Corrected: Correction

Open

EUS-Guided Biliary Drainage Versus ERCP for the Primary Palliation of Malignant Biliary Obstruction: A Multicenter Randomized Clinical Trial

Woo Hyun Paik, MD, PhD[1,2], Tae Hoon Lee, MD, PhD[3], Do Hyun Park, MD, PhD[4], Jun-Ho Choi, MD[5], Seon-Ok Kim, MSc[6], Sunguk Jang, MD[7], Dong Uk Kim, MD, PhD[8], Ju Hyun Shim, MD, PhD[4], Tae Jun Song, MD, PhD[4], Sang Soo Lee, MD, PhD[4], Dong-Wan Seo, MD, PhD[4], Sung Koo Lee, MD, PhD[4] and Myung-Hwan Kim, MD, PhD[4]

OBJECTIVES: **The goal of the study was to determine whether endoscopic ultrasound (EUS)-guided biliary drainage (EUS-BD) is comparable to conventional transpapillary stenting with endoscopic retrograde cholangiopancreatography (ERCP) in palliation of malignant distal biliary obstruction. Although ERCP for the palliation of malignant biliary obstruction is the standard of care, post-procedure pancreatitis and stent dysfunctions are not uncommon. While EUS-BD has garnered interest as a viable alternative when ERCP is impossible, its role as a primary palliation of malignant distal biliary obstruction is yet to be proven.**

METHODS: **We performed random allocation to EUS-BD or ERCP in 125 patients with unresectable malignant distal biliary obstruction at four tertiary academic referral centers in South Korea.**

RESULTS: **Technical success rates were 93.8% (60/64) for EUS-BD and 90.2% (55/61) for ERCP (difference 3.6%, 95% 1-sided confidence interval lower limit −4.4%, $P=0.003$ for noninferiority margin of 10%). Clinical success rates were 90.0% (54/60) in EUS-BD and 94.5% (52/55) in ERCP ($P=0.49$). Lower rates of overall adverse events (6.3% vs 19.7%, $P=0.03$) including post-procedure pancreatitis (0 vs 14.8%), reintervention (15.6% vs 42.6%), and higher rate of stent patency (85.1% vs 48.9%) were observed with EUS-BD. EUS-BD was also associated with more preserved quality of life (QOL) than transpapillary stenting after 12 weeks of the procedure.**

CONCLUSIONS: **This study demonstrated comparable technical and clinical success rates between EUS-BD and ERCP in relief of malignant distal biliary obstruction. Substantially longer duration of patency coupled with lower rates of adverse events and reintervention, and more preserved QOL were observed with EUS-BD (cris.nih.go.kr, Identifier: KCT0001396, https://cris.nih.go.kr/cris/search/search_result_st01_en.jsp?seq=9716&ltype=&rtype=).**

SUPPLEMENTARY MATERIAL accompanies this paper at https://doi.org/10.1038/s41395-018-0122-8

Am J Gastroenterol (2018) 113:987–997. https://doi.org/10.1038/s41395-018-0122-8

INTRODUCTION

Transpapillary stent placement with endoscopic retrograde cholangiopancreatography (ERCP) has been the preferred treatment modality for the palliation of malignant distal biliary obstruction [1–3]. However, a wide array of complications stemming from the procedure, including pancreatitis, cholangitis, and stent dysfunction resulting in untimely reintervention, has continued to pose a significant challenge [4, 5]. Reported combined rates of aforemen-

[1]Department of Internal Medicine, Seoul National University Hospital, Seoul, South Korea. [2]Ilsan Paik Hospital, Goyang, South Korea. [3]Department of Internal Medicine, Cheonan Hospital, Soonchunhyang University College of Medicine, Cheonan, South Korea. [4]Department of Internal Medicine, Division of Gastroenterology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea. [5]Department of Internal Medicine, Dankook University College of Medicine, Dankook University Hospital, Cheonan, South Korea. [6]Department of Clinical Epidemiology and Biostatistics, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea. [7]Digestive Disease Institute, Cleveland Clinic Foundation, Cleveland, OH, USA. [8]Department of Internal Medicine, Pusan National University School of Medicine, Pusan National University Hospital, Pusan, South Korea. These authors contributed equally to this article as first authors: Woo Hyun Paik, Tae Hoon Lee **Correspondence:** D.H.P. (email: dhpark@amc.seoul.kr)

Received 1 February 2018; accepted 11 April 2018; Published online 2 July 2018

tioned adverse event rate related to ERCP assisted transpapillary stenting range from 28% to 36% [6–8]. Acute pancreatitis is the most common adverse event for those undergoing the procedure, with reported rates between 2% and 18% [4, 6–8]. Compounding matters further, the presence of duodenal obstruction that can occur in later stages of malignancy or surgically altered anatomy often preclude accessing bile duct with ERCP [4].

Transmural stent placement under endoscopic ultrasound (EUS) guidance has emerged as an alternative procedure to percutaneous transhepatic biliary drainage after failed ERCP [9–12]. A recent meta-analysis reported EUS-guided biliary drainage (EUS-BD) to be a viable alternative to ERCP in relieving biliary obstruction when performed at institutions with procedural expertise [9]. Some theoretical advantages of EUS-BD over ERCP include (1) avoidance of traumatic papillary manipulation that can lead to acute pancreatitis, (2) ability to access bile duct even when ampulla cannot be approached endoscopically and (3) no need to place the stent through the biliary stricture [7, 11].

To date, only a small volume of retrospective studies comparing EUS-BD with conventional ERCP exists [4, 7], lacking a well-designed prospective randomized study with robust data. Therefore, we aimed to evaluate the noninferiority of EUS-BD compared to ERCP as a primary palliation method in relieving malignant distal biliary obstruction.

METHODS

Study design and participants

This study was a randomized, controlled, noninferiority trial conducted by four tertiary academic centers in South Korea. Patients were enrolled between May 2015 and January 2017 and were followed up until July 2017. The institutional review boards at each study center approved the protocol. The full protocol is included in Supporting document 1. We obtained informed consent with possible ERCP assisted transpapillary and EUS-guided transmural stenting before the start of procedure. This informed consent form may allow for timely other endoscopic method of biliary drainage in sedated patients with unsuccessful assigned procedure (transpapillary or transmural stenting) in same endoscopic session. All patients who presented with unresectable malignant distal biliary obstruction initially underwent endoscopic drainage procedure for biliary decompression. Unresectability in malignant distal biliary obstruction was determined by radiologist and surgeon based on computed tomography criteria and/or magnetic resonance imaging with or without EUS [12]. Inclusion criteria were as followed: (1) the presence of an unresectable malignant distal biliary obstruction (>2 cm distal to the hilum) with pathologic or radiologic diagnosis prior to endoscopic intervention, (2) >18 years old, (3) a Karnofsky index of 30% or greater, and (4) no serious or uncontrolled coexisting medical illness. Exclusion criteria included a hilar biliary obstruction, uncorrectable coagulopathy, history of allergy to radiocontrast agents, and refusal to participate in the study.

Enrolled patients were randomized in a 1:1 ratio to ERCP or EUS-BD without risk stratification. We obtained sequentially numbered, opaque, sealed envelopes with computer-generated random numbers using a block randomization (block size of 4) from a statistician. The patients were blinded to the procedures that they had undergone, and the statistician (S.O.K.) who analyzed the data were also blinded to the treatment arms that the patients had been enrolled. All authors had access to the study data and reviewed and approved the final manuscript.

Study oversight. After obtaining written informed consent, the randomization assignment was opened by one of the attending nurses, and the allocation sequence was concealed from all patients and operators before procedure. The study coordinators collected data, and the statistician (S.O.K.) analyzed the data and vouched for the completeness and accuracy of the analyses. An independent data and safety monitoring board provided regulatory oversight. No endoscopic accessory, device, and stents were donated by the manufacturer.

Definition and outcome measurements

The technical success was defined as the placement of the metal stent across the stricture site via the papilla (ERCP) or across the stomach or the duodenum (EUS-BD), along with the flow of the contrast medium and/or bile through the stent [13]. Clinical success was defined as the completion of stent placement with reduction of total serum bilirubin levels to less than half of the pretreatment level within one week and/or less than a quarter of the pretreatment level within four weeks [13]. Procedure-related adverse events were defined according to the Common Terminology Criteria for Adverse Events v 3.0 and 4.0. Early (procedure-related) or late adverse events were defined according to the timing (within 14 days after the procedure in early, or after 14 days in late adverse events) [14]. Detailed definitions, degree of adverse events, reintervention, and stent occlusion were defined following ASGE report [14]. Post-ERCP pancreatitis was defined as new or worsening abdominal pain persisting for at least 24 h and requiring analgesics after ERCP in conjunction with an elevation in serum amylase or lipase levels greater than three times the normal upper limit. The grading of severity was as follows: mild, requiring prolongation of planned admission for 3 days or less; moderate, requiring 4–10 days of hospitalization; severe, requiring >10 days of hospitalization, intensive care, or surgical intervention [14]. Stent patency (time to recurrent biliary obstruction; patients were censored at last follow-up or death) was defined as the time between stent placement and the occurrence of cholangitis, stent revision, or other biliary interventions [6]. Tumor ingrowth after EUS-guided transmural stenting was defined as tumor ingrowth in uncovered portion of partially covered metal stent which was placed inside the bile duct. Duodenal invasion was diagnosed when duodenal erosions, ulcers or strictures thought to have been caused by malignancy were observed by radiologic or endoscopic images at the time of procedures, regardless of whether they were confirmed pathologically [15].

The primary outcome of interest was technical success rate. The secondary outcomes of interest were rates of clinical success, adverse events, and reintervention along with stent patency duration, and quality of life (QOL). Clinical symptoms and laboratory examinations were recorded at baseline and at 1, 7, and 28 days after the procedures in both groups. QOL was estimated by using

European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) at baseline, at 4 weeks, and at 12 weeks. We followed up the patients for at least 6 months after the procedures or until death.

Study intervention

Prophylactic antibiotics was administered before the start of the intervention. Sedation for the procedure was performed using the following sequences: Both midazolam (0.05 mg/kg body weight; 1 mg if aged >70 or ASA class III) and meperidine 25 mg (12.5 mg if age >70 or ASA class III) were given at the initiation of sedation. Thereafter, repeated doses of 10–20 mg propofol were administered to reach and maintain a moderate level of sedation. Since rectal indomethacin was not available during study period [16], no patient had taken rectal indomethacin in present study.

ERCP. ERCP assisted transpapillary stenting was performed using a standard duodenoscope in patients with normal anatomy whereas cap-assisted forward viewing scope was used in patients with Billroth II or Roux-en-Y anatomy and duodenal invasion. Following biliary cannulation with a sphincterotome, contrast was injected to obtain cholangiogram. After the confirmation of successful bile duct cannulation, biliary sphincterotomy was performed. Finally, self-expandable metal stent was placed across the papilla and the length of stricture. The metal stents were chosen usually based on the tumor involvement of the cystic duct: If tumor involves the cystic duct, 10 mm diameter uncovered metal stent (WallFlex; Boston Scientific, Natick, MA) was used, and, otherwise, 10 mm diameter fully covered metal stent (BONA; Standard Sci Tech Inc, or MI-Tech Seoul, South Korea) was used. In patients with clinically significant duodenal obstruction, partially covered or uncovered metallic stent was placed in same session.

EUS-BD. EUS-guided transmural stenting was performed either as a choledochoduodenostomy (CDS, Supplementary Figure **1A**) or a hepaticogastrostomy (HGS, Supplementary Figure **1B**) using a linear array echoendoscope and one-step dedicated stent introducer (DEUS; Standard Sci Tech Inc, Seoul, South Korea). This dedicated stent introducer has a tapered metal tip which functions as a push-type dilator without the need for predilation or use of elcetrocautery [17]. It has an ultra-taperd 3F catheter with a 4F smooth tapered metal tip for simple puncture of the transmural fistula tract, without the need for fistula tract dilation devices after a 19-G needle puncture [16, 17]. The 7F outer sheath of the delivery catheter provides good pushability and adequate resistance [17, 18]. The preloaded self-expandable metallic stent (SEMS) included in the device has an uncovered portion (8 mm in diameter and 15 mm in length) to allow for better anchoring and preventing occlusion of side branches in the biliary tree, when placed in the liver. The covered portion (silicone membrane, 6 mm in diameter and 35–85 mm in length) extends transmurally to prevent intraperitoneal bile leakage. Proximal (anchoring flaps) and distal (funnel-shaped uncovered wire mesh in the bile duct portion) anti-migration features are also present (Supplementary Figure **1C**).

The procedural detail of transmural placement of SEMS are as follows. The dilated common bile duct or intrahepatic duct was accessed with a 19-gauge fine-aspiration needle, and a 0.025-inch guide wire was placed, preceded by confirmation cholangiogram. A one-step dedicated stent introducer was then advanced over guide wire, and the deployment of metal stent ensued. For the deployment of this all-in-one device into the bile duct, the axis of the introducer was kept toward the hilar portion in CDS and parallel to the central intrahepatic duct in HGS [17, 18]. In patients with clinically significant duodenal obstruction, partially covered or uncovered metallic stent was placed in same session.

The choice of EUS-HGS or CDS. Based on our modified algorithm from previous protocols [12, 18]. HGS was considered in patients with malignant distal biliary obstruction and duodenal bulb invasion (e.g., gastric outlet obstruction), periampullary duodenal invasion with compromised duodenal bulb, or surgically altered anatomy. In patients with malignant distal biliary obstruction and periampullary tumor infiltration with distal duodenal invasion, CDS was considered first. Otherwise, HGS or CDS was performed by the discretion of endoscopists. Four experienced endoscopists (D.H.P., W.H.P., T.H.L., J.-H.C.) participating in the study have >1200–4500 lifetime experiences in ERCP and have performed 100–500 EUS procedures for pancreatobiliary diseases annually [12].

Sample size calculation

Technical feasibility and safety studies of EUS-BD after failed ERCP or inaccessible papilla due to anatomic variations have been reported [4, 7]. However, no study that considered EUS-BD as a primary treatment option for the palliation of malignant distal biliary obstruction exists to date. Furthermore, given the novelty of this technique, we believe some detailed elaboration of technical success rate is appropriate. Therefore, we designed this study based on noninferiority to demonstrate technical feasibility between EUS-BD and ERCP as a primary palliation of unresectable malignant distal biliary obstruction.

The primary analysis was a noninferiority comparison between ERCP and EUS-BD for technical success rates. The assumed technical success rate for transpapillary approach was 95% [4]. We set a margin of noninferiority for a technical success rate between ERCP and EUS-BD as 10% according to the results of a pooled analysis and after a discussion with the contributing physicians, who stated that this noninferiority margin of 10% would be clinically relevant [19]. To achieve a statistical power of 80% with the assumption of a type I error rate of 5%, a total of 118 (59 per group) was calculated. Considering a 5% of drop-out rate, we calculated a final sample size of 124 patients (62 per group).

Statistical analysis

The noninferiority hypothesis for primary outcome was assessed using the one-sided Z-test of the difference in the technical success rate and the margin of noninferiority. The characteristics of the study groups were compared using Student *t* tests for continuous variables and a Pearson chi-square test or the Fisher exact test for categorical variables. Overall survival and stent patency were calculated by the Kaplan-Meier method with use of the log-rank test. The changes in QOL scores were calculated as the difference from baseline to the 4 or 12 weeks, and analyzed by Mann-Whitney test to compare the study groups. A P value of less than 0.05 was

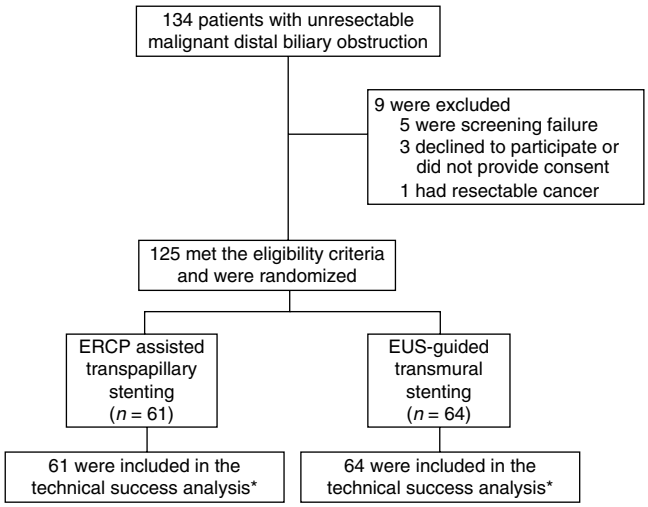

Fig. 1 Flow diagram of enrolled patients.
*Technical success rates were calculated by intention-to-treat analysis

considered statistically significant. Statistical analyses were performed using SAS version 9.4 (SAS Institute).

RESULTS

Study population

A total of 125 patients were enrolled and completed the study during median follow-up of 155 days (interquartile range [IQR], 100–234 days, Fig. 1). The presence of malignancy was confirmed by the review of available histologic and/or cytologic specimen by dedicated GI pathologists. A total of 61 patients underwent ERCP, and 64 patients underwent EUS-BD. Baseline characteristics of the two study groups were similar with the exception of sex (Table 1). The duodenal invasion was present in 33 patients (26.4%), each 15 patients (24.6%) in ERCP and 18 patients (28.1%) in EUS-BD.

Primary outcome

Technical success rates were 93.8% (60/64) in EUS-BD and 90.2% (55/61) in ERCP. The treatment difference was 3.6% (90% confidence interval −4.4 to 11.6%). Because the lower limit of the confidence interval for the treatment difference (−4.4%) exceeded the noninferiority margin of −10%, noninferiority was shown for technical success ($P=0.003$). Six patients from the ERCP group and four patients in EUS-BD group who failed initial biliary drainage with initial approach (due to duodenal obstruction ($n=5$) or surgically altered anatomy ($n=1$) in the ERCP group and insufficient bile duct dilatation in EUS-BD group) were allowed to cross over to the other modality to receive successful treatment in same endoscopic session. Therefore, no percutaneous drainage was required in all enrolled patients.

Secondary outcomes

Clinical success rates were 90.0% (54/60) with EUS-BD and 94.5% (52/55) with ERCP ($P=0.49$, per-protocol analysis). Median procedure time was significantly shorter with EUS-BD than with ERCP (5 (IQR 3–12) vs. 11 (IQR 7–18) min, $P<0.001$, Table 2). The median length of hospital stay was also shorter among EUS-BD group compared to ERCP group (4 (IQR 3–5) vs. 5 (IQR 4–6) days, $P=0.03$).

A lower rate of early (procedure-related) adverse events was observed with EUS-BD compared to ERCP (6.3% vs 19.7% respectively, $P=0.03$), particularly in terms of procedure-related pancreatitis (0 vs 14.8%, $P=0.001$). The severity of procedure-related pancreatitis was mild degree in seven patients and moderate degree in two patients. ERCP-related pancreatitis rate was more frequent in nonpancreatic cancer group compared to pancreatic cancer group without statistical difference (12.5% vs 19%, $P=.71$). There were no serious procedure-related adverse events, including death. The late adverse events rate was also significantly lower in EUS-BD (4.7% in EUS-BD vs 19.4% in ERCP group, $P=0.01$). The rates of mild and moderate adverse events were 26.2% and 13.1% in ERCP group, and 6.3% and 4.7% in EUS-BD group, respectively (Table 2).

In subgroup analysis of duodenal invasion, the duodenal invasion was present in 33 patients (26.4%), each 15 patients (24.6%) in ERCP and 18 patients (28.1%) in EUS-BD. Clinical outcome was similar between the two groups, however, the rate of technical success tended to be higher among EUS-BD group compared to ERCP group without statistical significance (94.4% vs. 66.7%, $P=0.07$, Table 3). Remaining subgroup analysis in patients without duodenal invasion or surgically altered anatomy, showed similar result with main outcomes (Table 4).

In EUS-BD group, the technical success rates of choledochoduodenostomy (CDS) and hepaticogastrostomy (HGS) were 90.6% (29/32) and 96.9% (31/32), respectively. One-step fistula dilation with dedicated introducer was performed in 46 patients (76.7%) on an intention-to-treat analysis. The rate of clinical success, adverse events, reintervention, stent patency, and overall survival were similar between CDS and HGS (Supplementary Table **1**).

Higher stent patency rate at 6 months (85.1% vs. 48.9%, $P=0.001$, Fig. 2a) and longer mean patency time (208 days vs. 165 days), along with lower reintervention rate (15.6% vs. 42.6%, $P=0.001$) were observed with EUS-BD. There was no significant difference in overall survival between two groups (Fig. 2b). In subgroup analysis, there was no difference in stent patency between EUS-CDS and HGS (Fig. 2c), and between in patients with duodenal invasion and those without (Fig. 2d). No significant factor predicting reintervention was identified except biliary drainage method (Supplemetary Table **2**).

The changes in QOL scores, indicating preservation of existing quality of life, were less in EUS-BD group compared with ERCP group after 12 weeks of the procedure in terms of global (4.17 vs −9.03, $P=0.001$), and parts of functional (emotional, 1.62 vs −9.72, $P=0.001$; cognitive, 0.93 vs −11.11, $P=0.003$) and symptom scale (fatigue, −3.40 vs 8.02, $P=0.02$; pain, −17.59 vs 4.63, $P=0.01$; financial difficulties, 2.78 vs 18.52, $P=0.01$) (Fig. 3).

DISCUSSION

This is the first prospective, multicenter, randomized study comparing EUS-BD with ERCP as a primary modality for the

Table 1 Baseline characteristics[a]

Variables	ERCP ($n=61$)	EUS-BD ($n=64$)	All patients ($n=125$)
Age – mean (range), yr	68.4 (46, 88)	64.8 (40, 90)	66.6 (40, 90)
Sex (male: female)	26:35	41:23	67:58
ASA class[b]			
I	5	5	10
II	52	54	106
III	4	5	9
Etiology of biliary obstruction			
Pancreatic cancer	40	38	78
Cholangiocarcinoma	8	3	11
Gallbladder cancer	4	4	8
Ampulla of Vater cancer	3	5	8
Stomach cancer	2	4	6
Duodenal cancer	1	2	3
Hepatocellular carcinoma	1	0	1
Others	2	8	10
Common bile duct diameter (mm)	15.0±3.9	15.7±4.0	15.4±3.9
Intrahepatic duct diameter (mm)	—	5.57±2.49[c]	—
Total bilirubin (mg/dL)			
Initial	7.7±6.4	8.3±7.2	8.0±6.8
1 week	2.8±4.5	3.0±3.2	2.9±3.8
4 weeks	1.5±2.9	1.5±2.4	1.5±2.7
Alkaline phosphatase (U/L)			
Initial	497.4±272.8	527.4±331.3	512.8±303.3
1 weeks	296.8±171.7	343.3±394.5	321.2±309.1
4 weeks	172.4±118.8	204.9±324.5	189.2±247.2
Surgically altered anatomy			
Billroth-II	0	1	1
Roux-en-Y	1	3	4
Duodenal invasion			
Type 1	8	7	15
Type 2	2	4	6
Type 3	5	7	12
[d]Systemic chemotherapy – no. (%)	26 (42.6)	37 (57.8)	63 (50.4)

[a]Plus-minus values are means±SD. There were no significant differences between the two groups in any baseline characteristics except sex ($P=0.02$)
[b]The ASA physical status classification system is a system for assessing the fitness of patients before surgery: I. normal healthy patient, II. a patient with mild systemic disease, and III. A patient with severe systemic disease
[c]EUS-HGS group
[d]Systemic chemotherapy was performed at least 2 sessions after biliary drainage

palliative treatment of malignant biliary obstruction. Previous studies comparing ERCP with surgical or percutaneous intervention have demonstrated the superiority of ERCP in terms of safety and efficacy [1, 2, 20]. Therefore, ERCP has become the standard of care for the treatment of biliary obstruction since 1990s. Reported technical success rate of transpapillary stenting with ERCP ranges from 90% to 95% [4]. However, ERCP assisted transpapillary approach for malignant biliary obstruction may have inherent drawbacks, including traumatic injury of main pancreatic duct and stent occlusion by tumor growth [21]. Post-procedure

Table 2 Safety profile and procedure-related outcomes of ERCP and EUS-BD

	Intention-to-treat analysis			Per-protocol analysis		
Outcome measures, *n* (%)	**ERCP (*n*=61)**	**EUS-BD (*n*=64)**	***P*-value**	**ERCP (*n*=55)**	**EUS-BD (*n*=60)**	***P*-value**
Procedure time, median (IQR), min[a]	11 (7–18)	5 (3–12)	<0.001	14 (8–20)	5 (3–9)	<0.001
Follow up period, median (IQR), days	165 (99–253)	144 (101–209)	0.45	165 (99–253)	142 (90–209)	0.41
Adverse events						
Early (≤2 weeks, procedure-related)	12 (19.7)[b]	4 (6.3)[b]	0.03	12 (21.8)	2 (3.3)	0.003
Late (>2 weeks)	12 (19.4)[c]	3 (4.7)[c]	0.01	12 (21.8)	3 (5.0)	0.008
Procedure-related pancreatitis	9 (14.8)	0	0.001	8 (14.5)	0	0.002
Mild/Moderate/Severe	16 (26.2)/8 (13.1)/0	4 (6.3)/3 (4.7)/0	0.001	16 (29.1)/7 (12.7)/0	4 (6.7)/2 (3.3)/0	<0.001
Mortality						
Procedure-related	0	0		0	0	
Disease progression	51(83.6)	46 (71.9)		46 (83.6)	43 (71.7)	
Cardiopulmonary complication	0	2 (3.1)		0	2 (3.3)	
Reintervention rate	26 (42.6)[d]	10 (15.6)[d]	0.001	24 (43.6)	9 (15.0)	0.001
Reintervention method			<0.001			<0.001
ERCP	22	0		20	0	
EUS-BD	3	9[e]		3	8[e]	
PTBD	1	1		1	1	
Hospital stay, median (IQR), days	5 (4–6)	4 (3–5)	0.03	5 (4–6)	4 (3–5)	0.008

PTBD percutaneous transhepatic biliary drainage

[a]Procedure time was defined as time from biliary cannulation to stent placement in ERCP group, and time from needle puncture of the dilated bile duct to stent placement in EUS-BD group. In cases of difficult cannulation (defined as failed biliary access within 5 min of attempt), we performed early precut fistulotomy for cannulation by experts without involvement of trainees and duodenal intubation time was not included within procedure time

[b]Early adverse events included acute pancreatitis (*n*=9), acute cholecystitis (*n*=2), stent migration (*n*=1) in ERCP group and self-limited pneumoperitoneum (*n*=2), bile peritonitis (*n*=1), and acute cholangitis (*n*=1) in EUS-BD group

[c]Late adverse events included acute cholangitis (*n*=6), acute cholecystitis (*n*=3), and stent occlusion (*n*=3) in ERCP group and acute cholangitis (n=3) in EUS-BD group

[d]In ERCP group, 26 reinterventions were required due to stent clogging (*n*=14), tumor in/overgrowth (*n*=9), stent migration (*n*=1), acute cholecystitis (*n*=1), and biloma (*n*=1). In EUS-BD group, 10 reinterventions were required due to stent clogging (*n*=6), stent migration (*n*=2), and tumor in/overgrowth (*n*=2)

[e]As reintervention, these patients underwent stent reinsertion via the previous transmural fistula

pancreatitis from pancreatic duct injury and stent occlusion due to tumor ingrowth or overgrowth often results in untimely reintervention as well as prolonged hospitalization. Currently EUS-BD is used as a rescue option when ERCP is not successful [9, 18]. Failure with initial attempt results in multiple procedure, incurring a significant increase in health and financial burden. Previous retrospective studies comparing EUS-BD and ERCP as the first-line treatment option for malignant distal biliary obstruction showed comparable safety and efficacy [4, 7]. In this multicenter prospective study, we demonstrated comparable technical and clinical success rates between EUS-BD and ERCP. Furthermore, substantially lower rates of adverse outcomes (including post-procedure pancreatitis and stent occlusion requiring reintervention) coupled with more preserved QOL after 12 weeks of the procedure, were observed with EUS-BD.

The technical success rate of ERCP achieved in our study is comparable to previous reported rates despite including significant number of patients with duodenal invasion that are often excluded in other studies [11, 20, 22, 23]. Although duodenal invasion was observed in 26.4% (33 patients) in entire group, only six patients (9.8%) from ERCP group (*n*=61) failed to gain ampullary access. Thus, the rate of clinically significant duodenal obstruction rate in ERCP group observed in our study (9.8%) is on par with of 8% rate of previous literature [24], especially considering the study centers involved are the aggregate of cancer treatment institutions. The presence of duodenal invasion confers more advanced degree of malignant process, hence introducing a heterogeneity among the study population. Even so, a clear advantage of EUS-BD over ERCP is in those patients with duodenal obstruction precluding access of ampulla with a duodenoscope.

Lower rates of procedure-related adverse events observed with EUS-BD (6.3% vs 19.7%, $P=0.03$), especially in the rates of post-procedure pancreatitis (0% with transmural approach vs 14.8% with transpapillary approach, $P=0.001$), carry significant clinical

Table 3 Comparison of transpapillary and transmural stent placement in patients with duodenal invasion

Outcome measures	ERCP ($n=15$)	EUS-BD ($n=18$)	*P* value
Technical success, *n* (%)[a]	10 (66.7)	17 (94.4)	0.07
Clinical success, *n* (%)[a]	13 (86.7)	13 (72.2)	0.41
Procedure time, min (range)	8.7 (3.3, 15.0)	5.7 (3.3, 15.0)	0.64
Adverse events, *n* (%)			0.31
Early (≤2 weeks, procedure-related)	3 (20.0)	1 (5.6)	
Late (>2 weeks)	4 (26.7)	1 (5.6)	
Mortality, *n*			0.61
Procedure-related	0	0	
Disease progression	14	14	
Cardiopulmonary complication	0	1	
Reintervention rate, *n* (%)	7 (46.7)	4 (22.2)	0.14
Reintervention method, *n*			0.62
ERCP	6	3	
EUS-BD	1	0	
PTBD	0	1	
Hospital stay, median (IQR), days	5 (3, 8)	5 (4, 6)	0.88

[a]Technical success was calculated according to a per-protocol analysis, and clinical success was calculated according to an intention-to-treat analysis

Table 4 Comparison of transpapillary and transmural stent placement in patients without duodenal invasion or surgically altered anatomy

Outcome measures	ERCP ($n=45$)	EUS-BD ($n=43$)	*P* value
Technical success, *n* (%)	45 (100)	40 (93.02)	0.11
Clinical success, *n* (%)	39 (86.7)	39 (90.7)	0.73
Procedure time, min (range)	14 (10, 20)	4.8 (3.2, 11.8)	<0.001
Adverse events, *n* (%)			
Early (≤2 weeks, procedure-related)	9 (20)	3 (6.9)	0.07
Late (>2 weeks)	8 (17.4)	2 (4.7)	0.09
Mortality, *n*	37	30	0.17
Procedure-related	0	0	
Disease progression	37	29	
Cardiopulmonary complication	0	1	
Reintervention rate, *n* (%)	18 (40)	5 (11.6)	0.003
Reintervention method, *n*			1.00
ERCP	15	5	
EUS-BD	2	0	
PTBD	1	0	
Hospital stay, median (IQR), days	5 (4, 6)	4 (3, 5)	0.01

implications including shorter length of stay (4 in EUS-BD group vs 5 days in ERCP group, $P=0.03$) and likely lower cost of care. The rate of post-ERCP pancreatitis in the current study appears higher than previous studies looking into post-ERCP pancreatitis among patients with malignant biliary obstruction receiving metallic stent [25]. The varying incidence of post-ERCP pancreatitis has been considered as a result of multiple factors including heterogeneity of enrolled patients, nature of study design, definition criteria of pancreatitis, and thoroughness of follow-up [26]. More difficult biliary cannulation due to given higher rate of advanced disease state with duodenal invasion may contribute to the increased incidence of post-ERCP pancreatitis. Also, metallic stent itself and nonpancreatic cancer may increase the rate of pancreatitis. A study by Kawakubo and colleagues [27] showed that the patients undergoing ERCP for the obstructive jaundice from nonpancreatic malignancy developed a significantly higher rate (16.1%) of post ERCP pancreatitis compared to the patients with obstructive jaundice from pancreatic malignancy (3.1%). Regarding rate of pancreatitis with SEMS a study by Tol and colleagues [28] for preoperative biliary drainage in patients with resectable pancreatic cancer showed higher rate of pancreatitis (18%) with SEMS compared to the patients that received plastic stent. As described in our result section, the nonpancreatic cancer group demonstrated higher rate of pancreatitis without reaching statistical difference (12.5% vs 19%, $P=0.71$). The incidence (14.8%) of post-ERCP pancreatitis in this study is comparable to the rate (16.1%) reported among the similar group of patients, and can be attributed to the fact that all of them had naïve papilla prior to metal stent insertion, which is a well-recognized risk factor for post-ERCP pancreatitis [7]. The role of routine endoscopic sphincterotomy before placement of metal stent is still controversial and no clear guideline exist. Endoscopic sphincterotomy itself is an independent risk factor of post-ERCP pancreatitis, and it may also be related with high rate of PEP in this study. Our study protocol adopted utilization of a dedicated one-step device for tract dilation and stent introduction for transmural stenting. We believe this has contributed to curtailing the rates of adverse outcomes by decreasing the risk of bile leak and delayed luminal injury from electrocautery [29]. Furthermore, this device may expedite the process of EUS-BD (without further fistula tract dilation) resulting in shortened procedure time compared with ERCP (5 vs 11 min, $P<0.001$).

The stent patency rate at 6 months was higher with EUS-BD compared to ERCP (85.1% vs 48.9% respectively, $P=0.001$) with the lower rate of reintervention (15.6% for transmural vs 42.6% for transpapillary, $P=0.001$). The rates of stent patency and reintervention among the ERCP group were comparable to that of previous literatures [30, 31]. Longer duration of stent patency and less

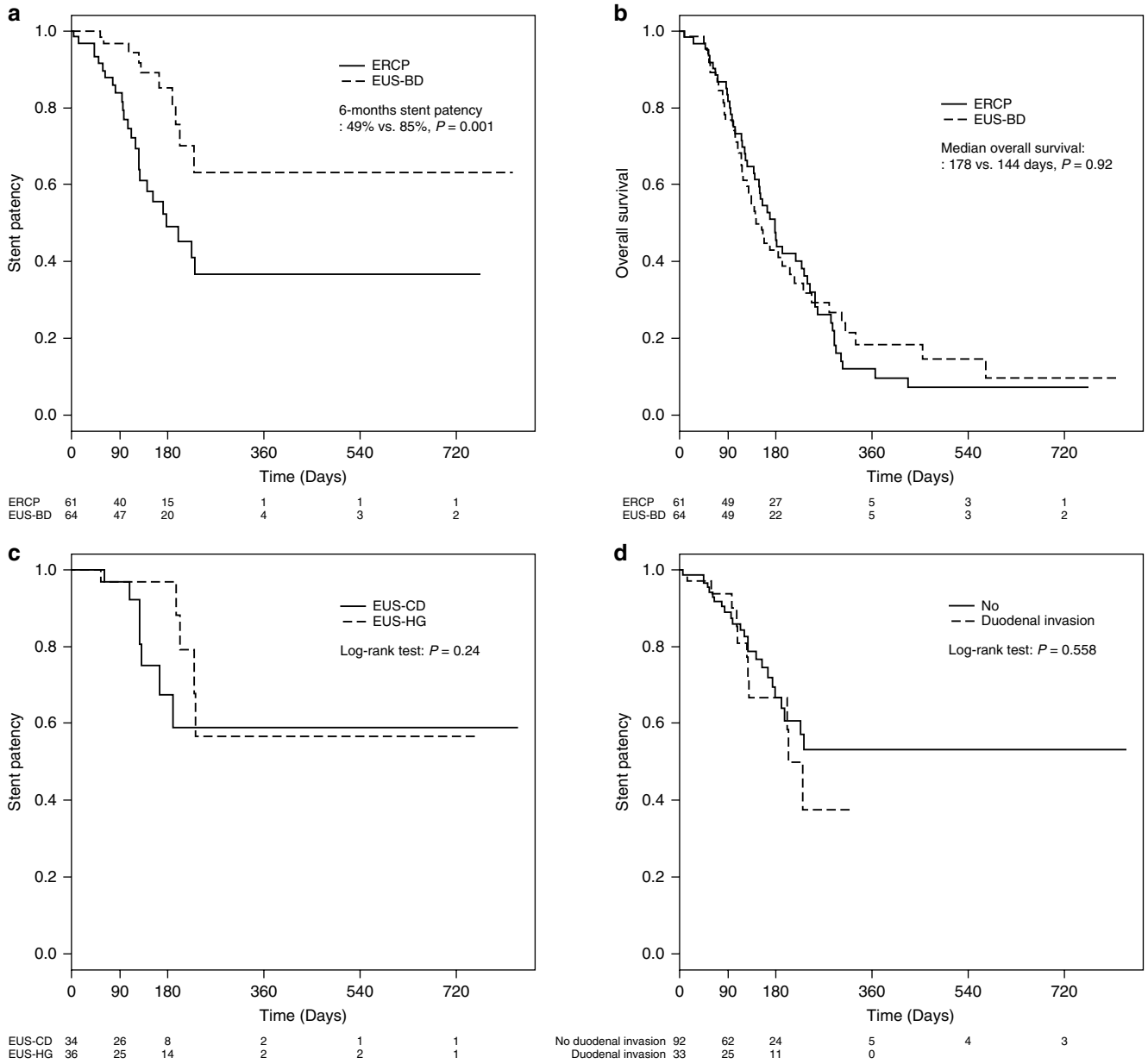

Fig. 2 Kaplan–Meier analysis with the log-rank test for stent patency (**a**) and overall survival (**b**) in ERCP and EUS-BD group, stent patency in EUS-CD and EUS-HG (**c**), and stent patency in patients with duodenal invasion and those without (**d**)

need for reintervention observed with EUS-BD can be attributed to lower risk of tumor ingrowth and/or overgrowth with transmural stenting which bypasses the site of malignant stricture. The comparison of QOL scores using the EORTC QLQ-C30 assessment between EUS-BD and ERCP showed more favorable outcomes with EUS-BD, specifically in terms of change in QOL scores regarding global, functional (emotional and cognitive), and symptom scale (fatigue, pain, and financial difficulties) between baseline and 12 weeks. The negative trends observed in some components QOL assessment among the ERCP group can be attributed to the relatively higher procedural adverse event and reintervention rate compared to EUS-BD group.

Our study has several limitations. First, technology available for the study—one step stent introducer—is not available in United States, limiting applicability of our study's efficiency and safety. With additional studies confirming its safety and efficacy, it is our expectation that the device will be available outside South Korea in near future. Second, EUS-BD is performed in a small number of high-volume academic center due to its perceived procedural complexity and the need for dedicated devices [32, 33]. This will limit its generalizability. However, it can be overcome with training of additional endoscopists and dissemination of the technology. This study suggests the need for devices and accessories tailor-made specifically for effective and safe EUS-BD.

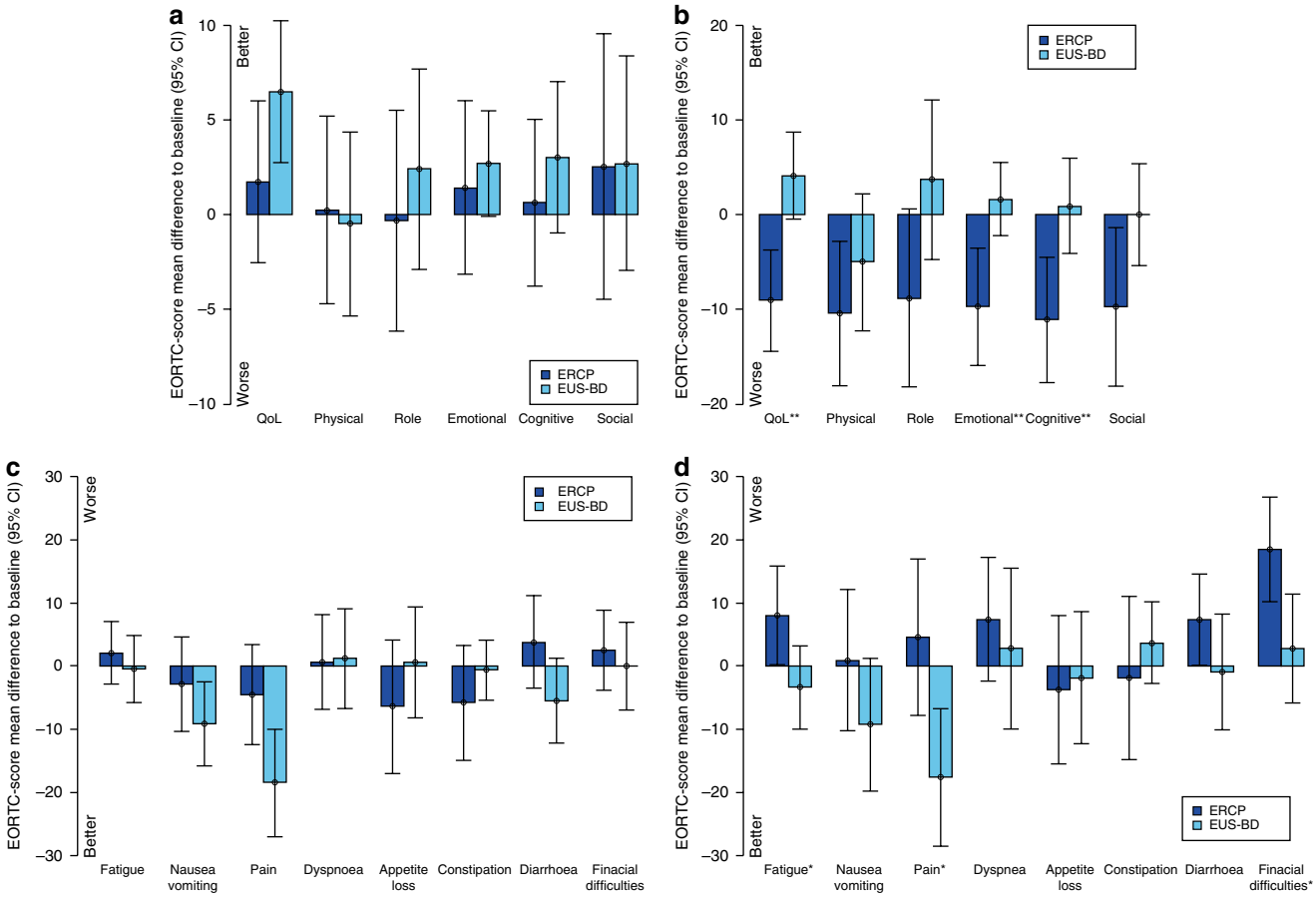

Fig. 3 Quality of life was estimated by using EORTC QLQ-C30. **a** Changes in global health status and functional scales between baseline and 4 weeks after the procedure. **b** Changes in global health status and functional scales between baseline and 12 weeks after the procedure. **c** Changes in symptom scale between baseline and 4 weeks after the procedure. **d** Changes in symptom scale between baseline and 12 weeks after the procedure. EUS-BD was associated with more preserved QOL than ERCP after 12 weeks of the procedure regrading global (4.17 vs −9.03, $P=0.001$), and parts of functional (emotional, 1.62 vs −9.72, $P=0.001$; cognitive, 0.93 vs −11.11, $P=0.003$) and symptom scale (fatigue, −3.40 vs 8.02, $P=.02$; pain, −17.59 vs 4.63, $P=0.01$; financial difficulties, 2.78 vs 18.52, $P=0.01$). $^{*}P<0.05$.$^{**}P<0.01$

Third, EUS-BD is often performed after failed conventional ERCP [25]. Even in countries such as Japan and Korea where skills of interventional endoscopy are abound, only a small number of expert endoscopists perform EUS-BD as the first-line treatment of malignant biliary obstruction [7, 34, 35]. Furthermore, the acceptance of EUS-BD as a viable alternative to ERCP has been slow, in part because of long track record of efficacy and safety with ERCP. Nevertheless, as ERCP has its own limitation, [16] mounting evidence of technical feasibility and safety, which is also the primary goal of this study, should encourage measured yet persistent engagement with EUS-BD.

In conclusion, EUS-BD and PTBD had similar levels of efficacy for the primary palliation of unresectable malignant distal biliary obstruction based on rates of technical and clinical success. Furthermore, several robust clinical advantages (lower adverse outcomes with no risk of pancreatitis, longer stent patency with less need of reintervention, and more preserved QOL) were recognized with EUS-BD over ERCP, warranting further evaluation.

CONFLICT OF INTEREST

Guarantor of the article: Do Hyun Park, MD, PhD.

Specific author contributions: Study concept and design: DHP. Recruitment of participants and acquisition of data: DHP, WHP, THL, and JHC. Endoscopic interventions: WHP, THL, JHC, and DHP. Analysis and interpretation of data: SOK, THL, JHC, DUK, JHS, TJS, SSL, and SJ. Statistical analysis: SOK, WHP, THL, JHC, and DHP. Drafting of the manuscript: WHP, THL, JHC, and DHP. Critical revision of manuscript for important intellectual content: SJ, DUK, JHS, TJS, SSL, DWS, SKL, MHK, and DHP. Study supervision: SSL, DWS, SKL, MHK, and DHP.

Financial Support: This research was supported by a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute, funded by the Ministry of Health and Welfare, Republic of Korea (HI14C0139, HI17C0055), and partly supported by the Soonchunhyang University Research Fund. The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Potential competing interests: None

Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Endoscopic ultrasound (EUS)-guided transmural biliary drainage (EUS-BD) has been used as a rescue alternative when transpapillary stent placement with endoscopic retrograde cholangiopancretography (ERCP) is impossible.
- ✓ However, EUS-BD as a primary palliation of unresectable malignant distal biliary obstruction remains unknown.

WHAT IS NEW HERE

- ✓ In this randomized clinical trial, EUS-BD are comparable to ERCP for the primary palliation of unresectable malignant distal biliary obstruction in terms of technical and clinical success.
- ✓ Lower rates of overall adverse events without post-procedure pancreatitis, higher rate of stent patency with a less intervention, and more preserved quality of life were observed with EUS-BD.
- ✓ EUS-BD may be a good, safe, and promising treatment modality for the first-line palliation of unresectable malignant distal biliary obstruction.

REFERENCES

1. Speer AG, Cotton PB, Russell RC, et al. Randomised trial of endoscopic versus percutaneous stent insertion in malignant obstructive jaundice. Lancet. 1987;2:57–62.
2. Moss AC, Morris E, Mac Mathuna P. Palliative biliary stents for obstructing pancreatic carcinoma. Cochrane Database Syst Rev. 2006;19:CD004200.
3. Inamdar S, Slattery E, Bhalla R, et al. Comparison of adverse events for endoscopic vs percutaneous biliary drainage in the treatment of malignant biliary tract obstruction in an inpatient national cohort. JAMA Oncol. 2016;2:112–7.
4. Dhir V, Itoi T, Khashab MA, et al. Multicenter comparative evaluation of endoscopic placement of expandable metal stents for malignant distal common bile duct obstruction by ERCP or EUS-guided approach. Gastrointest Endosc. 2015;81:913–23.
5. Isayama H, Kawabe T, Nakai Y, et al. Cholecystitis after metallic stent placement in patients with malignant distal biliary obstruction. Clin Gastroenterol Hepatol. 2006;4:1148–53.
6. Lee JH, Krishna SG, Singh A, et al. Comparison of the utility of covered metal stents versus uncovered metal stents in the management of malignant biliary strictures in 749 patients. Gastrointest Endosc. 2013;78:312–24.
7. Kawakubo K, Kawakami H, Kuwatani M, et al. Endoscopic ultrasound-guided choledochoduodenostomy vs. transpapillary stenting for distal biliary obstruction. Endoscopy. 2016;48:164–9.
8. Tol JA, van Hooft JE, Timmer R, et al. Metal or plastic stents for preoperative biliary drainage in resectable pancreatic cancer. Gut. 2016;65:1981–7.
9. Wang K, Zhu J, Xing L, et al. Assessment of efficacy and safety of EUS-guided biliary drainage: a systematic review. Gastrointest Endosc. 2016;83:1218–27.
10. Giovannini M, Moutardier V, Pesenti C, et al. Endoscopic ultrasound-guided bilioduodenal anastomosis: a new technique for biliary drainage. Endoscopy. 2001;33:898–900.
11. Khashab MA, Van der Merwe S, Kunda R, et al. Prospective international multicenter study on endoscopic ultrasound-guided biliary drainage for patients with malignant distal biliary obstruction after failed endoscopic retrograde cholangiopancreatography. Endosc Int Open. 2016;4:E487–96.
12. Lee TH, Choi JH, Park do H, et al. Similar efficacies of endoscopic ultrasound-guided transmural and percutaneous drainage for malignant distal biliary obstruction. Clin Gastroenterol Hepatol. 2016;14:1011–9.
13. Park DH, Koo JE, Oh J, et al. EUS-guided biliary drainage with one-step placement of a fully covered metal stent for malignant biliary obstruction: a prospective feasibility study. Am J Gastroenterol. 2009;104:2168–74.
14. Cotton PB, Eisen GM, Aabakken L, et al. A lexicon for endoscopic adverse events: report of an ASGE workshop. Gastrointest Endosc. 2010;71:446–54.
15. Ohtsubo K, Watanabe H, Mouri H, et al. Endoscopic findings of upper gastrointestinal lesions in patients with pancreatic cancer. JOP. 2012;13:420–6.
16. Elmunzer BJ, Scheiman JM, Lehman GA, et al. A randomized trial of rectal indomethacin to prevent post-ERCP pancreatitis. N Engl J Med. 2012;366:1414–22.
17. Park do H, Lee TH, Paik WH, et al. Feasibility and safety of a novel dedicated device for one-step EUS-guided biliary drainage: A randomized trial. J Gastroenterol Hepatol. 2015;30:1461–6.
18. Park DH, Jeong SU, Lee BU, et al. Prospective evaluation of a treatment algorithm with enhanced guidewire manipulation protocol for EUS-guided biliary drainage after failed ERCP (with video). Gastrointest Endosc. 2013;78:91–101.
19. Khan MA, Akbar A, Baron TH, et al. Endoscopic ultrasound-guided biliary drainage: a systematic review and meta-analysis. Dig Dis Sci. 2016;61:684–703.
20. Smith AC, Dowsett JF, Russell RC, et al. Randomised trial of endoscopic stenting versus surgical bypass in malignant low bileduct obstruction. Lancet. 1994;344:1655–60.
21. Matsubayashi H, Fukutomi A, Kanemoto H, et al. Risk of pancreatitis after endoscopic retrograde cholangiopancreatography and endoscopic biliary drainage. HPB. 2009;11:222–8.
22. Maydeo A, Kwek BE, Bhandari S, et al. Single-operator cholangioscopy-guided laser lithotripsy in patients with difficult biliary and pancreatic ductal stones (with videos). Gastrointest Endosc. 2011;74:1308–14.
23. Uchino R, Isayama H, Tsujino T, et al. Results of the Tokyo trial of prevention of post-ERCP pancreatitis with risperidone-2: a multicenter, randomized, placebo-controlled, double-blind clinical trial. Gastrointest Endosc. 2013;78:842–50.
24. Shah A, Fehmi A, Savides TJ. Increased rates of duodenal obstruction in pancreatic cancer patients receiving modern medical management. Dig Dis Sci. 2014;59:2294–8.
25. Coté GA, Kumar N, Ansstas M, et al. Risk of post-ERCP pancreatitis with placement of self-expandable metallic stents. Gastrointest Endosc. 2010;72:748–54.
26. Lazaraki G, Katsinelos P. Prevention of post ERCP pancreatitis: an overview. Ann Gastroenterol. 2008;21:27–38.
27. Kawakubo K, Isayama H, Nakai Y, et al. Risk factors for pancreatitis following transpapillary self-expandable metal stent placement. Surg Endosc. 2012;26:771–6.
28. Tol JA, van Hooft JE, Timmer R, et al. Metal or plastic stents for preoperative biliary drainage in resectable pancreatic cancer. Gut. 2016;65:1981–7.
29. Park DH, Jang JW, Lee SS, et al. EUS-guided biliary drainage with transluminal stenting after failed ERCP: predictors of adverse events and long-term results. Gastrointest Endosc. 2011;74:1276–84.
30. Ma KW, Chan ACY, She WH, et al. Efficacy of endoscopic self-expandable metal stent placement versus surgical bypass for inoperable pancreatic cancer-related malignant biliary obstruction: a propensity score-matched analysis. Surg Endosc. 2018;32:971–6.
31. Kitano M, Yamashita Y, Tanaka K, et al. Covered self-expandable metal stents with an anti-migration system improve patency duration without increased complications compared with uncovered stents for distal biliary obstruction caused by pancreatic carcinoma: a randomized multicenter trial. Am J Gastroenterol. 2013;108:1713–22.
32. Vila JJ, Perez-Miranda M, Vazquez-Sequeiros E, et al. Initial experience with EUS-guided cholangiopancreatography for biliary and pancreatic duct drainage: a Spanish national survey. Gastrointest Endosc. 2012;76:1133–41.
33. Paik WH, Lee NK, Nakai Y, et al. Conversion of external percutaneous transhepatic biliary drainage to endoscopic ultrasound-guided hepaticogastrostomy after failed standard internal stenting for malignant biliary obstruction. Endoscopy. 2017;49:544–8.
34. Hara K, Yamao K, Mizuno N, et al. Endoscopic ultrasonography-guided biliary drainage: who, when, which, and how? World J Gastroenterol. 2016;22:1297–303.
35. Hara K, Yamao K, Niwa Y, et al. Prospective clinical study of EUS-guided choledochoduodenostomy for malignant lower biliary tract obstruction. Am J Gastroenterol. 2011;106:1239–45.