with stent patency but also a longer survival period according to multivariate Cox regression analysis. In our study, an inadequate ALP/GGT decline rather than a bilirubin decline in the blood appeared to be a more sensitive marker of slower bile flow. The decreased bile flow promoted the adherence of proteins and bacteria to the inner wall of the stent and consequently enhanced the risk of clogging.[23,24] Therefore, the higher risk of biliary tract infection may explain why an inadequate ALP/GGT decline was associated with poor overall survival in our study.

The tendency of patients with duodenal invasion to experience PC-SEMS occlusion in requires further investigation. One multicenter, retrospective study conducted by Hamada et al[15] revealed that duodenal invasion was a risk factor for early SEMS dysfunction in patients with pancreatic cancer according to multiple logistic regression analysis. In our study, the PC-SEMS was placed across the papilla of Vater in all cases, which may have further predisposed the patients to duodenobiliary reflux of duodenal residues and subsequently resulted in the formation of bacterial biofilms and sludge in the bile duct.[25] Nevertheless, in our study, duodenal invasion, which was diagnosed clinically based on endoscopic instead of pathologic findings, was not a factor associated with PC-SEMS occlusion.

This study has several strengths. First, it was carried out on a homogeneous group of patients with malignant biliary obstruction due to unresectable pancreatic cancer, which was an independent factor for recurrent biliary obstruction and is considered to be more aggressive with a poorer prognosis than other causative tumors.[11] Second, we only used PC-SEMS in our study because the causes of stent occlusion may differ somewhat with the type and characteristics of SEMSs, including axial and radial forces.[26]

Nonetheless, this study also has several limitations. First, it is retrospective and has potential biases. Second, the study population was relatively small and obtained from only a single center. Third, our study lacked data about the precise anticancer regimen and the evaluation of treatment response, which may have impacted the results of the stent occlusion and survival in our study. Fourth, we did not have data pertaining to stent migration, a known drawback of covered SEMS compared with uncovered SEMS.[27,28]

In conclusion, we found that inadequate ALP/GGT decline was not only a predictor of the occlusion of first inserted PC-SEMS but also a poor prognostic factor in patients with unresectable pancreatic cancer. According to our findings, we recommended that clinicians routinely monitor serum levels of ALP and GGT in addition to total bilirubin before and after PC-SEMS placement to identify patients with malignant biliary obstruction at higher risk of stent occlusion.

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