

Retrospective Cohort Study

Lower incidence of complications in endoscopic nasobiliary drainage for hilar cholangiocarcinoma

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Abstract

AIM: To identify the most effective endoscopic biliary drainage technique for patients with hilar cholangiocarcinoma.

METHODS: In total, 118 patients with hilar cholangiocarcinoma underwent endoscopic management [endoscopic nasobiliary drainage (ENBD) or endoscopic biliary stenting] as a temporary drainage in our institution between 2009 and 2014. We retrospectively evaluated all complications from initial endoscopic drainage to surgery or palliative treatment. The risk factors for biliary reintervention, post-endoscopic retrograde cholangiopancreatography (post-ERCP) pancreatitis, and percutaneous transhepatic biliary drainage (PTBD) were also analyzed using patient- and procedure-related characteristics. The risk factors for bilateral drainage were examined in a subgroup analysis of patients who underwent initial unilateral drainage.

RESULTS: In total, 137 complications were observed in 92 (78%) patients. Biliary reintervention was required in 83 (70%) patients. ENBD was significantly associated with a low risk of biliary reintervention [odds ratio (OR) = 0.26, 95%CI: 0.08-0.76, $P = 0.012$]. Post-ERCP pancreatitis was observed in 19 (16%) patients. An absence of endoscopic sphincterotomy was significantly associated with post-ERCP pancreatitis (OR = 3.46, 95%CI: 1.19-10.87, $P = 0.023$). PTBD was required in 16 (14%) patients, and Bismuth type III or IV cholangiocarcinoma was a significant risk factor (OR = 7.88, 95%CI: 1.33-155.0, $P = 0.010$). Of 102 patients with initial unilateral drainage, 49 (48%) required bilateral drainage. Endoscopic sphincterotomy (OR = 3.24, 95%CI: 1.27-8.78, $P = 0.004$) and Bismuth II, III, or IV cholangiocarcinoma (OR = 34.69, 95%CI: 4.88-736.7, $P < 0.001$) were significant risk factors for bilateral drainage.

CONCLUSION: The endoscopic management of hilar cholangiocarcinoma is challenging. ENBD should be selected as a temporary drainage method because of its low risk of complications.

Key words: Hilar cholangiocarcinoma; Endoscopic nasobiliary drainage; Endoscopic biliary stenting; Endoscopic sphincterotomy; Complications

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Core tip: This retrospective study evaluated the risk of complications associated with a temporary endoscopic biliary drainage for hilar cholangiocarcinoma. Endoscopic nasobiliary drainage (ENBD) had a significantly lower incidence of biliary complications than biliary stenting. Endoscopic sphincterotomy significantly reduced the rate of post-endoscopic retrograde cholangiopancreatography pancreatitis, but was associated with bilateral drainage. Therefore, ENBD should be selected as a temporary biliary drainage method for patients with hilar cholangiocarcinoma.

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INTRODUCTION

Surgery is the only curative treatment for patients with hilar cholangiocarcinoma, and the routine use of preoperative biliary drainage should be avoided^[1,2]. However, preoperative drainage is mandatory to assess the surgical resectability and obtain pathological

confirmation^[3,4]. In other words, surgical resectability cannot be accurately assessed before biliary drainage.

Endoscopic biliary drainage is widely accepted as the standard therapy for palliation of malignant biliary obstruction^[5,6]. Because of severe complications and tumor seeding, percutaneous transhepatic biliary drainage (PTBD) is not recommended as a routine preoperative drainage method^[7,8]. Therefore, endoscopic nasobiliary drainage (ENBD) is usually selected for temporary biliary drainage in patients with hilar cholangiocarcinoma, especially in high-volume centers. In patients who are not candidates for surgery after a work-up for resectability, endoscopic biliary drainage using a self-expandable metallic stent is often performed because of the long stent patency^[6,9].

No studies have evaluated the safety of endoscopic biliary drainage as a bridge to definitive surgery or palliative treatment in patients with hilar cholangiocarcinoma. The aim of this study was to evaluate the complications associated with temporary endoscopic biliary drainage in patients with hilar cholangiocarcinoma from the initial biliary drainage to the definitive surgery or palliative treatment.

MATERIALS AND METHODS

Study design

This retrospective study was performed at a tertiary care university hospital in which > 50 cases of major hepatectomy are performed every year. The prospectively collected endoscopy database at our department was searched for patients who underwent biliary drainage of hilar cholangiocarcinoma for temporary purpose from 2009 to 2014. We excluded patients who underwent PTBD or self-expandable metallic stent (SEMS) placement as an initial drainage technique. In patients who underwent curative surgery, all complications that occurred from initial drainage to surgery were reviewed. In the remaining patients, all complications that occurred from initial drainage to palliative treatment were assessed. Palliative treatment included SEMS placement, bypass surgery, and permanent PTBD. The severity of each complication was defined by a lexicon from the American Society for Gastrointestinal Endoscopy. The study was approved by the institutional review board of Hokkaido University Hospital (014-044) and complied with the Health Insurance Portability and Accountability Act regulations (UMIN000017178).

Endoscopic management of hilar cholangiocarcinoma

Written informed consent was obtained from each patient before endoscopic retrograde cholangiopancreatography (ERCP). In our institution, the initial drainage technique for patients with hilar cholangiocarcinoma is usually unilateral ENBD to the future remnant liver lobe^[8]. However, in other hospitals, the selection of initial drainage technique depended on each endoscopist. In patients who had previously

Table 1 Patient characteristics (N-118)

Age, yr (mean, SD)	69 (9)
Male/female	74/44
Preoperative bilirubin, mg/dL (median, range)	2.0 (0.5–24.9)
Bismuth I/II/IIIa/IIIb/IV, <i>n</i>	18/25/35/5/35
Initial biliary drainage at our institutions, <i>n</i> (%)	43 (36)
Initial drainage ENBD/EBS, <i>n</i>	85/33
Unilateral/bilateral, <i>n</i>	102/16
Sphincterotomy, <i>n</i> (%)	74 (63)
PTPE, <i>n</i> (%)	54 (46)
Surgery, <i>n</i> (%)	71 (60)
Time to surgery, days (median, range)	62 (4-233)

ENBD: Endoscopic nasobiliary drainage; EBS: Endoscopic biliary stenting; PTPE: Percutaneous transhepatic portal vein embolization.

undergone drainage, biliary reintervention with ENBD was considered in the following situations: Catheter obstruction, segmental cholangitis, spontaneous catheter dislocation, accidental ENBD tube removal, and/or ENBD-induced duodenal ulcer formation. Catheter obstruction was diagnosed in patients with a high fever ($> 38^{\circ}\text{C}$) and elevated serum hepatobiliary enzyme concentrations. Segmental cholangitis was defined as cholangitis that occurred in an undrained area. In patients with catheter obstruction, the previous endoscopic biliary stent (EBS) or ENBD tube was exchanged for an ENBD tube in the same segment. In patients with segmental cholangitis, an additional ENBD tube was placed in the segment in which cholangitis was suspected. PTBD was performed in patients with segmental cholangitis if ENBD failed or after severe post-ERCP pancreatitis.

Resectability assessment

The criteria for surgical resectability were basically determined according to our previous study^[10,11], and some patients with advanced age or comorbid diseases did not undergo surgery. Portal vein embolization was performed as necessary^[12]. If the patient was determined to have unresectable disease, endoscopic SEMS placement, PTBD, or bypass surgery was performed as a palliative treatment.

Statistical analysis

Results are reported as mean \pm SD for quantitative variables and as percentage for categorical variables. We analyzed the risk factors for all complications, biliary reintervention, and PTBD using age, sex, Bismuth type I/II/III or IV cholangiocarcinoma, total bilirubin concentration before initial drainage, EBS placement/ENBD, unilateral/bilateral disease, and sphincterotomy. Risk factors for post-ERCP pancreatitis were evaluated using age, sex, EBS placement/ENBD, unilateral/bilateral disease, and sphincterotomy. In patients who underwent unilateral initial drainage, we evaluated risk factors for bilateral drainage using these factors.

Table 2 Complications

Initial drainage	ENBD (<i>n</i> = 85)	EBS (<i>n</i> = 33)
ENBD dislocation	20	6
EBS occlusion	8	14
ENBD occlusion	14	7
Contralateral cholangitis	25	12
Accidental ENBD extubation	2	2
Cholecystitis	0	3
Liver abscess	0	2
ENBD induced ulcer	0	1
Inappropriate location	1	1
Pancreatitis	12	7
(Mild/moderate/severe)	(5/2/5)	(3/2/2)

ENBD: Endoscopic nasobiliary drainage; EBS: Endoscopic biliary stenting.

Statistical analysis was performed by JMP version 11 (SAS Institute Inc., Cary, NC, United States).

RESULTS

Patient characteristics

During the study period, 125 patients underwent endoscopic biliary evaluation and drainage for temporary purpose at our institution. Two patients were excluded because of previous PTBD placement at the previous hospital. Five patients who underwent SEMS placement at the time of initial drainage were also excluded. Therefore, 118 patients were included and evaluated in this study. The patients' baseline characteristics are shown in Table 1. Eighty-five patients underwent ENBD for initial drainage, while the remaining underwent EBS placement. One hundred and two patients underwent unilateral initial drainage and 16 underwent bilateral drainage. Seventy-four patients underwent endoscopic sphincterotomy at the time of the initial drainage. The initial drainage was performed at other hospitals in 75 patients. Seventy-one patients underwent definitive surgery, while the remaining underwent palliative treatment. Palliative treatment included SEMS placement or PTBD. The median time to the final treatment was 64 d (range: 4-233 d).

Complications

Between the initial drainage and final treatment, 118 complications in 92 patients were observed (Table 2). Biliary reintervention was required in 83 (70%) patients; the incidence was 35%, 53%, and 63% within 30, 60, and 90 d, respectively. The reasons for biliary reintervention were contralateral cholangitis ($n = 37$), ENBD dislocation ($n = 26$), EBS occlusion ($n = 22$), ENBD occlusion ($n = 21$), accidental ENBD removal ($n = 4$), inappropriate tube location ($n = 2$), and ENBD-induced duodenal ulcer formation ($n = 1$). PTBD was required in 16 (14%) patients with contralateral cholangitis but who underwent failed endoscopic drainage. Post-ERCP pancreatitis was observed in 19 patients; the severity was mild in eight, moderate in four, and severe in seven.

Table 3 Risk factors for biliary reintervention

	OR	95%CI	P value
Age (+1 yr)	1.01	0.96-1.06	0.626
Female/male	1.23	0.50-3.14	0.650
Bismuth I	1		
Bismuth II	1.53	0.38-9.19	0.555
Bismuth IIIa/b/IV	2.06	0.68-6.11	0.195
Preoperative Bil (+ 1 mg/dL)	0.97	0.91-1.05	0.492
EBS/ENBD	3.80	1.32-13.02	0.012
Unilateral/bilateral	2.62	0.74-9.20	0.132
Sphincterotomy	1.32	0.53-3.25	0.551

ENBD: Endoscopic nasobiliary drainage; EBS: Endoscopic biliary stenting.

Table 4 Risk factors for percutaneous transhepatic biliary drainage

	OR	95%CI	P value
Age (+1 yr)	0.96	0.92-1.08	0.220
Female/male	2.48	0.73-8.71	0.143
Bismuth I	1		
Bismuth II	0.54	0.02-15.15	0.683
Bismuth IIIa/b/IV	10.15	1.62-214.7	0.010
Sphincterotomy	2.36	0.69- 9.43	0.178
EBS/ENBD	2.63	0.70-9.89	0.149
Unilateral/bilateral	8.77	1.09-214.7	0.040
Preoperative bilirubin (+ 1 mg/dL)	1.02	0.93-1.12	0.604

ENBD: Endoscopic nasobiliary drainage; EBS: Endoscopic biliary stenting.

In 102 patients who underwent initial unilateral drainage, 49 (48%) required bilateral drainage.

Risk factors for biliary reintervention

Multivariate analysis showed that EBS placement was a significant risk factor for biliary reintervention (OR = 3.80, 95%CI: 1.32-13.02, *P* = 0.012). ENBD was significantly associated with a low risk of biliary reintervention (OR = 0.26, 95%CI: 0.08-0.76, *P* = 0.012) and *vice versa* (Table 3).

Risk factors for PTBD

Multivariate analysis showed that patients with Bismuth III and IV cholangiocarcinoma (OR = 10.15, 95%CI: 1.62-214.7, *P* = 0.010) and initial unilateral drainage (OR = 8.77, 95%CI: 1.09-214.7, *P* = 0.040) were significant risk factors for PTBD (Table 4).

Risk factors for post-ERCP pancreatitis

Multivariate analysis showed that absence of endoscopic sphincterotomy was significantly associated with post-ERCP pancreatitis (OR = 3.46, 95%CI: 1.19-10.87, *P* = 0.023) (Table 5).

Risk factors for bilateral drainage

In the multivariate analysis of 102 patients, those with Bismuth II/III/IV cholangiocarcinoma (OR = 34.69, 95%CI: 4.88-736.7, *P* < 0.001) and the presence of endoscopic sphincterotomy (OR = 4.43, 95%CI:

Table 5 Risk factors for post-endoscopic retrograde cholangio-pancreatography pancreatitis

	OR	95%CI	P value
Age (+1 yr)	0.95	0.89-1.01	0.078
Female/male	1.45	0.48-4.36	0.501
EBS/ENBD	2.24	0.70-7.09	0.171
Unilateral/bilateral	1.46	0.31-11.24	0.661
No sphincterotomy	3.46	1.19-10.87	0.023

ENBD: Endoscopic nasobiliary drainage; EBS: Endoscopic biliary stenting.

Table 6 Risk factors for bilateral drainage (n = 102)

	OR	95%CI	P value
Age (+1 yr)	0.95	0.89-1.01	0.077
Female/male	1.76	0.66-4.91	0.259
EBS/ENBD	3.12	0.97-11.26	0.056
Bismuth I	1		
Bismuth II	34.69	4.88-736.7	< 0.001
Bismuth IIIa/b/IV	1.12	0.36-3.53	0.843
Sphincterotomy	4.43	1.61-13.51	0.004
Preoperative bilirubin	1.07	0.98-1.17	0.156

ENBD: Endoscopic nasobiliary drainage; EBS: Endoscopic biliary stenting.

1.61-13.51, *P* = 0.004) were significant risk factors for bilateral drainage (Table 3).

DISCUSSION

In this study, endoscopic biliary drainage of hilar cholangiocarcinoma for temporary purpose had a high morbidity rate. However, ENBD was associated with a significantly lower risk of biliary reintervention than EBS placement. Endoscopic sphincterotomy reduced the risk of post-ERCP pancreatitis, but was significantly associated with bilateral drainage.

The treatment strategy for hilar cholangiocarcinoma depends on the surgical resectability. Surgical resectability was determined not only by the tumor itself but also the presence of jaundice, liver function test results, performance status, and/or comorbid diseases. Endoscopic biliary drainage is usually necessary after endoscopic biopsy of the bile duct to prevent post-ERCP cholangitis. We previously demonstrated that ENBD is the most suitable preoperative drainage method for hilar cholangiocarcinoma because it is associated with a lower complication rate than are EBS and PTBD^[8]. Preoperative drainage did not affect the mortality rate among jaundiced patients with hilar cholangiocarcinoma^[13,14]. In a recent study, surgeons preferred endoscopic biliary drainage to PTBD to avoid tumor seeding and severe complications^[7,15]. Actually, during the study period, only two patients underwent PTBD as the initial biliary drainage method. This study showed that ENBD is still the most suitable initial temporary drainage method for the management of hilar cholangiocarcinoma. This means that ENBD should be selected as a tem-

porary drainage method in jaundiced patients with hilar cholangiocarcinoma regardless of the surgical resectability. In previous studies involving patients who were not candidates for surgical resection, an endoscopic SEMS was deployed in place of an ENBD tube because of the longer patency duration than a plastic stent^[9,16].

Post-ERCP pancreatitis is an unresolved problem in endoscopic biliary drainage^[17,18]. Prophylactic pancreatic stenting and rectal indomethacin has been recommended to prevent post-ERCP pancreatitis^[19]. This study showed that endoscopic sphincterotomy can reduce the incidence of post-ERCP pancreatitis without prophylactic pancreatic stenting or rectal indomethacin, which is consistent with the findings of previous retrospective studies^[15,20]. However, endoscopic sphincterotomy did not reduce the incidence of post-ERCP pancreatitis in patients with distal malignant biliary obstruction before ENBD^[21,22]. The risk of post-ERCP pancreatitis was higher in patients with hilar cholangiocarcinoma than in patients with pancreatic cancer^[22]. The effect of endoscopic sphincterotomy before endoscopic biliary drainage for hilar cholangiocarcinoma on post-ERCP pancreatitis should be clarified in a randomized prospective study.

PTBD was historically a standard preoperative management technique for hilar cholangiocarcinoma^[23]. However, the development of endoscopic biliary drainage and the high risk of severe complications rendered it salvage therapy^[4]. In the present study, 14% of patients required PTBD for the management of contralateral cholangitis, and highly advanced biliary stricture was significantly associated with PTBD. This is consistent with previous reports^[24]. Although multiple ENBD is possible, surgeons and endoscopists should understand the limitations of ENBD, especially for highly advanced hilar cholangiocarcinoma^[4].

There is still controversy regarding the superiority of unilateral or bilateral drainage for management of hilar malignant biliary obstruction. In the present study, 49% of patients who underwent unilateral initial drainage required bilateral drainage until the surgery or palliative treatment because of contralateral cholangitis. In patients with unresectable malignant hilar biliary obstruction, bilateral drainage was associated with a longer stent patency time than was unilateral drainage. However, bilateral drainage was sometimes technically difficult, especially in patients with highly advanced biliary strictures^[25]. Additional studies are required to compare unilateral and bilateral endoscopic biliary drainage for temporary biliary drainage.

This study had several limitations. This was a retrospective nonrandomized study. Each endoscopist chose the endoscopic biliary drainage method and necessity of endoscopic sphincterotomy. The usefulness of inside stent placement for temporary preoperative drainage was recently reported^[26]. The superiority of ENBD to inside stent placement requires clarification in future studies. Furthermore, few patients in this study underwent preoperative neoadjuvant therapy, in which

the preoperative period was much longer. The safety of surgery after SEMS placement was reported, and temporary SEMS placement should be evaluated^[27].

Endoscopic biliary drainage for temporary purpose in patients with hilar cholangiocarcinoma has a high morbidity rate. Until surgical resectability is determined, ENBD should be selected for temporary endoscopic biliary drainage because of its low reintervention rate. Endoscopic sphincterotomy should be considered to prevent post-ERCP pancreatitis. Further studies are required to identify a more suitable management technique for patients with hilar cholangiocarcinoma.

COMMENTS

Background

Surgery is the only curative treatment for patients with hilar cholangiocarcinoma, and the routine use of preoperative biliary drainage should be avoided. However, surgical resectability cannot be always accurately assessed before biliary drainage. No studies have evaluated the safety of endoscopic biliary drainage as a bridge to definitive surgery or palliative treatment in patients with hilar cholangiocarcinoma.

Research frontiers

The authors previously reported endoscopic nasobiliary drainage (ENBD) is the most suitable for preoperative biliary drainage in patients with hilar cholangiocarcinoma. The authors provide support to the preference of ENBD for both preoperative and palliative biliary drainage in patients with hilar cholangiocarcinoma.

Innovations and breakthroughs

ENBD had a significantly lower incidence of biliary complications than biliary stenting in patients with hilar cholangiocarcinoma.

Applications

Endoscopic biliary drainage for temporary purpose in patients with hilar cholangiocarcinoma has a high morbidity rate. Until surgical resectability is determined, ENBD should be selected for temporary endoscopic biliary drainage because of its low reintervention rate.

Terminology

ENBD is one of the biliary drainage methods. The advantage of ENBD over biliary stenting is the monitoring of bile, cholangiography, bile cytology, and removability. The disadvantage is the discomfort of the patients.

Peer-review

In this retrospective study, the authors end up into some conclusions, the majority of which are well known from previous studies. What is new is that according to their findings ENBD was a better approach and with lower complications.

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