Percutaneous transpapillary biliary stent placement for distal malignant biliary obstruction: Outcomes and survival analysis

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ABSTRACT

Background/Aims: *For distal malignant biliary obstruction (MBO), a percutaneous metal stent is usually inserted by the transpapillary method. However, stent-related complications and recurrent biliary obstruction following transpapillary stent placement are concerns, and survival analysis of patients with distal MBO has rarely been done.*

Materials and Methods: *From January 2012 to March 2016, 104 patients underwent transpapillary uncovered metal stent placement for distal MBO at our institution. Clinical success, complications, recurrent biliary obstruction rates, and predictors of survival were analyzed.*

Results: *Of the total 104 patients, clinical success after stent insertion was achieved in 93 patients (90.3%). Major complications were observed in 24 patients (23.1%), which were as follows: cholangitis in 19 patients; pancreatitis in four patients; and biloma in one patient. Recurrent biliary occlusion was observed in 28 patients (26.9%). The median overall survival period was 162 days. The 3-, 6-, and 12-month overall survival rates after stent insertion were 64.4%, 41.3%, and 10.6%, respectively. Results of multivariate analysis indicated that metastatic carcinoma compared with ampullary carcinoma (HR=3.82; 95% CI, 1.30-11.24; p=0.015) and longer biliary stricture (HR=1.04; 95% CI, 1.02-1.06; p<0.001) were independent risk factors for worse survival after metal stent insertion.*

Conclusion: *Transpapillary stent placement was found to be effective with acceptable complication rates for treating distal MBO. Primary tumor and length of biliary stricture were found to be statistically significant independent prognostic factors for survival.*

Keywords: *Biliary stent, malignant biliary obstruction, outcomes, prognostic factors, transpapillary*

INTRODUCTION

Distal malignant biliary obstruction (MBO) is commonly caused by pancreatic carcinoma, cholangiocarcinoma, or metastatic carcinoma. At presentation, most patients are not candidates for curative resection secondary to local spread or distant metastases (1-3). For those patients, percutaneous biliary stenting has become the established palliative treatment owing to its low rate of complications and mortality (3-6), and this treatment contributes to the regression of symptoms and improvement in quality of life (QoL) of patients (7-11).

Because distal biliary obstruction develops near the papilla in most patients with MBO, a metallic biliary stent is placed with one end in the duodenum to ensure better bile drainage (12,13). Generally, recurrent biliary obstruction and infectious complications following the transpapillary procedure are concerns (14). However, results of recent studies have revealed that percutaneous stent placement across the main duodenal papilla seems to prevent early infectious complications (15,16). In addition, at least in the short-to-medium term, cholangitis is not a critical problem, and transpapillary stent placement continues to be used to prevent tumor overgrowth in patients with MBO (17,18).

In the series of studies evaluated here, in the majority of patients, stents remained patency for the remainder of the patient's life (11,19). Thus, particular efforts should be made to identify factors predictive of survival in patients with distal malignant biliary strictures. There is a paucity of studies that have evaluated factors that may impact survival in patients with distal MBO, such as patient-, tumor-, and stent-related characteristics (20-22). However, in the setting of limited data concerning clinical outcomes of percutaneous stent insertion in patients with distal MBO, predictors of survival following transpapillary stent insertion have not been fully illustrated or analyzed.

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Therefore, large-scale studies are needed to investigate the safety and efficacy of percutaneous transpapillary stent insertion in patients with distal MBO and to determine which subgroups of patients with distal MBO would benefit from stents placed across the sphincter of Oddi.

We conducted this retrospective study to evaluate the outcomes of uncovered metal stent insertion by the percutaneous transpapillary method for patients with distal MBO. We also attempted to clarify the predictive factors of overall survival.

MATERIAL AND METHODS

The study procedures followed the guidelines of the World Medical Association Declaration of Helsinki and were approved by the Ethics Committee of the First Affiliated Hospital with Nanjing Medical University. For this retrospective study, formal consent of the patients was not required.

Patient population

From January 2012 to March 2016, percutaneous transhepatic metal stents were placed in 368 patients with MBO at our institution. In all cases, diagnoses were based on radiological and laboratory examinations, with or without pathological results. Exclusion criteria were as follows: hilar lesions (185 patients); double stent placement (44 patients); previous surgery of the biliary tract (10 patients); metal stent insertion combined with a plastic stent for internal drainage (11 patients). In addition, those who were lost to follow-up (18 patients) were also excluded. Finally, 104 patients were enrolled in this study. Of these, 59 patients were diagnosed based on pathological results.

Clinical data of patients from the medical records and follow-up telephone calls were retrospectively collected. They included age, sex, primary tumor, preoperative external drainage, level of total bilirubin, length of biliary stricture, performance status, and complications.

Therapeutic strategy of stent insertion

Before stent insertion, contrast-enhanced abdominal computed tomography, magnetic resonance imaging, or both were performed for all patients. Broad-spectrum antibiotics were administered to the patients before the procedure.

Percutaneous transhepatic stent placement was performed under fluoroscopic guidance. If no combined infections or hemobilia developed during the percutaneous transhepatic biliary drainage (PTBD) procedure, the stent was inserted at the same time. If the patient developed infection or experienced bleeding, external drainage was performed 2-7 days before stent insertion. After obtaining the cholangiograms, the location and length of the biliary stricture were confirmed. The stent was inserted by the transpapillary method with the distal end protruding into the duodenum. In addition, an 8.5-F external drainage catheter was placed in some patients to check stent function after stent placement. The uncovered stents used in this study were E-Luminexx stents (Bard, Germany), which were 8 mm in diameter and 6 or 8 cm in length.

Patients were followed up at an outpatient clinic and were advised to immediately report to the hospital if fever or jaundice developed. For patients who presented with recurrent jaundice, complete blood count was assessed and upper abdomen-enhanced CT imaging was performed. After stent dysfunction was detected, repeat drainage was conducted if possible. All patients were followed up until September, 2016.

Study endpoints and definitions

Distal MBO is typically defined as a biliary stricture located at or below the orifice of the cystic duct. The primary endpoint was overall survival. The survival period was defined as the period from initial stent placement to death or to the end of follow-up. Clinical success was defined as a decrease in serum bilirubin level to <50% of the pretreatment value within two weeks of stent placement. All complications were divided into major or minor according to the guidelines issued by the Society of Interventional Radiology Standards of Practice Committee. Complications such as cholangitis, pancreatitis, and bleeding were diagnosed based on the TOKYO criteria (23). Recurrent biliary obstruction was defined as recurrent jaundice, an increase in serum bilirubin levels, or biliary dilation, as observed on imaging findings (23). Basically, time to recurrent biliary obstruction was regarded as a pure interval between stent insertion and recurrent biliary obstruction.

Statistical analysis

Statistical analysis was performed using SAS 9.3. Data are presented as mean and standard deviation for continuous variables and as frequency and percent for categorical variables. Univariate analysis was performed using a Cox regression model. A multivariate Cox regression model was used to evaluate independent prognostic factors. A forward or backward variable selection method was used to select the covariates by applying an alpha=0.2 removal criteria. p value of <0.05 was considered statistically significant.

RESULTS

Patient characteristics

Patient characteristics are summarized in Table 1. Primary tumor of MBO was cholangiocarcinoma in 19 cases, gallbladder carcinoma in eight cases, pancreatic carcinoma in 43 cases, ampullary carcinoma in six cases, and metastatic tumor in 28 cases. Metastasis originated from gastric carcinoma in 24 cases, colon carcinoma in three cases, and ovarian carcinoma in one case.

Clinical outcomes and complications

Stents were percutaneously inserted in all patients. Clinical success was achieved in 93 (90.3%) patients. Among the remaining 11 patients, the serum level of bilirubin increased after stent insertion in two of the patients, at which point the reserved external drainage catheter was opened. Three patients for whom clinical success was not achieved died one month after stent insertion. For another six patients, the serum bilirubin level decreased after one month into the follow-up period without any further interventional treatment.

Table 1. Patients characteristics for distal malignant biliary obstruction.

Variables	N
Age (years: mean ± SD)	65.9±12.4
Gender (male/female)	74/30
Primary disease	
Cholangiocarcinoma	19
Gallbladder cancer	8
Pancreatic cancer	43
Ampullary carcinoma	6
Metastatic tumor*	28
Performance status	
0	5
1	79
2	20
Total bilirubin (mg/dL: mean ± SD)	13.8±7.1
Pre-drainage	33
Length of stricture (mm: mean ± SD)	28.8±10.7

*Metastatic tumor (28 cases) included gastric carcinoma in 24 cases, colon carcinoma in three cases, and ovarian carcinoma in one case.

The complication of procedure-related bleeding was observed in four patients, all of whom recovered completely without transfusion. Major complications were observed in 24 patients (23.1%): cholangitis in 19 patients; pancreatitis in four patients; and biloma in one patient. All cases of pancreatitis occurred immediately after stent placement. Patients with pancreatitis showed a mean amylase level of 1467.0 IU/L (range 705.6-2551.8). All cases of cholangitis and pancreatitis resolved after 5-7 days of conservative treatment. The patient who developed biloma was managed successfully after external drainage.

Recurrent biliary obstruction and survival

Recurrent biliary obstruction was observed in 28 (26.9%) patients. Of these, 15 patients underwent external drainage, and one patient underwent another stent insertion. The remaining 12 patients did not undergo re-intervention owing to their poor clinical condition. In patients with recurrent biliary obstruction, the median time to recurrent biliary obstruction was 115 days (range 20-750 days). The median time to recurrent biliary obstruction was 144.5 days for all patients. The median survival time for patients with recurrent biliary obstruction who underwent re-intervention was longer than that for those who did not undergo re-intervention (102 vs. 21 days, $p<0.001$).

Based on the results of univariate and multivariate analyses, age [HR=1.04; 95% confidence interval (CI), 1.00-1.08; p=0.047] was found to be a statistically significant independent prognostic factor associated with recurrent biliary obstruction within 90 days of stent insertion (Table 2). Furthermore, we tried to evaluate the predictors of time to recurrent biliary obstruction, but no independent predictors of time to recurrent biliary obstruction were found (Table 3).

In total, 95 patients (91.3%) died after stent insertion during the follow-up period. Six patients died within 30 days of stent insertion. The causes of death were recorded as follows: cardiopulmonary failure in one patient, septic shock in two patients, and rapid progression of primary tumor in three patients. The median survival time was 162 days for all patients, 144 days for patients with cholangiocarcinoma, 162 days for patients with gallbladder carcinoma, 194 days for patients with pancreatic carcinoma, 67 days for patients with metastatic carcinoma, and 267 days for patients with ampullary carcinoma. The 3-month, 6-month, and 12-month cumulative survival rates were 64.4%, 41.3%, and 10.6%, respectively, in all patients (Figure 1).

Table 2. Univariate and multivariate analyses of recurrent biliary obstruction within 90 days in patients with distal malignant biliary obstruction

Variables	Univariate HR (95% CI)	p	Multivariate HR (95% CI)	p
Age (years)	1.03 (0.99-1.06)	0.115	1.04 (1.00-1.08)	0.047
Gender (male/female)	0.73 (0.30-1.79)	0.494	-	-
Primary disease				
Cholangiocarcinoma	-	-	-	-
Gallbladder cancer	0.16 (0.02-1.55)	0.114	0.19 (0.02-1.92)	0.160
Pancreatic cancer	0.38 (0.12-1.18)	0.095	0.38 (0.12-1.22)	0.104
Metastatic tumor	2.00 (0.61-6.55)	0.252	2.42 (0.70-8.33)	0.161
Ampullary carcinoma	0.22 (0.02-2.28)	0.205	0.18 (0.017-1.94)	0.159
Total bilirubin (mg/dL)	1.00 (1.00-1.00)	0.583	-	-
Pre-drainage	0.88 (0.37-2.06)	0.764	-	-
Length of stricture (mm)	1.02 (0.98-1.06)	0.303	-	-

CI: confidence interval.
Forward selection with an alpha level of removal of 0.20 was used. The following variables were removed from the model: age and pre-drainage.

Table 3. Univariate and multivariate analyses of time to recurrent biliary obstruction in patients with distal malignant biliary obstruction

Variables	Univariate HR (95% CI)	p	Multivariate HR (95% CI)	p
Age (years)	1.49 (0.63-3.57)	0.366	-	-
Gender (male/female)	1.44 (0.91-2.29)	0.119	0.99 (0.40-2.47)	0.989
Primary disease				
Cholangiocarcinoma	0.32 (0.07-1.42)	0.132	0.32 (0.07-1.44)	0.136
Gallbladder cancer	0.00 (0.00-0.00)	0.991	0.00 (0.00-0.00)	0.991
Pancreatic cancer	0.33 (0.10-1.06)	0.062	0.33 (0.10-1.08)	0.067
Metastatic tumor	1.14 (0.35-3.73)	0.833	1.14 (0.35-3.73)	0.833
Ampullary carcinoma	-	-	-	-
Total bilirubin (mg/dL)	1.00 (1.00-1.00)	0.830	-	-
Pre-drainage	0.84 (0.38-1.83)	0.653	-	-
Length of stricture (mm)	1.01 (0.97-1.05)	0.757	-	-

CI: confidence interval.
Backward selection with an alpha level of removal of 0.20 was used. The following variables were removed from the model: age pre-drainage; and length of stricture.

Based on the results of univariate and multivariate analyses, metastatic carcinoma compared with ampullary carcinoma (HR=3.82; 95% CI, 1.30-11.24; p=0.015) and length of biliary stricture (HR=1.04; 95% CI, 1.02-1.06; p<0.001) were found to be statistically significant independent prognostic factors associated with survival (Table 4).

DISCUSSION

The primary aims of the usage of metal stents for distal MBO were palliation of jaundice, improvement of QoL, and creation of opportunities for anti-tumor therapy that could prolong survival time. The results of our study suggested that for patients with distal MBO, uncovered

Table 4. Univariate and multivariate analyses of overall survival of patients with distal malignant biliary obstruction.

Variables	Univariate HR (95% CI)	p	Multivariate HR (95% CI)	p
Age (years)	0.99 (0.97-1.01)	0.319	-	-
Gender (male/female)	1.44 (0.91-2.29)	0.119	1.52 (0.93-2.48)	0.096
Primary disease				
Cholangiocarcinoma	3.31 (1.11-9.91)	0.032	2.76 (0.89-8.54)	0.078
Gallbladder cancer	3.71 (1.09-12.65)	0.036	3.23 (0.91-11.44)	0.070
Pancreatic cancer	1.99 (0.70-5.64)	0.197	1.68 (0.58-4.88)	0.339
Metastatic tumor	4.49 (1.54-13.09)	0.006	3.82 (1.30-11.24)	0.015
Ampullary carcinoma	-	-	-	-
Performance status				
0	0.44 (0.13-1.50)	0.190	-	-
1	0.71 (0.42-1.20)	0.207	-	-
2	-	-	-	-
Total bilirubin (mg/dL)	1.00 (1.00-1.00)	0.145	-	-
Pre-drainage	1.04 (0.67-1.61)	0.852	-	-
Length of stricture (mm)	1.04 (1.02-1.06)	<.001	1.04 (1.02-1.06)	<0.001

CI: confidence interval.
Backward selection with an alpha level of removal of 0.20 was used. The following variables were removed from the model: age and pre-drainage.

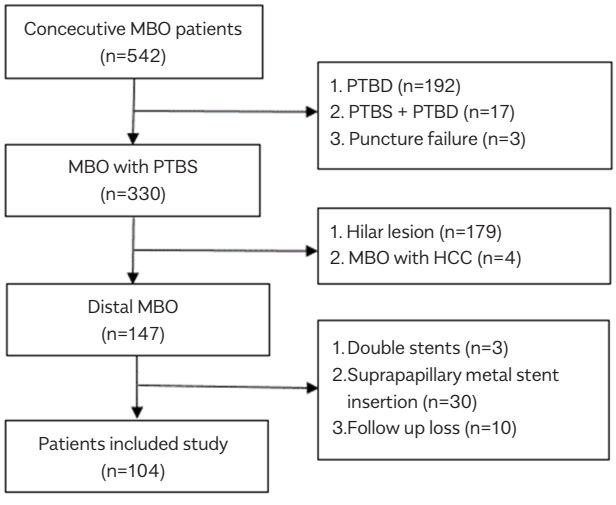

Figure 1. Flowchart of patients' inclusion and exclusion.
MBO: malignant obstructive jaundice; PTBD: percutaneous transhepatic biliary drainage; PTBS: percutaneous transhepatic biliary stent; HCC: hepatocellular carcinoma.

metal stent insertion performed using the percutaneous transpapillary method is a safe and effective therapeutic modality with an acceptable rate of complications. In this study, we analyzed potential prognostic factors including patient and tumor characteristics. The results obtained indicated that primary tumor and length of biliary stricture were independent prognostic factors for overall survival.

Because of the limited life expectancy of patients with unresectable malignant cancer, the most important goal for palliative stent placement is to maintain patency until the patient's death to minimize the re-intervention rate (24). In the present study, approximately two-thirds of patients remained occlusion free until death. In the majority of these patients, the causes of death were disease progression and poor clinical condition, which were not directly related to recurrent biliary obstruction. The rate of recurrent biliary obstruction associated with transpapillary stent implantation was 26.9%, which was acceptable considering the rates observed in previous studies on distal MBO (13,14,18). Here, we hypothesized that distal MBO has better stent patency than proximal biliary stricture (25) because of the lower incidence of tumor

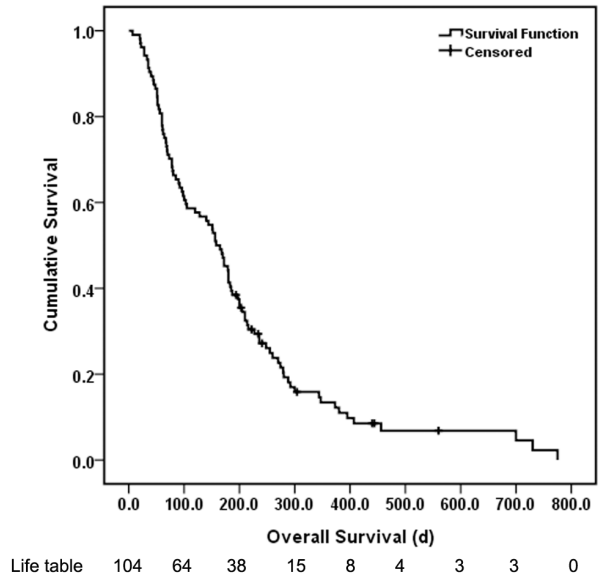

Figure 2. Cumulative overall survival rate after percutaneous transpapillary stent placement for distal malignant biliary obstruction. The median survival time was 162 days. The 3-month, 6-month, and 12-month cumulative survival rates were 64.4%, 41.3%, and 10.6%, respectively.

overgrowth. The patients included in the current study underwent stenting across the sphincter of Oddi, which could have maintained better bile drainage (16). In previous studies, the frequency of stent-related cholangitis owing to transpapillary stent insertion varied from 6.3% to 23.5% (14,18). The rate of occurrence of cholangitis in the present study was 18.3% (19/104), and the values discussed herein fall within the ranges cited in these earlier studies. For these complications, although the suspected cause was duodenobiliary reflux, tumor growth was found to be the major cause of recurrent biliary obstruction, and this finding is inconsistent with those reported in previous studies on uncovered metallic stents (13,17). In fact, clinical evidence has not yet proven that impaired function of the main duodenal papilla triggers cholangitis or vice versa. Here, cholangitis was not the main cause of death; it has always been treated conservatively (4,11,26). Although four patients (one with cholangiocarcinoma, one with gallbladder cancer, one with gastric carcinoma, and one with pancreatic cancer) included in the current study (3.8%) developed procedure-related acute pancreatitis, the rate of occurrence of acute pancreatitis was relatively low. In other reports, the rate was 6.3%-14.9% (18,27). Finally, recovery of all four patients was smooth after conservative treatment, and none of them developed serious acute pancreatitis.

In the current study, the median survival time was 162 days for all patients, which was similar to that reported in previous studies (4,28). The median survival times of patients with ampullary carcinoma, pancreatic carcinoma, gallbladder carcinoma, cholangiocarcinoma, and metastatic carcinoma were 267, 194, 162, 144, and 67 days, respectively. Multivariate analysis revealed that patients with ampullary carcinoma have a better survival rate than those with metastatic carcinoma (267 vs. 67 days, p=0.03). In general, the prognosis of patients with metastatic carcinoma was dismal because of the rapid invasion of neighboring organs and frequent distant metastasis. The median survival of patients with MBO caused by metastatic carcinoma has been reported to be 2.6-3.5 months (21,29). Considering the recommendations made by the current consensus and guidelines (30), plastic stents and novel biliary stents loaded with radiation seeds may be more suitable for patients with distal MBO owing to metastatic carcinoma, and this should be analyzed in further studies.

The length of the biliary stricture provided valuable information for the selection of the proper method for biliary drainage and type of stent. In the current study, the mean length of biliary strictures was 28.8 mm, which was similar to that stated in previous reports (5,11,13,19). Results of univariate and multivariate analyses initially showed the length of the biliary stricture to be a strong predictive factor of survival. Tumor size was proven to be a predictor of survival for patients with biliary tract cancer (20). However, tumor size was almost impossible to measure because of the tumors' asymmetrical growth patterns, especially in extrahepatic cholangiocarcinoma. To some extent, the biliary stricture length was an index of tumor size neighboring the biliary tract. In other words, longer biliary strictures were associated with advanced biological behavior (28). In the current study, 8-cm stents were more frequently used, and the results indicated that the length of the stent was sufficient to prevent tumor overgrowth (6).

We found that age was a predictive factor for recurrent biliary obstruction. A previous study evaluated the risk factors for stent patency, and its results revealed that older age was associated with a shorter patency (31). The reason for the association between age and recurrent biliary obstruction was unclear. The reasons may include the following. First, after stent placement, cholangitis is more commonly developed in the elderly (32). In the present study, the incidence of cholangitis was higher than that in patients aged <68 years of age [11/48 (22.9%) vs. 8/56

(14.3%), p=0.256]. It was believed that repeated episodes of cholangitis contributed to recurrent biliary obstruction (26). Second, less anti-tumor therapy was noted in the elderly, and lack of local tumor control may easily lead to tumor ingrowth through the stent mesh and stent occlusion for uncovered stent. However, further studies on the relationship between age and recurrent biliary obstruction are needed.

This study had some limitations. First, it was a retrospective study with some inevitable bias. Second, there were several primary tumor patterns with different prognoses. The number of patients with each tumor type could be insufficient from a statistical perspective. Third, chemo- or radiotherapy after stent insertion was not analyzed in this study.

In conclusion, the current study demonstrated that percutaneous transpapillary uncovered metal stent insertion is an effective means of treating patients with distal MBO and has acceptable complication rates. Primary tumor and length of biliary stricture were found to be significant independent prognostic factors associated with survival in these patients.

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Supplemental Table 1. Tumor Stage based on the 8th American Joint Committee on Cancer (AJCC).

Primary disease	Stage II	stage III	stage IV	Total
Cholangiocarcinoma	0	9	10	19
Gallbladder cancer	0	3	5	8
Pancreatic cancer	11	8	24	43
Metastatic tumor	0	0	28	28
Ampullary carcinoma	3	2	1	6
Total	14	22	68	104

Supplemental Table 2. Univariate and multivariate analyses of the overall survival of patients with distal malignant biliary obstruction.

Variables	Univariate HR (95% CI)	p value	Multivariate HR (95% CI)	p
Age (years)	0.99 (0.97-1.01)	0.319	-	-
Gender (male/female)	1.44 (0.91-2.29)	0.119	1.52 (0.93-2.48)	0.096
Primary disease				
Cholangiocarcinoma	3.31 (1.11-9.91)	0.032	2.76 (0.89-8.54)	0.078
Gallbladder cancer	3.71 (1.09-12.65)	0.036	3.23 (0.91-11.44)	0.070
Pancreatic cancer	1.99 (0.70-5.64)	0.197	1.68 (0.58-4.88)	0.339
Metastatic tumor	4.49 (1.54-13.09)	0.006	3.82 (1.30-11.24)	0.015
Ampullary carcinoma	-	-	-	-
Performance status				
0	0.44 (0.13-1.50)	0.190	-	-
1	0.71 (0.42-1.20)	0.207	-	-
2	-	-	-	-
Total bilirubin (mg/dL)	1.00 (1.00-1.00)	0.145	-	-
Pre-drainage	1.04 (0.67-1.61)	0.852	-	-
Length of stricture (mm)	1.04 (1.02-1.06)	<0.001	1.04 (1.02-1.06)	<0.001

CI: confidence interval.
Backward selection with an alpha level of removal of 0.20 was used. The following variables were removed from the model: age and pre-drainage

Supplemental Table 3. Univariate and multivariate analyses of the time to recurrent biliary obstruction in patients with distal malignant biliary obstruction patients.

Variables	Univariate HR (95% CI)	p	Multivariate HR (95% CI)	p
Age (years)	1.49 (0.63-3.57)	0.366	-	-
Gender (male/female)	1.44 (0.91-2.29)	0.119	0.99 (0.40-2.47)	0.989
Primary disease				
Cholangiocarcinoma	0.32 (0.07-1.42)	0.132	0.32 (0.07-1.44)	0.136
Gallbladder cancer	0.00 (0.00-0.001)	0.991	0.00 (0.00-0.001)	0.991
Pancreatic cancer	0.33 (0.10-1.06)	0.062	0.33 (0.10-1.08)	0.067
Metastatic tumor	1.14 (0.35-3.73)	0.833	1.14 (0.35-3.73)	0.833
Ampullary carcinoma	-	-	-	-
Total bilirubin (mg/dL)	1.00 (1.00-1.00)	0.830	-	-
Pre-drainage	0.84 (0.38-1.83)	0.653	-	-
Length of stricture (mm)	1.01 (0.97-1.05)	0.757	-	-

CI: confidence interval.
Backward selection with an alpha level of removal of 0.20 was used. The following variables were removed from the model: age, pre-drainage, and length of stricture.