Efficacy of EUS-guided and ERCP-guided biliary drainage for malignant biliary obstruction: prospective randomized controlled study

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Background and Aims: ERCP-guided biliary drainage (ERCP-BD) is a criterion standard treatment for malignant biliary obstruction when curative surgery is not an option. Alternative methods such as percutaneous transhepatic biliary drainage would significantly lower the quality of life. EUS-guided biliary drainage (EUS-BD) has been developed and performed by experienced endoscopists. Therefore, the aims of this study were to evaluate the efficacy and safety of EUS-BD compared with ERCP in malignant biliary obstruction.

Methods: The prospective randomized controlled study was conducted, and 30 patients were enrolled: 15 for each EUS-BD and ERCP-BD arms. The technical success, procedural time, clinical success, and adverse events were evaluated.

Results: Thirty patients had extrahepatic malignant biliary tract obstruction (19 men, 11 women). Twenty-seven patients had unresectable pancreatic ductal adenocarcinomas, 1 patient had distal common bile duct cancer, and 2 patients had metastatic malignant lymphadenopathy. There were no significant differences both in terms of technical success rate and clinical success rate (100% vs 93% and 93% vs 100% in ERCP-BD vs EUS-BD, respectively; $P = 1.00$, $P = 1.00$). Four patients (31%) had tumor ingrowth–caused stent dysfunction in the ERCP-BD group, whereas 2 patients had food impaction and 2 patients had stent migration in the EUS-BD group. No significant procedure-related adverse events occurred in either group.

Conclusions: This prospective randomized controlled study suggests that EUS-BD has similar safety to ERCP-BD. EUS-BD was not superior to ERCP-BD in terms of relief of malignant biliary obstruction. EUS-BD may have fewer cases of tumor ingrowth but may also have more cases of food impaction or stent migration. (Clinical trial registration number: NCT01421836.) (Gastrointest Endosc 2018;88:277-82.)

Abbreviations: ERCP-BD, ERCP-guided biliary drainage; EUS-BD, EUS-guided biliary drainage; PDAC, pancreatic ductal adenocarcinoma.

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EUS has evolved from a purely diagnostic imaging modality to an interventional procedure that enabled minimally invasive treatment modality to interventional radiologic and surgical techniques.[1] The criterion standard treatment of obstructive jaundice has been ERCP with biliary stent placement, with a success rate of greater than 95% in expert hands and a frequency of adverse events of approximately 8%.[2-4] Patients with malignant biliary obstruction often have inaccessible papilla because of duodenal invasion and altered anatomy from the previous surgeries, and these comprise most of the failed ERCP cases.[5]

Percutaneous transhepatic biliary drainage has been the standard of care after failed ERCP in patients with malignant biliary obstruction. However, quality of life can be compromised by this type of biliary drainage. Lee et al[6] reported that EUS-guided biliary drainage (EUS-BD) has emerged as an effective alternative strategy for percutaneous transhepatic biliary drainage after failed ERCP. The reported overall technical success rate of EUS-BD in expert centers has reached 93%, and the clinical success rate ranged from 92% to 100%.[7-11] In addition, EUS-BD may not have a tumor ingrowth problem, which has been the most difficult problem after successful ERCP with biliary stent placement (ERCP–guided biliary drainage [ERCP-BD]) for malignant biliary obstruction. Therefore, EUS-BD potentially may be the first-line biliary drainage procedure, but standardizing the technique of EUS-BD is still required.

The aims of this study were to evaluate the efficacy and safety of EUS-BD compared with ERCP-BD in patients with malignant biliary obstruction. Therefore, the technical success, procedural time, clinical success, and adverse events were evaluated.

METHODS

Study patients and randomization

A prospective, randomized, and controlled trial was conducted to evaluate the efficacy and safety of EUS-BD compared with ERCP-BD in patients with malignant biliary obstruction. Written informed consent for the procedure was obtained from all patients. The study was approved by the institutional ethics committee (IRB no 2011-03-101). Patients with an initial diagnosis of malignant biliary obstruction were assessed using the following eligibility criteria. The inclusion criteria of the study were malignant distal biliary obstruction and no eligibility for the curative surgical resection because of advanced stage of malignancies or accompanied comorbidities. The exclusion criteria were hilar involvement in malignancy, coagulation disorder, history of an upper GI operation, and refusal or inability to provide informed consent. The study patients were randomized in a 1:1 ratio to the EUS-BD and ERCP-BD groups. Randomization number was delivered as sequentially numbered, opaque, sealed envelopes with computer-generated using a block randomization.

Thirty patients were enrolled: 15 for each study arm, EUS-BD and ERCP-BD, respectively. Two study patients initially enrolled as pancreatic ductal adenocarcinoma (PDAC) with liver metastasis were not found to have metastatic nodules in liver with further evaluation after the biliary drainage and underwent operation for surgical resection. They underwent Whipple operation 10 days after biliary drainage and were excluded from each group (Fig. 1). All authors had access to the study data and reviewed and approved the final manuscript.

Interventions

One of the top ERCP and EUS experts who had a median experience of 12 years in interventional pancreatobiliary procedures performed both ERCP-BD by papillary approach and EUS-BD with transmural stent placement (Fig. 2). Study patients were treated with prophylactic intravenous antibiotics before the procedure and underwent conscious sedation. ERCP-BD and EUS-BD were performed as follows.

The ERCP-BD group underwent ERCP by using a therapeutic duodenoscope (TJF-260; Olympus Medical Systems, Tokyo, Japan). Sphincterotomy or balloon dilatation was performed before stent insertion in all patients. The delivery system was inserted into the bile duct over the guidewire (.025- or .035-inch Visiglide; Olympus) after cholangiography to evaluate the biliary stricture. A self-expandable metal stent, consisting of an uncovered sleeve part and a fully covered body part (Hanarostent, Seoul, South Korea), which has antimigration system, was placed over the guidewire. The diameter of the stent was 10 mm, whereas its length (40, 60, or 80 mm) was determined according to the length of the stricture.

EUS-BD was also performed using a curved linear echoendoscope (Olympus) that was positioned in the duodenum. After visualization of bile duct in suprapancreatic area, a transduodenal puncture was done by using a 19-gauge EUS-FNA needle (EchoTip Ultra; Cook Medical, Bloomington, Ind). After the transduodenal puncture with the EUS-FNA needle, bile was aspirated and a cholangiogram was acquired afterward, confirming the route from duodenum to the bile duct system. A guidewire (.025- or .035-inch Visiglide; Olympus) was passed into the bile duct. Once the guidewire was placed, a 6F cystotome (Endo-flex, Voerde, Germany) and a Hurricane balloon with a 4-mm diameter (Boston Scientific, Marlborough, Mass) were introduced along with the guidewire, and track dilation was done. The same self-expandable metal stent (Hanarostent) was placed over the guidewire under EUS and fluoroscopic system. The diameter of the stent was 10 mm and its length (40, 60, or 80 mm) determined.

Sample size calculation

We assumed that the average period of patency was reported as follows: ERCP with biliary stent placement at 143 days and EUS-BD at 212 days.[12,13] We used an average period of maintaining the stent in ERCP-BD and the EUS-BD group;

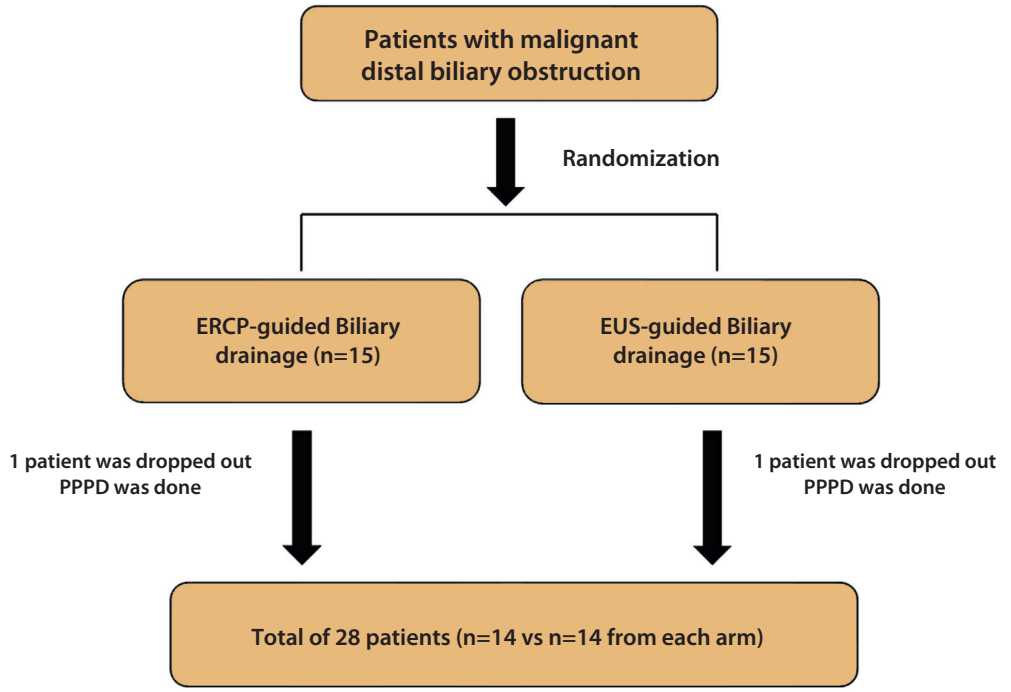

Figure 1. Schematic flowchart of the study design. *PPPD*, pylorus-preserving pancreaticoduodenectomy.

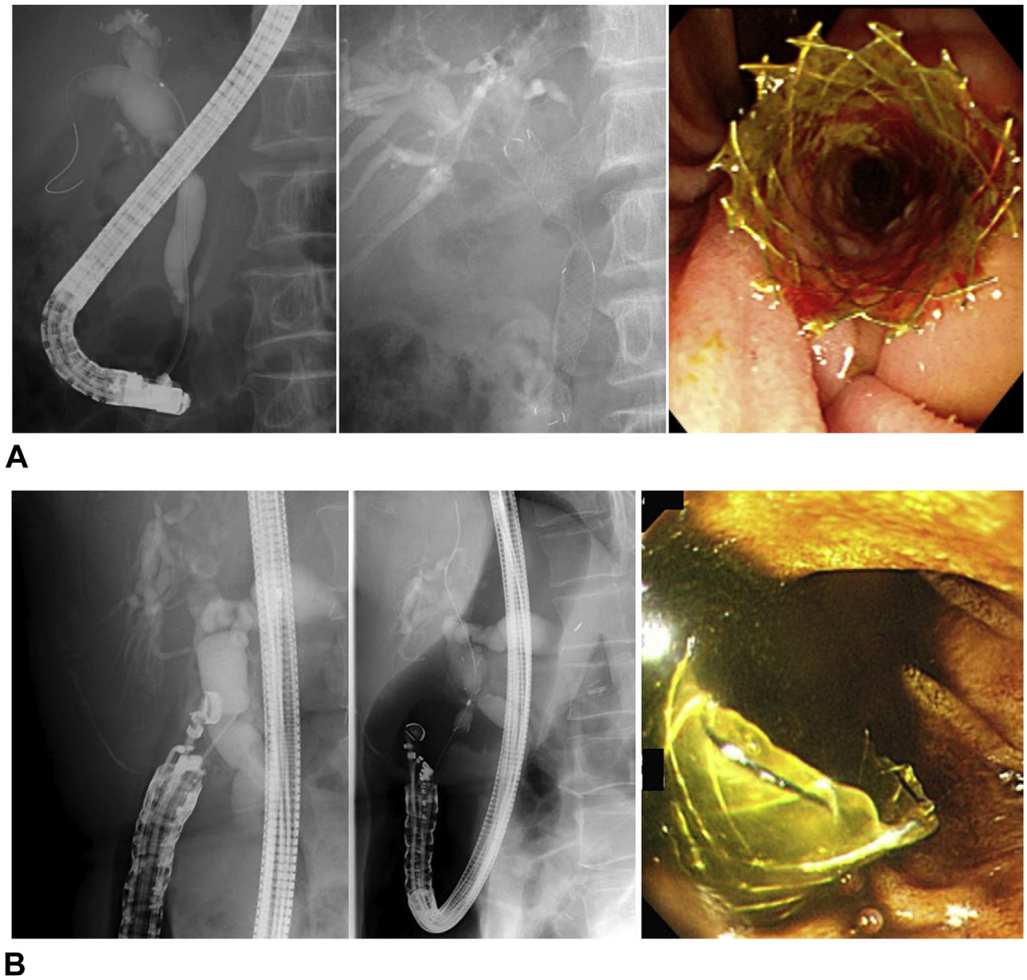

Figure 2. A, ERCP with biliary stent placement. **B,** EUS-guided biliary drainage.

TABLE 1. Baseline characteristics of study patients

	ERCP-BD (n = 14)	EUS-BD (n = 14)	*P* value
Mean age, y (± SD)	65.4 ± 9.3	66.8 ± 8.0	.68
Sex, M:F	8:6	9:5	.70
Diagnosis			
Pancreatic ductal adenocarcinoma	12	14	.48
Malignant LAP	2	0	
Median follow-up, days (IQR)	147 (73-273)	95 (78-210)	.60
Stage, III:IV	5:9	5:9	1.00
Median total bilirubin, mg/dL (IQR)	9.9 (7.5-20.4)	7.5 (4.8-14.0)	.45
Median aspartate aminotransferase, U/L (IQR)	130 (90-213)	69 (51-95)	.01
Median alanine aminotransferase, U/L (IQR)	138 (84-315)	73 (49-145)	.04
Median ALP, U/L (IQR)	428 (307-522)	385 (195-596)	.70

ERCP-BD, ERCP-guided biliary drainage; *EUS-BD*, EUS-guided biliary drainage; *SD*, standard deviation; *LAP*, lymphadenopathy; *IQR*, interquartile range; *ALP*, alkaline phosphatase.

143 and 212 days with 50 and 60 days standard deviation, respectively, with a power of .8 and an α of .05. This would require 11 patients in each group, and therefore a total of 22 study patients. Considering dropouts and patients lost to follow-up, we also allowed for an attrition rate of 10% to ~15% and enrolled 15 patients in each group.

Follow-up and outcome measurement

The primary endpoint was to measure the stent patency defined as the interval (in days) between the time of stent insertion and the time of stent occlusion or death of the patient for each study arm. The secondary endpoints were clinical success rate and safety: (1) a decrease in bilirubin level more than 50% of the pretreatment value within the first month without recurrent cholangitis or biliary sepsis and (2) any procedure-related adverse events such as acute cholecystitis, acute pancreatitis, bile peritonitis, perforation, or bleeding. In addition, a technical success rate and procedural time were also compared between ERCP-BD and EUS-BD groups.

Laboratory examinations and clinical symptoms were regularly evaluated during the admitted days and outpatient clinic at 1, 3, 5, 7, 15, and 30 days after the procedure. In terms of long-term follow-up, the enrolled patients were seen on days 45, 60, and 90 from the procedure. Survival and morbidity data were also acquired by the study coordinators and audited by a safety monitoring board.

Statistical analysis

Analysis was carried out using the SPSS 23.0 software package (IBM, Armonk, NY). Results were reported as mean ± standard deviation for quantitative variables and percentages for categorical variables. Continuous variables were analyzed using a *t* test, and categorical data were compared using the χ^2 test. Cumulative stent patency was analyzed by the Kaplan-Meier method. A $P < .05$ was considered to be statistically significant.

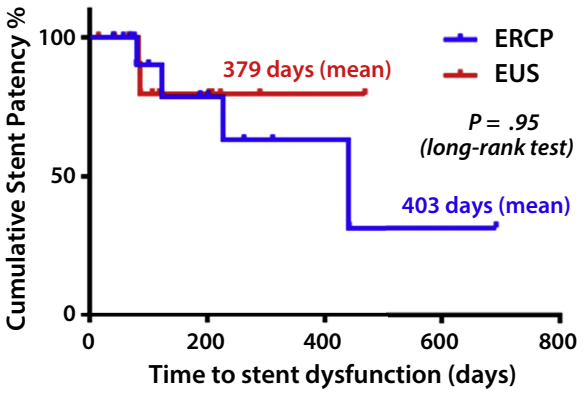

Figure 3. Comparison of the stent patency.

RESULTS

Study patients

The prospective randomized controlled study was conducted, and 30 patients were enrolled: 15 for each ERCP-BD and EUS-BD study arms (Fig. 1). Two patients were initially diagnosed as PDAC with liver metastases and enrolled in each study arm but later were considered to have liver abscess rather than metastasis. They underwent pancreaticoduodenectomy 10 days after biliary stent placement. The median age of each group was 65 and 67 years old in the ERCP-BD and EUS-BD groups, respectively. In the ERCP-BD group, 12 of 14 patients (86%) had biliary obstruction caused by PDAC and 2 patients had metastatic lymphadenopathy. In EUS-BD group, all 14 patients had malignant biliary obstruction caused by PDACs. The median follow-up duration for the ERCP-BD and EUS-BD groups was 145 and 95 days, respectively. Also, the median total bilirubin level was measured as 9.9 and 7.5 mg/dL in the ERCP-BD and EUS-BD groups, respectively. Overall, there was no statistically significant difference between the 2 groups in

TABLE 2. Outcomes of study patients

	ERCP-BD (n = 14)	EUS-BD (n = 14)	*P* value
Mean stent patency, days (± SD)	403 ± 84	379 ± 55	.72
Technical success,* n (%)	14 (100)	13 (92.8)	1.00
Clinical success, n (%)	13/14 (92.8)	13/13 (100)	1.00
Mean procedural time, min (± SD)	31 ± 21	43 ± 24	.20

ERCP-BD, ERCP-guided biliary drainage; *EUS-BD*, EUS-guided biliary drainage; *SD*, standard deviation.
*One patient failed in the EUS-BD group and underwent ERCP-BD instead of EUS-BD.

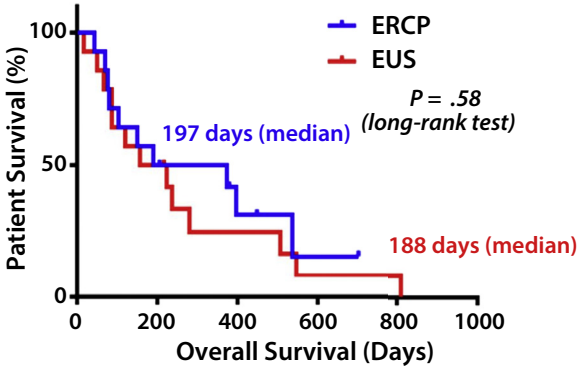

Figure 4. Kaplan-Meier curve of overall survival.

terms of clinical parameters; age, sex, diagnosis, follow-up duration, stage, and liver function tests (Table 1).

Outcome of study patients

Stent patency for ERCP-BD was 403 days compared with EUS-BD 379 days ($P = .95$) (Fig. 3, Table 2). The median overall survival of the study patients was 197 days (Fig. 4), and there was no significant difference between the 2 groups: ERCP-BD group, 197 days, versus EUS-BD group, 188 days ($P = .58$). Biliary obstruction was relieved after the procedure: 93% (13/14 patients) in the ERCP-BD group and 100% in the EUS-BD group. The procedure time was 31 minutes for the ERCP-BD group and 43 minutes for the EUS-BD group ($P = .20$). There were no significant differences in terms of technical and clinical success rate or procedural time between the ERCP-BD and EUS-BD groups.

Stent dysfunction and adverse events

The technical success rate in the ERCP-BD group was 100%, and 1 patient with metastatic lymphadenopathy from NSCLC in the EUS-BD group failed the procedure and ERCP-BD was then performed (Table 3). Although the clinical success rate was defined by a decrease in bilirubin level more than 50% of the pretreatment value within the first month without recurrent cholangitis or biliary sepsis, we analyzed the cause of stent dysfunction and frequencies of stent revision between the 2 study groups during the follow-up period. In 4 of 13 patients (31%) treated with ERCP-BD, there was stent dysfunction because of tumor ingrowth. In the EUS-BD group, 4 of 13 patients (31%) had stent dysfunction because of food impaction (2) or stent migration (2); however, no further intervention was needed because of the formation of a choledochoduodenal fistula tract after EUS-BD. We observed no cases of acute cholecystitis, acute pancreatitis, bile peritonitis, bowel perforation, or bleeding after the biliary drainage procedure in either group.

TABLE 3. Stent dysfunction and adverse events

	ERCP-BD (n = 14)	EUS-BD (n = 14)	*P* value
Stent dysfunction	4/13 (30.8%)	2/13 (15.4%)	.65
Tumor ingrowth	4	0	.047
Food impaction	0	2	
Adverse events	0	0	1.00
Cholecystitis	0	0	
Acute pancreatitis	0	0	
Bile peritonitis	0	0	
Perforation	0	0	
Bleeding	0	0	

ERCP-BD, ERCP-guided biliary drainage; *EUS-BD*, EUS-guided biliary drainage.

DISCUSSION

It has been well established that ERCP-BD is a criterion standard treatment for malignant biliary obstruction when curative surgery is not an option, typically reaching a success rate of more than 95% in expert hands with very low adverse events.[2-4] However, it is often found that patients with malignant biliary obstruction have duodenal invasion or altered anatomy from previous surgeries, which prevents success in biliary stent placement with ERCP. EUS-BD has been developed and performed by experienced endoscopists, with reports that it could be performed safely in failed cases of ERCPs.[2,4,14-20] Still, the indication for EUS-BD has been limited to failed biliary cannulation during ERCP, surgical anatomy, previously failed ERCP, cancer with duodenal invasion, and duodenal stent covering the ampulla.[18]

In this study, we have evaluated the feasibility of EUS-BD as a first treatment option and tried to show that the EUS-BD procedure is technically very efficient and can be safely performed compared with conventional ERCP-BD. This study compared ERCP-BD and EUS-BD as the first treatment option in a randomization and prospective protocol. The study was powered to detect a clinically relevant difference in stent patency, and none was observed. Other secondary outcomes also appeared to be similar between the ERCP-BD and EUS-BD groups, including technical and clinical success rates, overall

survival, procedural time, adverse event rate, and stent dysfunction rate. More importantly, the causes of stent dysfunction were quite different between the 2 groups. The major cause of stent dysfunction in the ERCP-BD group was tumor ingrowth and required additional stent insertion. On the other hand, the EUS-BD group had stent dysfunction because of food impaction, which was treated with a balloon catheter to pull out the impacted food material from the inside of the stent. Interestingly, 2 patients we described as having stent dysfunction did not require further intervention because of the development of a permanent biliary-enteric fistula at the stent site. Although our study supports the feasibility and performance of EUS-BD as an effective biliary drainage procedure, the technique still required dedicated expertise as with all complex endoscopic procedures and may not be applicable outside of expert centers.[19,20]

Some limitations in this study should be considered. First, it is a prospective interventional study design within a single center. The study therefore could have selection and referral bias. Further multicenter studies are needed to extrapolate our result in other centers. Recently, a novel, fully covered, lumen-apposing metal stent has been developed for EUS-BD. At the time of designing this study, we had to choose among the available stents because the lumen-apposing metal stent was not available. Instead, we performed both procedures with the partially covered stent with a distal flare end to prevent bile leakage and migration.

Here, we report a prospective randomized controlled study that suggests that EUS-BD has similar biliary drainage durability compared with ERCP-BD in malignant biliary obstruction. Preliminary data on our secondary outcomes suggest that the patterns and consequences of stent failure are different, with more tumor ingrowth requiring repeat stent placement with ERCP-BD and more food impactions and stent migrations that did not require repeat stent placement with EUS-BD. Further stent improvements are needed to prevent food impaction. Further study is needed to evaluate the impact of iatrogenic-therapeutic choledochoduodenal fistula made by EUS-BD to deliver more-effective treatment to the patients with malignant biliary obstruction.

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