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CLINICAL INVESTIGATION BILIARY

Predictors of Recurrent Biliary Obstruction Following Percutaneous Uncovered Metal Stent Insertion in Patients with Distal Malignant Biliary Obstruction: An Analysis Using a Competing Risk Model

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Abstract

Objective To evaluate predictive factors of recurrent biliary obstruction (RBO) following percutaneous uncovered metal stent placement for unresectable distal malignant biliary obstruction (MBO) by using a competing risk model.

Materials and Methods Between March 2012 and March 2016, 119 patients underwent percutaneous uncovered metal stent placement with distal MBO at our institution. Univariate and multivariate analyses were conducted to identify the prognostic factors for RBO using a competing risk model.

Results The median overall survival period was 170 days (range 19–775 days). Recurrent biliary obstruction before death was observed in 34 patients (28.6%). The 3-, 6-, and 12-month cumulative incidences of RBO were 14.3%, 21.0%, and 27.7%, respectively. A multivariate analysis indicated that ampullary carcinoma compared with metastatic carcinoma (hazard ratio [HR] = 4.86; 95% confidence interval [CI], 1.74–13.54; $P = 0.003$) and a stent insertion above the sphincter of Oddi (HR 2.49; 95% CI, 1.11–5.62; $P = 0.028$) were the independent risk factors for RBO when we considered death to be a competing risk.

Conclusion Ampullary carcinoma and stent insertion above the sphincter of Oddi were risk factors for RBO in these patients who received percutaneous transhepatic stent placement.

Keywords Biliary tract neoplasms · Jaundice, Obstructive · Self-expandable metallic stents · Recurrence · Regression analysis

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Introduction

Distal malignant biliary obstruction (MBO) is commonly caused by pancreatic carcinoma, ampullary carcinoma, cholangiocarcinoma, or metastatic carcinoma. Most patients at presentation are not candidates for curative resection secondary to local spreading or distant metastases [1–3]. For these patients, percutaneous biliary stenting is an alternative palliative treatment [3–7].

In cases of distal MBO, the frequency of recurrent biliary obstruction (RBO) after metal stent insertion was reported to be 24.2–41.0% [8–12]. After recurrence, some patients could not reap any benefit from another drainage procedure. Thus, it is important to identify the subgroup of patients with distal MBO who would benefit the most or the least from a metal stent placement.

Thus far, many researchers have evaluated factors that affect stent patency for patients with proximal and distal MBO [13–17]. Conventional methods such as the Kaplan–Meier method with the logrank test and Cox's proportional hazard model are widely used to evaluate these outcomes. In these statistical methods, a particular problem arises when the focus is on "competing risks" (i.e., death without

RBO), which can affect the probability of the occurrence of the event of interest (RBO) [18, 19]. That is, RBO can no longer be observed when death occurs. In the presence of competing risks, traditional statistical methods may overestimate the actual incidence of the event of interest, leading to inappropriate risk stratification and a false interpretation of the data [19–21].

Therefore, we conducted the present retrospective study of 119 patients with distal MBO to clarify the predictive factors of RBO, considering death to be a competing risk.

Materials and Methods

The procedures followed in this study conformed to the guidelines of the World Medical Association Declaration of Helsinki and were approved by the Ethics Committee of our institution (Ethical review no. 2017-SR-307). Furthermore, written informed consent was not required for this retrospective study.

Patients

In this study, we retrospectively reviewed patients with MBO who presented at our institution between March 2012 and March 2016. The inclusion criteria for the study population were as follows: (1) patient age $\geq$ 18 years, (2) first-time metal stent insertion, and (3) unresectable disease or intolerable surgery. The exclusion criteria were as follows: (1) hilar biliary stricture, (2) Eastern Cooperative Oncology Group (ECOG) Scale of Performance Status grade 3 or 4, (3) long-segment biliary stricture needs double-stent placement, (4) previous biliary tract surgery, (5) duodenal stent placement prior to the biliary stent, and (6) lost in follow-up. Ultimately, 119 patients were enrolled in this study (Fig. 1). The indications of percutaneous approach for MBO included: failed endoscopic drainage (n = 7); the previous upper gastrointestinal surgery (n = 27); and after multidisciplinary discussion and informed consent from patients, patients were willing and recommended to receive percutaneous approach primarily (n = 85). The malignant diagnosis basis of these patients was: 74 patients had pathological results (43 patients had surgery history and 31 patients underwent biopsy), and 45 patients had disease progression on clinical manifestations, laboratory results, and imaging findings.

The patients' clinical data, including their medical records and follow-up visit data, were collected retrospectively. These data included age, gender, type of primary tumor, duration of jaundice, performance status score, preoperative external drainage, initial total bilirubin level, cholangitis prior to stent insertion, ascites, intrahepatic metastasis, location of the distal end of the stent, complications, chemotherapy following stent insertion, and RBO and survival status.

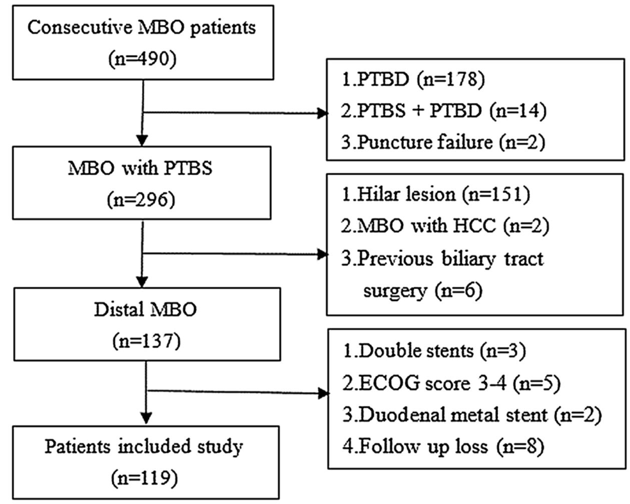

Fig. 1 Patient inclusion flowchart. *MBO* malignant biliary obstruction, *PTBD* percutaneous transhepatic biliary drainage, *PTBS* percutaneous transhepatic biliary stent, *HCC* hepatocellular carcinoma

Therapeutic Strategy of Stent Insertion

Before percutaneous transhepatic biliary stenting, contrast-enhanced abdominal computed tomography (CT) and/or magnetic resonance imaging (MRI) were performed in all of the patients. Furthermore, broad-spectrum antibiotics were given to the patients before the procedure.

Stents were placed percutaneously under monitored anesthesia care. The position and the length of the stricture were confirmed using a cholangiogram. The stent was selected and then deployed across the obstructed segment. In patients who had stent placement above the sphincter of Oddi (SO), we usually kept a maximum of 2 cm at the proximal and distal margins over the stricture. If the stent should be placement across the SO, the distal end of the stent protruding into the duodenum was 1.0 cm. The self-expandable uncovered metal stents used in this study were E-Luminexx stents (Bard, Germany) with a diameter of 8 mm and a length of 6 or 8 cm. Besides, an external drainage catheter (8.5F, COOK, US) was placed in 22 cases duo to pre-procedure cholangitis, poor biliary drainage, non-fully expended stent, or hemobilia after stenting. The catheter was removed after infection controlled and contrast media flowed easily through the stent after repeat cholangiography.

Patients were followed up by telephone interview, outpatient clinics, or local hospitals. They were advised to report to the interventional radiologists if fever or jaundice developed. For patients who presented with recurrent jaundice, complete blood count and contrast-enhanced abdominal CT and/or MRI were performed. After the detection of stent dysfunction, repeated biliary drainage was conducted if possible. The cutoff date of the follow-up was December 31, 2017.

Definitions

Clinical success was defined as a decrease in the serum bilirubin level to less than 50% of the pre-treatment value within 2 weeks after the stent placement [22]. According to TOKYO criteria, cholangitis was diagnosed when a fever > 38 °C continued > 24 h with cholestasis and leukocytosis observed and when there is neither biliary dilation on imaging studies nor a define finding of stent occlusion [22]. RBO was defined as recurrent jaundice, an increase in the serum bilirubin level, and biliary dilation as revealed by the imaging results [22]. When a patient died without recurrent jaundice, we considered the patient's death to be a competing risk. Basically, stent patency was regarded as a pure interval between stent insertion and recurrent jaundice. The survival period was defined as the period from the initial stent placement to the patient's death.

Statistical Analysis

The occurrence of RBO was the event of interest. Univariate and multivariate analyses of the predictive factors of RBO were performed using a proportional hazards model proposed by Fine and Gray, considering death without RBO to be a competing event. Accordingly, these variables considered in this model included age, sex, primary tumor, duration of jaundice, performance status score, preoperative external drainage, initial total bilirubin level (before any biliary drainage), cholangitis (prior to stent insertion), ascites, intrahepatic metastasis, location of the distal end of the stent (a stent insertion above or across the SO), and chemotherapy after stent insertion [23–25].

Then, an additional analysis was conducted in the absence of the competing risk: treating RBO as the end point and death without RBO as censored. Standard univariate and multivariate Cox's proportional hazards models were used to evaluate the predictive factors of RBO.

Factors with $P < 0.2$ in the univariate analysis were considered to be the potential predictors of RBO and were further analyzed in the multivariate analysis. A P value of less than 0.05 was considered statistically significant. Fine and Gray's competing risks regression analysis and Cox's regression analysis were performed with SAS, version 9.4.

Results

Patient Characteristics

The primary tumor of MBO was cholangiocarcinoma in 21 cases, gallbladder carcinoma in 9 cases, pancreatic carcinoma in 50 cases, ampullary carcinoma in 9 cases, and metastatic tumor in 30 cases. The metastasis originated from gastric carcinoma in 27 cases, colon carcinoma in 1 case, and ovarian carcinoma in 2 cases. The stent was placed across the SO in 91 cases and above the SO in 28 cases. The patient characteristics are summarized in Table 1.

Clinical Outcomes

After the stent placement procedure, clinical success was achieved in 107 (89.9%) patients. The following procedure-related complications were observed in 18 patients: early cholangitis in 14 patients (4 patients accompany with missed clinical success), acute pancreatitis in 2 patients, biloma in 1 patient, and hemobilia in 1 patient.

After the last follow-up visit, all of the considered patients died. The median survival time was 170 days (range: 19–775 days). RBO was observed in 34 (28.6%)

Table 1 Patients characteristics for distal malignant biliary obstruction

Variables	*N*/Mean ± SD
Age (years)	65.5 ± 12.3
Gender (male/female)	86/33
Primary disease	
Metastatic tumour[a]	30
Cholangiocarcinoma	21
Gallbladder cancer	9
Pancreatic cancer	50
Ampullary carcinoma	9
Duration of jaundice (days)	16.9 ± 13.2
ECOG score (0 + 1/2)	88/31
Ascites	26
Intrahepatic metastasis	43
Total bilirubin (μmol/L)	232.2 ± 114.2
Pre-drainage	39
Location of distal end of stent	
Duodenum	91
Bile duct	28
Chemotherapy	31

[a]Metastatic tumor (30 cases) included gastric carcinoma in 27 cases, colon carcinoma in 1 case, and ovarian carcinoma in 2 cases

ECOG Eastern cooperative oncology group patients. In the RBO cases, the median time to RBO was 92.5 days (range 20–750 days). Figure 2 illustrates the cumulative incidences of RBO estimated using a competing risk analysis and the Kaplan–Meier method. When death without RBO was considered a competing risk, the cumulative incidences of RBO at 3, 6, and 12 months were 14.3%, 21.0%, and 27.7%, respectively. Using the Kaplan–Meier method, we estimated the cumulative incidences of RBO at 3, 6, and 12 months to be 16.0%, 26.8%, and 45.8%, respectively.

Risk Factors for RBO

The cumulative incidences of RBO calculated using a competing risk analysis are shown in Fig. 3 (patients with different primary tumors, $P = 0.0004$) and Fig. 4 (stent insertion above and across the SO, $P = 0.028$).

We analyzed the risk factors for RBO using Fine and Gray's competing risks regression analysis. In the multivariate analysis, the statistically significant variables were primary tumor ($P = 0.0004$) and the location of the distal end of the stent ($P = 0.028$). The hazard ratio (HR) for ampullary carcinoma against metastatic carcinoma was 4.86 (95% confidence interval [CI], 1.74–13.54). With respect to the location of the distal end of the stent, the risk of RBO increased in patients with a stent insertion above SO (HR 4.86; 95% CI, 1.74–13.54; $P = 0.003$) (Table 2).

A second analysis was conducted using Cox's regression model and ignoring the competing risk. As shown in Table 3, the predictors of primary tumor ($P = 0.101$) and the location of the distal end of the stent ($P = 0.061$) did not differ significantly to influence the RBO.

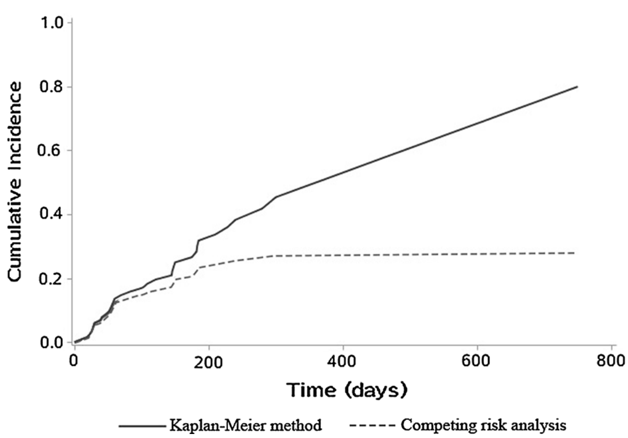

Fig. 2 Cumulative incidence curves of recurrent biliary obstruction obtained using a competing risk analysis and the Kaplan–Meier method

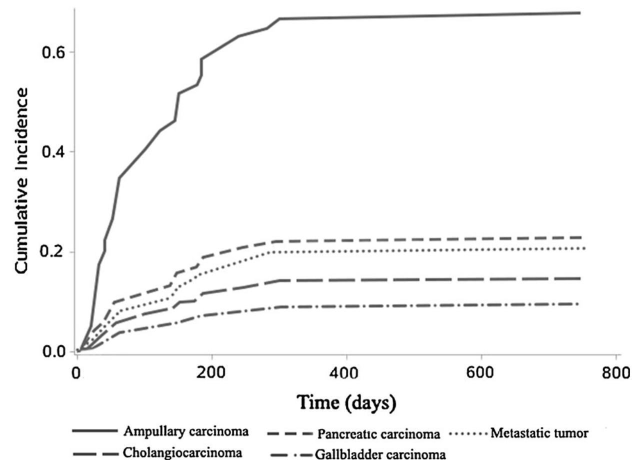

Fig. 3 Cumulative incidence of recurrent biliary obstruction according to the primary tumors, estimated using a competing risk analysis ($P = 0.0004$). Death without recurrent biliary obstruction was considered to be a competing risk

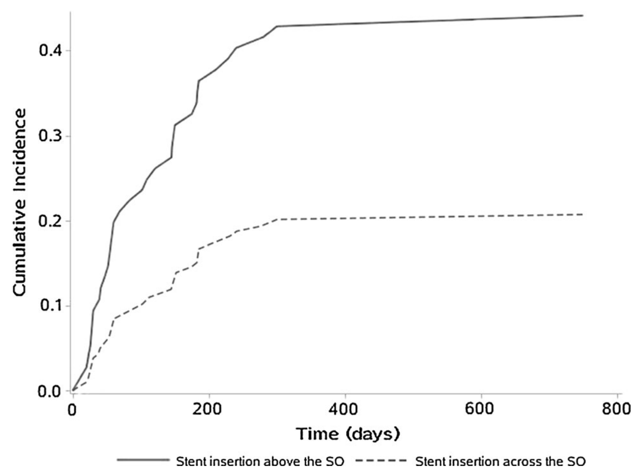

Fig. 4 Cumulative incidence of recurrent biliary obstruction according to the location of the distal end of the stent, estimated using a competing risk analysis ($P = 0.028$). Death without recurrent biliary obstruction was considered to be a competing risk

Discussion

The primary aims of self-expandable metal stents for MBO were palliation of jaundice and improvement of the patient's quality of life. In most of the studies evaluating stent outcomes, RBO is the event of primary interest, and death without RBO is considered a censoring event [13, 14, 16, 17]. Unlike previous studies, our study investigated the risk factors for RBO, considering death without RBO to be a competing risk event. Our study indicated that the type of primary tumor and the location of the distal end of the stent are independent prognostic factors of RBO in a competing risk model.

Compared with the standard Cox's model, the competing risk model used in the risk factor analysis of RBO in

Table 2 Univariate and multivariate analysis for risk factors for RBO using fine and gray model

	Univariate		Multivariate	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Gender (male)	0.94 (0.46–1.93)	0.868		
Age	0.99 (0.97–1.02)	0.867		
Primary disease		0.003		0.0004
Metastatic tumor	1.00 (reference)		1.00 (reference)	
Cholangiocarcinoma	0.59 (0.17–1.96)	0.393	0.64 (0.19–2.14)	0.478
Gallbladder cancer	0.33 (0.04–2.81)	0.312	0.37 (0.04–3.12)	0.362
Pancreatic cancer	0.82 (0.35–1.92)	0.642	1.09 (0.43–2.71)	0.849
Ampullary carcinoma	3.12 (1.29–7.47)	0.011	4.86 (1.74–13.54)	0.003
Duration of jaundice	0.99 (0.97–1.02)	0.861		
ECOG score (2)	0.72 (0.31–1.68)	0.456		
Ascites	0.75 (0.31–1.81)	0.518		
Intrahepatic metastasis	0.97 (0.48–1.96)	0.939		
Total bilirubin	1.00 (0.99–1.00)	0.548		
Pre-drainage	0.99 (0.48–2.04)	0.997		
Stent insertion above the SO	1.75 (0.85–3.58)	0.125	2.49 (1.11–5.62)	0.028
Chemotherapy	1.09 (0.54–2.21)	0.792		

HR hazard ratio, *CI* confidence interval, *RBO* recurrent biliary obstruction, *SO* sphincter of Oddi, *ECOG* Eastern Cooperative Oncology Group

Table 3 Univariate and multivariate analysis for risk factors for RBO using Cox model

	Univariate		Multivariate	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Gender (male)	1.06 (0.51–2.25)	0.865		
Age	0.99 (0.97- 1.02)	0.671		
Primary tumor		0.170		0.101
Metastatic tumor	1.00 (reference)		1.00 (reference)	
Cholangiocarcinoma	0.55 (0.17–1.79)	0.324	0.66 (0.19–2.17)	0.659
Gallbladder cancer	0.33 (0.04–2.62)	0.293	0.41 (0.05–3.29)	0.401
Pancreatic cancer	0.62 (0.26–1.46)	0.273	0.92 (0.35–2.43)	0.873
Ampullary carcinoma	1.78 (0.63–5.05)	0.274	2.95 (0.88–9.83)	0.078
Duration of jaundice	1.00 (0.97–1.03)	0.978		
ECOG score (2)	0.81 (0.35–1.88)	0.632		
Ascites	1.42 (0.57–3.51)	0.452		
Intrahepatic metastasis	1.34 (0.65–2.73)	0.429		
Total bilirubin	1.00 (0.99–1.00)	0.361		
Pre-drainage	0.95 (0.46–1.96)	0.895		
Stent insertion above the SO	1.86 (0.90–3.85)	0.091	2.31 (0.96–5.53)	0.061
Chemotherapy	0.82 (0.38–1.73)	0.601		

HR hazard ratio, *CI* confidence interval, *RBO* recurrent biliary obstruction, *SO* sphincter of Oddi, *ECOG* Eastern Cooperative Oncology Group

patients with distal MBO revealed different risk associations. The risk factors for RBO, such as the type of primary tumor and the location of the distal end of the stent, were not statistically significant when death was not considered a competing risk event. The two abovementioned methods yielded different results for the same data, making us question which method was optimal. Several researchers have reported that in populations with a high mortality rate, such as patients with MBO, including a competing risk in the study model is more appropriate [19, 20]. In this study, we calculated and compared the cumulative incidences of RBO by using the conventional Kaplan–Meier method and a competing risk analysis (Fig. 2). We observed that the Kaplan–Meier method overestimated the cumulative incidence of RBO as compared to the competing risk analysis. These results further support the idea that a competing risk model should be considered in the evaluation of stent patency for the management of distal MBO.

Ampullary carcinoma was identified as a risk factor for RBO following uncovered metal stent insertion when death was considered a competing risk. Although ampullary cancer is a relatively uncommon malignancy and has a better prognosis than pancreatic or bile duct carcinoma [26, 27], in this study, recurrent jaundice was observed in 7 (7/9, 77.8%) patients with ampullary cancer. Similarly, upon observing the outcomes of 17 patients with ampullary carcinoma treated with an uncovered metal stent, Su et al. [28] found a high rate (88.2%) of stent dysfunction. Ampullary cancer seems to grow most commonly as a soft and friable expansive mass, resulting in easy infiltration through a metallic mesh [28]. Given that the main cause of MBO is tissue ingrowth in the uncovered metal stent [11, 25, 29], a plastic stent or covered metal stent with an anti-migration system [30] may be more suitable for patients with distal MBO in ampullary carcinoma.

Several previous reports have compared the effects of the placement of a self-expandable metal stent above and across the SO from the viewpoint of stent patency, but with conflicting results [8, 9, 31, 32]. Huang et al. [9] compared 47 cases of stent placement above the SO with 51 cases of stent placement across the SO and found that RBO were more frequently observed in patients with stent placement across the SO. They suggested that, in patients with MBO, biliary stents should be placed above the SO if papillary lesions are not invaded. However, after observing 155 patients treated with metal stent insertion, Jo et al. [8] concluded that stent placement across the SO did not increase RBO or shorten patency time compared with stent placement above the SO. To clarify this issue, we estimated and compared the cumulative incidence of RBO by using the competing risk model; we found that the cumulative incidence of RBO of a stent insertion above the SO was significantly higher than that of a stent insertion across the SO (Fig. 4). One explanation might be that placing a stent with one end in the duodenum ensures better bile drainage. Furthermore, the aggravated angulation of the bile duct below the stent and the unexpected narrowing distal to the stent have been reported to lead to poor stent patency [32]. Thus far, no consensus has been reached on whether a stent placed above causes more stent occlusion than the one placed across the SO. Further studies, including randomized, controlled clinical trials, are required to resolve this controversy.

The current study also had some limitations. First, it was a retrospective study with some inevitable bias. Second, other factors such as duodenal invasion, which were proven to be associated with stent patency in previous studies [16], were not analyzed in the present study. Because 7 patients received duodenal condition evaluation by endoscopy, duodenal function of other 112 patients was evaluated according to the following aspects indirectly: (1) symptoms shown by the patients; (2) any duodenal invasion found on contrast-enhanced CT/MR images; (3) after catheter across the stricture, checking duodenal and bowel function by contrast media infusion. Based on these findings, fifteen cases were suspected with mild duodenal invasion. However, it was still difficult to evaluate whether the duodenum invaded or not intuitively. Third, the number of patients with ampullary cancer enrolled in our study was small, and further large-scale studies on the stent patency of ampullary cancer are required. Moreover, a small subset of patients undergoing regional intra-arterial chemotherapy or radiotherapy after stent insertion was not analyzed in this study.

In conclusion, the current study demonstrated that ampullary carcinoma and a stent insertion above the SO were significant independent prognostic factors associated with RBO in patients with distal MBO.

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Compliance with Ethical Standards

Conflict of interest No conflict of interest to declare.

Ethical Approval Study protocol followed the guidelines of the World Medical Association Declaration of Helsinki and was approved by the Ethics Committee of our institution (Ethical review no. 2017-SR-307). For this retrospective study, formal consent was not required.

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