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Long-term outcomes and risk factors of recurrent biliary obstruction after permanent endoscopic biliary stenting for choledocholithiasis in high-risk patients

Running Head: Permanent EBS for choledocholithiasis

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Abstract

Aim: To elucidate the long-term outcomes of permanent endoscopic biliary stenting (EBS) and risk factors for recurrent biliary obstruction (RBO) in high-risk or elderly patients with common bile duct (CBD) stones.

Methods: The electronic database of Hakodate Municipal Hospital was searched to identify elderly or high-risk patients with CBD stones who underwent initial permanent EBS using a plastic stent without stone removal and was followed without re-intervention until symptoms between April 2011 and May 2019.

Results: Among a total of 47 patients (19 males [40.4%]; median age, 86 [interquartile range, 80–90] years). RBO and death without biliary disease occurred in 14 (29.8%) and 19 (40.4%) patients, respectively. The cumulative RBO rates at 20, 40, and 60 months were 22.1%, 31.8%, and 35.5%, respectively. The median periods until RBO were 13.0 and 38.0 months in the

group with the CBD stone diameter ≥ 15 mm and 11–14mm, respectively, and the date was not reached in the group with the CBD stone diameter ≤ 10 mm. The cumulative RBO incidence rates were significantly different among the three groups based on the CBD stone diameter (competing risk analysis, $P < 0.01$). Multivariate analysis showed that an increase in CBD stone diameter predicted the increased risk of RBO (hazard ratio per 1 mm, 1.26, $P = 0.01$).

Conclusions: Permanent EBS is a feasible option for high-risk patients with small CBD stones.

Keywords: Endoscopic biliary stenting; Permanent endoscopic biliary stenting; Common bile duct stone; Recurrent biliary obstruction; Long-term outcome

Introduction

Choledocholithiasis is a common biliary disease that requires medical attention and intervention. Endoscopic retrograde cholangiopancreatography (ERCP) with endoscopic sphincterotomy (ES) is a globally used procedure for common bile duct (CBD) stone removal [1-3], which is successful in 80%–95% of the cases [4,5]. However, successful endoscopic removal of the CBD stones is sometimes difficult in patients with large or impacted stones and those with CBD stone-related acute cholangitis, especially in high-risk patients with comorbidities. Endoscopic biliary stenting (EBS) using plastic stents (PSs) is a safe alternative procedure in the short term for elderly and high-risk patients [6,7]. Several studies demonstrated the long-term benefits of EBS [7-9], whereas other studies reported that the long-term complications increased with time following EBS; therefore, replacement or removal of the biliary stents has been recommended after 3–6 months [10-12]. However, the long-term benefits of permanent EBS remain even less clear. Data on the incidence of long-term recurrent biliary obstruction (RBO) and risk factors associated with RBO are limited.

The aim of the current study was to examine the clinical outcomes of permanent EBS in elderly and high-risk patients with choledocholithiasis and the time to RBO in those with

PSs, with the aim to identify the risk factors for RBO of the PSs.

Patients and methods

Study design

In this retrospective cohort study conducted at Hakodate Municipal Hospital, the hospital database was searched to identify consecutive high-risk patients with acute cholangitis associated with choledocholithiasis who underwent emergent ERCP according to the Japanese guidelines [13] between April 2011 and May 2019. The inclusion criteria were the following: 1) permanent EBS to improve acute cholangitis associated with choledocholithiasis at initial ERCP or permanent EBS converted from endoscopic nasobiliary drainage (ENBD) during second ERCP, 2) EBS without stone removal, 3) clinical findings attributable to infection that improved within seven days after the initial ERCP, and 4) refusal of further endoscopic removal of CBD stones due to poor patient characteristics based on severe comorbidities or older age. The exclusion criteria were the following: 1) CBD stones not confirmed by any imaging studies including ultrasonography, endoscopic ultrasonography, computed tomography, magnetic resonance cholangiopancreatography, and ERCP, 2) history of ES or endoscopic papillary balloon dilation, 3) biliary stent or nasobiliary tube that was

already placed, 4) history of gastrointestinal tract reconstruction, 5) future periodic and scheduled change of a PS, 6) conversion to stone removal in patients without symptoms, 7) biliary stricture regardless of the presence of benign or malignant disease, and 8) refusal of the patient or their family to enroll in the study.

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki (6th revision, 2008) as reflected in *a priori* approval by the study institution's Human Research Committee. The study was approved by the Institutional Review Board of Hakodate Municipal Hospital (2019-60).

Endoscopic procedures

All endoscopic procedures were performed by one of the four experienced endoscopists (R.S., H.N., H.Y., and T.K.) who collectively perform >150 ERCP procedures per year and have completed >500 ERCP procedures in total. ERCP was performed under conscious sedation. Briefly, a therapeutic duodenoscope (TJF-240 or JF-260V; Olympus Medical Systems, Tokyo, Japan) was used with the standard station approach. After bile duct cannulation, the bile duct was filled with a contrast medium until the CBD stones were visualized. Following the ERCP, a PS was inserted and positioned with its proximal end lying in the CBD above the stones and

the distal end lying free in the duodenum. Permanent EBS was achieved using a 7- or 8.5-Fr straight PS (QuickPlaceV[®], Olympus Medical Systems; Flexima[™], Boston Scientific Japan, Tokyo, Japan) or a 7-Fr double pigtail PS (Through&pass[®], Gadelius Medical, Tokyo, Japan). The straight PS was the standard device until June 2017 at the study institution, whereas the double pigtail PS has been the standard device afterwards. The number of PS was based on each endoscopist's discretion. ES was performed at the discretion of the endoscopist. In our institute, patients, who were not high-risk, underwent endoscopic stone removal or scheduled change of a plastic stent; permanent EBS was chosen only in high-risk patients.

Patient follow-up

During the follow-up visits, physical examination and liver function tests were performed. The patients were advised to return to the emergency department if clinical symptoms, such as fever, right hypochondriac pain and jaundice, developed. All patients were followed until August 2019 or death.

Definitions

RBO was defined as exacerbation of cholangitis and/or jaundice requiring biliary intervention

after the PS insertion [14]. RBO was classified based on the underlying causes of occlusion and stent migration. Adverse events following the initial permanent EBS were assessed according to the severity grading system of the American Society for Gastrointestinal Endoscopy lexicon [15]. Early and late adverse events were defined as those occurring within 30 days and more than 30 days of permanent EBS, respectively. The Eastern Cooperative Oncology Group (ECOG) performance status scores ranging from 0 to 4 were also used [16]. High-risk patient was defined as follows: 1) The American society of anesthesiologist's physical status classification >3 and 2) An ECOG performance status of 4 under the conditions as following: coagulopathy (prothrombin time/international normalized ratio ≥ 1.5), thrombocytopenia (platelet count $< 50,000/\text{mL}$), inability to stop anticoagulation therapy, and refusal of the patient or their family to undergo additional stone removal and periodic replacement of a PS.

Outcome measures

The endpoints were details of RBO of the PS, cumulative RBO incidence rate, and RBO incidence rates based on the diameter of the largest CBD stone determined by ERCP (≤ 10 mm, 11-14 mm and $15 \text{ mm} \leq$). The risk factors associated with RBO were evaluated by

multivariate analysis using the following variables: age (per year), sex (male or female), CBD diameter (per 1 mm), number of CBD stones (per stone), diameter of largest CBD stone (per 1 mm), computed tomography-positive stone (present or absent), post-cholecystectomy (present or absent), gallbladder stones (present or absent), ursodesoxycholic acid (use or non-use), EBS session (first or second ERCP), ES (present or absent), PS type (straight or double pigtail), and PS diameter (7- or 8.5-Fr). Adverse events following the initial permanent EBS were also analyzed.

Statistical analysis

Statistical analyses were performed using the free software EZR [17]. Data were presented as medians (range, interquartile range) for nonparametric variables and percentages for categorical variables. Survival was estimated from the day of initial permanent EBS until death or final follow-up period using the Kaplan-Meier method. The cumulative RBO incidence rate and differences in cumulative RBO incidence rates among groups based on the largest CBD stone diameter were evaluated by competing risk analysis [18], accounting for death without biliary disease as a competing risk. The risk factors for RBO were analyzed using the Fine-Gray regression [19] to account for the competing event of death without

biliary disease. Factors with a P value < 0.05 in the univariate analysis were included in the multivariate analysis. Differences were considered statistically significant at a P value of < 0.05 .

Results

The database search identified 1298 patients who underwent ERCP between April 2011 and May 2019 at Hakodate Municipal Hospital. Among these, 47 consecutive high-risk patients who fulfilled the study criteria were included in the final analyses.

Baseline characteristics

The study included 19 males and 28 females with a median age of 86 (range, 59–97; interquartile range, 80–90) years. 26 patients underwent permanent EBS during the initial ERCP, whereas 21 patients underwent permanent EBS during the second ERCP after cholangitis had improved by ENBD performed during the first ERCP. All patients underwent permanent EBS using only one PS. The baseline patient characteristics and the details of permanent EBS are shown in Table 1. The median follow-up period (range, interquartile

range) after the permanent EBS was 354 (9-2729, 177-907) days. The survival rates after initial permanent EBS are shown in Figure 1; the median period of survival was 32.6 months.

Outcome measures

The details of the permanent EBS outcomes are shown in Table 2. Briefly, RBO occurred in 14 patients (28.6%), among whom obstruction and stent migration occurred in 12 and 2 patients, respectively. The cumulative RBO incidence rates of the entire cohort at 20, 40 and 60 months were 22.1%, 31.8%, and 35.5%, respectively, as shown in Figure 2A. The cumulative RBO incidence rates were significantly different among the three groups based on the largest CBD stone diameter ($P < 0.01$) (Figure 2B). Although the median periods until RBO were 13.0 and 38.0 months in the group with the largest CBD stone diameter ≥ 15 mm and 11–14 mm, respectively, the date was not reached in the group with the largest CBD stone diameter ≤ 10 mm.

To evaluate the risk factors for RBO, we performed univariate analysis of the patient characteristics and permanent EBS-related factors. In univariate analysis, a wide CBD diameter and a large CBD stone diameter were associated with increased risk for RBO. The

results of the multivariate analysis revealed that a large CBD stone diameter predicted the risk of RBO (hazard ratio, 1.26; 95% confidence interval, 1.05–1.51; $P = 0.01$; Table 3).

During the study period, 20 patients (42.6%) suffered from 21 adverse events (Table 4). The RBO occurred in 14 patients. Of these, death was due to RBO in 3 (6.4%) patients, who were bedridden with an ECOG performance status score of 4, and the families refused endoscopic or percutaneous procedures; all three patients consequently died from cholangitis. The remaining 11 patients with RBO were treated successfully with additional ERCP, which included PS exchange in 10 patients and conversion to endoscopic stone removal in one patient.

Discussion

The current study is the first to elucidate cumulative RBO rates and to determine risk factors for RBO after initial permanent EBS in high-risk patients with choledocholithiasis.

The current study revealed that the risk of RBO was significantly increased with increasing CBD stone size, which might be due to two reasons. First, the bile duct lumen might have been smaller in the patients with large CBD stones compared to those with small CBD stones. Even in the case of complete luminal obstruction of the PS, bile can flow through alongside the PS [20], especially in patients with small CBD stones. Additionally, EBS using PSs shaves down and fragments CBD stones [6,21,22]. The increase in the CBD stone size might have caused more biliary sludge, which might have consequently occluded the lumen of the PS and the CBD.

Several studies previously recommended that the biliary stents should be replaced or removed after 3–6 months [10-12]. In their study, Mohammed *et al.* reported that cholangitis with blocked stents, which was synonymous with the RBO definition used in the current study, occurred in 9 of the 17 patients (52.9 %) in the permanent stent insertion group and that 5 of the 9 patients presented within 12 months [11]. The authors concluded that planned annual stent exchange would not have affected the outcome; however, they did not show the

details of the CBD stones or the endoscopic procedures. Conversely, Di Giorgio *et al.* conducted a randomized, prospective, multi-center trial and showed that the best stent management to avoid cholangitis was stent change at defined intervals, which was every three months in that study [10]. One limitation of that study was the inclusion of only large CBD stones with a mean diameter ranging from 17 to 19 mm. Overall, these findings together with the current study results indicate that periodic stent changing and conversion to stone removal should be considered in patients with large CBD stones. However, in many cases extraction of small CBD stones may be relatively ease, but the procedure is sometimes unsuccessful because of a number of factors including general status, use of antithrombotic agent, anatomical deformation and patient's wish. Permanent stent insertion might be allowed in elderly or high-risk patients with small CBD stones such as those with a diameter ≤ 10 mm included in the current study. Further studies are needed to determine the precise time interval to develop RBO based on the CBD stone size and to assess the interval of PS exchanges.

In the current study, all 11 patients with RBO who did not refuse endoscopic procedures were successfully treated with additional ERCP. A PS can act as a nidus for new CBD stone formation around the PS after long-term stent placement, and complete CBD stone removal is sometimes difficult [23]. However, previous studies about forgotten

long-term PSs showed that all patients underwent successful additional endoscopic procedures, including not only CBD stone removal but also PS removal due to the absence of additional CBD stones, PS exchange, and additional PS insertion [12,23,24]. These findings in combination with the current study results indicate that additional endoscopic procedures are relatively easy even in patients with choledocholithiasis and long-term PSs who develop RBO. Nevertheless, follow-up is necessary so that prompt endoscopic procedure can be reestablished in the RBO.

There are several limitations in the current study. First, this was a single-center retrospective study. A validation study with a large cohort is required to determine the precise time interval to develop RBO based on the CBD stone size. Further, the permanent EBS method was based on each endoscopist's discretion. Finally, the relationship between RBO and the state of the extracted PSs was not evaluated.

In conclusion, permanent EBS using a PS without stone removal is a feasible option for elderly or high-risk patients with small CBD stones.

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Tables

Table 1. Baseline characteristics and details of permanent EBS

Male/female, n	19/28
Age, median (range, IQR), years	86 (59–97, 80–90)
Underlying disease, n (%)	
Elderly with ECOG performance status 4	15 (31.9)
Severe dementia	8 (17.0)
Cerebrovascular disease	7 (14.9)
Heart failure	6 (12.8)
Advanced malignant disease	6 (12.8)
Neurological disease	3 (6.4)
Liver cirrhosis	1 (2.1)
Respiratory failure	1 (2.1)
Diameter of CBD, median (range, IQR), mm	14 (6–31, 10–17)
Number of CBD stones, median (range, IQR), n	2 (1–20, 1–5)
Diameter of largest CBD stone, median (range, IQR), mm	10 (2–21, 8–12)
CT-positive CBD stone, n (%)	34 (72.3)

Post-cholecystectomy, n (%)	9 (19.1)
Presence of gallbladder stones, n (%)	23 (48.9)
Use of UDCA after permanent EBS, n (%)	17 (36.2)
Permanent EBS at initial ERCP, n (%)	26 (55.3)
Presence of ES, n (%)	7 (14.9)
Type of PS, n (%)	
Straight	40 (85.1)
Double pigtail	7 (14.9)
Diameter of the PS, n (%)	
7-Fr	32 (68.1)
8.5-Fr	15 (31.9)

CBD, common bile duct; CT, computed tomography; EBS, endoscopic biliary stenting;

ECOG, Eastern Cooperative Oncology Group; ES, endoscopic sphincterotomy; ERCP,

endoscopic retrograde cholangiopancreatography; IQR, interquartile range; PS, plastic stent;

UDCA, ursodesoxycholic acid

Table 2. Outcomes of the permanent EBS

RBO, n (%)	14 (29.8)
Death without biliary disease, n (%)	19 (40.4)
Survival without RBO, n (%)	14 (29.8)

EBS, endoscopic biliary stenting; RBO, recurrent biliary obstruction

Table 3. Univariate and multivariate analyses of risk factors for RBO

	Univariate analysis	Multivariate analysis
	HR (95%CI) <i>P</i> value	HR (95%CI) <i>P</i> value
Age (per year)	1.03 (0.98–1.08) 0.28	
Male vs. female	1.64 (0.61–4.46) 0.33	
Diameter of CBD (per 1 mm)	1.10 (1.03–1.17) < 0.01*	1.01 (0.91–1.11) 0.92
Number of CBD stone (per stone)	1.02 (0.93–1.11) 0.75	
Diameter of largest CBD stone (per 1 mm)	1.27 (1.13–1.42) < 0.01*	1.26 (1.05–1.51) 0.01*
CT-positive vs. CT-negative stone	0.93 (0.32–2.71) 0.89	
Post-cholecystectomy vs. no surgery	1.05 (0.27–4.02) 0.95	
Gallbladder stones present vs. absent	1.55 (0.55–4.38) 0.41	
UDCA use vs. non-use	2.36 (0.85–6.49) 0.10	
Permanent EBS at first vs. second ERCP	0.40 (0.14–1.15) 0.09	
ES present vs. absent	1.42 (0.43–4.68) 0.56	
Straight vs. double pigtail PS	0.67 (0.15–3.01) 0.61	
8.5-Fr vs. 7-Fr PS	1.75 (0.67–4.58) 0.26	

CBD, common bile duct; CT, computed tomography; EBS, endoscopic biliary stenting; ES,

endoscopic sphincterotomy; ERCP, endoscopic retrograde cholangiopancreatography; PS, plastic stent; UDCA, ursodesoxycholic acid

Table 4. Adverse events

	Mild	Moderate	Severe	Fatal
Early (≤ 30 days), n				
RBO	0	1	0	0
Cholangitis not requiring ERCP	0	1	0	0
Pancreatitis	1	2	1	0
Cholecystitis	0	1	0	0
Delayed (≥ 30 days), n				
RBO	0	8	2	3
Cholecystitis	0	0	1	0

ERCP, endoscopic retrograde cholangiography; RBO, recurrent biliary obstruction

Figure legends

Figure 1. Cumulative survival time.

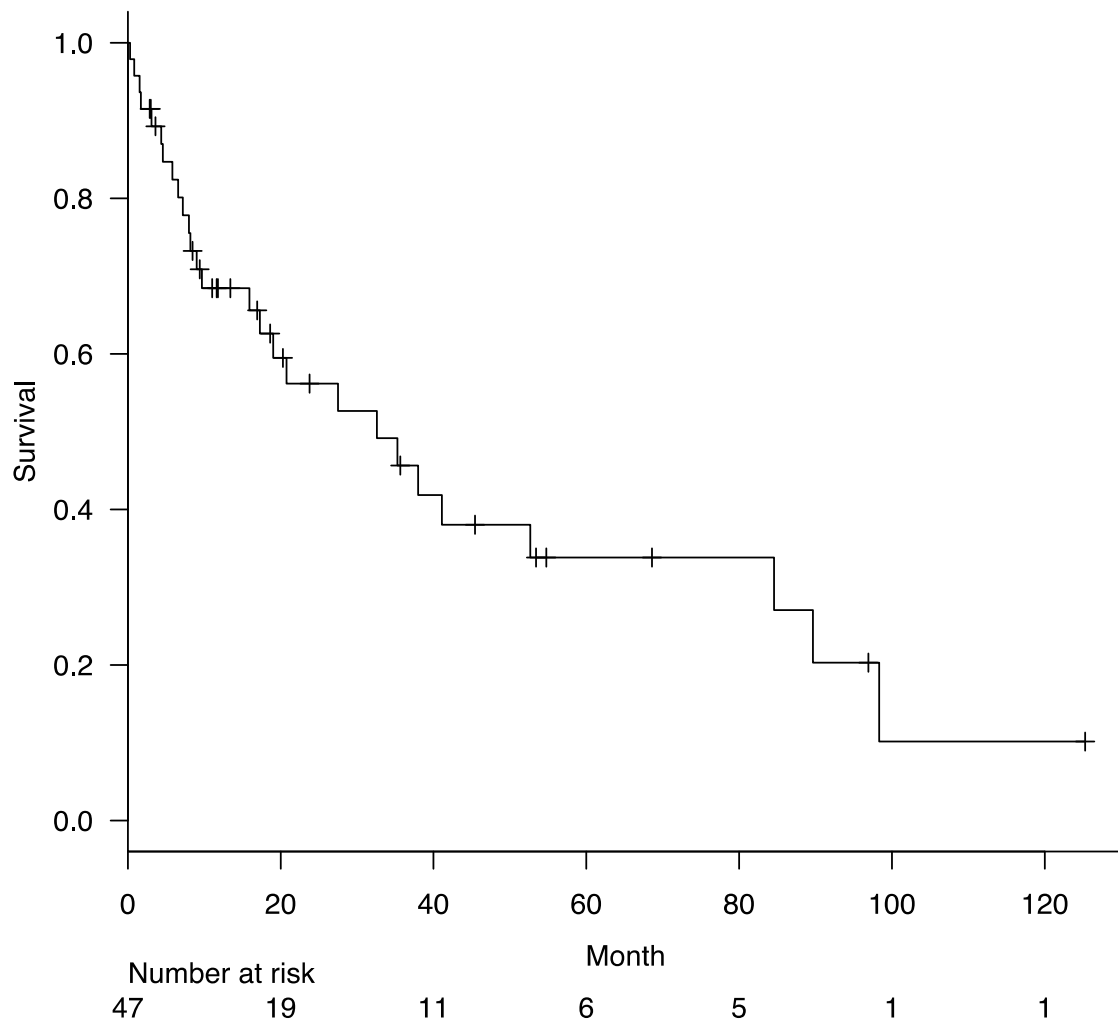
Figure 2.

(A) Cumulative incidence of recurrent biliary obstruction (RBO).

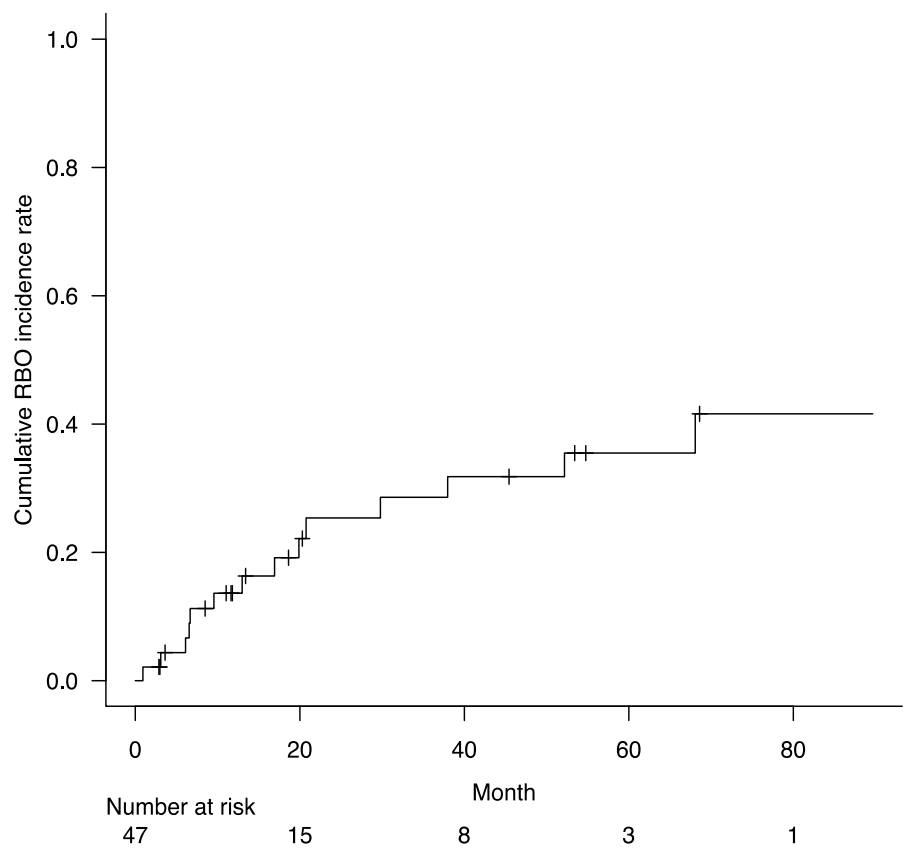
(B) The cumulative RBO incidence rates were significantly different among the three groups

based on the largest common bile duct stone diameter (≤ 10 mm, 11-14 mm and $15 \text{ mm} \leq$)

(Gray test, $P < 0.01$).



(A)



(B)

