Risk factors for dysfunction of preoperative endoscopic biliary drainage for malignant hilar biliary obstruction

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This retrospective study was approved by the Institutional Review Board of Hokkaido University Hospital (018-0403).

Abstract

Background: Few studies have focused on the risk factors for dysfunction of endoscopic biliary drainage (EBD) in preoperative patients with malignant hilar biliary obstruction (MHBO).

Methods: We searched the database between February 2011 and December 2018 and identified patients with MHBO who underwent radical operation. The rate of dysfunction of the initial EBD, risk factors for dysfunction of the initial EBD and survival after surgery were retrospectively evaluated.

Results: We analyzed a total of 131 patients [95 males (72.5%); mean age, 69.5(±7.3) years; Bismuth-Corlette classification (BC) I/II/IIIa/IIIb/IV, 50/26/22/17/16; hilar cholangiocarcinoma/gall bladder cancer, 115/16]. Dysfunction of the initial EBD occurred in 28patients (21.4%). The cumulative incidences of dysfunction of the initial EBD in all patients were 18.4%, 38.2% and 47.0% at 30, 60 and 90days, respectively (Kaplan–Meier method). The rate of dysfunction of the initial EBD increased in patients with BC-IV (*P*=0.03). Multivariate analysis showed that BC-IV and pre-EBD cholangitis were significantly associated with the occurrence of dysfunction of the initial EBD. Survival rates were not significantly different according to the initial biliary drainage methods and presence/absence of the initial EBD dysfunction.

Conclusions: Dysfunction of the initial EBD frequently occurs in patients with the BC-IV and those with pre-EBD cholangitis.

Keywords: Endoscopic biliary drainage, Preoperative biliary drainage, Malignant hilar biliary obstruction, Hilar cholangiocarcinoma, Gall bladder cancer

Abbreviations:

BC, Bismuth-Corlette classification; EBD, endoscopic biliary drainage; EBS, endoscopic biliary stenting; ENBD, endoscopic nasobiliary drainage; ERC, endoscopic retrograde cholangiography; MHBO, malignant hilar biliary obstruction; PTBD, percutaneous transhepatic biliary drainage; PTPE, percutaneous transhepatic portal vein embolization; T-BIL, total bilirubin

Introduction

Secure treatment of malignant hilar biliary obstruction (MHBO) remains challenging. Surgical resection is the only effective method for radical cure of primary MHBOs, which are caused by cholangiocarcinoma and gallbladder cancer.[1-3] In many cases, preoperative biliary drainage is needed in order to assess the surgical resectability and obtain pathological confirmation.[4] There are various procedures for preoperative biliary drainage for MHBO, including percutaneous transhepatic biliary drainage (PTBD) and endoscopic biliary drainage (EBD) comprising endoscopic nasobiliary drainage (ENBD) and endoscopic biliary stenting (EBS) by a plastic stent. PTBD is not recommended as a routine preoperative drainage procedure because of the possibility of tumor seeding and severe complications.[5,6] The Japanese guideline for the management of preoperative MHBO recommends ENBD as the first-line approach.[4] EBS frequently causes stent occlusion and frequently requires biliary re-interventions;[6,7] however, EBS is often selected because some patients cannot tolerate ENBD placement for a long time.

There have been several studies that focused on complications caused by EBD and need for re-intervention.[6-10] During the preoperative waiting period, dysfunction of EBD frequently results in the need for biliary re-interventions and postponement of surgery, occasionally leading to abort of surgery due to tumor progression. However, few studies have focused on the risk factors for dysfunction of EBD in patients with MHBO.

The aim of the present study was to identify risk factors for dysfunction of EBD in preoperative patients with MHBO.

Patients and methods

This was a retrospective cohort study conducted at Hokkaido University Hospital, a tertiary referral center. We searched the database for consecutive patients with MHBO who underwent radical surgical resection at Hokkaido University Hospital (Department of Gastroenterological Surgery I and Department of Gastroenterological Surgery II) between February 2011 and December 2018, and we identified them for this study. The inclusion criteria were 1) diagnosis of cholangiocarcinoma or gallbladder cancer by histopathological analyses of surgical specimens, 2) main biliary stricture being located within 2 cm from the hepatic hilum, 3) functional success after the initial EBD, and 4) patient's or their families' agreement to enrollment in this study by the opt-out form. In the present study, functional success was defined as 1) a decrease in serum total bilirubin (T-BIL) from > 2.0 mg/dL to ≤ 2.0 mg/dL, 2) a decrease in serum T-BIL by half from > 2.0 mg/dL or 3) 50% or more decrease of hepatobiliary enzymes in the case of serum T-BIL being 2.0 mg/dL or less within fourteen days after biliary drainage. The exclusion criteria were 1) having undergone PTBD before the initial EBD, 2) multiple EBD tubes/stents, 3) removal of an EBD tube at the discretion of the endoscopist or surgeons because of a lose biliary stricture after EBD, 4) having received preoperative chemotherapy or radiation therapy, and 5) refusal for enrollment in this study by the patients or their families. For simplifying analysis of the risk of the initial EBD dysfunction, we excluded the patients with multiple EBD tubes/stents.

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki (6th revision, 2008) as reflected in *a priori* approval by the study institution's Human Research Committee. The study was approved by the Institutional Review Board of Hokkaido University Hospital (018-0403).

Endoscopic retrograde cholangiography and EBD procedure

Endoscopic retrograde cholangiography (ERC) was performed under conscious sedation. A therapeutic duodenoscope (TJF-240 or TJF-260V; Olympus Medical Systems Co., Tokyo, Japan) was used with the standard station approach. Selective bile duct cannulation was performed using the wire-guided cannulation method. If this method failed, the double-guidewire technique or precut papillotomy was performed at the discretion of the endoscopist. After bile duct cannulation, the bile duct was filled with a contrast medium until the intrahepatic bile ducts were visualized. If there was no filling of the intrahepatic bile ducts on ERC, a guidewire was advanced to the tip of a graphic catheter, through the stricture, and into the dilated bile duct in the future remnant lobe through the stricture. ERC was performed until the intrahepatic bile ducts in the future remnant lobes were visualized. Following the ERC, endoscopic transpapillary multiple biopsies from the primary lesions and other lesions were performed under fluoroscopic guidance using biopsy forceps. Preoperative EBD was performed in the future remnant lobe using a single EBD tube/stent. In general, the future remnant lobe will usually be the left lobe in patients with Bismuth-Corlette classification (BC) I, BC-II, BC-IIIa, or BC-IV because carcinoma frequently involves the right hepatic artery. On the other hand, the future remnant lobe will be the right lobe in patients with BC-IIIb because of the site of the primary tumor.

The endoscopist used a single EBD tube/stent. ENBD was chosen as the first EBD procedure based on the Japanese guideline[4] except for cases who rejected ENBD or assumed not to tolerate ENBD at the discretion of a primacy physician. Regarding the ENBD tube, the endoscopist firstly schemed to select a 6-Fr or 7-Fr tube; however, if insertion of such an ENBD tube was difficult, a 5-Fr ENBD tube was selected. Regarding the stent for EBS, the endoscopist fundamentally schemed to select a 7-Fr stent. The type of the used EBD tube/stent was a straight type or pigtail type. Endoscopic sphincterotomy was performed at the discretion of the endoscopist. When the scheduled surgical procedure was changed based on resectability assessment, additional EBD tubes/stents were placed in both the originally intubated area and a new future remnant lobe. A prophylactic pancreatic stent was inserted for preventing post-ERC pancreatitis in high-risk patients as previously reported.[11]

Dysfunction of EBD was defined as occlusion or dislocation of an EBD tube/stent. Occlusion of an EBD tube/stent was defined as 1) a decrease in the amount of bile flow by more than 50% compared with that the day before the event and not being revised by washout or 2) increases in serum hepatobiliary enzymes which can improve after exchange of the tube/stent. Contralateral segmental cholangitis was presumed as an adverse event in this study, because it is caused by tumor-related obstruction, not by EBD tube/stent dysfunction. Dislocation of an ENBD tube/stent for EBS was defined as migration of the tip of the tube/stent from the original drainage area as assessed by a roentgenogram. Self-removal of the ENBD tube by a patient was defined as dislocation of ENBD. Pre-EBD cholangitis was defined as cholangitis that occurred before the initial EBD and that was improved with the initial EBD. Adverse events of the initial EBD were graded according to the severity grading system of the American Society for Gastrointestinal Endoscopy lexicon.[12] Early and late adverse events were defined as those occurring within 14 days and more than 14 days of EBD, respectively. Contralateral segmental cholangitis was defined as cholangitis that occurred in an undrained area. In patients with contralateral segmental cholangitis, an additional EBD tube was placed in the segment in which the cholangitis had occurred. The contiguous extent of the primary tumor (T factor) and the absence/presence of regional lymph node metastasis were defined according to the classification of biliary tract cancers established by the Japanese Society of Hepato-Biliary-Pancreatic Surgery: 3rd English Edition.[13]

Outcome measures

The outcomes measures included rate and details of dysfunction of the initial EBD according to the BC grade and the biliary drainage method, risk factors for dysfunction of the initial EBD, and prognostic factors of survival: age (≤70 or >70 year), sex (male or female), final diagnosis (cholangiocarcinoma or gallbladder cancer), BC grade (I/II/IIIa/IIIb or IV), serum T-BIL level before the initial EBD (≤2.0 mg/dL or >2.0 mg/dL), cholangitis before the initial EBD (presence or absence), biliary drainage method (ENBD or EBS), diameter of the EBD tube/stent (≤6-Fr or ≥7-Fr), type of the EBD tube/stent (straight or pigtail), endoscopic sphincterotomy (presence or absence), preoperative waiting period (≤60 days or >60 days), presence/absence of dysfunction of the initial EBD, presence/absence of percutaneous transhepatic portal vein embolization (PTPE) before surgery, presence/absence of PTBD until surgery, and N category by histopathological analyses of surgical specimens were used as covariates. Adverse events of the initial EBD were also analyzed.

Statistical analysis

Statistical analysis was performed using GraphPad Prism software 7.0 (GraphPad Software Inc., San Diego, CA) and the free software EZR.[13] Results are shown as means (SD) for quantitative variables, medians (range, IQR) for nonparametric variables, and percentages for categorical variables. The chi-squared test was conducted to compare adverse event rates between biliary drainage methods. The cumulative incidences of EBD dysfunction and survival from the day of surgery were estimated using the Kaplan–Meier method. The differences in BC grades and biliary drainage methods were evaluated by the log-rank test. The Mann–Whitney U test was conducted to compare the median follow-up period from the initial EBD between the two groups. The risk factors for dysfunction of the initial EBD and prognostic factors of survival were analyzed using the Cox proportional hazard model. Factors with a P value < 0.10 in the univariate analysis were then included in multivariate analysis. Differences were considered statistically significant at a P value of < 0.05.

Results

Baseline characteristics

By search of the database, 174 patients who underwent preoperative EBD and radical surgical resection were identified during the period, and 131 patients were finally analyzed in the present study (Figure 1). The baseline characteristics of the patients, and details of EBD and radical surgery are shown in Table 1. The patients included 95 males and 36 females with a mean age of 69.5 (± 7.3) years. The final diagnoses were cholangiocarcinoma in 115 patients and gallbladder cancer in 16 patients. BC grades were I in 50 patients, II in 26 patients, IIIa in 22 patients, IIIb in 17 patients and IV in 16 patients. Ninety-six patients underwent ENBD and 35 patients underwent EBS. An inside plastic stent (plastic stent intubated above the papilla) was placed in three patients (8.6%) in EBS group. All patients achieved a functional success and underwent radical surgical resection as scheduled. There was no patient for whom radical surgical resection was canceled due to intraoperative metastatic findings.

Dysfunction of the initial EBD

Dysfunction of the initial EBD occurred in 28 patients (21.4%). The details of dysfunction of the initial EBD were occlusion in 20 patients and dislocation in 8 patients. The cumulative rate of dysfunction of the initial EBD in all patients is shown in Figure 2A: 18.4%, 38.2% and 47.0% at 30, 60 and 90 days, respectively. The cumulative rate of dysfunction of the initial EBD in patients with BC-IV was higher than that in patients with BC-I/II/IIIa/IIIb ($P = 0.03$) (Fig. 2B), while they were not significantly different between patients with ENBD and those with EBS ($P = 0.09$).

Twenty-nine patients underwent radical resection without re-intervention during preoperative waiting period. Dysfunction of the initial EBD occurred in 28 patients. The remaining 74 patients underwent re-intervention for re-biopsy in 42 patients, conversion to another drainage method in 22 patients and adverse event including contralateral segmental cholangitis, pancreatitis and bleeding after endoscopic sphincterotomy in 10 patients.

To evaluate the factors influencing the risk factors of dysfunction of the initial EBD, we performed univariate analysis of the characteristics of the patients and EBD procedures (Table 2). The rates of dysfunction of EBD were significantly different between BC classes (P = 0.03). Dysfunction tended to occur in patients with pre-EBD cholangitis and EBS (P < 0.10). The results of multivariate analysis showed that patients with BC-IV and pre-EBD cholangitis were independent predictive factors of dysfunction of the initial EBD [hazard ratio = 3.36 (P = 0.01) and 32.9 (P = 0.03), respectively].

The median follow-up period from the initial EBD in patients with unplanned re-intervention (n=57) was longer than that in the other patients with planned re-intervention (n=74) (36 days verses 21 days, P = 0.01). Therefore, we also evaluated the factors influencing the risk factors of dysfunction of the initial EBD only in the 57 patients with unplanned re-intervention. The univariate analysis revealed that BC-IV was a significant risk factor of the initial EBD dysfunction (P = 0.04). Presence of pre-EBD cholangitis (n=11) was not a risk factor of the initial EBD dysfunction in this analysis [hazard ratio = 1.52 (95% CI 0.61-3.78), *P* = 0.37]. The result of multivariate analysis showed that BC-IV was an independent predictive factor of the initial EBD dysfunction [hazard ratio = 3.19 (95% CI 1.22-8.31), *P* = 0.02].

Adverse events

During the study period, 31 patients (23.7%) suffered from 31 adverse events (Table 3). The adverse events rates were 25.0% and 11.4% in patients with ENBD and those with EBS, respectively (*P* = 0.09). Pancreatitis occurred in 19 patients. One of those 19 patients had moderate pancreatitis due to compression of the pancreatic duct by an ENBD tube 21 days after the initial ENBD, and the event was successfully treated by addition of endoscopic nasopancreatic drainage. Contralateral segmental cholangitis occurred in seven patients. Six of those 7 patients underwent additional ENBD and one patient required percutaneous drainage because of difficulty in endoscopic re-intervention. One patient with cholecystitis underwent cholecystectomy three days after ENBD.

Survival rate

The survival rates after the curative surgery are shown in Figure 3A; the median of survival time in all cases was 3.8 years. The survival rates were not significantly different between the initial biliary drainage methods (ENBD versus EBS) ($P = 0.08$) (Figure 3B) and presence of dysfunction of the initial EBD ($P = 0.78$) (Figure 3C). The univariate analysis revealed that presence of PTBD until surgery and regional lymph node metastasis by histopathological analyses of surgical specimens were significant prognostic factors ($P < 0.05$), and that EBS, thin EBD tube/stent (≤ 6-Fr) and PTPE before surgery were candidates of prognostic factors ($P < 0.10$). The multivariate analysis revealed that presence of regional lymph node metastasis was an independent prognostic factor of survival (hazard ratio = 2.46, $P < 0.01$] (Table 4).

Discussion

This is the first study that focused on the risk factors for dysfunction of the initial EBD in preoperative patients with MHBOs. Nakai et al. reported that the rate of unplanned re-intervention, which is practically a synonym of dysfunction of the initial ENBD/EBS in the present study, was 31.0% in the both ENBD and EBS groups;[9] however, their study revealed only the incidence of EBD dysfunction and not the time to dysfunction of EBD. The preoperative waiting period is affected by various factors such as the necessity of repeated pathological confirmations and re-intervention for cholangitis and portal vein embolization. Dysfunction of EBD causes frequent biliary re-interventions and postponement of surgery, which can lead to cancellation of surgery due to tumor progression. Therefore, the prediction of time to dysfunction of EBD according to BC grade and the prevention are available for the preoperative patients with MHBO.

The present study revealed that dysfunction of EBD frequently occurred in patients with BC-IV. We therefore speculate that a large stricture length from the hilum to the peripheral bile duct in the future remnant liver negatively affects the patency and stability of an EBD tube as was previously reported.[8] In patients with BC-IV, the bile duct for EBD was the 2nd/3rd branch duct and was narrower than that for patients with BC-I-III because of spread of tumor. Therefore, even if the tip of an EBD tube is slightly misaligned due to movements of the upper gastrointestinal tract, dysfunction of EBD could frequently occur in patients with BC-IV.

In the multivariate analysis of risk factors of dysfunction of the initial EBD in all patients, pre-EBD cholangitis was one of the independent predictive factors. The patients with pre-EBD cholangitis undergo antibiotic treatment and EBD; however, bacterial proliferation before EBD can be one of the driving forces to sludge formation in biliary tracts after EBD,[14] which can lead to dysfunction of an EBD tube/stent. Meanwhile, in patients with unplanned re-intervention alone, pre-EBD cholangitis was not an independent risk factor of the initial EBD dysfunction. It was possible that the number of patients was small (n=57) or the effect of bias couldn't be fully excluded.

Nakai et al. also reported that unplanned re-intervention was associated with a poor prognosis in patients with MHBO resected.[9] The present study showed that the independent predictive factors of dysfunction of initial EBD were BC-IV and pre-EBD cholangitis. Therefore, the patients with such factors should undergo as early radical surgical resection as possible, or bilateral EBD should be considered at an early stage.

PTBD should be also considered for patients with BC-IV, but not endoscopic biliary drainage alone.

Previous studies showed that ENBD was superior to EBS and PTBD as a routine preoperative drainage technique.[4,6,7,15] However, some recent retrospective studies failed to show advantages of ENBD over EBS and PTBD as the initial preoperative biliary drainage in terms of unplanned re-interventions, adverse events and prognosis[9,10] as well as the present study. Further prospective studies are needed to determine precise times to dysfunctions of ENBD, EBS or PTBD and postoperative survivals, and to compare these drainage methods. In addition, as we didn't have data associating preoperative parameters with detailed postoperative complications in this study, future study should also include such a data and analysis. Meanwhile, the integrated inside EBS and ENBD catheter system was recently reported.[16] It is also necessary to investigate the new preoperative EBD method for patents with MHBO.

At present, neoadjuvant therapy is controversial in patients with biliary tract cancer. Recently, several studies have shown that neoadjuvant therapy, which includes chemotherapy and chemoradiation therapy, is useful for increasing resectability and extending the recurrence free-survival and overall survival in patients with biliary tract cancer.[17-20] If neoadjuvant therapy is selected, the preoperative waiting period will be extended compared with that in the case of upfront surgery. Management of ENBD is complicated for patients during neoadjuvant therapy. Therefore, EBS might be the most suitable method for the initial biliary drainage in terms of compliance during the period.

There are several limitations in the present study. First, this study was a single-center, retrospective, non-randomized study. Second, a primary physician chose EBD at their discretion in some cases. Third, patients who had received preoperative chemotherapy or radiation therapy were excluded from this study.

In conclusion, dysfunctions of the initial EBD frequently occur in patients with the BC-IV and those with cholangitis before EBD.

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Figure legends

Figure 1

Flow chart of the subjects in the present study.

EBD, endoscopic biliary drainage; EBS, endoscopic biliary stenting; ENBD, endoscopic nasobiliary drainage; PTBD, percutaneous transhepatic biliary drainage.

Figure 2

(A) Cumulative incidence of endoscopic biliary drainage (EBD) dysfunction.

(B) Cumulative incidence of EBD according to the Bismuth-Corlette classification (BC). The cumulative dysfunction rate of the initial EBD in patients with BC-IV was higher that in patients with BC-I/II/IIIa/IIIb (P = 0.03).

Figure 3

(A) Survival rate in all cases.

(B) Survival rates according to the biliary drainage methods. The survival rates were not significantly different between the EBD methods (P = 0.08).

(C) Survival rates according to the presence/absence of the EBD dysfunction. The survival rates were not significantly different (*P* = 0.78).

Tables

Table 1. Baseline characteristics of patients

Male / Female, n	95 / 36
Age, mean (±SD), years	69.5 (± 7.3)
Final diagnosis, n (%)	
Cholangiocarcinoma	115 (87.8)
Gallbladder cancer	16 (12.2)
Bismuth-Corlette classification, n	
I / II / IIIa / IIIb / IV	50 / 26 / 22 / 17 / 16
Laboratory data	
Total bilirubin, median (range), mg/dL	3.1 (0.4 – 26.6)
Alkaline phosphatase, median (range), U/L	1078 (204 – 5334)
γ-Glutamyltranspeptidase, median (range), U/L	745 (30 – 3222)
White blood cells, median (range), $/m^3$	5810 (2950 – 18700)
C-reactive protein, median (range), mg/dL	0.49 (0.02 – 14.63)
ICG-R15, median (range), % (n = 122)	8.9 (1.3 – 35.7)

Total bilirubin >2.0 mg/dL, n (%)	80 (61.1)
Pre-EBD cholangitis, n (%)	15 (11.5)
Assortment of the EBD	
ENBD, n (%)	96 (73.3)
≤ 6-Fr, n	75
≥ 7-Fr, n	21
EBS, n (%)	35 (26.7)
7-Fr, n	30
8.5-Fr, n	5
Type of the EBD tube, n (%)	
Straight	114 (87.0)
Pigtail	17 (13.0)
Endoscopic sphincterotomy, n (%)	62 (47.3)
Preoperative waiting period, median (range; IQR), days	63 (5 – 180; 50 – 83)
Percutaneous transhepatic portal vein embolization until surgery, n (%)	75 (57.3)

Surgical procedure, n	
Extrahepatic bile duct resection only	3
Hilar resection + pancreatoduodenectomy	16
Hilar resection + hepatectomy of segment 4a	1
Hilar resection + hepatectomy of segment 4a/5	1
Hilar resection + central bisegmentectomy of the liver	1
Hilar resection + left hepatectomy	25
Hilar resection + left hepatic trisegmentectomy	6
Left hepatectomy + pancreatoduodenectomy	7
Left hepatic trisegmentectomy+ pancreatoduodenectomy	1
Hilar resection + right hepatectomy	50
Hilar resection + hepatic trisegmentectomy	4
Right hepatectomy + pancreatoduodenectomy	15
Right hepatic trisegmentectomy+ pancreatoduodenectomy	1
T factor	
Hilar cholangiocarcinoma	

T1a/T1b/T2a/T2b/T3/T4a/T4b, n	2/1/3/46/21/15/3/10
Distal cholangiocarcinoma	
T1b/T2/T3a/T3b, n	2/10/2/1
Gallbladder cancer	
T3a/T3b/T4a/T4b, n	1/9/2/4
Presence of regional lymph node metastasis, n (%)	68 (51.9)

ICG-R15, indocyanine green retention value at 15 minutes; EBD, endoscopic biliary drainage; EBS, endoscopic biliary stenting; ENBD, endoscopic nasobiliary drainage

Table 2. Univariate and multivariate analyses of risk factors for dysfunction of the initial EBD.

	Univariate analysis		Multivariate analysis		
	n	*P*-value	Hazard ratio	95%CI	*P*-value
Age		0.65			
≤ 70 years	64				
> 70 years	67				
Sex		0.44			
Male	95				
Female	36				
Final diagnosis		0.64			
Cholangiocarcinoma	114				
Gallbladder cancer	17				
Bismuth-Corlette classification		0.04			
I/II/IIIa/IIIb	115		1		
IV	16		3.36	1.30-8.68	0.01

Serum T-BIL before initial EBD		0.49			
≤ 2.0 mg/dL	51				
> 2.0 mg/dL	80				
Cholangitis before initial EBD		0.08			
Absence	116		1		
Presence	15		2.91	1.14-7.47	0.03
Biliary drainage method		0.09			
ENBD	96		1		
EBS	35		2.11	0.97-4.59	0.06
Size of the EBD tube/stent		0.49			
≤ 6-Fr	56				
≥ 7-Fr	75				
Type of EBD tube/stent		0.43			
Straight	114				
Pigtail	17				
Endoscopic sphincterotomy		0.11			

Absence	69	
Presence	62	
Preoperative waiting period		0.12
> 60 days	71	
≤ 60 days	60	

EBD, endosocpic biliary dranage; EBS, endosocpic biliary stenting; ENBD, endoscopic nasobiliary drainage; T-BIL, total-bilirubin

Table 3. Adverse events.

	Mild	Moderate	Severe
Early (≤14 days), n			
Pancreatitis	12	6	0
Contralateral segmental cholangitis	0	2	0
Cholecystis	0	1	1
Bleeding	1	2	0
Delayed (≥15 days), n			
Pancreatitis	0	1	0
Contralateral segmental cholangitis	5	0	0

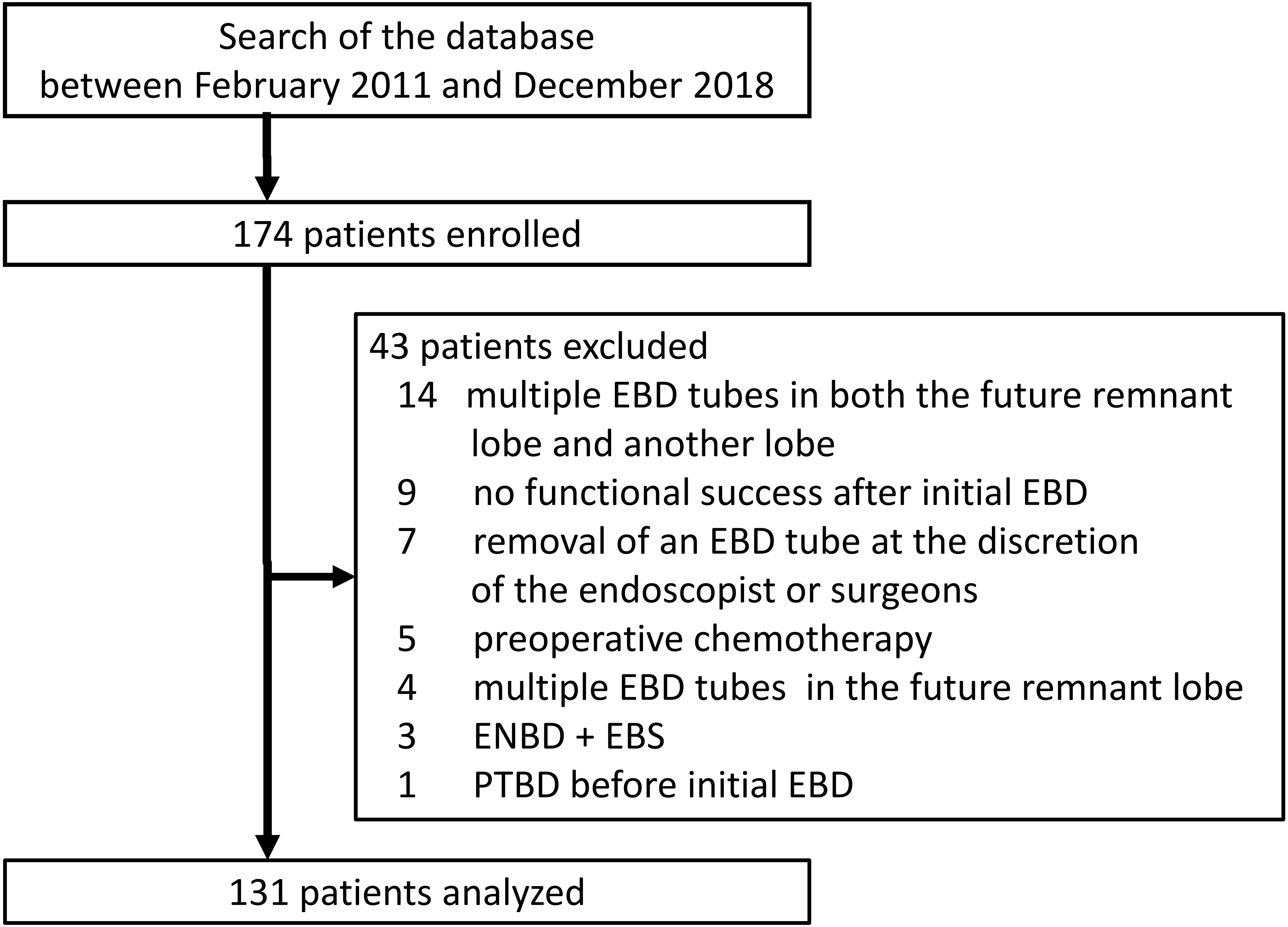
Table 4. Univariate and multivariate analyses of prognostic factors of survival

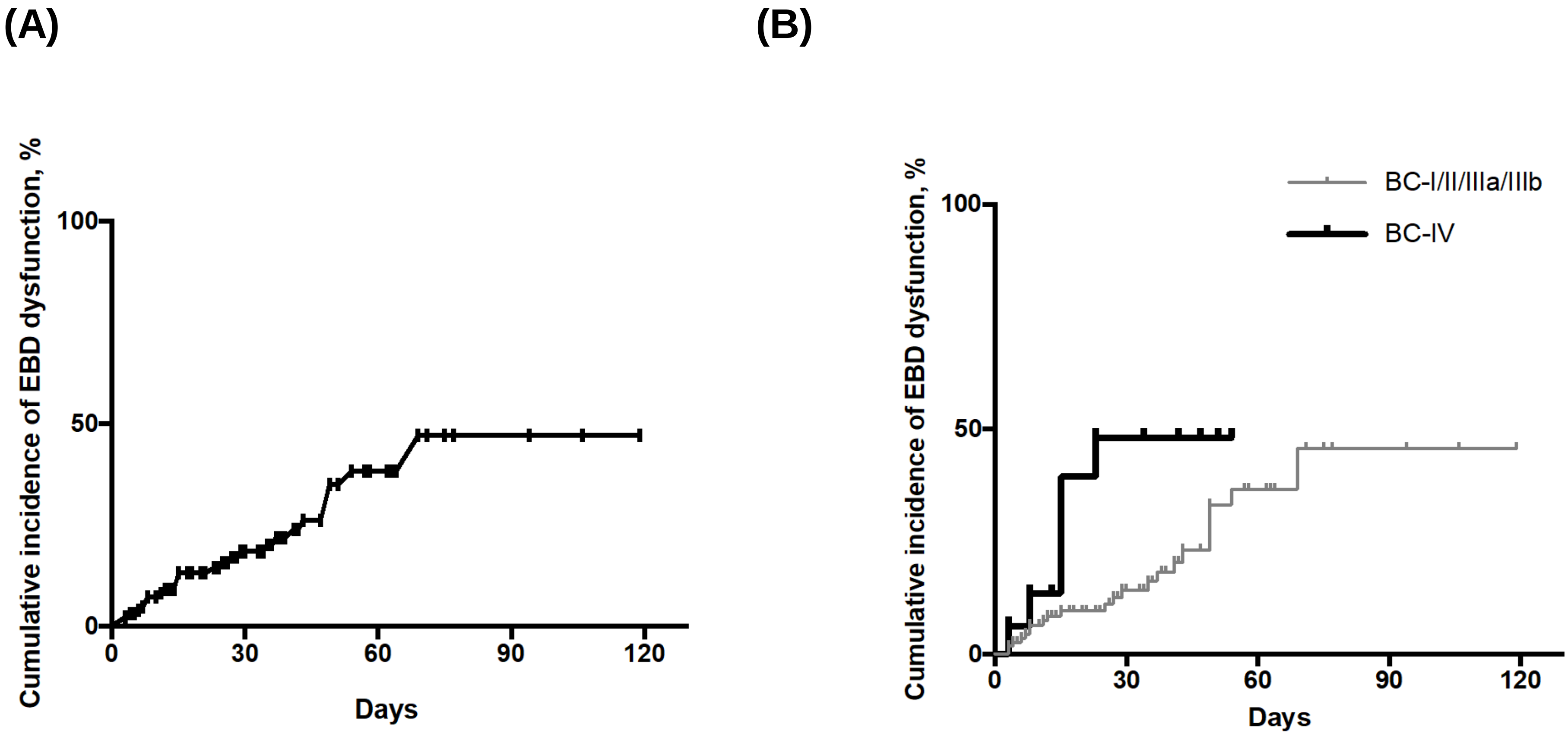
	Univariate analysis		Multivariate analysis		
	n	*P*-value	Hazard ratio	95%CI	*P*-value
Age		0.28			
≤ 70 years	64				
> 70 years	67				
Sex		0.66			
Male	95				
Female	36				
Final diagnosis		0.11			
Cholangiocarcinoma	114				
Gallbladder cancer	17				
Bismuth-Corlette classification		0.82			
I/II/IIIa/IIIb	115				
IV	16				
Serum T-BIL before initial EBD		0.15			

≤ 2.0 mg/dL	51				
> 2.0 mg/dL	80				
Cholangitis before initial EBD		0.66			
Absence	116				
Presence	15				
Biliary drainage method		0.08			
ENBD	96		1		
EBS	35		1.08	0.51-2.29	0.83
Size of an EBD tube/stent		0.07			
≤ 6-Fr	56		1		
≥ 7-Fr	75		0.78	0.40-1.56	0.49
Type of an EBD tube/stent		0.82			
Straight	114				
Pigtail	17				
Endoscopic sphincterotomy		0.72			
Absence	69				

Presence	62				
Preoperative waiting period		0.23			
> 60 days	71				
≤ 60 days	60				
Dysfunction of the initial EBD		0.78			
Absence	103				
Presence	28				
PTPE before surgery		0.13			
Absence	56				
Presence	75				
PTBD until surgery		0.03			
Absence	125		1		
Presence	6		2.22	0.86-5.72	0.10
Regional lymph node metastasis		< 0.01			
Absence	63		1		
Presence	68		2.46	1.46-4.15	< 0.01

EBD, endosocpic biliary dranage; EBS, endosocpic biliary stenting; ENBD, endoscopic nasobiliary drainage; PTBD, percutaneous transhepatic biliary drainage; PTPE, percutaneous transhepatic portal vein embolization; T-BIL, total-bilirubin


Search of the database
between February 2011 and December 2018
174 patients enrolled
43 patients excluded
14 multiple EBD tubes in both the future remnant lobe and another lobe
9 no functional success after initial EBD
7 removal of an EBD tube at the discretion of the endoscopist or surgeons
5 preoperative chemotherapy
4 multiple EBD tubes in the future remnant lobe
3 ENBD + EBS
1 PTBD before initial EBD
131 patients analyzed



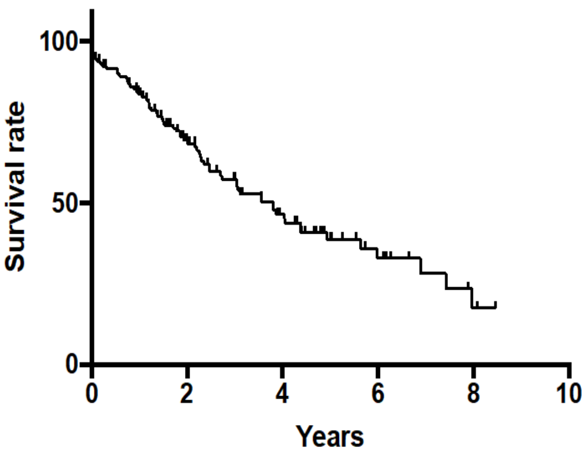
Number at risk (A)

131	55	15	3	0

Number at risk (B)

BC-I/II/IIIa/IIIb	115	50	15	3	0
BC-IV	16	5	0	0	0

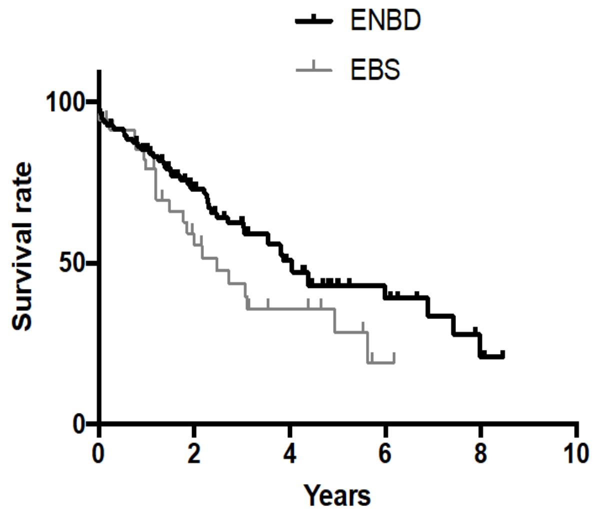
(A)



Number at risk

131	67	35	11	3

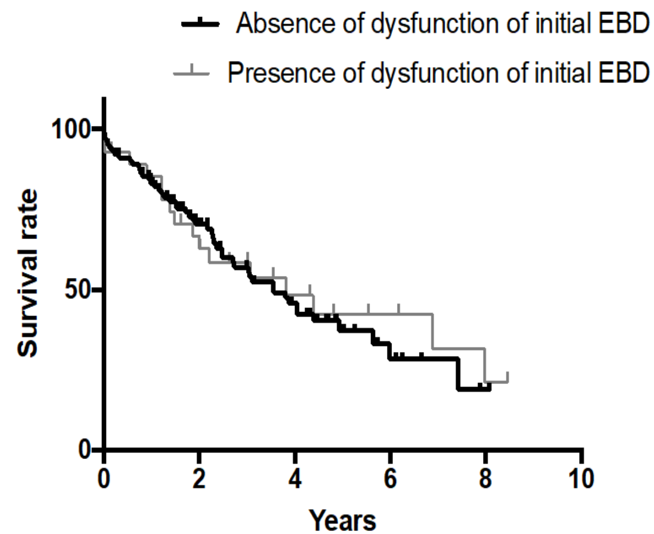
(B)



Number at risk

ENBD	96	52	28	10	3
EBS	35	15	7	1	0

(C)



Number at risk

Absence of dysfunction of initial EBD

103	51	26	6	1

Presence of dysfunction of initial EBD

28	16	9	5	2