DR. RYUNOSUKE HAKUTA (Orcid ID : 0000-0001-7653-7689)
DR. YOUSUKE NAKAI (Orcid ID : 0000-0001-7411-1385)
DR. TSUYOSHI HAMADA (Orcid ID : 0000-0002-3937-2755)

Article type : Original article

Endoscopic papillary large balloon dilation and endoscopic papillary balloon dilation both without sphincterotomy for removal of large bile duct stones: a propensity-matched analysis

Ryunosuke Hakuta,[1] MD, Shuhei Kawahata,[2] MD, PhD, Hirofumi Kogure,[1] MD, PhD, Yousuke Nakai,[1] MD, PhD, Kei Saito,[1] MD, PhD, Tomotaka Saito,[1] MD, PhD, Tsuyoshi Hamada,[1,3] MD, PhD, Naminatsu Takahara,[1] MD, PhD, Rie Uchino,[1] MD, PhD, Suguru Mizuno,[1] MD, PhD, Takeshi Tsujino,[1] MD, PhD, Minoru Tada,[1] MD, PhD, Naoya Sakamoto,[2] MD, PhD, Hiroyuki Isayama,[1,4] MD, PhD, and Kazuhiko Koike,[1] MD, PhD

R.H. and S.K. contributed equally as co-first authors.

Current affiliations:
1) Department of Gastroenterology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan
2) Department of Gastroenterology, Hokkaido University Graduate School of Medicine, Sapporo, Japan
3) Department of Oncologic Pathology, Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA, USA
4) Department of Gastroenterology, Graduate School of Medicine, Juntendo University, Tokyo, Japan

Each author's contribution: R.H., S.K., H.K., and Y.N.: conception and design of the study, analysis, and interpretation of the data, and drafting of the article. K.S., T.S., T.H., N.T., R.U., S.M., T.T., M.T., N.S., H.I., and K.K.: critical revision of the article for important intellectual content. All authors: final approval of the article. R.H. and S.K. contributed equally as co-first authors.

Running title: EPLBD vs. EPBD for large stones

Figures and tables: 3 figures and 3 tables.

Corresponding Author:
Yousuke Nakai, MD, PhD
Department of Gastroenterology, Graduate School of Medicine, The University of Tokyo
7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan
Tel.: +81-3-3815-5411

Fax: +81-3-5800-9801
E-mail: ynakai-tky@umin.ac.jp

Abstract

Objectives:

Endoscopic papillary larger balloon dilation (EPLBD) without endoscopic sphincterotomy (EST) may facilitate extraction of large bile duct stones through achieving adequate dilation of the ampulla. However, contrary to favorable long-term outcomes after endoscopic papillary balloon dilation (EPBD), that of EPLBD without EST has been little investigated. Therefore, we conducted a current study to evaluate short- and long-term outcomes of EPLBD without EST and EPBD after removal of large bile duct stones (LBDS; ≥ 10 mm).

Methods:

This retrospective study included patients without a previous history of EST, EPBD or EPLBD who underwent EPLBD without EST or EPBD for removal of LBDS. Each patient in the EPLBD without EST group was matched to a patient in the EPBD group using propensity scores.

Results:

Forty-four patients in each group were matched for the analysis. The baseline characteristics were balanced after propensity matching. The rate of complete stone removal in a single session was higher (80% vs. 16%, $P < 0.001$), and the number of ERCP sessions (1.3 ± 0.74 vs. 2.4 ± 1.5, $P < 0.001$) and the rate of lithotripsy use (30% vs. 80%, $P < 0.001$) were smaller in the matched EPLBD without EST group. Contrary to null between-group differences in early adverse events ($P = 0.99$), a cumulative rate of late biliary complications was higher in EPLBD without EST group ($P = 0.02$).

Conclusions:

EPLBD without EST showed higher efficacy for removal of LBDS but was associated with worse long-term outcomes when compared to EPBD.

Key words

choledocholithiasis, dilatation, endoscopic retrograde cholangiopancreatography, endoscopic sphincterotomy, lithotripsy

Introduction

Endoscopic sphincterotomy (EST) is widely accepted as a standard technique for the removal of bile duct stones during endoscopic retrograde cholangiopancreatography (ERCP).[1-3] Endoscopic papillary balloon dilation (EPBD) is a possible alternative to EST in cases of coagulopathy (e.g., patients with liver cirrhosis, on antithrombotic agents or on dialysis) because of its low risk of hemorrhage.[4-11] Another advantage of EPBD is its lower rate of late biliary events due to the preservation of sphincter of Oddi.[12-17] However, in addition to a risk of post-ERCP pancreatitis (PEP),[18-21] EPBD has a disadvantage at extraction of large bile duct stones (LBDS): The use of mechanical lithotripsy (ML), which is a possible risk factor for late biliary events after EPBD,[22,23] is more often necessary after EPBD.

Recently, efficacy and safety of endoscopic papillary large balloon dilation (EPLBD) were reported for removal of LBDS.[24-28] Although EST is often performed prior to EPLBD, EPLBD without EST is also reported as an similar short term results to EPLBD with EST.[29-32] The potential advantage of EPLBD without EST over EPLBD

with EST is a low risk of hemorrhage or perforation, lower cost, shorter procedure time and possibility of preservation of sphincter function. However, long-term outcomes after EPLBD without EST has been little investigated.[32-36] Therefore, we conducted this retrospective study to compare short- and long-term outcomes of EPLBD without EST and EPBD after endoscopic removal of LBDS. Propensity score based matching analysis was performed to mitigate bias due to potential confounders.

Methods

Study design

This is a single center, matched cohort analysis to compare short-term and long-term outcomes of EPLBD without EST and EPBD for removal of LBDS. The consecutive data on patients undergoing endoscopic treatment of LBDS at The University of Tokyo was retrospectively collected from our prospectively collected database and the hospital medical records. Written informed consent was obtained from each patient before the procedure. This study was conducted according to the guidelines in the Helsinki Declaration and was approved by the ethics committee at The University of Tokyo Hospital.

Patients

Patients without a previous history of EST, EPBD or EPLBD who underwent EPLBD without EST or EPBD for removal of LBDS (≥ 10 mm) between November 1994 and April 2017 were included in this study. The exclusion criteria were as follows: 1) patients with Billroth-II or Roux-en-Y reconstruction, 2) patients who underwent EPLBD with EST, 3) patients with acute pancreatitis, and 4) patients who

were lost to follow up within 30 days after discharge. The primary outcome of this study was late biliary complications (> 30 days). The secondary outcomes were the rate of complete stone removal in a single session, the number of ERCP sessions for complete stone removal, the rate of lithotripsy use and early adverse events.

Endoscopic procedures

After obtaining cholangiogram and confirming the presence of bile duct stones, the diameter of distal bile duct was measured on the cholangiogram. In cases who underwent EPBD, a 6- to 10-mm balloon catheter (Eliminator; CONMED Japan, Tokyo, Japan, Hurricane^{TM} RX; Boston Scientific Japan, Tokyo, Japan or ZARA; Century Medical, Tokyo, Japan) was used for balloon dilation. EPBD procedure was performed as previously described.[7,37] Briefly, ballooning time of EPBD was 2 minutes until June 1999, 5 minutes from July 2013 to September 2014, and 15 seconds in the other period.

EPLBD was introduced to our institution in March 2008. EPLBD without EST was performed using a 12- to 20-mm balloon catheter (CRE wire-guided balloon dilator [12–15mm, 15–18mm or 18–20mm]; Boston Scientific Japan or Giga [10–12, 13–15, 16–18mm]; Century Medical). The balloon was inflated gradually with diluted contrast medium under the endoscopic and fluoroscopic guidance and was deflated immediately after the disappearance of the waist of the balloon. The EPLBD or EPBD balloon size was selected according to the size of bile duct stones but not to exceed the diameter of the distal bile duct.

Stone extraction was performed using a basket and/or retrieval balloon catheter.[38] When the stone diameter was larger than the size of EPBD or EPLBD balloon and could not be removed without fragmentation, lithotripsy, either

endoscopic mechanical lithotripsy (EML), electrohydraulic shockwave lithotripsy (EHL), extracorporeal shockwave lithotripsy (ESWL) or the combination, was performed. If complete stone removal was not achieved within approximately one hour, a biliary stent or a nasobiliary catheter was placed, and the residual stones were removed in the following sessions without repeating EPBD or EPLBD. Complete stone removal was confirmed using intraductal ultrasonography or balloon-occluded cholangiography.

Evaluation of early and late adverse events

All patients were hospitalized at least one night after ERCP to follow possible early adverse events. Hematologic examinations, including complete blood count, liver function tests, pancreatic enzymes, and C-reactive protein level, were performed 18–24 hours after the procedure. Abdominal radiography, ultrasound, or computed tomography (CT) was performed when needed. Early adverse events (within 30 days after the procedure) and their severity were defined according to the lexicon by American Society of Gastrointestinal Endoscopy.[39]

Patients with complete stone clearance were included in the analysis of long-term outcomes. Clinical symptoms (fever, abdominal pain, and jaundice), hematologic examinations including liver function test and abdominal ultrasound were followed every 3–6 months excepting patients with poor performance status who could not visit outpatient service. Pneumobilia, which is an indication for the loss of sphincter function,[16] was confirmed by abdominal ultrasound in the follow-up period. Bile duct stone recurrences were confirmed using abdominal CT, magnetic resonance cholangiopancreatography, and/or endoscopic ultrasonography. Cholangitis and cholecystitis as late adverse events were defined according to the

current version of the Tokyo guidelines for management of acute cholangitis and cholecystitis (Japanese Society of Hepato-Biliary-Pancreatic Surgery).[40,41]

Propensity score matching

We performed propensity score matching because between-group differences in baseline characteristics in the total cohort could influence our primary outcome. The propensity score of undergoing EPLBD without EST or EPBD was calculated using a multivariable logistic regression model. Bile duct diameter and gallbladder status were previously reported as risk factors for stone recurrence after EPLBD or EPBD.[22,32,33,35,36] Furthermore, age and gender were different between the two groups in the total cohort and number of stones could associate whether to perform EPLBD or EPBD. Taking these into account, the following characteristics of patients were included in the model: age (continuous), gender (female vs. male), number of stones (continuous), bile duct diameter (continuous), gallbladder status (categorical: post cholecystectomy, cholecystectomy after removal of bile duct stones, gallbladder stones in situ or no gallbladder stones).

Subsequently, each patient in the EPLBD without EST group was matched to a patient in the EPBD group with the nearest neighbor method using a caliper range of 0.25 of the standard deviation of the pooled propensity scores (i.e., 0.13 * 0.25 = 0.03).

Statistical analysis

Categorical variables were compared using the chi-square test or Fisher's exact test as appropriate. Continuous variables were compared using the Wilcoxon rank sum test. The cumulative rate of late biliary complications was estimated using the

Kaplan–Meier methods and compared using the log-rank test.

All statistical analyses and matching were performed using EZR software (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R software (The R Foundation for Statistical Computing, Vienna, Austria, version 3.4.1). More precisely, EZR is a modified version of R commander (version 2.4-0) that was designed to add statistical functions frequently used in biostatistics.[42]

Results

A total of 307 patients without a previous history of EST or EPBD underwent EPLBD or EPBD for removal of LBDS from November 1994 to April 2017 (**Figure 1**), and 232 patients met the criteria of this study; 47 and 185 patients underwent EPLBD without EST or EPBD, respectively. Using the algorithm described above, 44 patients who underwent EPLBD without EST were successfully matched to 44 patients who underwent EPBD.

In the total cohort, the baseline characteristics were statistically significantly different between the EPLBD without EST and EPBD groups in terms of gender and age. The propensity matching well balanced these differences between the two groups (**Table 1**). The details of EPBD and EPLBD balloon are also shown in **Table 1**. While the balloon size was 8 mm in 90% of the EPBD group, it was 12–14 mm in 61% of the matched EPLBD group.

The details of the procedure and early adverse events of ERCP are summarized in **Table 2**. Complete stone removal during the index hospitalization was achieved in 100% in both groups. The rate of complete stone removal in a single session was

80% in the matched EPLBD without EST group compared with 16% in the matched EPBD group ($P < 0.001$). The number of ERCP sessions and the rate of lithotripsy use were statistically significantly smaller in the matched EPLBD without EST group (mean ± standard deviation, 1.3 ± 0.74 vs. 2.4 ± 1.5, $P < 0.001$, and 30% vs. 80%, $P < 0.001$, respectively). The early adverse events did not differ significantly between the two groups ($P = 0.99$). Four PEP (9.1%) developed in each group ($P = 0.99$). There was one severe PEP with prolonged hospitalization (18 days) in the matched EPLBD without EST group, which improved with conservative treatment without any interventions. Although antithrombotics were administered 32% in the matched EPLBD without EST group and 23% in the matched EPBD group ($P = 0.47$), both groups did not develop bleeding.

Late biliary complications are shown in **Table 3** and **Figure 2**. The follow-up period was statistically significantly shorter in the matched EPLBD without EST group (22 vs. 58 months in the matched EPLBD without EST and EPBD group, $P < 0.001$). Overall late biliary complications occurred in nine (21%) in the matched EPLBD without EST group and three (6.8%) in the matched EPBD group, respectively ($P = 0.12$). While one cholangitis, 3 cholecystitis, and 1 liver abscess developed as late complications in the matched EPLBD without EST group, there was no biliary tract infection as late complications in the matched EPBD group. The cumulative rates of late biliary complications in the matched EPLBD without EST and EPBD group were 14% vs. 4.5% at 1 year, 16% vs. 6.8% at 2 years ($P = 0.02$ by the log-rank test, **Figure 2**). During the follow-up period, pneumobilia was observed 53% in the matched EPLBD without EST group compared with 19% in the matched EPBD group, respectively ($P = 0.006$).

Discussion

This retrospective propensity score-based matching study was conducted to evaluate the short- and long-term outcome of EPLBD without EST and EPBD after endoscopic removal of LBDS. The rate of late biliary complications was higher in the matched EPLBD without EST group compared with the matched EPBD group. Regarding the safety, EPLBD without EST did not increase early adverse events of ERCP compared to EPBD. The rate of lithotripsy use and the number of ERCP sessions for complete stone removal were significantly lower, and the rate of complete stone removal in a single session was higher in the matched EPLBD without EST group, suggesting its higher efficacy of removal of LBDS.

The cumulative rate of late biliary complications was statistically significantly higher in the matched EPLBD without EST group in this study. Recently, accumulating evidence suggests better long-term outcomes of EPBD compared to EST for endoscopic removal of small bile duct stones because of the preserved sphincter function.[15-17] EPLBD is considered to potentially preserve sphincter function and reduce late biliary complications by avoiding the preceding EST (**Figure 3**). However, in our study, the rate of pneumobilia was higher (53%) in EPLBD group, suggesting the impairment of Oddi function,[16] and we failed to demonstrate preferable long-term outcomes of EPLBD without EST contrary to our assumption. Despite the null events of biliary tract infection as late biliary complications in the matched EPBD group, 11% in the matched EPLBD without EST group developed cholangitis, cholecystitis and liver abscess. Regularly follow-up imaging studies performed regardless of symptoms in our study cohort might increase late biliary complications but the presence of pneumobilia is known to be associated with late biliary complications. [34]

Although EPLBD without EST was associated with increased late biliary complications, it improved the rate of complete stone removal in a single session and reduced the rate of lithotripsy use and the number of ERCP sessions for complete stone removal.[28,43] The lower usage of EML did not reduce the procedure time in a first session in the match EPLBD without EST group. The increased rate of complete stone removal in a single session potentially prolong procedure time. Despite the improved effectiveness of stone removal in EPLBD without EST which could reduce medical cost, early adverse events including PEP did not differ between the two groups. EPLBD is reportedly associated with a lower PEP rate compared with EPBD,[19,44] contrary to our results in which the methods for PEP reduction (i.e., pancreatic stent placement and rectal NSAIDs)[45,46] between the groups is comparative. Considering the association between narrow bile duct and PEP,[47] our study population with a large bile duct may have a low risk of PEP even after EPBD. In this study, all patients, including even with null physical symptoms, were hospitalized after ERCP and underwent both physical examinations and blood tests. This strategy potentially increased PEP rate due to overestimation of mild pancreatitis.

EPBD provided better long-term outcomes with less late biliary complications but cannot be a first-line treatment for LBDS given its less effectiveness of stone removal. Young patients with LBDS who have longer life expectancy might gain benefits from EPBD, though most of LBDS are diagnosed in elderly patients. Cholecystectomy should be performed to reduce late biliary complications but the risk of late biliary complications in patients with gallbladder left in situ after EPBD was relatively low in cases with a large bile duct or large bile duct stones.[48] In those cases, bile duct stones are likely to be primary stones rather than secondary stones migrated

from the gallbladder. Recurrence of primary bile duct stones are possible even after cholecystectomy, and it is still unclear whether cholecystectomy should be performed in all cases with gallstones after endoscopic treatment of LBDS or not.[49] This should be confirmed in a large-scale data.

It still remains controversial whether EPLBD should be preceded by EST or not. While short-term outcomes such as early adverse events and effectiveness of stone removal were reportedly not different between EPLBD with and without EST,[44,50,51] there has been no comparative studies on the long-term outcomes of EPLBD with and without EST to date. Our study results suggested that long-term outcomes after EPLBD without EST appeared comparable to those of EPLBD with EST in the previous studies.[33,35] The omission of EST prior to EPLBD might be more simple and cost-effective, but there are some concerns about potential risks of PEP. The previous reports and guidelines did not suggest higher incidence of PEP in EPLBD without EST compared to EPLBD with EST.[44,51] In our study, PEP developed in 9.1% including one severe case, which appeared higher than previous reports.[29-32,44] Although, longer ballooning time decreased PEP during EPBD in the previous RCT,[52] we did not find any differences between 5-minute and 15-second EPBD,[37] and the effect of longer ballooning time during EPLBD is still controversial.[53] At least, EPLBD without EST could be indicated when EST is difficult or risky (i.e., cases with coagulopathy or with surgically altered anatomy).

There were some limitations which should be acknowledged in this study. First, it was a single center, retrospective study and the selection bias may exist. However, consecutive patients who underwent EPBD or EPLBD without EST for endoscopic removal of LBDS during the study period were included. Furthermore, the propensity score based matching well balanced the baseline characteristics between the two

groups. Second, the shorter follow-up period in the matched EPLBD without EST group was another limitation of this study. Nevertheless, prolonged follow-up period of EPLBD without EST group could not alter the positive result in late biliary complications. Finally, a relatively small sample size limited the statistical power of this study. The one-to-two matching further decreased sample size in each group (leaving only 30 patients in EPLBD without EST group), and failed to increase power. However, it is unlikely that EPLBD without EST would demonstrate less late biliary events and a future study should be focused on the population best fit for this procedure.

In conclusion, EPLBD without EST for endoscopic removal of LBDS allowed a high single session success rate but might be associated with a higher cumulative incidence of late biliary complications compared to EPBD. The role of EPLBD without EST as compared to EST, EPBD, and EPLBD with EST is yet to be determined.

Conflict of Interest

We declare that we have no conflicts of interest.

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TABLE 1. Baseline characteristics of the total and propensity-matched cohorts for EPLBD without EST and EPBD for removal of large bile duct stones.

	Total cohort			**Matched cohort**		
	EPLBD without EST (n = 47)	**EPBD** (n = 185)	***P* value**	**EPLBD without EST** (n = 44)	**EPBD** (n = 44)	***P* value**
Gender, male/female	18/29 (38%/62%)	114/71 (62%/38%)	0.005	18/26 (41%/59%)	18/26 (41%/59%)	0.99
Age, years*	80 (71–85, 53–91)	77 (67–83, 12–97)	0.013	80 (71–85, 53–91)	77 (69–83, 40–96)	0.26
ASA-PS score, 1/2/3/4	14/25/8/0 (30%/53%/17%/0%)	58/89/35/3 (31%/48%/19%/1.6%)	0.95	14/23/7/0 (32%/52%/16%/0%)	12/26/6/0 (27%/59%/14%/0%)	0.83
Bile duct diameter, mm	13 (12–15)	13 (11–16)	0.26	13 (12–15)	13 (10–16)	0.18
Maximum stone diameter, mm	13 (12–15)	12 (10–15)	0.19	13 (11–15)	14 (10–15)	0.91
Number of stones	2 (1–3)	2 (1–4)	0.33	2 (1–3)	2 (1–3)	0.78
Periampullary diverticulum	20 (43%)	103 (56%)	0.14	20 (46%)	25 (57%)	0.39
Previous gastrectomy	1 (2.1%)	13 (7.0%)	0.31	1 (2.3%)	0	0.99
Gallbladder status			0.56			0.81
Post cholecystectomy	6 (13%)	27 (15%)		6 (14%)	6 (14%)	
Cholecystectomy after removal of bile duct stones	13 (28%)	36 (20%)		10 (23%)	14 (32%)	
Gallbladder stones in situ	17 (36%)	83 (45%)		17 (39%)	14 (32%)	
No gallbladder stones	11 (23%)	39 (21%)		11 (25%)	10 (23%)	

Balloon diameter, mm			
6/8/10		1/157/27 (0.5%/85%/15%)	0/40/4 (0%/91%/9.1%)
12–14/15–17/18–20	30/16/1 (64%/34%/2.1%)	27/16/1 (61%/36%/2.3%)	

Data are expressed as number (percentage) of patients within a given group or as median (interquartile ranges).

* Age are expressed as median (interquartile ranges, ranges).

ASA-PS, American Society of Anesthesiologists Physical Status Classification; EPBD, endoscopic papillary balloon dilation; EPLBD, endoscopic papillary large balloon dilation; EST, endoscopic sphincterotomy

TABLE 2. Outcomes of stone removal and early adverse events in the matched EPLBD without EST and EPBD groups.

	EPLBD without EST (n = 44)	**EPBD** (n = 44)	***P* value**
Procedures			
Complete stone removal during the index hospitalization	44 (100%)	44 (100%)	NA
Complete stone removal in a single session	35 (80%)	7 (16%)	< 0.001
Number of sessions			< 0.001
1	35 (80%)	7 (16%)	
2	6 (14%)	26 (59%)	
≥ 3	3 (6.8%)	11 (25%)	
Use of lithotripsy	13 (30%)	35 (80%)	< 0.001
EML/ESWL/EHL	12/4/1 (27%/9.1%/2.3%)	35/4/6 (80%/9.1%/14%)	
Procedure time in a first session, minutes	45 (35–56)	45 (40–63)	0.26
Pancreatic stent placement	5 (11%)	5 (11%)	0.99
Rectal NSAIDs	2 (4.5%)	0	0.49
Early adverse events			
Overall	4 (9.1%)	5 (11%)	0.99
Pancreatitis	4 (9.1%)	4 (9.1%)	0.99
Mild/moderate/severe	3/0/1 (6.8%/0%/2.3%)	2/2/0 (4.5%/4.5%/0%)	0.43
Cholangitis	0	1 (2.3%)	0.99
Cholecystitis	0	1 (2.3%)	0.99
Bleeding	0	0	NA
Perforation	0	0	NA
Mortality	0	0	NA

Data are expressed as number (percentage) of patients within a given group or as median (interquartile ranges).

EHL, electrohydraulic lithotripsy; EML, endoscopic mechanical lithotripsy; EPBD, endoscopic papillary balloon dilation; EPLBD, endoscopic papillary large balloon dilation; EST, endoscopic sphincterotomy; ESWL, extracorporeal shockwave lithotripsy; NA, not available; NSAIDs, nonsteroidal anti-inflammatory drugs

TABLE 3. Long-term outcomes of the matched EPLBD without EST and EPBD groups.

	EPLBD without EST (n = 44)	**EPBD** (n = 44)	***P* value**
Follow-up period, month	22 (11–38)	58 (27–93)	< 0.001
Pneumobilia*	19 (53%)	7 (19%)	0.006
Overall late biliary complications	9 (21%)	3 (6.8%)	0.12
Time to overall late biliary complications, days	225 (104–411)	333 (185–405)	0.99
Bile duct stone recurrence	5 (11%)	3 (6.8%)	0.71
Time to bile duct stone recurrence, days	165 (104–225)	333 (185–405)	0.99
Cholangitis	1 (2.3%)	0	0.99
Time to cholangitis, days	411		NA
Cholecystitis	3 (6.8%)	0	0.24
Time to cholecystitis, days	259 (156–706)		NA
Liver abscess	1 (2.3%)	0	0.99
Time to liver abscess, days	165		NA

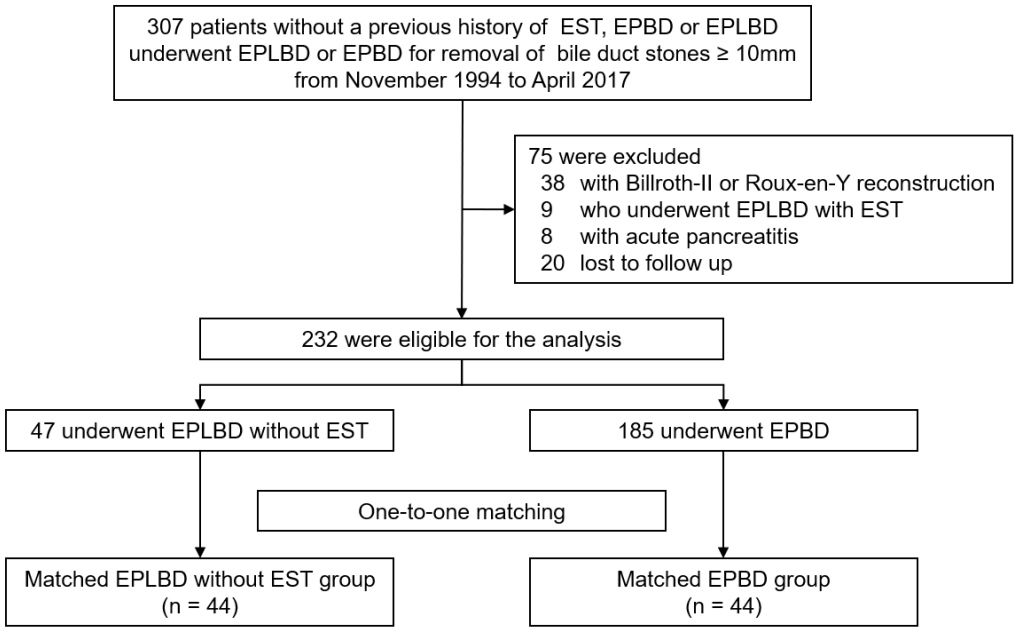
Data are expressed as number (percentage) of patients within a given group or as median (interquartile ranges).

* Ultrasound sonography was not performed 8 patients in each group during the follow-up period.

EPBD, endoscopic papillary balloon dilation; EPLBD, endoscopic papillary large balloon dilation; EST, endoscopic sphincterotomy; NA, not available

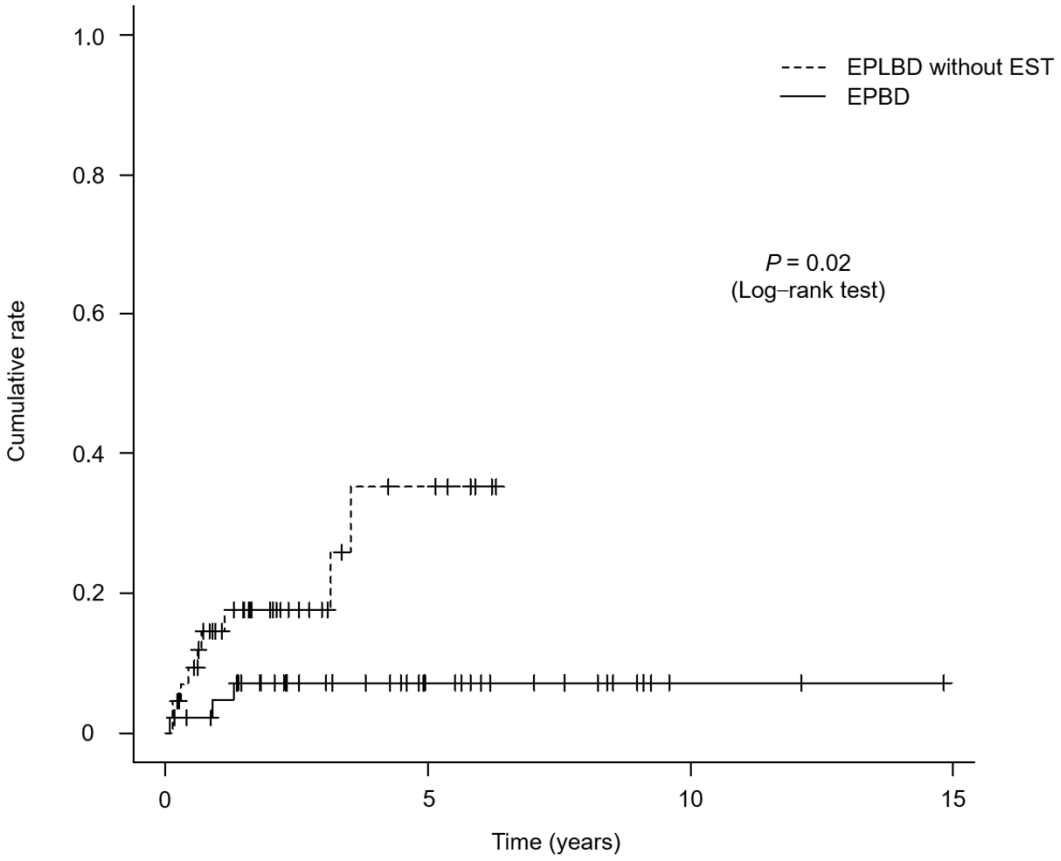
Figure Legends

Figure 1. Flowchart of patient selection into the matched groups of EPLBD without EST group and EPBD group for removal of large bile duct stones.



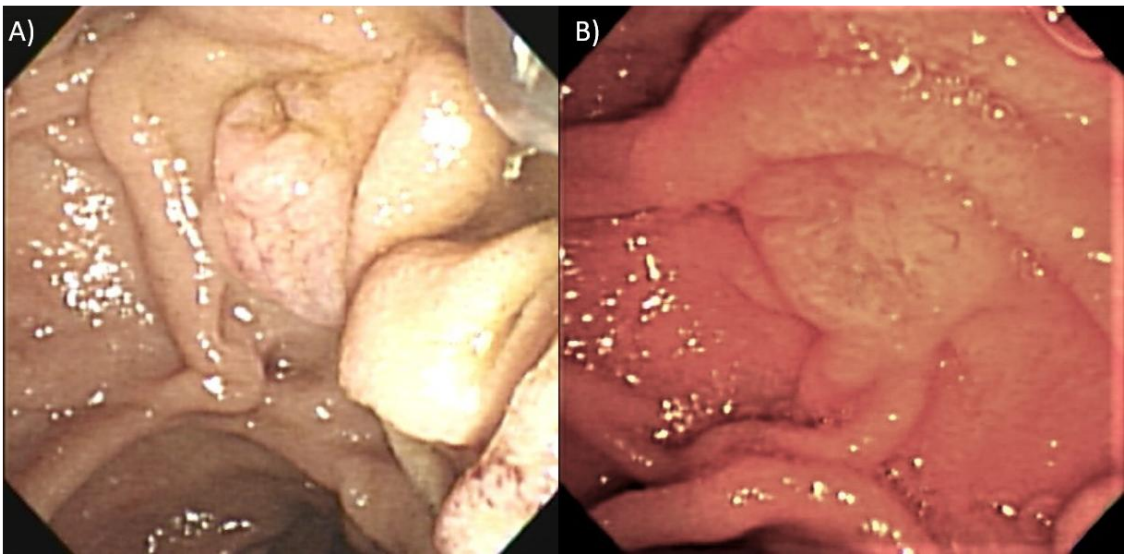
EPBD, endoscopic papillary balloon dilation; EPLBD, endoscopic papillary large balloon dilation; EST, endoscopic sphincterotomy

Figure 2. Cumulative rates of late biliary complications using the Kaplan–Meier method. Small vertical bars on the graphs indicate censored cases. The cumulative rate was higher in the matched EPLBD without EST group.



EPBD, endoscopic papillary balloon dilation; EPLBD, endoscopic papillary large balloon dilation; EST, endoscopic sphincterotomy

Figure 3. Endoscopic images of major papilla at the time of reintervention one year after EPLBD without EST or EPBD.
A) Major papilla after EPLBD without EST
B) Major papilla after EPBD



EPBD, endoscopic papillary balloon dilation; EPLBD, endoscopic papillary large balloon dilation; EST, endoscopic sphincterotomy