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Research Article

Endoscopic nasobiliary drainage comparable with endoscopic biliary stenting as a preoperative drainage method for malignant hilar biliary obstruction: A multicenter retrospective study

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Short Title: ENBD is comparable with EBS

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Abstract

Introduction: Preoperative endoscopic biliary drainage (PEBD) for malignant hilar biliary obstruction (MHBO) is widely accepted. Recent PEBD consists of endoscopic nasobiliary drainage (ENBD), conventional endoscopic biliary stenting (CEBS) with plastic stents across the papilla, and endoscopic biliary inside stenting (EBIS) with plastic stents above the papilla, while ENBD is the primary procedure in Asian countries. Thus, we aimed to compare the efficacy of ENBD with those of CEBS and EBIS as a means of PEBD for MHBO.

Methods: We retrospectively identified patients with MHBO who underwent upfront surgery between January 2011 and December 2018 in a multicenter setting. The outcome measures were cumulative dysfunction of PEBD, risk factors for PEBD dysfunction, and adverse events.

Results: We analyzed a total of 219 patients, comprising: 163males (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 (*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 were not significantly different among PEBD groups (*P*=0.70).

Conclusion: ENBD as a means of PEBD for MHBO is comparable with CEBS and EBIS in rates of dysfunction and adverse events.

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 because of the possibility of tumor seeding and severe complications [8, 9]. Preoperative endoscopic biliary drainage (PEBD) is widely accepted as the standard preoperative biliary drainage technique in Japan [10]. Endoscopic nasobiliary drainage (ENBD) is the primary procedure for PEBD, according to Japanese guidelines [4]. Previous studies have reported that ENBD has advantages, including less adverse events, such as tube/stent occlusion with cholangitis, and re-interventions over endoscopic biliary stenting (EBS) as a PEBD method [8, 11]. Currently, ENBD is frequently performed in Japanese high-volume centers [10]. However, the method typically involves the external fistula, which has been shown to decrease the quality of life during the preoperative waiting period. In addition, some recent studies have failed to show an advantage of ENBD over EBS as a PEBD method [12-14]. Conventional endoscopic biliary stenting (CEBS) is performed using 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, which was demonstrated in patients with malignant biliary obstruction, including MHBO [15, 16], as well as in patients with unresectable MHBO [16, 17]. However, the most suitable PEBD method remains controversial. Meanwhile, multiple EBD procedures are frequently performed before the final decision on the surgical strategy. It is not known whether the initial EBD method affects tube/stent dysfunction and complications of PEBD at the final decision on the surgical strategy. Furthermore, because of the advent of EBIS and revision of preoperative management protocols in the last decade [10], re-evaluation of the typical PEBD methods that are implemented in surgical care is needed.

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

Materials 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. We retrospectively searched for consecutive patients with MHBO who underwent radical surgical resection between January 2011 and December 2018 from the hospital databases. 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.

We previously conducted a single-center, retrospective study to identify the risk factors for the initial endoscopic procedures for dysfunction of endoscopic biliary drainage (EBD) in preoperative patients with MHBO [14]. Although the inclusion/exclusion criteria and target procedures were different between the previous study and this study, many of the enrolled patients in the previous study were also included in this multicenter, retrospective study.

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki (2013 revision), as reflected in prior approval by the Human Research Committee of the relevant institutions. This study was approved by the Institutional Review Board at Hokkaido University Hospital (018-0392) and other study institutions and was registered in the UMIN-CTR (clinical trial registration number: UMIN000040605).

Endoscopic management for MHBO

Written informed consent was obtained from all patients prior to endoscopic retrograde cholangiography and EBD/PEBD. ENBD tubes or plastic stents were used for the initial EBD (initial ENBD, iENBD/initial CEBS, iCEBS/initial EBIS, iEBIS)/PEBD. In general, the biliary drainage technique for patients with MHBO is single biliary drainage of 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 the surgical strategy made by the cancer board of each institution required it. ENBD was the first-choice procedure for PEBD in the participating institutions, according to Japanese guidelines [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 could be selected, as well as ENBD and CEBS. If the preoperative waiting period would be extended at the final decision on the surgical strategy, ENBD could be converted to CEBS/EBIS. Some patients who were referred to the participating institutions for workup of MHBO had undergone CEBS/EBIS previously at other hospitals. The selection of the biliary drainage technique (ENBD/CEBS/EBIS) and endoscopic sphincterotomy were performed at the sole discretion of the endoscopist.

Definitions

PEBD was defined as EBD during the preoperative waiting period and divided into three groups: preoperative ENBD (pENBD), preoperative CEBS (pCEBS), and preoperative EBIS (pEBIS). 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 (Figure 1). Before PEBD, one or more EBD procedures as re-intervention could be performed to assess the surgical resectability/pathological confirmation, improve cholangitis, or convert from single to multiple biliary drainage due to the final decision on the surgical strategy.

PEBD dysfunction was defined as occlusion or dislocation of the 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 [18], and 2) elevation of serum hepatobiliary enzyme levels, any of which can improve after exchange of the tubes/stents. When bile flow in an ENBD tube stopped or extremely decreased, bile reflow after flushing an ENBD tube with physiological saline was not defined as occlusion of an ENBD tube. 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 was defined as the dislocation of an ENBD tube.

Functional success was defined as (a) a decrease in serum total bilirubin from >2.0 mg/dL to ≤2.0 mg/dL, (b) a decrease in serum total bilirubin by half from >2.0 mg/dL, (c) 50% or more decrease in hepatobiliary enzyme levels in the case of serum T-BIL being 2.0 mg/dL or less within 14 days after

biliary drainage, or (d) no increase in serum total bilirubin > 2.0 mg/dL and of hepatobiliary enzymes in the case of biliary decompression previously.

In the present study, the type of hilar biliary obstruction in patients with gallbladder cancer, as well as that in patients with 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 because 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 and improved with conservative treatment. Pancreatitis, bleeding, and perforation related to the endoscopic biliary stenting/tubing procedure, and their severity was defined according to the American Society for Gastrointestinal Endoscopy lexicon [19]. Acute cholecystitis and cholangitis were defined according to the 2018 Tokyo guidelines [20].

Outcome measures

The primary outcome measure of the present study was the cumulative dysfunction of PEBD according to the PEBD method. The secondary outcomes measures were functional success, details of PEBD duration and dysfunction, and risk factors for PEBD dysfunction: 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); and percutaneous transhepatic portal vein embolization (PTPE) before surgery (presence or absence) were used as covariates. Adverse events associated with PEBD were also analyzed.

Statistical analysis

Statistical analysis was performed using the free software EZR [21]. Results are shown as means (standard deviation) for quantitative variables, medians (interquartile range) for nonparametric

variables, and percentages for categorical variables. A one-way ANOVA was conducted to compare continuous variables among the PEBD methods. The Kruskal–Wallis test was conducted to compare the median values of the preoperative waiting period among the PEBD methods. Categorical variables were compared using the chi-squared test or Fisher's exact test, as appropriate. The cumulative incidences of PEBD dysfunction were estimated using the Kaplan–Meier method, and the differences among PEBD methods were evaluated using the log-rank test. Patients who underwent radical surgical resection, re-intervention, or conversion to another EBD method without dysfunction of PEBD or drainage-related adverse events were regarded as censored. The risk factors for PEBD dysfunction were analyzed using the Cox proportional hazards model. Factors with a *P*-value < 0.20 in the univariate analysis, were included in the multivariate analysis. Differences were considered statistically significant at $P < 0.05$.

Results

Baseline characteristics

The database searched for the retrieval of 219 consecutive patients who were finally analyzed in the present study (Figure 2). The baseline characteristics of the patients are shown in Table 1. The patients included 163 men and 56 women, 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 as follows: I, 68; II, 49; IIIa, 43; IIIb, 30; and IV, 29. ENBD, CEBS, and EBIS were performed using the PEBD method in 160 (pENBD), 31 (pCEBS), and 28 patients (pEBIS), respectively. A total of 157 patients (71.7%) had undergone one or more EBDs before PEBD. There were no significant differences in the percentage of patients who underwent one or more EBD procedures before PEBD (multiple EBD procedures) among the three groups (pENBD: 68.1% vs. pCEBS: 74.2% vs. pEBIS: 89.3%, $P = 0.06$). The incidence rates of cholangitis before PEBD in the pENBD, pCEBS, and pEBIS groups were 23.1%, 16.1%, and 25.0%, respectively, and were not significantly different among the PEBD groups ($P = 0.70$).

The initial EBD methods were ENBD in 159 patients (iENBD), CEBS in 52 patients (iCEBS), and EBIS in 8 patients (iEBIS). A flowchart of the initial EBD method for PEBD is shown in Figure 3. The main reasons for the additional EBD are listed in Table 2.

The functional success rates of PEBD in the pENBD, pCESB, and pEBIS groups were 100% (160/160), 100% (31/31), and 100% (28/28), respectively. All patients underwent radical surgical resection as scheduled. The median preoperative waiting period of the entire cohort was 41 days

(interquartile range, 26–56) and was not significantly different among the PEBD groups (P = 0.55). The rates of endoscopic sphincterotomy at PEBD were 53.1%, 45.2%, and 39.3% in the pENBD, pCEBS, and pEBIS groups, respectively, and were not significantly different among the groups (P = 0.32). Details of the PEBD status and radical surgical resection are shown in Table 3.

Primary outcome

The median follow-up durations (interquartile range) of PEBD in the pENBD, pCEBS, and pEBIS groups were 30.5 days (14–47), 23.0 days (14–49), and 24.0 days (8–42), respectively, and were not significantly different among them (P = 0.54). 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 4A). The dysfunction rates of PEBD in the pENBD, pCEBS, and pEBIS groups were 25.0% (40/160), 35.5% (11/31), and 24.1% (7/28), respectively (P = 0.45). The cumulative dysfunction rates of PEBD were not significantly different among the PEBD methods (P = 0.60) (Figure 4B).

We also analyzed the patients according to the initial EBD method, to identify the effect of the initial EBD method on the dysfunction of PEBD. The dysfunction rates of the iENBD, iCEBS, and iEBIS groups during the preoperative period were 26.4% (42/159), 28.8% (15/52), and 12.5% (1/8), respectively, and were not significantly different among the groups (P = 0.77). The cumulative dysfunction rates of PEBD were also not significantly different among the groups (P = 0.65).

Secondary outcomes

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 EBD 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 a univariate analysis of patient characteristics and PEBD procedures related to dysfunction (Table 4). The PEBD dysfunction rates were significantly different between BC classes (I, II, IIIa, and IIIb vs. IV) ($P = 0.01$). The results of the multivariate analysis showed that BC-IV was an independent predictive factor for PEBD dysfunction (hazard ratio = 2.01, $P = 0.02$).

There were significant differences in the distributions of BC grades among the three PEBD methods ($P < 0.01$). Therefore, we also evaluated the predictive factors for PEBD dysfunction in patients with BC-IIIa, IIIb, and IV (Table 5). Multivariate analysis revealed that the hazard ratio was higher in the CEBS group (hazard ratio = 2.51, $P = 0.04$). BC-IV was also an independent predictive factor for PEBD dysfunction (hazard ratio = 2.54, $P = 0.02$).

Adverse events of PEBD

During the study period, 42 patients (19.2%) experienced 42 adverse events (Table 6). The adverse event rates were 20.6% (33/160), 12.9% (4/31), and 17.9% (5/28) in the pENBD, pCEBS, and pEBIS groups, respectively, and were not significantly different among the PEBD groups ($P = 0.70$). No severe adverse events were observed in this 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 of these 16 patients 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 the addition of endoscopic nasopancreatic drainage. Acute cholecystitis occurred in three patients (moderate in two patients and mild in one patient). One patient with moderate cholecystitis underwent percutaneous transhepatic gallbladder drainage, whereas the remaining two patients with cholecystitis were successfully treated with conservative therapy. Bleeding after endoscopic sphincterotomy occurred in one patient undergoing ENBD; the patient was successfully treated with endoscopic hemostasis, and the ENBD tube was replaced.

Comparison between the ENBD and EBS (CEBS/EBIS) groups

We also evaluated the baseline characteristics of the patients, details of PEBD procedures, dysfunctions of PEBD, and rates of adverse events between the pENBD and preoperative EBS (pEBS) (pCEBS/pEBIS) groups. The BC grades in the pENBD group were as follows: I in 44 patients (27.5%), II

in 42 patients (26.3%), IIIa in 28 patients (17.5%), IIIb in 24 patients (15.0%), and IV in 22 patients (13.7%); and in the pEBS group, I was present in 24 patients (40.7%), II in 7 patients (11.9%), IIIa in 15 patients (25.4%), IIIb in 6 patients (10.2%), and IV in 7 patients (11.8%). The distribution of BC grades was not significantly different between the two groups (P = 0.07). The sizes of ENBD tubes were 5-Fr in 81 patients (50.6%) and ≥ 6-Fr in 79 patients (49.4%) in the pENBD group, and those of the largest stents were 5-Fr in 4 patients (6.8%) and ≥ 6-Fr in 55 patients (93.2%) in the pEBS group (P <0.01). The two groups did not differ significantly in terms of other baseline characteristics and PEBD procedures. The dysfunction rates of PEBD in the pENBD and pEBS groups were 25.0% (40/160) and 30.5% (18/59), respectively (P = 0.49). The cumulative dysfunction rates of PEBD were not significantly different between the pENBD and pEBS groups (P = 0.37) (Figure 5). The adverse event rates in the pENBD and pEBS groups were 20.6% (33/160) and 15.3% (9/59), respectively, and were not significantly different between the two groups (P = 0.44).

Discussion/Conclusion

The present study revealed that ENBD was comparable with CEBS and EBIS in terms of the rates of PEBD dysfunction or adverse events in patients with MHBO. 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, 11], more recent studies have shown that there were no significant differences between ENBD and CEBS [12-14], as well as the present study. 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 to those of ENBD; therefore, any PEBD method can be selected for different purposes in cases with short preoperative periods. However, EBS, especially EBIS, should be selected in cases with long preoperative periods in order to prevent a decline in quality of life. Meanwhile, the sub-analysis of the present study in patients with BC-III and IV indicated that CEBS would have a high incidence of PEBD dysfunction, as well as a previous study [8].

To date, few previous studies have focused on the efficacy of EBIS as a PEBD method in patients with MHBO who underwent upfront radical surgery. A previous retrospective study in preoperative patients with malignant biliary strictures showed that the average stent patency was significantly longer in the EBIS group than in the CEBS group (85.2 verses 49.1 days, P <0.05) [15]. However, the study included patients with distal biliary stricture in addition to MHBO, as well as those who received neoadjuvant therapy. Other previous studies in patients with unresectable MHBO have also

revealed that stent patency in the EBIS group was significantly longer than that in the CEBS group [16, 17]. Therefore, we hypothesized that the cumulative dysfunction rate of PEBD for MHBO in the EBIS group was lower than that in the CEBS group. Recently, a single-center, retrospective study revealed that EBIS was a possible alternative to ENBD as a bridge to a definitive operation for patients with resectable MHBO [22]. Thus, further prospective studies with a larger cohort are needed to accurately compare these PEBD methods for patients with MHBO.

In the multivariate analysis of risk factors for dysfunction of PEBD, BC-IV was found to be an independent predictive factor, which 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 [14]. 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 to the present study. First, this was a retrospective, non-randomized study. Second, selection bias could not be fully avoided because there were few differences among the participating institutions regarding the selection of the PEBD method, assessment of resectability, and the final operative strategy. Third, this study included patients with MHBO who underwent radical surgery (per-protocol analysis), but not all patients with MHBO who would be candidates for radical surgery (intention-to-treat analysis). Our per-protocol analysis could not accurately determine the technical success rate in clinical practice. Fourth, patients who 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 may differ 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 to evaluate the postoperative survival times.

In conclusion, ENBD is comparable with CEBS and EBIS in patients with MHBO who undergo upfront radical surgery. However, further prospective studies with larger cohorts are needed to accurately compare these PEBD methods for patients with MHBO.

Statements

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Statement of Ethics

Study approval statement: This study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki (2013 revision), as reflected in prior approval by the Human Research Committee of the relevant institutions. This study was approved by the Institutional Review Board at Hokkaido University Hospital (018-0392) and other study institutions, and was registered in UMIN-CTR (clinical trial registration number: UMIN000040605).

Consent to participate statement: This study was a retrospective observational study and did not necessarily require written informed consent because it was a study that used only information such as medical records without using samples. Informed consent to participate in the study was obtained from the patients or their families using an opt-out form.

Conflict of Interest Statement

Author A.K. has received consultant fee from Gadelius Medical and lecture fee from Olympus Medical Systems. The other authors declare no Conflict of Interests for this article.

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Author Contributions

R.S. designed the research, performed the research (data acquisition and data analysis), and wrote the manuscript; M.K. performed the research (data analysis) and wrote the manuscript and critical revision; T.H., M.Y., H.I., H.Y., and M.O. performed the research (data acquisition) and critically reviewed the manuscript; A.K. supervised the entire research; all authors read and approved the final manuscript.

Data Availability Statement

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants but are available from the corresponding author M.K.

References

1. Hirano S, Kondo S, Tanaka E, Shichinohe T, Tsuchikawa T, Kato K, et al. Outcome of surgical treatment of hilar cholangiocarcinoma: a special reference to postoperative morbidity and mortality. J Hepatobiliary Pancreat Sci. 2010 Jul;17(4):455-62.

2. Nasu Y, Tanaka E, Hirano S, Tsuchikawa T, Kato K, Matsumoto J, et al. The prognosis after curative resection of gallbladder cancer with hilar invasion is similar to that of hilar cholangiocarcinoma. J Hepatobiliary Pancreat Sci. 2012 May;19(3):274-80.

3. Nasu Y, Hirano S, Tsuchikawa T, Shichinohe T. Aggressive surgery for locally advanced gallbladder cancer with obstructive jaundice: result of a prospective study. Dig Surg. 2016;33(3):213-9.

4. Miyazaki M, Yoshitomi H, Miyakawa S, Uesaka K, Unno M, Endo I, et al. Clinical practice guidelines for the management of biliary tract cancers 2015: the 2nd English edition. J Hepatobiliary Pancreat Sci. 2015 Apr;22(4):249-73.

5. Farges O, Regimbeau JM, Fuks D, Le Treut YP, Cherqui D, Bachellier P, et al. Multicentre European study of preoperative biliary drainage for hilar cholangiocarcinoma. Br J Surg. 2013 Jan;100(2):274-83.

6. Tamada K, Ido K, Ueno N, Kimura K, Ichiyama M, et al. Preoperative staging of extrahepatic bile duct cancer with intraductal ultrasonography. Am J Gastroenterol. 1995 Feb;90(2):239-46.

7. Tamada K, Tomiyama T, Wada S, Ohashi A, Satoh Y, Ido K, et al. Endoscopic transpapillary bile duct biopsy with the combination of intraductal ultrasonography in the diagnosis of biliary strictures. Gut. 2002 Mar;50(3):326-31.

8. Kawakami H, Kuwatani M, Onodera M, Haba S, Eto K, Ehira N, et al. Endoscopic nasobiliary drainage is the most suitable preoperative biliary drainage method in the management of patients with hilar cholangiocarcinoma. J Gastroenterol. 2011 Feb;46(2):242-8.

9. Hirano S, Tanaka E, Tsuchikawa T, Matsumoto J, Kawakami H, Nakamura T, et al. Oncological benefit of preoperative endoscopic biliary drainage in patients with hilar cholangiocarcinoma. J Hepatobiliary Pancreat Sci. 2014 Aug;21(8):533-40.

10. Chaudhary RJ, Higuchi R, Nagino M, Unno M, Ohtsuka M, Endo I, et al. Survey of preoperative management protocol for perihilar cholangiocarcinoma at 10 Japanese high-volume centers with a combined experience of 2,778 cases. J Hepatobiliary Pancreat Sci. 2019 Nov;26(11):490-502.

11. Kawakubo K, Kawakami H, Kuwatani M, Haba S, Kudo T, Taya YA, et al. Lower incidence of complications in endoscopic nasobiliary drainage for hilar cholangiocarcinoma. World J Gastrointest Endosc. 2016 May 10;8(9):385-90.

12. Nakai Y, Yamamoto R, Matsuyama M, Sakai Y, Takayama Y, Ushio J, et al. Multicenter study of endoscopic preoperative biliary drainage for malignant hilar biliary obstruction: E-POD hilar study. J Gastroenterol Hepatol. 2018 May;33(5):1146-53.

13. Jo JH, Chung MJ, Han DH, Park JY, Bang S, Park SW, et al. Best options for preoperative biliary drainage in patients with Klatskin tumors. Surg Endosc. 2017 Jan;31(1):422-9.

14. Sugiura R, Kuwatani M, Kato S, Kawakubo K, Kamachi H, Taketomi A, et al. Risk factors for dysfunction of preoperative endoscopic biliary drainage for malignant hilar biliary obstruction. J Hepatobiliary Pancreat Sci. 2020 Nov;27(11):851-9.

15. Kobayashi N, Watanabe S, Hosono K, Kubota K, Nakajima A, Kaneko T, et al. Endoscopic inside stent placement is suitable as a bridging treatment for preoperative biliary tract cancer. BMC Gastroenterol. 2015 Feb 5;15:8.

16. Kubota K, Hasegawa S, Iwasaki A, Sato T, Fujita Y, Hosono K, et al. Stent placement above the sphincter of Oddi permits implementation of neoadjuvant chemotherapy in patients with initially unresectable Klatskin tumor. Endosc Int Open. 2016 Apr;4(4):E427-33.

17. Inatomi O, Bamba S, Shioya M, Mochizuki Y, Ban H, Tsujikawa T, et al. Threaded biliary inside stents are a safe and effective therapeutic option in cases of malignant hilar obstruction. BMC Gastroenterol. 2013 Feb 14;13:31.

18. Kiriyama S, Kozaka K, Takada T, Strasberg SM, Pitt HA, Gabata T, et al. Tokyo Guidelines 2018: diagnostic criteria and severity grading of acute cholangitis (with videos). J Hepatobiliary Pancreat Sci. 2018 Jan;25(1):17-30.

19. Cotton PB, Eisen GM, Aabakken L, Baron TH, Hutter MM, Jacobson BC, et al. A lexicon for endoscopic adverse events: report of an ASGE workshop. Gastrointest Endosc. 2010 Mar;71(3):446-54.

20. Yokoe M, Hata J, Takada T, Strasberg SM, Asbun HJ, Wakabayashi G, et al. Tokyo Guidelines 2018: diagnostic criteria and severity grading of acute cholecystitis (with videos). J Hepatobiliary Pancreat Sci. 2018 Jan;25(1):41-54.

21. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant. 2013 Mar;48(3):452-8.

21. Takahashi Y, Sasahira N, Sasaki T, Inoue Y, Mise Y, Sato T, et al. The role of stent placement above the papilla (inside-stent) as a bridging therapy for perihilar biliary malignancy: an initial experience. Surg Today. DOI: 10.1007/s00595-021-02268-8.

Figure Legends

Figure 1.

Definition of preoperative endoscopic biliary drainage (PEBD) and preoperative waiting period in the present study

EBD, endoscopic biliary drainage; MHBO, malignant hilar biliary obstruction; pCEBS, preoperative conventional endoscopic biliary stenting; PEBD, preoperative endoscopic biliary drainage; pEBIS, preoperative endoscopic biliary inside stenting; pENBD, preoperative endoscopic nasobiliary drainage

Figure 2.

Flow chart of the present study

EBD, endoscopic biliary drainage; GI, gastrointestinal; MHBO, malignant hilar biliary obstruction; NAC, neoadjuvant chemotherapy; pCEBS, preoperative conventional endoscopic biliary stenting; PEBD, preoperative endoscopic biliary drainage; pEBIS, preoperative endoscopic biliary inside stenting; pENBD, preoperative endoscopic nasobiliary drainage; PTBD, percutaneous transhepatic biliary drainage.

Figure 3.

Flow chart of convert of EBD method to PEBD

CEBS, conventional endoscopic biliary stenting; EBD, endoscopic biliary drainage; EBIS, endoscopic biliary inside stenting; ENBD, endoscopic nasobiliary drainage; iCEBS, initial conventional endoscopic biliary stenting; iEBIS, initial endoscopic biliary inside stenting; iENBD, initial endoscopic nasobiliary drainage; pCEBS, preoperative conventional endoscopic biliary stenting; PEBD, preoperative endoscopic biliary drainage; pEBIS, preoperative endoscopic biliary inside stenting; pENBD, preoperative endoscopic nasobiliary drainage.

Figure 4.

(A) Cumulative incidence of preoperative endoscopic biliary drainage (PEBD) dysfunction.

(B) Cumulative incidence of PEBD according to the PEBD method (pENBD/pCEBS/pEBIS). The cumulative dysfunction rates of PEBD were not significantly different among the PEBD methods (*P* = 0.60).

Figure 5.

Cumulative incidence of preoperative endoscopic biliary drainage (PEBD) dysfunction according to the PEBD method (pENBD and pEBS [pCEBS/pEBIS]). The cumulative dysfunction rates of PEBD were not significantly different between the pENBD and pEBS groups (*P* = 0.37).

Tables

Table 1. Baseline characteristics of patients

	All (n = 219)	pENBD (n = 160)	pCEBS (n = 31)	pEBIS (n = 28)	*P*-value
Age, mean (± SD), years	69.7 (± 7.6)	69.2 (± 7.4)	71.7 (± 7.4)	70.3 (± 8.5)	0.23
Sex, n (%)					0.56
Male	163 (74.4)	116 (72.5)	24 (77.4)	23 (82.1)	
Female	56 (25.6)	44 (27.5)	7 (22.6)	5 (17.9)	
Final diagnosis, n (%)					0.82
Cholangiocarcinoma	188 (85.8)	136 (85.0)	27 (87.1)	25 (89.3)	
Gallbladder cancer	31 (14.2)	24 (15.0)	4 (12.9)	3(10.7)	
Bismuth-Corlette classification, n (%)					< 0.01
I	68 (31.1)	44 (27.5)	16 (48.5)	8 (28.6)	
II	49 (22.4)	42 (26.2)	5 (15.1)	2 (7.1)	
IIIa	43 (19.6)	28 (17.5)	6 (18.2)	9 (32.2)	
IIIb	30 (13.7)	4 (15.0)	4 (12.1)	2 (7.1)	
IV	29 (13.2)	22 (13.8)	0	7 (25.0)	
Cholangitis before PEBD, n (%)					
	49 (22.4)	37 (23.1)	5 (16.1)	7 (25.0)	0.70
Pancreatitis due to EBD/PEBD procedures, n (%)					
	37 (16.9)	26 (16.3)	7 (22.6)	4 (14.3)	0.64
Initial EBD method, n (%)					< 0.01
iENBD	159 (72.6)	127 (79.4)	15 (48.4)	17 (60.7)	
iCEBS	52 (23.7)	31 (19.4)	16 (51.6)	5 (17.9)	
iEBIS	8 (3.7)	2 (1.2)	0	6 (21.4)	
One or more re-intervention by EBD before PEBD, n (%)					

	157 (71.7)	109 (68.1)	23 (74.2)	25 (89.3)	0.06

EBD: Endoscopic biliary drainage, iCEBS: Initial conventional endoscopic biliary stenting, iEBIS: Initial endoscopic biliary inside stenting, iENBD: Initial endoscopic nasobiliary drainage, pCEBS: Preoperative conventional endoscopic biliary stenting, PEBD: Preoperative endoscopic biliary drainage, pEBIS: Preoperative endoscopic biliary inside stenting, pENBD: preoperative endoscopic nasobiliary drainage

Table 2. Details of endoscopic biliary drainage (EBD) before preoperative EBD (PEBD)

	All (n = 219)	iENBD (n = 159)	iCEBS (n = 52)	iEBIS (n = 8)	*P*-value
No re-intervention, n (%)	62 (28.3)	51 (32.1)	8 (15.4)	3 (37.5)	0.04
One or more re-intervention by EBD before PEBD, n (%)	157 (71.7)	108 (67.9)	44 (84.6)	5 (62.5)	
Main reason of the additional EBD, n (%) (n=157)					< 0.01
Re-biopsy	82 (52.2)	55 (50.9)	24 (54.5)	3 (60.0)	
Tube/stent dysfunction	30 (19.1)	19 (17.6)	11 (25.0)	0	
Conversion from iENBD to CEBS/EBIS for quality of life improvement	22 (14.0)	22 (20.4)	0	0	
Conversion from single to multiple biliary drainage due to the surgical strategy	10 (6.4)	9 (8.3)	1 (2.3)	0	
Conversion from iCEBS/iEBIS to ENBD to monitor bile output or to perform cholangiography via ENBD tube	9 (5.7)	0	7 (15.9)	2 (40.0)	
Adverse event related to the initial EBD procedure	4 (2.6)	3 (2.8)	1 (2.3)	0	

CEBS: conventional endoscopic biliary stenting, EBD: Endoscopic biliary drainage, EBIS: endoscopic biliary inside stenting, ENBD: endoscopic nasobiliary drainage, iCEBS: Initial conventional endoscopic biliary stenting, iEBIS: Initial endoscopic biliary inside stenting, iENBD: Initial endoscopic nasobiliary drainage, pCEBS: Preoperative conventional endoscopic biliary stenting, PEBD: Preoperative endoscopic biliary drainage, pEBIS: Preoperative endoscopic biliary inside stenting, pENBD: preoperative endoscopic nasobiliary drainage

Table 3. Details of preoperative endoscopic biliary drainage (PEBD) and radical surgical resection

	All (n = 219)	pENBD (n = 160)	pCEBS (n = 31)	pEBIS (n = 28)	*P*-value
Preoperative waiting period, median (interquartile range), days					
	41 (26–56)	41 (26–55)	43 (22–61)	40 (26–58)	0.55
Number of the PEBD tubes, n (%)					0.19
Single	188 (85.8)	109 (68.1)	26 (83.9)	21 (75.0)	
Multiple	63 (28.8)	51 (31.9)	5 (16.1)	7 (25.0)	
Size of the largest PEBD tube/stent, n (%)					< 0.01
5-Fr	85 (38.8)	81 (50.6)	1 (3.2)	3 (10.7)	
6-Fr	70 (32.0)	68 (42.5)	1 (3.2)	1 (3.6)	
≥ 7-Fr	64 (29.2)	11 (6.9)	29 (93.6)	24 (85.7)	
Type of PEBD tubes/stents, n (%)					0.17
Straight	186 (84.9)	132 (82.5)	27 (87.1)	27 (96.4)	
Pigtail	33 (15.1)	28 (17.5)	4 (12.9)	1 (3.6)	
History of endoscopic sphincterotomy at PEBD, n (%)					
	110 (50.2)	85 (53.1)	14 (45.2)	11 (39.3)	0.32
Percutaneous transhepatic portal vein embolization until surgery, n (%)					
	129 (58.9)	98 (61.3)	11 (35.5)	20 (71.4)	0.01
Surgical procedure, n (%)					< 0.01
Bile duct resection (+ hepatectomy of segment 4a/5)					
	13 (6.0)	8 (5.0)	5 (16.1)	0	
Hilar resection + pancreatoduodenectomy					
	22 (10.0)	11 (6.9)	8 (25.8)	3 (10.7)	
Left hepatectomy/left hepatic trisegmentectomy					
	55 (25.1)	42 (26.2)	6 (19.4)	7 (25.0)	

Right hepatectomy/right hepatic trisegmentectomy				
	97 (44.3)	75 (46.9)	7 (22.6)	15 (53.6)
Hepatectomy/hepatic trisegmentectomy + pancreatoduodenectomy				
	32 (14.6)	24 (15.0)	5 (16.1)	3 (10.7)

pCEBS: Preoperative conventional endoscopic biliary stenting, PEBD: Preoperative endoscopic biliary drainage, pEBIS: Preoperative Initial endoscopic biliary inside stenting, pENBD: preoperative endoscopic nasobiliary drainage

Table 4. Univariate and multivariate analyses of risk factors for dysfunction of preoperative endoscopic biliary drainage (PEBD)

	Univariate analysis		Multivariate analysis		
	n	*P*-value	Hazard ratio	95%CI	*P*-value
Age		0.20			
< 75 years	161				
≥ 75 years	58				
Sex		0.97			
Male	163				
Female	56				
Final diagnosis		0.93			
Cholangiocarcinoma	188				
Gallbladder cancer	31				
Bismuth-Corlette classification		0.01			
I/II/IIIa/IIIb	190		1		
IV	29		2.10	1.12–3.93	0.02
Cholangitis before PEBD		0.26			
Absence	170				
Presence	49				
Pancreatitis due to EBD/PEBD procedures		0.26			
Absence	182				
Presence	37				
Initial EBD method		0.66			
iENBD	159				
iCEBS	52				

iEBIS	8				
PEBD method		0.60			
pENBD	160				
pCEBS	31				
pEBIS	28				
Number of PEBD tubes/stents		0.79			
Single	156				
Multiple	63				
Size of the largest PEBD tube/stent		0.18			
5-Fr	85		1		
≥ 6-Fr	134		0.76	0.45–1.30	0.32
Type of PEBD tubes/stents		0.88			
Straight	186				
Pigtail	33				
History of endoscopic sphincterotomy		0.30			
Absence	109				
Presence	110				
Preoperative waiting period		0.77			
≤ 40 days	105				
> 40 days	114				
PTPE until surgery		0.60			
Absence	90				
Presence	129				

CI: Confidential interval, EBD: Endoscopic biliary drainage, iCEBS: Initial conventional endoscopic biliary stenting, iEBIS: Initial endoscopic biliary inside stenting, iENBD: Initial endoscopic nasobiliary drainage, pCEBS: Preoperative

conventional endoscopic biliary stenting, PEBD: Preoperative endoscopic biliary drainage, pEBIS: Preoperative Initial endoscopic biliary inside stenting, pENBD: preoperative endoscopic nasobiliary drainage, PTPE: Percutaneous transhepatic portal vein embolization

Table 5. Univariate and multivariate analyses of risk factors for dysfunction of preoperative endoscopic biliary drainage (PEBD) in patients with Bismuth-Corlette classification (BC) IIIa, IIIb, and IV

	Univariate analysis		Multivariate analysis		
	n	*P*-value	Hazard ratio	95%CI	*P*-value
Age		0.60			
< 75 years	79				
≥ 75 years	23				
Sex		0.35			
Male	74				
Female	28				
Final diagnosis		0.71			
Cholangiocarcinoma	90				
Gallbladder cancer	12				
Bismuth-Corlette classification		0.15			
IIIa/IIIb	73		1		
IV	29		2.54	1.17–5.50	0.02
Cholangitis before PEBD		0.89			
Absence	84				
Presence	18				
Pancreatitis due to EBD/PEBD procedures		0.31			
Absence	81				
Presence	21				
Initial EBD method		0.89			
iENBD	74				
iCEBS	23				

iEBIS	5				
PEBD method		0.13			
pENBD	74		1		
pCEBS	10		2.51	1.01–6.25	0.04
pEBIS	18		0.36	0.10–1.21	0.10
Number of PEBD tubes/stents		0.62			
Single	60				
Multiple	42				
Size of the largest PEBD tube/stent		0.65			
5-Fr	51				
≥ 6-Fr	51				
Type of PEBD tubes/stents		0.58			
Straight	88				
Pigtail	14				
History of endoscopic sphincterotomy		0.31			
Absence	51				
Presence	51				
Preoperative waiting period		0.80			
≤ 40 days	51				
> 40 days	51				
PTPE until surgery		0.60			
Absence	42				
Presence	60				

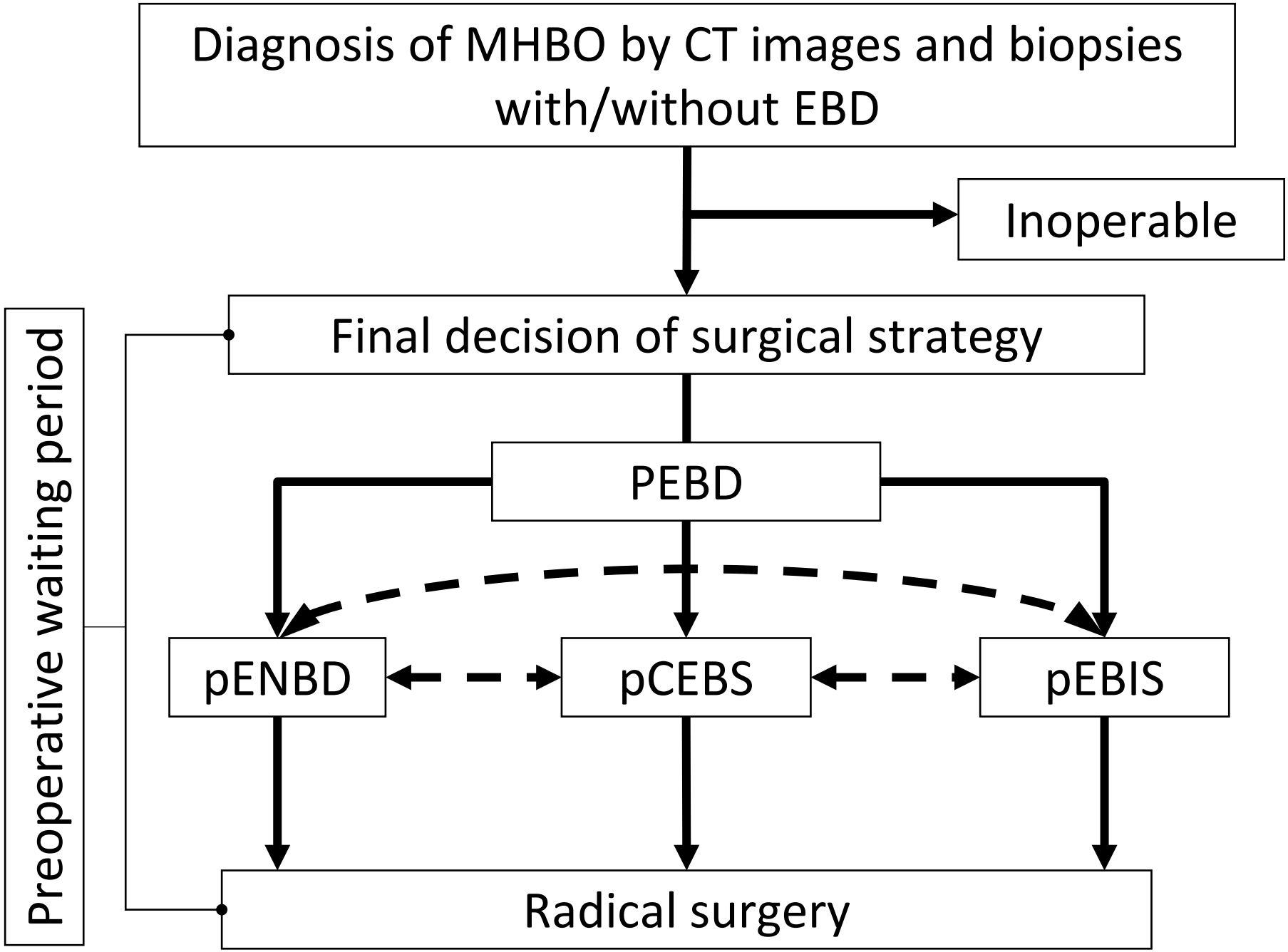
CI: Confidential interval, iCEBS: Initial conventional endoscopic biliary stenting, iEBIS: Initial endoscopic biliary inside stenting, iENBD: Initial endoscopic nasobiliary drainage, pCEBS: Preoperative conventional endoscopic biliary stenting,

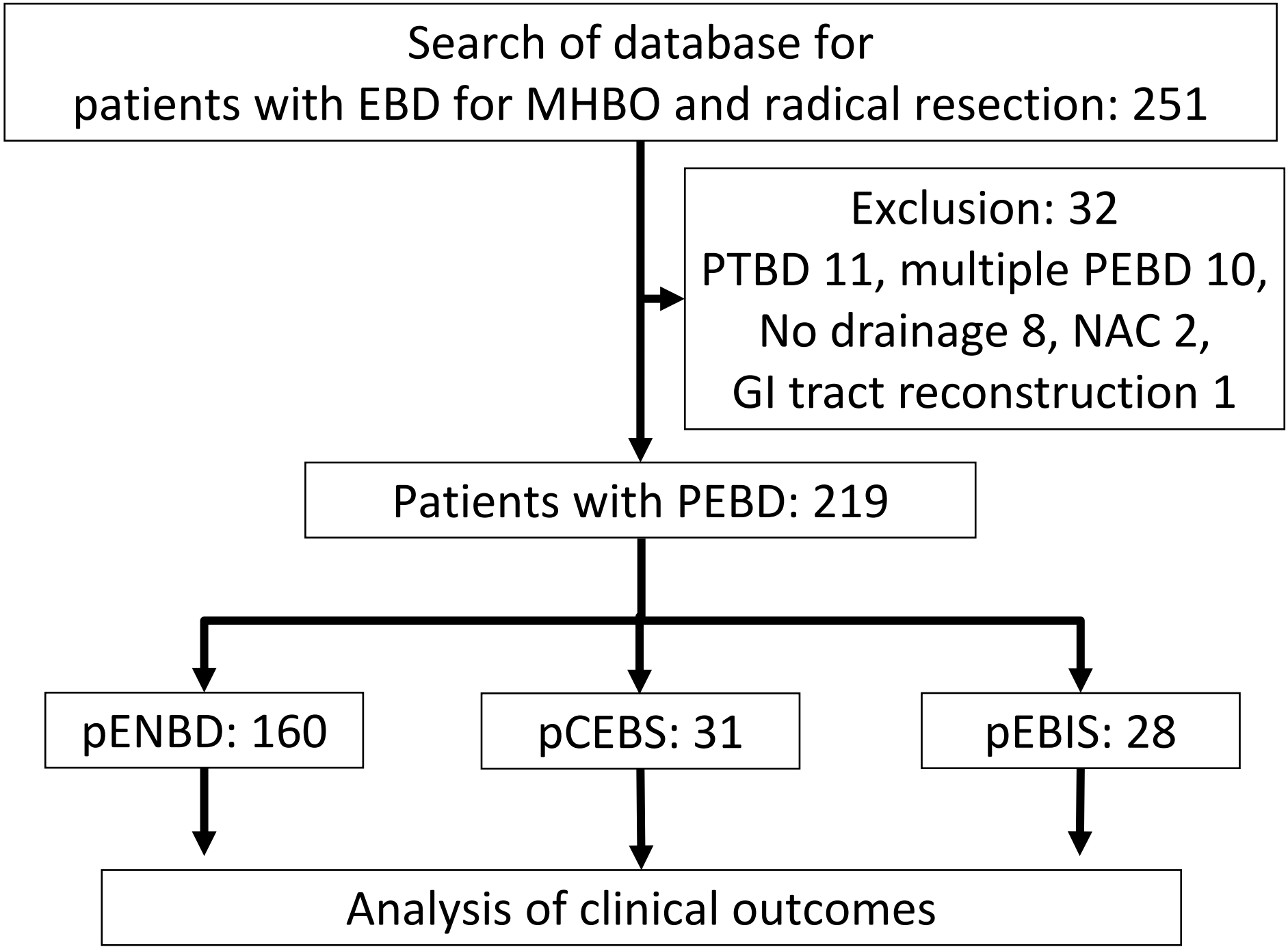
PEBD: Preoperative endoscopic biliary drainage, pEBIS: Preoperative Initial endoscopic biliary inside stenting, pENBD: preoperative endoscopic nasobiliary drainage, PTPE: Percutaneous transhepatic portal vein embolization

Table 6. Adverse events of preoperative endoscopic biliary drainage (PEBD)

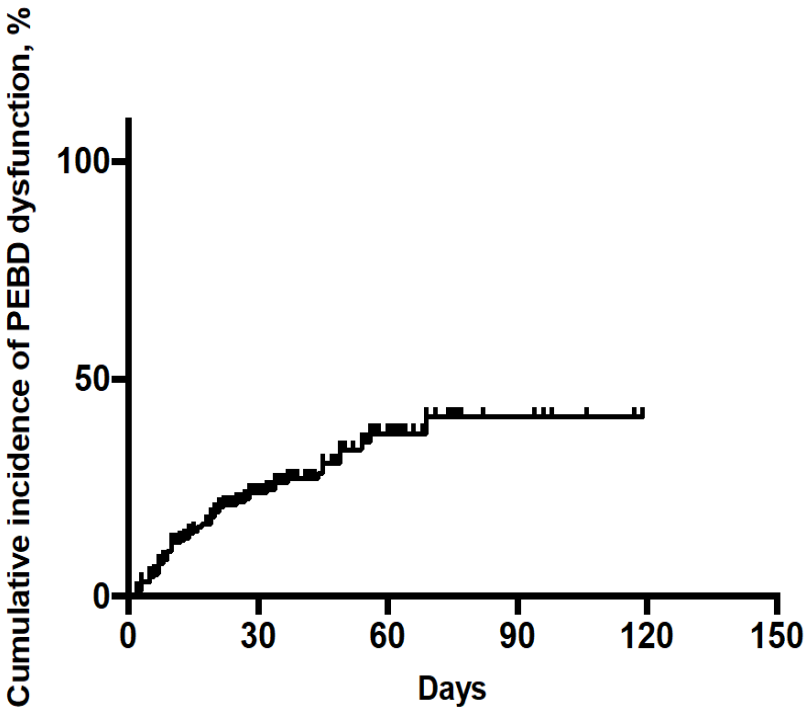
	All (n = 219)	pENBD (n = 160)	pCEBS (n = 31)	pEBIS (n = 28)	*P*-value
All adverse event, n (%)	42 (19.2)	33 (20.6)	4 (12.9)	5 (17.9)	0.70
Severe/moderate/mild, n	0/24/18	0/20/13	0/3/1	0/1/4	0.22
Contralateral segmental cholangitis, n (%)					
	11 (5.0)	10 (6.3)	0	1 (3.6)	0.47
Ipsilateral segmental cholangitis without re-intervention, n (%)					
	10 (4.6)	6 (3.8)	1 (3.2)	3 (11.1)	0.22
Pancreatitis, n (%)	16 (7.3)	14 (8.8)	1 (3.2)	1 (3.6)	0.57
Cholecystis, n (%)	3 (1.4)	2 (1.3)	1 (3.2)	0	0.61
Bleeding, n (%)	1 (0.5)	1 (0.6)	0	0	1

pCEBS: Preoperative conventional endoscopic biliary stenting, pEBIS: Preoperative Initial endoscopic biliary inside stenting, pENBD: preoperative endoscopic nasobiliary drainage


Diagnosis of MHBO by CT images and biopsies with/without EBD
Inoperable
Final decision of surgical strategy
Preoperative waiting period
PEBD
pENBD
pCEBS
pEBIS
Radical surgery

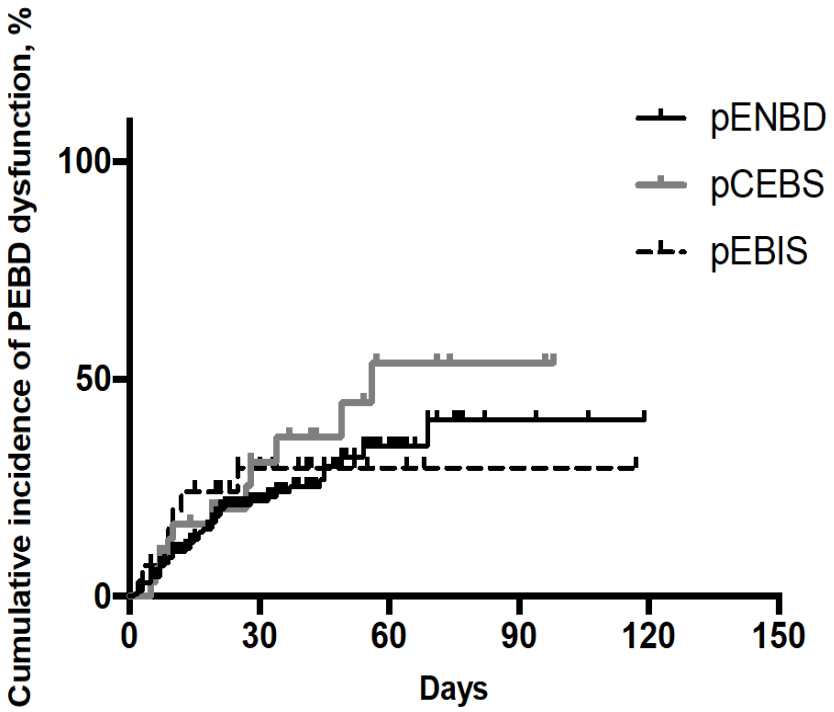

Search of database for
patients with EBD for MHBO and radical resection: 251
Exclusion: 32
PTBD 11, multiple PEBD 10,
No drainage 8, NAC 2,
GI tract reconstruction 1
Patients with PEBD: 219
pENBD: 160
pCEBS: 31
pEBIS: 28
Analysis of clinical outcomes

(A)

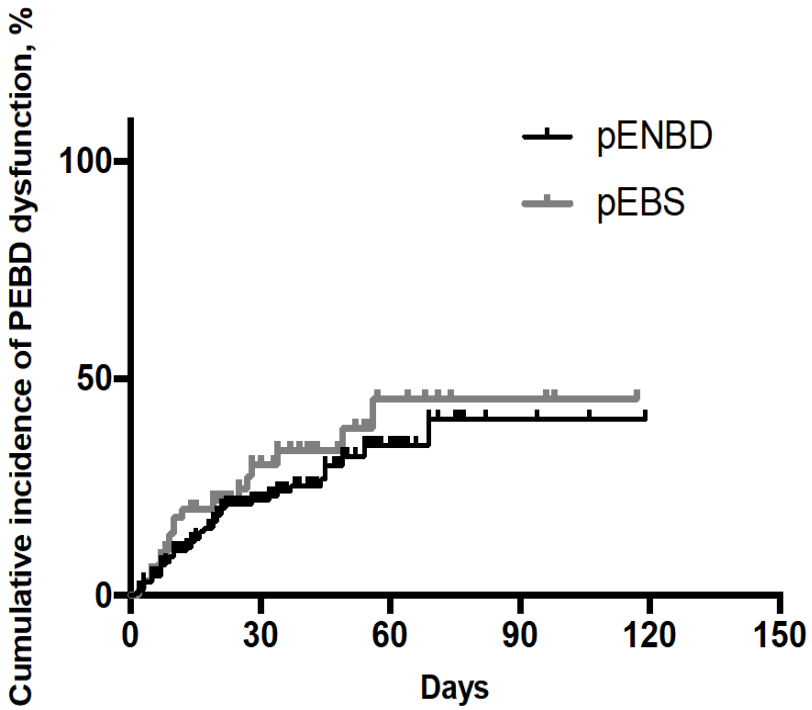


Number at risk					
	219	105	26	6	0

(B)

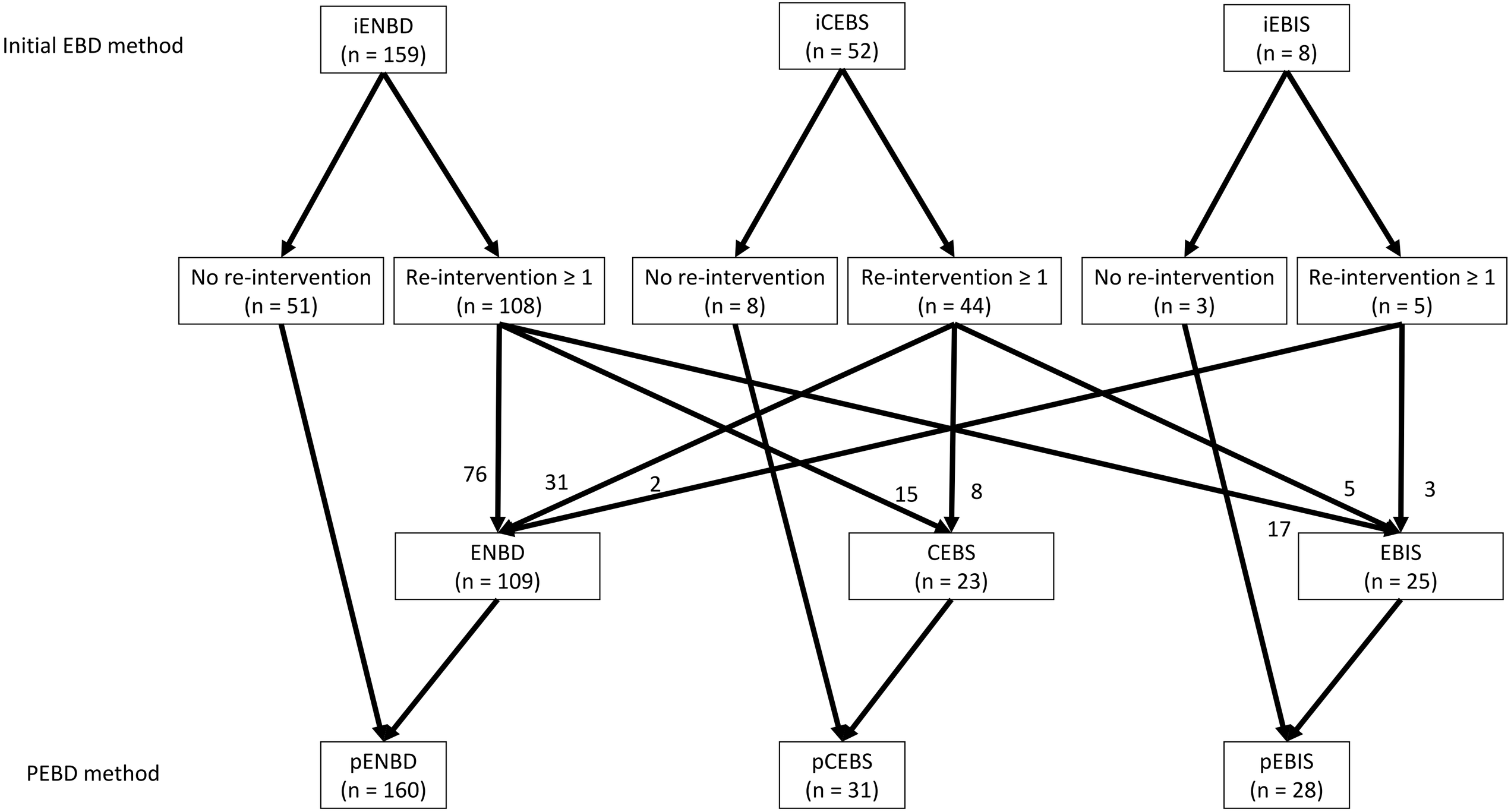


Number at risk					
pENBD	160	81	19	3	0
pCEBS	31	12	4	2	0
pEBIS	28	12	3	1	0



Number at risk

pENBD	**160**	**81**	**19**	**3**	**0**
pEBS	**59**	**24**	**7**	**3**	**0**


Initial EBD method
iENBD
(n = 159)
iCEBS
(n = 52)
iEBIS
(n = 8)
No re-intervention
(n = 51)
Re-intervention ≥ 1
(n = 108)
No re-intervention
(n = 8)
Re-intervention ≥ 1
(n = 44)
No re-intervention
(n = 3)
Re-intervention ≥ 1
(n = 5)
76
31
2
15
8
5
3
17
ENBD
(n = 109)
CEBS
(n = 23)
EBIS
(n = 25)
PEBD method
pENBD
(n = 160)
pCEBS
(n = 31)
pEBIS
(n = 28)