

**Preoperative course of patients undergoing endoscopic naso-biliary drainage
during the management of resectable perihilar cholangiocarcinoma**

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ABSTRACT

Background: Although there are many studies on technical outcomes of endoscopic nasobiliary drainage (ENBD), no authors reported on preoperative course of patients undergoing ENBD. The aim of this study was to investigate the course of patients with ENBD during the waiting
5 period.

Methods: Patients who underwent resection of perihilar cholangiocarcinoma (PHCC) between January 2013 and September 2017 were retrospectively reviewed.

Results: During the study period, 191 consecutive patients underwent surgical resection of PHCC after ENBD. Of the study patients, 154 (80.6%) patients were discharged, returned to their home, then re-
10 admitted for surgery. The remaining 37 patients were continuously hospitalized. The number of cholangitis events during the waiting period was 0 in 120 patients, 1 in 59 patients, 2≤ in 12 patients. Endoscopic re-intervention was needed in 52 patients. The median length between the first admission and surgery was 37 days (range, 12 to 197 days) in the entire cohort; it was longer in patients with portal vein embolization than in those without (43 vs 27 days, P<0.001).

15 **Conclusions:** In patients undergoing resection of PHCC, ENBD is widely tolerable with relatively low incidence of cholangitis and thus recommended for preoperative biliary drainage.

INTRODUCTION

Percutaneous transhepatic biliary drainage (PTBD), endoscopic biliary stenting (EBS), and endoscopic naso-biliary drainage (ENBD) have been used as established biliary drainage methods for perihilar cholangiocarcinoma (PHCC). However, controversy exists regarding the optimal technique among these three methods [1-4]. PTBD has been widely used with high success rates, but has a serious problem: the potential risk of seeding metastasis [5-8]. EBS is less invasive and physiological but has a high incidence of ascending cholangitis, especially in patients with Bismuth type III and IV tumors [9-12]. ENBD is less frequently associated with ascending cholangitis compared to EBS [9-13]. Considering these characteristics, the Japanese Clinical Practice Guidelines for Biliary Tract Cancer strongly recommends the use of ENBD [14]. Accordingly, ENBD is now the first option for preoperative biliary drainage for PHCC in most Japanese centers [9,13,15,16]. However, placing ENBD is uncomfortable for patients due to nasopharyngeal irritation [12]. This “patient-unfriendly” nature hinders the widespread use of ENBD in countries outside of Japan. So far, there are no studies on preoperative course of patients with ENBD during the waiting period until surgery; thus, nothing is known about this issue.

The aims of this retrospective study were to review patients who underwent resection of PHCC after ENBD and to verify whether preoperative management using ENBD is appropriate.

METHODS

Study Population

Between January 2013 and September 2017, consecutive patients who underwent resection of PHCC at the First Department of Surgery, Nagoya University Hospital, were retrospectively reviewed from a prospectively maintained database. This study was approved by the Human Research Review Committee of Nagoya University Hospital (Approval number 2018-0071)

Preoperative management during the first hospitalization

Preoperative management was described in detail in the present authors' previous report [16]. Briefly, cholangiography, computed tomography, and ultrasonography were used for the preoperative workup. Patients who had jaundice and/or dilated bile ducts in the future remnant lobe routinely underwent percutaneous or endoscopic biliary drainage [15,17]. Portal vein embolization was performed when the liver remnant was less than 40%, according to a previously reported method [18]. Liver function was evaluated by the indocyanine green test [19].

ENBD was performed using JF 260V and TJF 260V endoscopes (Olympus Medical Systems, Tokyo, Japan). After assessing the longitudinal and lateral tumor progression by intraductal ultrasonography and forceps biopsy, an ENBD pigtail-shaped catheter was inserted without endoscopic sphincterotomy [15]. Patients who were diagnosed as having unresectable tumor underwent EBS or self-expandable metallic stent according to endoscopists' preference.

Bile drained from the ENBD catheter was replaced orally or via a naso-duodenal tube to maintain the intestinal integrity, as reported previously (**Figure 1**) [20]. Preoperative monitoring of bile culture was performed routinely at least once a week [21,22].

After finishing the preoperative workup mentioned above, some patients scheduled for surgery were discharged and returned to their homes. Before discharge, they were educated by nurses in the management of the ENBD catheter, including the fixing method of the catheter (**Figure 1**), bile storage and replacement, and other points (e.g., do not pull, hitch, or bend the catheter). **We also instructed the patients to visit hospital if bile volume decreased and/or if fever >38.0°C developed. For the patients who lived far from Nagoya, we provided for close contact with doctors at local hospital.** The patients were required to measure and document their body weight, body temperature, and the volume of bile drained externally every day at home.

Preoperative cholangitis was diagnosed when the patient's body temperature was higher than

38.5°C in the presence of a positive bile culture. Cholangitis was treated by the appropriate administration of antibiotics according to the susceptibility of the specific microorganism detected by the surveillance of the bile culture, with or without endoscopic re-intervention [21,22].

Statistics

5 The results are expressed as the medians with ranges unless otherwise specified. The statistical analysis was performed using a Mann-Whitney U test for continuous variables. $P < 0.05$ was considered statistically significant. Analyses were performed using JMP 13 (SAS Institute Inc., Cary, NC).

10 **RESULTS**

Patient demographics

During the study period, 240 consecutive patients underwent the surgical resection of PHCC. Of these, 33 patients without jaundice had no preoperative biliary drainage, and the remaining 207 underwent drainage, including ENBD with (n=11) or without PTBD (n=180), PTBD alone (n=12), 15 and self-expandable metallic stent (n=4). Most of PTBD had been performed at local hospital before referral. The current study involved the 191 patients who underwent ENBD, including 140 men and 51 women with a median age of 70 years (range, 36 to 89 years).

Bismuth tumour types in the 191 patients were as follows: type I in 21 patients, type II in 26 patients, type III in 55 patients, and type IV in 89 patients: thus, 75% of the patients had Bismuth type 20 III or IV tumours.

Treatment during the first hospitalization

At previous hospitals before referral to our clinic, EBS had been placed in 67 patients (including one patient with PTBD), ENBD in 46 patients (including one patient with PTBD) and ENBD + EBS in 5 patients. The remaining 73 patients had not undergone any biliary drainage. The serum total

bilirubin concentration upon admission to our clinic was 4.1 mg/dl (0.5 to 29.9 mg/dl).

After admission, ENBD was placed in the 73 biliary drainage-naïve patients. All EBSs previously placed in the 67 patients were removed and replaced with ENBD. In 42 of the 51 patients who had received ENBD at previous hospitals, the existing ENBD was replaced with a new one. All endoscopic procedures were performed within 3 days after the admission. The final number of ENBD catheter placed was 1 in 139 patients, 2 in 49 patients, and 3 in 3 patients. The site of ENBD catheter placed was right-sided in 94 patients, left-sided in 77 patients, and bilateral in 20 patients. After ENBD placement, 8 patients underwent additional PTBD for treatment of segmental cholangitis. Preoperative portal vein embolization was performed in 114 (59.7%) patients.

Of the 191 study patients, 154 (80.6%) patients (group A, **Figure 2**) were discharged and returned to their homes. The remaining 37 patients (group B, **Figure 2**) continued hospitalization until surgery, either due to the short waiting time to surgery (n=31) or the treatment of cholangitis and/or ENBD catheter troubles requiring re-intervention (n=6). Regarding portal vein embolization, 106 (68.8%) of the former 154 patients underwent this radiological intervention, while only 8 (21.6%) of the latter 37 patients underwent the intervention (P<0.01).

Follow-up after discharge

In the 154 patients who had been discharged to their homes to await surgery, 129 (67.5%) patients (group A-1) had uneventful waiting periods until surgery. The remaining 25 patients were urgently re-admitted to the hospital before planned admission due to ENBD catheter troubles: in 24 patients, catheter troubles were successfully treated by an endoscopic approach, while in the remaining one patient additional PTBD was performed. Twelve (group A-2) of the 25 patients were again discharged, while the remaining 13 patients (group A-3) continued hospitalization until surgery (**Figure 2**).

Volume of bile drained externally thorough the ENBD catheter

The volume of bile drained externally through the ENBD catheter was measured daily by the nurse in charge during the hospitalization and by the patients themselves at home. The bile volume per day was relatively stable unless catheter occlusion /dislocation occurred. The mean volume per day for 3 days was 567 mL (range, 87 to 2327 mL) approximately one week after ENBD placement, and 588 mL (range, 43 to 2440 mL) one week before surgery.

Number of cholangitis events and re-interventions during the waiting period

The number of cholangitis events during the waiting period (between the first admission and surgery) was 0 in 120 patients, 1 in 59 patients, 2 in 7 patients, and 3 in 5 patients, with a median of 0 (range, 0 to 3). The number of patients who had cholangitis events was 3 (14.3%) in Bismuth type I, 7 (26.9%) in Bismuth type II, 21 (38.2%) in Bismuth type III, and 40 (44.9%) in Bismuth type IV.

The number of endoscopic re-interventions during the waiting period was 0 in 139 patients, 1 in 47 patients, 2 in 3 patients, and 3 in 2 patients, with a median of 0 (range, 0 to 3). The causes of re-intervention were additional drainage (n=26), catheter occlusion (n=17), catheter dislocation (n=9), re-biopsy (n=5), and accidental removal (n=2). The relationship between cholangitis and re-intervention is summarized in **Table 1**. No patients intentionally removed the ENBD catheter.

Time between the first admission and surgery

The lengths of the first hospitalization, the home stay, and between the first admission and surgery are summarized in **Table 2**. The median length between the first admission and surgery was 37 days (range, 12 to 197 days) in the entire cohort; it was significantly longer in group A than in group B because few patients in group B underwent portal vein embolization. In this regard, the median length between the first admission and surgery was significantly longer in patients with portal vein embolization (43 days, range 19 to 197 days) than in those without (27 days, range 7 to 82 days) (P<0.001).

In 11 patients, the lengths between the first admission and surgery were longer than 90 days

(Table 3). All 11 patients underwent portal vein embolization, and 5 patients received neoadjuvant chemotherapy using gemcitabine + cisplatin. Such a long waiting time was attributable to the slow hypertrophy of the non-embolized hepatic segments (future remnant segments) and/or the performance of neoadjuvant chemotherapy. Despite these difficult conditions, all 11 patients tolerated ENBD and underwent resection (4 right hepatopancreatoduodenectomy, 4 right trisectionectomy, 1 left trisectionectomy and 2 right hemihepatectomy).

Surgery

All surgeries were performed after the patient's serum total bilirubin level had decreased to <2mg/dL. In case of cholangitis, surgery was postponed for at least 2 weeks after the cholangitis had subsided. Of the 191 study patients, 5 patients underwent extrahepatic bile duct resection without hepatectomy, while the remaining 186 patients underwent hepatectomy, including left hepatectomy (n=57), left trisectionectomy (n=46), right hepatectomy (n=62), right trisectionectomy (n=20), and central bisectionectomy (n=1). All hepatectomies were combined with *en bloc* resection of the caudate lobe and extrahepatic bile duct. Combined pancreatoduodenectomy was performed in 29 (15.2%) patients. Combined portal vein and/or hepatic artery resection was performed in 73 (38.2%) patients. Operative mortality (90-day) was 1.6% (=3/191).

DISCUSSION

Several authors have reported that ENBD is superior to EBS for preoperative biliary drainage in patients with malignant distal and perihilar obstruction due to the lower risk of cholangitis [9-13]. A recent systematic review and meta-analysis demonstrated that ENBD is better than EBS in terms of the preoperative cholangitis rate, the postoperative pancreatic fistula rate, the incidence of stent dysfunction, and morbidity [10]. The only one randomized controlled trial investigated the incidence of severe drainage-related complications of EBS (n=27) or PTBD (n=27) in patients with resectable

PHCC [23]. The results were dismal with high cholangitis rate (59% in PTBD and 37% in EBS) and high mortality rate before surgery (41% in PTBD and 11% in EBS); thus this trial was prematurely stopped. It is evident that preoperative cholangitis is a major determinant of hepatic insufficiency and postoperative liver failure-related death [24-27]. Therefore, hepatobiliary surgeons should choose the biliary drainage method with a lower risk of cholangitis, especially in patients who must undergo major hepatectomy for PHCC. In this series, 120 (62.8%) of the 191 patients had no cholangitis during the waiting period and only 12 (6.2%) patients had two or more events of cholangitis, even though 75% of the cohort had Bismuth type III or IV tumours.

In our clinic, PTBD was the method primarily chosen for patients requiring drainage prior to 2005 [17]. After approximately 2006, the drainage strategy gradually changed from PTBD to ENBD due to the increasing evidence of PTBD-related seeding metastasis [5-8]. Currently, ENBD is routinely utilized, and PTBD is used only when endoscopic drainage is not feasible. In this series, ENBD was performed in 191 (92.3%) of 207 patients who underwent preoperative biliary drainage for PHCC.

The greatest disadvantage of ENBD is the low patient tolerance due to nasopharyngeal irritation. So far, no authors have reported on the preoperative course of patients who underwent ENBD as preoperative biliary drainage for PHCC. The current study clearly showed that ENBD is widely “tolerable” with relatively low incidence of cholangitis. The median length between the first admission and surgery was as long as 37 days, mainly due to portal vein embolization; however, approximately 80% of the cohort was discharged from the hospital and could stay at home. Some troubles related to biliary drainage occurred during the waiting period, but they could be managed successfully. In addition, the ENBD catheter was accidentally removed in 2 patients but was never removed intentionally by the patients themselves. This high tolerability may be attributable to patient education, in which the current authors eagerly explain that ENBD is indispensable for successful surgery. In any

case, the authors trust that both Eastern and Western patients can tolerate ENBD similarly to Japanese patients.

Another disadvantage of ENBD is that it is not physiological. This method promotes external drainage, which could impair intestinal barrier function [28,29]. Previously, the present authors
5 demonstrated that bile replacement during external biliary drainage can restore the intestinal barrier function in patients with biliary obstruction, primarily due to the repair of physical damage to the intestinal mucosa [20]. Yoshida et al. also showed in their prospective study that bile replacement improved liver and general immune function [30]. As a countermeasure against this disadvantage, the authors have used bile replacement for more than 15 years as reported previously [16,20]. So far, there
10 have been no adverse effects related to bile replacement.

The main limitation of this study was its retrospective nature and the fact that it was a single-centre study. Therefore, unexpected bias cannot be completely ruled out. **The second limitation was no comparison between ENBD and other drainage methods. During the study period, no patients received EBS at our clinic, and only a few patients underwent PTBD: thus, it was too difficult to**
15 **conduct such comparison.** Another limitation or bias was related to the skill of the endoscopists. The success rate of ENBD and trouble-shooting after drainage depends on the skill of endoscopists, which is largely different from institutes to institutes. Fortunately, the present authors' clinic has skillful endoscopists, which likely contributed largely to the satisfactory outcomes presented here [15].

In conclusion, ENBD, despite unfriendly nature, is widely tolerable in patients undergoing
20 resection of PHCC. This drainage method is safe and less associated with cholangitis and should thus be recommended for preoperative biliary drainage.

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Figure Legends

Figure 1. Fixing method of the ENBD catheter. The ENBD catheter (blue arrow) was fixed firmly at 3 points including the nasal alar, cheek, and neck. This particular patient could not drink bile; thus, a naso-duodenal tube (red arrow) was also placed for bile replacement.

5 **Figure 2.** Progress between the first admission and surgery. Some patients (group A) were discharged from the hospital until surgery, while the others (group B) continued hospitalization until surgery.

Group A patients were divided into the following 3 subgroups: group A-1, patients who had uneventful waiting period; group A-2, patients who were re-admitted to the hospital before planned admission due to ENBD catheter trouble and who were again discharged after treatment; group A-3, patients who
10 were re-admitted to the hospital before planned admission due to ENBD catheter trouble and who continued hospitalization until surgery.



Figure 1

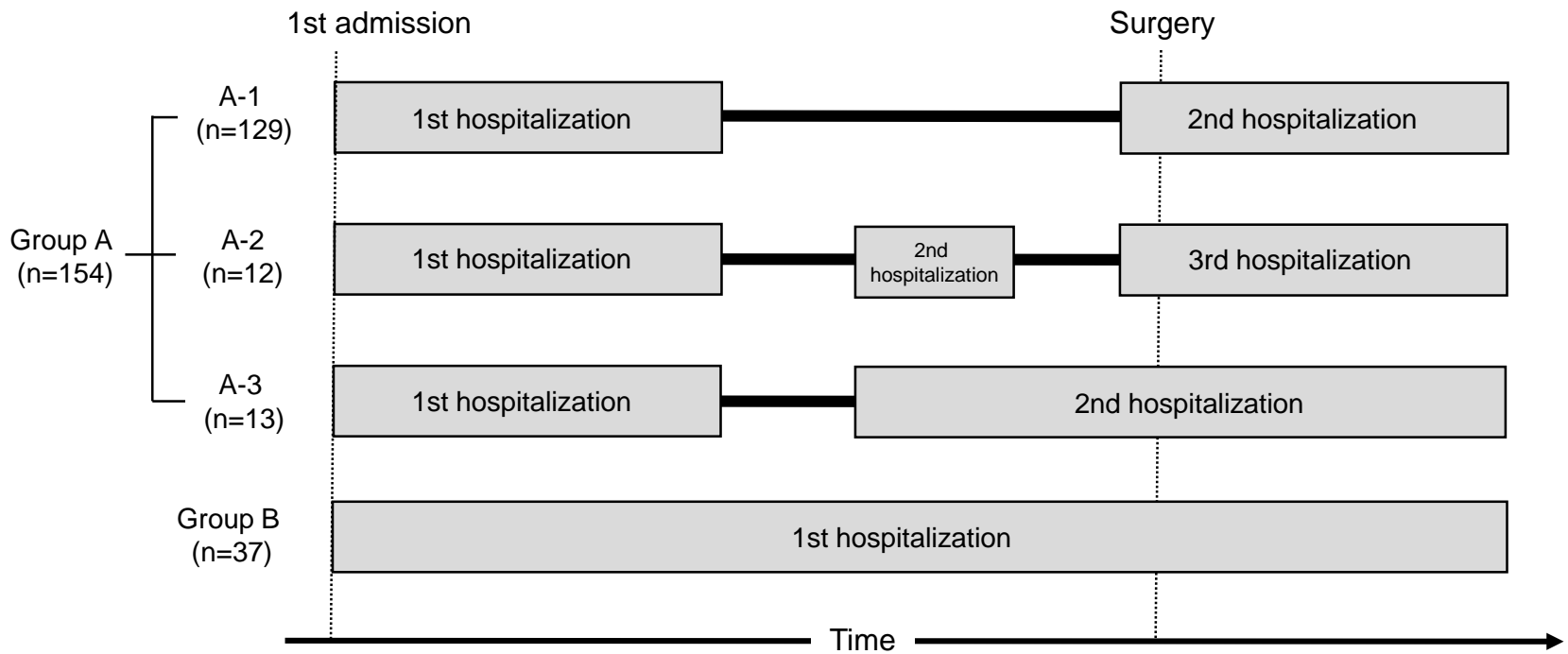


Figure 2

Table 1. Relationship between cholangitis and re-intervention during waiting period

		Number of re-intervention			
		0	1	2	3
Number of cholangitis events	0	94	24	2	0
	1	37	19	1	2
	2	5	2	0	0
	3	3	2	0	0

Table 2. Length of waiting period until surgery

Length of the period	Group A (n=154)			Group B (n=37)	P*
	A-1 (n=129)	A-2 (n=12)	A-3 (n=13)		
First hospitalization (days)	16 (6 - 48)	13 (7 - 30)	15 (6 - 24)	-	-
	----- 16 (6 - 48) -----				
Stay at home after discharge (days)	15 (2 - 126)	34 (19 - 164)	13 (4 - 37)	-	-
	----- 17 (2 - 164) -----				
Between the 1st admission and surgery (days)	41 (14 - 146)	63 (38 - 197)	39 (24 - 76)	22 (7 - 82)	<0.001
	----- 41 (14 - 197) -----				
	----- 37 (7 - 197) -----				

*, between group A and group B.

Table 3. Details of 11 patients whose waiting period was longer than 90 days

	Sex	Age	Length between 1st admission and surgery (days)	Length of stay at home during waiting time (days)	Number of ENBD placed	Number of event of cholangitis during waiting period	Re-intervention of ENBD during waiting period	Portal vein embolization	Neoadjuvant chemotherapy	Surgery*	Follow-up (months)
Case 1	Male	65	197	160	1	1	3	Yes	Yes	S1,5,6,7,8 + PD	NED (9)
Case 2	Male	65	146	126	1	0	0	Yes	Yes	S1,5,6,7,8 + PD	DOD (20)
Case 3	Male	62	114	91	1	1	0	Yes	No	S1,5,6,7,8	NED (42)
Case 4	Male	55	114	100	3	0	1	Yes	Yes	S1,5,6,7,8 + PD	NED (30)
Case 5	Male	73	108	81	2	2	0	Yes	No	S1,4,5,6,7,8	NED (38)
Case 6	Male	64	103	61	1	2	0	Yes	No	S1,4,5,6,7,8	NED (48)
Case 7	Male	80	97	40	2	1	0	Yes	No	S1,2,3,4,5,8	NED (41)
Case 8	Male	66	94	64	1	0	1	Yes	No	S1,5,6,7,8 + PD	AWD (28)
Case 9	Male	77	93	45	1	1	3	Yes	No	S1,4,5,6,7,8	NED (13)
Case 10	Male	51	93	71	1	0	0	Yes	Yes	S1,4,5,6,7,8	DOD (32)
Case 11	Male	78	93	64	1	2	0	Yes	Yes	S1,5,6,7,8	DOSC (1)

PD, pancreatoduodenectomy; NED, no evidence of disease; DOD, died of disease; AWD, alive with disease: **DOSC, died of surgical complication.**

*, expressed as Couinaud's hepatic segments resected.