**Abstract**

**Background:** Preoperative endoscopic biliary drainage (PEBD) is widely accepted for use in patients with hilar malignant biliary obstruction (MHBO). PEBD consists of endoscopic nasobiliary drainage (ENBD), conventional endoscopic biliary stenting (CEBS) with plastic stents across the papilla, and novel endoscopic biliary inside stenting (EBIS) with plastic stents above the papilla. We aimed to compare the efficacy of EBIS with ENBD and CEBS, and to evaluate the usefulness of EBIS for MHBO as a means of PEBD.

**Methods:** We retrospectively identified patients with MHBO who underwent upfront radical resection without percutaneous transhepatic biliary drainage between January 2011 and December 2018 in a multicenter setting. The outcome measures were cumulative dysfunction of PEBD, survival rate, risk factors for PEBD dysfunction, prognostic factors of survival, and adverse events.

**Results:** We analyzed a total of 219 patients, comprising: 163 males (74.4%); mean age, 69.7 (± 7.6) years; Bismuth-Corlette classification (BC) I, II, IIIa, IIIb, and IV in 68, 49, 43, 30, and 29 patients, respectively; and diagnosis of hilar cholangiocarcinoma and gall bladder cancer in 188 and 31 patients, respectively. PEBD procedures were performed in 160 patients with ENBD, 31 patients with CEBS, and 28 patients with EBIS. PEBD dysfunction occurred in 58 patients (26.5%), and the cumulative dysfunction rates were not significantly different among PEBD methods (Log-rank test, *P* = 0.60). Multivariate analysis showed that BC-IV was significantly associated with the occurrence of PEBD dysfunction (hazard ratio = 2.10, *P* = 0.02). The adverse event rates and survival rates were not significantly different among PEBD groups (*P* ≥ 0.05). In addition, age ≥ 75 years was an independent prognostic factor of survival (hazard ratio = 1.57, *P* = 0.04).

**Conclusion:** EBIS is feasible and can be of use as a PEBD method.

**Introduction**

Surgical treatment alone can offer long-term survival in patients with primary malignant hilar biliary obstruction (MHBO), including hilar cholangiocarcinoma and gallbladder cancer [1-3]. Although it remains unclear whether preoperative biliary drainage can reduce morbidity and mortality in patients with MHBO [4, 5], drainage is frequently necessary following assessment of the surgical resectability and pathological confirmation [6, 7]. Percutaneous transhepatic biliary drainage (PTBD) is not recommended as the first preoperative drainage procedure due to the possibility of tumor seeding and severe complications [8, 9]. As such, preoperative endoscopic biliary drainage (PEBD) is widely accepted as the standard preoperative biliary drainage in Japan [10]. Endoscopic nasobiliary drainage (ENBD) is the primary procedure for PEBD according to the Japanese guideline [4], while that is one of the external fistulas and can delay the quality of life during the preoperative waiting period. In addition, some studies have failed to show an advantage of ENBD over endoscopic biliary stenting as a PEBD method, and the most suitable method of PEBD remains controversial [11-13].

For preoperative patients with MHBO, conventional endoscopic biliary stenting (CEBS) is performed with plastic stents across the major papilla. Meanwhile, recent studies have indicated that novel endoscopic biliary inside stenting (EBIS) is superior to CEBS as a bridging treatment to surgery with plastic stents above the papilla; this was true in patients with malignant biliary obstruction, including MHBO [14, 15], as well as in patients with unresectable MHBO [15, 16]. However, the benefits of EBIS as a PEBD method for patients with MHBO are yet to be determined.

The aim of this multicenter retrospective study was to compare novel EBIS with ENBD and CEBS as a PEBD method, and to evaluate the usefulness of EBIS for patients with MHBO who underwent upfront radical surgery.

**Patients and methods**

**Study design**

This was a multicenter retrospective study conducted at Hokkaido University Hospital, Teine-Keijinkai Hospital, Sapporo Medical University, Tonan Hospital, Iwamizawa Municipal General Hospital, NTT East Sapporo Hospital, and Hakodate Municipal Hospital. A prospectively collected database was searched for consecutive patients with MHBO who underwent radical surgical resection between January 2011 and December 2018. The inclusion criteria were as follows: 1) Diagnosis of primary malignant biliary tract cancer based on pathological evidence, 2) main biliary stricture located within 2 cm from the hepatic hilum, 3) history of PEBD until surgery, and 4) patients’ or their families’ agreement to participate in this study by the opt-out form. The exclusion criteria were as follows: 1) History of PTBD before radical surgery, 2) history of multiple PEBD methods (ENBD + CEBS, ENBD + EBIS, or CEBS + EBIS) as a PEBD method, 3) history of preoperative chemotherapy or radiation therapy for MHBO, 4) history of gastrointestinal tract reconstruction, and 5) refusal to participate in this study by either the patients or their families.

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki (6th revision, 2008), as reflected in prior approval by the Human Research Committee of the relevant institutions. The study was approved by the Institutional Review Board at each institution, and was registered in UMIN-CTR (clinical trial registration number: UMIN000040605).

**Endoscopic management for MHBO**

Written informed consent was obtained from the patients prior to endoscopic retrograde cholangiography and endoscopic biliary drainage (EBD)/PEBD. ENBD tubes or plastic stents were used for EBD/PEBD. In general, the biliary drainage technique for patients with MHBO is single biliary drainage to the future remnant liver lobe. However, additional EBD was performed when cholangitis was suspected in the non-drainage area, or when the final decision on surgical strategy made by the cancer board of each institution required it. ENBD was the first choice procedure for PEBD according the Japanese guideline [4], except for patients who rejected the procedure, or those who were intolerant to ENBD. If the distance from the distal end of the biliary stricture to the sphincter of Oddi was at least 2 cm, EBIS can be selected, as well as ENBD and CEBS. The selection of biliary drainage technique (ENBD/CEBS/EBIS) and endoscopic sphincterotomy were at the discretion of the endoscopist.

**Definitions**

PEBD was defined as EBD during the preoperative waiting period. The preoperative waiting period was defined as the duration from the final decision on the surgical strategy by each institutional cancer board for radical surgery (Fig. 1).

Dysfunction of PEBD was defined as occlusion or dislocation of ENBD tubes or plastic stents of CEBS/EBIS. Occlusion of an ENBD tube or plastic stent of CEBS/EBIS was defined as follows: 1) Acute cholangitis as defined in the Tokyo guideline 2018 [17], and 2) elevation of serum hepatobiliary enzyme levels, any of which can improve after exchange of the tubes/stents. Dislocation of an ENBD tube or a plastic stent of CEBS/EBIS was defined as dislodgement of the tip of the tubes/stents from the original position to an inappropriate site, as assessed by a roentgenogram. In the present study, removal of an ENBD tube by a patient themselves was defined as dislocation of an ENBD tube.

In the present study, the type of hilar biliary obstruction in patients with gallbladder cancer or hilar cholangiocarcinoma was classified according to the Bismuth-Corlette grade (BC).

Regarding adverse events, contralateral segmental cholangitis was defined as cholangitis that occurred in an undrained area. When contralateral segmental cholangitis occurred, an additional ENBD tube or plastic stent of CEBS/EBIS was placed in the undrained area. In this study, contralateral segmental cholangitis was regarded as an adverse event, since it is mainly caused by tumor-related obstruction. Ipsilateral segmental cholangitis was defined as cholangitis that occurred in the same lobe as the drained area. Pancreatitis, bleeding, and perforation related to the endoscopic biliary stenting/tubing procedure, and their severities were defined according to the American Society for Gastrointestinal Endoscopy lexicon [18]. Acute cholecystitis and cholangitis were defined as outlined in the Tokyo guideline 2018 [19].

**Outcome measures**

The primary outcome measure of the present study was cumulative dysfunction of PEBD according to the PEBD method. The secondary outcomes measures were details of PEBD dysfunction, survival rate, risk factors for PEBD dysfunction, and prognostic factors of survival: age (< 75 or ≥ 75 year); sex (male or female); final diagnosis (cholangiocarcinoma or gallbladder cancer); BC grade (I, II, IIIa, IIIb, or IV); cholangitis before PEBD (presence or absence); pancreatitis due to EBD/PEBD procedures (presence or absence); biliary drainage method (ENBD, CEBS, or EBIS); number of intubated PEBD tubes/stents (single or multiple); diameter of the largest PEBD tube/stent (≤ 6-Fr or ≥ 7-Fr); type of PEBD tubes/stents (straight or pigtail); endoscopic sphincterotomy (presence or absence); preoperative waiting period (≤ 40 days or > 40 days); PEBD dysfunction (presence or absence); and percutaneous transhepatic portal vein embolization (PTPE) before surgery (presence or absence) were used as covariates. Adverse events of PEBD were also analyzed.

**Statistical analysis**

Statistical analysis was performed using the free software EZR [20]. Results are shown as means (SD) for quantitative variables, medians (interquartile range) for nonparametric variables, and percentages for categorical variables. One-way ANOVA was conducted to compare continuous variables among PEBD methods. The Kruskal-Wallis test was conducted to compare the median vales of the preoperative waiting period among PEBD methods. Categorical variables were compared using the chi-squared test or Fisher’s exact test, as appropriate. The cumulative incidences of PEBD dysfunction, and survival time from the day of radical surgery were estimated using the Kaplan-Meier method, and the differences among PEBD methods were evaluated by the log-rank test. The risk factors for dysfunction of PEBD, and prognostic factors of survival were analyzed using the Cox proportional hazard model. Factors with a *P*-value < 0.20 in the univariate analysis were included in multivariate analysis. Differences were considered statistically significant at a *P*-value < 0.05.

**Results**

**Baseline characteristics**

The database search led to retrieval of 219 consecutive patients who were finally analyzed in the present study (Fig. 2). The baseline characteristic of the patients are shown in Table 1. The patients included 163 males and 56 females, with a mean age of 69.7 (± 7.6) years. The final diagnoses were cholangiocarcinoma in 188 patients and gallbladder cancer in 31 patients. The BC grades were I in 68 patients, II in 49 patients, IIIa in 43 patients, IIIb in 30 patients, and IV in 29 patients. ENBD, CEBS, and EBIS were performed as the PEBD method in 160, 31, and 28 patients, respectively.

All patients demonstrated functional success and underwent radical surgical resection as scheduled. The median preoperative waiting period of the entire cohort was 41 days (interquartile range, 26–56), and were not significantly different among PEBD groups (*P* = 0.55). A total of 160 patients (73.1%) underwent EBD at least once before PEBD. Details of the PEBD status and radical surgical resection are shown in Table 2.

**Primary outcome**

Dysfunction of PEBD occurred in 58 patients (26.5%); among whom, occlusion and stent migration occurred in 34 and 24 patients, respectively. The cumulative dysfunction rates of PEBD in all patients were 23.8%, 37.4%, and 41.3% at 30, 60, and 90 days, respectively (Figure 3A). The cumulative dysfunction rates of PEBD were not significantly different among PEBD methods (*P* = 0.60) (Figure 3B).

**Secondary outcome**s

**Details of outcomes of PEBD**

After PEBD, 137 patients (62.6%) underwent radical surgical resection without re-intervention. Dysfunction of PEBD occurred in 58 patients (26.4%). The remaining 24 patients (11.0%) underwent re-intervention for the following reasons: Contralateral segmental cholangitis in 11 patients; conversion to another endoscopic biliary drainage method without dysfunction of PEBD in 6 patients (conversion from external to internal drainage by patient requirement in 2 patients, and from internal to external drainage for bile monitoring in 4 patients); preventive tube exchange due to slight tube dislocation on roentgenogram in 5 patients; pancreatitis due to compression of the pancreatic duct by the ENBD tube in 1 patient; and bleeding after endoscopic sphincterotomy in 1 patient.

**Risk factors of PEBD dysfunction**

We performed univariate analysis of the characteristics of the patients and PEBD procedures related to dysfunction (Table 3). The PEBD dysfunction rates were significantly different between BC classes (I, II, IIIa, and IIIb verses IV) (*P* = 0.01). The results of multivariate analysis showed that BC-IV was an independent predictive factor of PEBD dysfunction (hazard ratio = 2.01, *P* = 0.02).

**Adverse events of PEBD**

During the study period, 42 patients (19.2%) suffered from 42 adverse events (Table 4). The adverse event rates were 20.6% (33/160), 12.9% (4/31), and 17.9% (5/28) in the ENBD, CEBS, and EBIS groups, respectively, and were not significantly different among PEBD groups (*P* = 0.70). There were no severe adverse events in the current study. The incidence rates of contralateral segmental cholangitis and ipsilateral segmental cholangitis were not significantly different among the PEBD groups. Pancreatitis occurred in 16 patients. One patient had moderate pancreatitis due to compression of the pancreatic duct by the ENBD tube 21 days after PEBD, and the event was successfully treated by addition of endoscopic nasopancreatic drainage. Acute cholecystitis occurred in three patients (moderate in 2 patients and mild in 1 patient). One patient with moderate cholecystitis underwent percutaneous transhepatic gallbladder drainage, whereas the remaining 2 patients with cholecystitis were successfully treated by conservative therapy. Bleeding after endoscopic sphincterotomy occurred in one patient undergoing ENBD; the patient was successfully treated by endoscopic hemostasis, and the ENBD tube was replaced.

**Survival rate**

The median survival time of the included patients was 4.0 years (95% confidence interval, 3.0–6.0), and was not significantly different among the ENBD, CEBS, and EBIS groups (*P* = 0.41). Univariate analysis revealed that age ≥ 75 years was a significant prognostic factor (*P* < 0.05), and that gallbladder cancer, cholangitis before PEBD, thick PEBD tubes/stents, and PTPE until surgery were potential prognostic factors (*P* < 0.20) (Table 5). Multivariate analysis revealed that age ≥ 75 years was an independent prognostic factor of survival (hazard ratio = 1.57, *P* = 0.04).

**Discussion**

This is the first study to focus on novel EBIS as a PEBD method in patients with MHBO who underwent upfront radical surgery. Moreover, no previous study has compared the efficacy between ENBD, CEBS, and EBIS as a PEBD method in patients with MHBO who underwent upfront radical surgery. One previous retrospective study in preoperative patients with malignant biliary strictures showed that the average stent patency was significantly longer in the EBIS group than that in the CEBS group (85.2 days verses 49.1 days, *P* < 0.05) [14]. However, the study included patients with distal biliary stricture in addition to MHBO, as well as who received neoadjuvant therapy. Other previous studies in patients with unresectable MHBO have also revealed that the stent patency in the EBIS group was significantly longer than that in the CEBS group [15, 16]. Therefore, we hypothesized that the cumulative dysfunction rate of PEBD for MHBO in the EBIS group was lower than that in the CEBS group; however, the present study did not show an advantage of EBIS over CEBS as a PEBD method. This may be due to the shorter preoperative waiting period in the present study (median, 41 days) than that in the previous study comparing CEBS and EBIS (mean, 96.3–96.8 days) [14]. In other words, both CEBS and EBIS would be available when the preoperative waiting period is short.

In the present study, there were no significant differences in rates of dysfunction or adverse events among the three PEBD groups. Although previous studies have reported that ENBD has advantages over CEBS as a PEBD method in terms of adverse events, including tube/stent occlusion with cholangitis, and re-interventions [8, 21], more recent studies showed that there were no significant differences between ENBD and CEBS [11-13]. The advantages of ENBD are the ability to monitor bile quality and output and to perform preoperative cholangiography via a drainage tube, while the disadvantage of the method is nasopharyngeal discomfort. The advantages and disadvantages of CEBS and EBIS are completely opposite from ENBD; therefore, any PEBD method can be selected for different purposes in cases with short preoperative periods. However, endoscopic biliary stenting, in particular, EBIS, should be selected in cases with long preoperative periods in order to prevent a decline in quality of life. Further prospective studies are needed to compare these PEBD methods for patients with MHBO.

In the multivariate analysis of risk factors of dysfunction of PEBD, BC-IV was found to be an independent predictive factor; this can be explained by the fact that the bile ducts for PEBD in BC-IV cases are the 2nd/3rd branch duct, and are narrower than those in BC-I-III as previously described [13]. Therefore, patients with BC-IV should undergo radical surgical resection as early as possible. In addition, because PEBD for MHBO, especially BC-IV MHBO, is occasionally technically difficult, PTBD should also be considered.

There are several limitations of the present study. First, this was a retrospective and non-randomized study. Second, selection bias could not be fully avoided because there were little differences among the participating institutions regarding the selection of the PEBD method, assessment of resectability and the final operative strategy. Third, patients who had received neoadjuvant therapy were excluded from this study. If neoadjuvant therapy is selected, the preoperative waiting period is extended compared to that in the case of upfront surgery, and the results might change according to the treatment strategy. Finally, we did not obtain postoperative parameters, such as liver failure and complications in this study. Future studies should include these parameters in order to evaluate postoperative survival times.

In conclusion, EBIS is feasible and can be used as an appropriate PEBD methods.