Published online: 2019-11-11

Endoscopic ultrasound-guided biliary drainage for distal malignant obstruction: a systematic review and meta-analysis of randomized trials

OPEN ACCESS

Authors
Corey S. Miller, Alan N. Barkun, Myriam Martel, Yen-I Chen

Institution
Division of Gastroenterology and Hepatology, McGill University Health Center, McGill University, Montréal, Quebec, Canada

submitted 25.4.2019
accepted after revision 29.7.2019

Bibliography
DOI https://doi.org/10.1055/a-0998-8129 |
Endoscopy International Open 2019; 07: E1563–E1573

eISSN 2196-9736

Corresponding author
Dr. Yen-I Chen, Division of Gastroenterology and Hepatology, McGill University Health Center, 1001 Decarie Blvd, Montréal, QC H4A 3J, Canada
Fax: +1-514-938-7050
yen-I.chen@mcgill.ca

Appendices
Online content viewable at:
https://doi.org/10.1055/a-0998-8129

ABSTRACT

Background and study aims Endoscopic ultrasound (EUS)-guided biliary drainage (BD) is increasingly used for distal malignant biliary obstruction, yet its safety and efficacy compared to endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic biliary drainage (PTBD) remain unclear. We performed a meta-analysis to improve our understanding of the role of EUS-BD in this patient population.

Methods We searched Embase, MEDLINE, CENTRAL, and ISI Web of Knowledge through September 2018 for randomized controlled trials (RCTs) comparing EUS-BD to ERCP-BD or PTBD as treatment of distal malignant biliary obstruction. Risk ratios (RRs) with 95 % confidence intervals (CIs) were combined using random effects models. The primary outcome was risk of stent/catheter dysfunction requiring reintervention.

Results Of six trials identified, three (n = 222) compared EUS-BD to ERCP-BD for first-line therapy; three others (n = 132) evaluated EUS-BD versus PTBD after failed ERCP-BD. EUS-BD was associated with a decreased risk of stent/catheter dysfunction overall (RR, 0.39; 95 %CI 0.27 – 0.57) and in planned subgroup analysis when compared to ERCP (RR, 0.41; 95 %CI 0.23 – 0.74) or PTBD (RR, 0.37, 95 %CI 0.22 – 0.61). Compared to ERCP, EUS was associated with a decreased risk of post-procedure pancreatitis (RR, 0.12; 95 % CI 0.01 – 0.97). No differences were noted in technical or clinical success.

Conclusions In a meta-analysis of randomized trials comparing EUS-BD to conventional biliary drainage modalities, no difference in technical or clinical success was observed. Importantly, EUS-BD was associated with decreased risks of stent/catheter dysfunction when compared to both PTBD and ERCP, and decreased post-procedure pancreatitis when compared to ERCP, suggesting the potential role for EUS-BD as an alternative first-line therapy in distal malignant biliary obstruction.

Introduction

Malignant biliary obstruction is a common complication of pancreatic cancer, often requiring decompression for symptomatic relief of jaundice and to allow for safe administration of chemotherapy [1]. Transpapillary stenting via endoscopic retrograde cholangiopancreatography (ERCP) is the recommended modality for decompression [2]; however, it is associated with significant adverse events including post-ERCP pancreatitis in 5 – 15 % of patients [3, 4]. Furthermore, recurrent obstruction due to delayed stent dysfunction occurs in up to 41 % [5] and is associated with considerable morbidity in this frail patient population while also representing a significant cost burden to the health care system [6].

Endoscopic ultrasound (EUS)-guided biliary drainage (BD), first described by Giovannini et al. in 2001 [7], is an increasingly

popular technique which creates a trans-duodenal (choledochoduodenostomy) or trans-gastric (hepatogastrostomy) bypass to the bile duct. In addition to its high technical and clinical success rate when performed in expert centers [8], this modality obviates the need for manipulation at the level of the papilla and bypasses the tumor site, which may decrease the risk of pancreatitis and delayed stent dysfunction from tumor tissue stent ingrowth or overgrowth. When compared to percutaneous transhepatic biliary drainage (PTBD) as second-line modality after failed ERCP in a recent meta-analysis [9], EUS-BD was associated with a decreased risk of reintervention and procedure-related adverse events, while demonstrating better clinical success. Only recently have the first randomized controlled trials (RCTs) been published comparing EUS-BD to ERCP as first-line therapy [10 – 12]; however, small sample sizes limit comparisons of critical outcomes. Previously reported systematic reviews evaluating EUS-BD [9, 13] are limited by mostly retrospective uncontrolled data; moreover, there are currently no meta-analyses comparing EUS-BD to first-line ERCP. We therefore conducted a systematic review and meta-analysis of RCTs to assess the efficacy and safety of EUS-BD compared to either PTBD or ERCP for decompression of distal malignant biliary obstruction.

Methods

This study was performed in accordance with the PRISMA statement for reporting systematic reviews and meta-analyses of RCTs [14].

Search strategy

Systematic searches were performed through September 2018 using MEDLINE, EMBASE, Cochrane, and ISI Web of knowledge. A highly sensitive search strategy was used to identify reports of RCTs with a combination of Medical Subject Heading terms and text words related to EUS and pancreatic cancer or common bile duct diseases (**Appendix 1**). Recursive searches, cross-referencing, and hand-searches were performed.

Study selection

All RCTs were included, both fully published and in abstract form, that compared EUS-BD to either PTBD or ERCP for decompression of distal malignant biliary obstruction. Trials were excluded if they included non-human subjects or were reported in neither English nor French. The eligibility of the studies was assessed independently by two investigators (CSM and MM), and if discrepancies were encountered, they were resolved by a third assessor (YC).

Data extraction and validity assessment

Data were extracted from included studies in a predetermined data sheet by one investigator and verified by a second. Extracted data included study information, comparator intervention, baseline characteristics, and outcome events. The Jadad score and Cochrane risk of bias tool were used to grade the quality of studies and to assess for potential bias, respectively.

Choice of outcomes

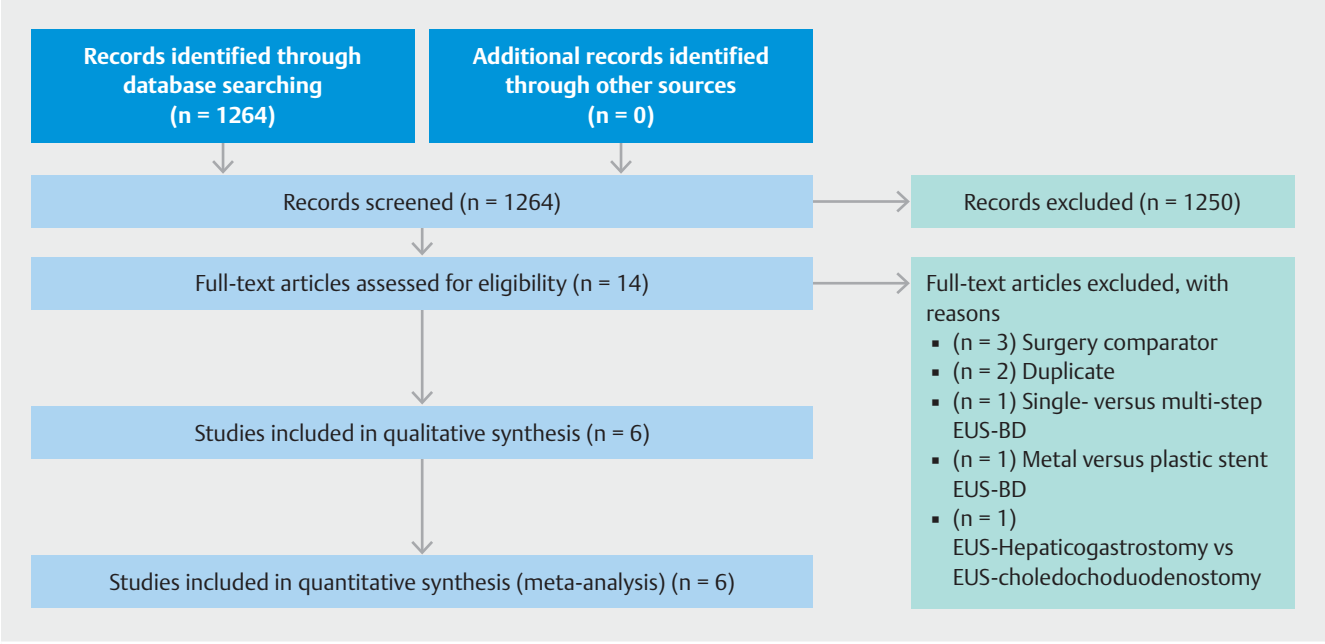
The primary outcome was risk of stent or catheter dysfunction requiring biliary reintervention, defined as the need for any unscheduled endoscopic, interventional or surgical procedure to improve biliary drainage after the index drainage. Secondary outcomes included technical success, clinical success, procedure time, adverse events, post-procedure pancreatitis, tumor tissue stent in/overgrowth, stent clogging, and stent migration. Clinical success was defined as a 50 – 75 % reduction in serum bilirubin within 1 – 4 weeks post-drainage. Adverse events were defined according to the ASGE report [15] or the Common Terminology Criteria for Adverse Events [16]. Post-procedure pancreatitis was generally defined as typical abdominal pain post-procedure with an elevated amylase or lipase of greater than three times the upper limit of normal [15].

Addressing clinical heterogeneity

Qualitative comparisons were performed to assess the heterogeneity of patient populations, interventions, and outcomes across studies, guiding possible subgroup analyses. A priori subgroup analyses by comparator were performed. Sensitivity analyses were performed according to full publication status of trials. Post hoc sensitivity analyses were performed excluding a trial that used a stent apparatus available only in South Korea [11]. The identification and handling of statistical heterogeneity are described below.

Statistical analysis

For each outcome and in every comparison, effect sizes were calculated with risk ratios (RR) for categorical variables. Random effects models were applied to all comparisons to determine corresponding overall effect sizes and their confidence intervals using the DerSimonian and Laird method [17]. If no heterogeneity was noted, results from the corresponding fixed effects models using the Mantel–Haenszel method were also reported. The presence of heterogeneity across studies for a given outcome was defined using Chi-squared tests of homogeneity with a 0.10 significance level [18]. The Higgins I^2 statistic [19] was calculated to quantify the proportion of variation in treatment effects attributable to between-study heterogeneity. Values of 25 %, 50 %, and 75 % represent low, moderate, and high heterogeneity, respectively. To identify possible sources of statistical heterogeneity, sensitivity analyses were performed, excluding studies one by one. A continuity correction was added to each trial with zero events using the reciprocal of the opposite treatment arm size to ensure that comparisons with double-zero events did not significantly affect the heterogeneity or P value [20]. For all comparisons, publication bias was evaluated using the Begg adjusted rank correlation test [21] and the Egger regression asymmetry test [22]. Summary statistics were expressed as means and standard deviations. All statistical analyses were done using Meta package in R version 3.2.1 (R Foundation for Statistical Computing, Vienna, Austria, 2008).



▶ **Fig. 1** Flow diagram of study selection. BD, biliary drainage; EUS, endoscopic ultrasound.

Results

Included studies, quality assessment and publication bias

The search yielded 1264 citations (▶ **Fig. 1**). After screening based on title and abstract, 14 articles were reviewed in full. Of these, six trials randomizing 354 patients were included [10 – 12, 23 – 25]. Three trials (n = 222) compared EUS-BD to ERCP-BD for first-line therapy [10 – 12], and three trials (n = 132) compared EUS-BD to PTBD after failed ERCP-BD [23 – 25]. One of the latter was reported only in abstract form [25]. In terms of EUS-BD technique, all studies specified the use of self-expanding metal stents, with the exception of one study [25] which did not specify this. Three trials used only choledochoduodenostomy [10, 12, 23], two further included hepatogastrostomy [11, 24], and one included even antegrade transpapillary stenting [25]. ▶ **Table 1** summarizes the studies included.

The modified Jadad quality scores ranged from 1 to 3 points out of a possible score of 5, with a mean of 2.5 ± 0.8. The Cochrane risk of bias tool revealed a low potential for selection bias across studies (**Appendix 2**). All trials were single-blinded; however, double-blinding in this clinical context is not feasible. No statistical heterogeneity was noted with the exception of the stent clogging analysis ($P = 0.07$) (▶ **Table 2**). Publication bias was noted for the primary outcome analysis (Begg, $P < 0.01$).

Primary and secondary outcomes

In the primary outcome analysis, EUS-BD was associated with a decreased risk of stent/catheter dysfunction requiring reintervention (RR, 0.39; 95 %CI 0.27 – 0.57) (▶ **Fig. 2**, ▶ **Table 2**). Prespecified subgroup analysis by comparator demonstrated a decreased risk of stent/catheter dysfunction associated with EUS-BD compared to ERCP as primary therapy (RR, 0.41; 95 %CI 0.23 – 0.74) as well as compared to PTBD as second-line therapy after failed ERCP (RR, 0.37, 95 %CI 0.22 – 0.61).

EUS-BD was associated with a decreased risk of tumor in/overgrowth overall (RR, 0.18; 95 %CI 0.06 – 0.62) and compared to ERCP (RR, 0.18; 95 %CI 0.05 – 0.69), but no statistically significant difference was observed compared to PTBD alone in subgroup analysis (▶ **Fig. 3**, ▶ **Table 2**). Pooled estimates for stent clogging and migration were inconclusive due to wide confidence intervals. Although no difference was observed overall, compared to ERCP, EUS-BD was associated with a decreased risk of post-procedure pancreatitis (RR, 0.12; 95 %CI 0.01 – 0.97) (▶ **Fig. 3**). A decreased risk of adverse events was associated with EUS-BD both in the overall analysis (RR, 0.56; 95 %CI 0.34 – 0.94) and when solely compared to PTBD (RR, 0.59; 95 % CI 0.39 – 0.87); but there was no difference compared to ERCP (▶ **Fig. 4**). There were no differences observed in technical (▶ **Fig. 4**) or clinical success and there was no difference in procedure time compared to ERCP.

Sensitivity analyses

Results from sensitivity analyses were concordant with the main analysis (▶ **Table 2**). In a post hoc analysis removing Paik et al. [11] from the ERCP-BD comparator subgroup, there was no significant difference found for risk of stent/catheter dysfunction, tumor in/overgrowth or post-procedure pancreatitis.

▶ **Table 1** Characteristics of studies included in the systematic review.

Authors	Year	Country	Groups	ITT Patients, n	Female, %	Mean age, y	Median follow-up, d	Mean, CBD, mm
Artifon et al. [23]	2012	Brazil	EUS-BD	13	31	63.4	80[1]	13.7
			PTBD	12	33	71.0	75[1]	11.9
Bang et al. [10]	2018	USA	EUS-BD	33	48	69.4	190	13.3
			ERCP-BD	34	32	69.2	174	12.5
Giovannini et al. [25]	2015	France	EUS-BD	20	10	NR	NR	NR
			PTBD	21	52			
Lee et al. [24]	2016	Korea	EUS-BD	34	24	66.5	≥3 mo	11.2
			PTBD	32	25	68.4	≥3 mo	12.6
Paik et al. [11,38]	2018	Korea	EUS-BD	64	36	64.8	144	15.7
			ERCP-BD	61	57	68.4	165	15.0
Park et al. [12]	2018	Korea	EUS-BD	15	33	66.8	95	NR
			ERCP-BD	15	40	65.4	147	

BD, biliary drainage; CBD, common bile duct; ERCP, endoscopic retrograde cholangiopancreatography; ITT, intention-to-treat; NR, not reported, PTBD, percutaneous transhepatic biliary drainage.
[1] Mean value.

Discussion

Although ERCP as primary therapy with PTBD as second line have been the standard of care for decompression of distal malignant biliary obstruction for several decades, EUS-BD has emerged as a viable alternative with several potential advantages. Our meta-analysis is the first, to our knowledge, to compare EUS-BD to ERCP for primary treatment and the first meta-analysis of RCTs to evaluate the safety and efficacy of EUS-BD overall. Overall, compared to conventional modalities, EUS-BD was associated with decreased stent/catheter dysfunction requiring reintervention (RR, 0.39; 95 %CI 0.27 – 0.57), tumor in/overgrowth (RR, 0.18; 95 %CI 0.06 – 0.62), and adverse events (RR, 0.56; 95 %CI 0.34 – 0.94) with comparable technical (RR, 1.00; 95 %CI 0.95 – 1.06) and clinical success (RR, 1.02; 95 %CI 0.95 – 1.09). Our subgroup findings are consistent with previous data [9] demonstrating that EUS-BD outperforms PTBD as a salvage approach after failed ERCP with decreased risk of stent or catheter dysfunction requiring reintervention (RR, 0.37, 95 %CI 0.22 – 0.61) and adverse events (RR, 0.59; 95 %CI 0.39 – 0.87). Our data further suggest that EUS-BD is favorable over ERCP as the primary modality for distal malignant biliary obstruction in terms of risks of stent dysfunction (RR, 0.41; 95 %CI 0.23 – 0.74), tumor in/overgrowth (RR, 0.18; 95 %CI 0.05 – 0.69), and post-procedure pancreatitis (RR, 0.12; 95 %CI 0.01 – 0.97), while comparable in terms of safety as represented by adverse events (RR, 0.67; 95 %CI 0.16 – 2.79).

The decreased risk of stent dysfunction requiring reintervention favoring EUS-BD over ERCP or PTBD is of great clinical significance not only because of the diminished morbidity in this often-frail patient population, but also because of the potential impact on oncological outcomes. For patients with metastatic pancreatic cancer with a good performance status, there is a clear survival benefit to FOLFIRINOX therapy [26], which would be necessarily delayed by the need for reintervention. Furthermore, even among resectable patients, in whom a recent trial demonstrated an unprecedented median survival of 54.4 months after adjuvant FOLFIRINOX [27], there may be a benefit to neoadjuvant chemotherapy administration. It has been suggested that preoperative chemotherapy may improve surgical outcomes, treat micrometastasis, and identify those whose disease will inevitably progress, all while patients are less likely to suffer serious side effects [28]. Indeed, a meta-analysis of 5520 patients with non-metastatic pancreatic adenocarcinoma demonstrated an impressive 85 % R0 resection rate (no residual tumor) among all patients who underwent resection after neoadjuvant therapy [29]. Thus, there is currently a push towards neoadjuvant therapy for all resectable pancreatic cancer and not only for borderline resectable disease needing downstaging. Optimal biliary drainage is becoming increasingly crucial as limiting the rate of stent dysfunction may have a significant impact on systemic therapy administration and, ultimately, oncological outcomes. It should be noted that, in the small cohort of patients who underwent resection in the study by Bang et al. [10], EUS-guided choledochoduodenostomy did not seem to impact negatively on surgical outcomes. From a practical efficiency perspective, EUS has the unique ability to achieve decompression and acquire precise tissue diagnosis at the same setting. As the technique of EUS-BD continues to improve along with the introduction of dedicated devices, it may prove to be a preferred drainage modality over ERCP for distal malignant biliary obstruction.

The fear of adverse events and well-described technical challenges with EUS-BD are likely major barriers to the implementa-

▶ **Table 2** Primary and secondary outcomes, subgroup and sensitivity analyses.

	Studies, n	Patients, n	RR (95 %CI)	Heterogeneity		Egger	Beggs
				P value	I^2 (%)		
Primary outcome							
Stent/catheter dysfunction	5	311	0.39 (0.27; 0.57)	0.89	0	*P* = 0.08	*P* < 0.01
▪ Only fully published	5	311	0.39 (0.27; 0.57)	0.89	0		
▪ Continuity correction	5	311	0.39 (0.27; 0.57)	0.93	0		
▪ Fixed effects model	5	311	0.39 (0.27; 0.58)	0.89	0		
▪ Compared to ERCP	3	220	0.41 (0.23; 0.74)	0.76	0		
▪ Excluding Paik et al.	2	95	0.59 (0.16; 2.25)	0.65	0		
▪ Compared to percutaneous	2[1]	39	0.37 (0.22; 0.61)	–	–		
Secondary outcome							
Technical success	6	352	1.00 (0.95; 1.06)	0.60	0	*P* = 0.46	*P* = 0.48
▪ Only fully published	5	211	0.99 (0.94; 1.05)	0.82	0		
▪ Continuity correction	6	352	1.00 (0.95; 1.06)	0.60	0		
▪ Fixed effects model	6	352	1.01 (0.96; 1.07)	0.60	0		
▪ Compared to ERCP	3	220	1.00 (0.93; 1.08)	0.52	0		
▪ Excluding Paik et al.	2	95	0.95 (0.85; 1.07)	0.76	0		
▪ Compared to percutaneous	3	132	1.01 (0.92; 1.11)	0.27	27		
Clinical success	5	311	1.02 (0.95; 1.09)	0.92	0	*P* = 0.73	*P* = 0.40
▪ Only fully published	5	311	1.02 (0.95; 1.09)	0.92	0		
▪ Continuity correction	5	311	1.02 (0.95; 1.09)	0.92	0		
▪ Fixed effects model	5	311	1.01 (0.93; 1.09)	0.92	0		
▪ Compared to ERCP	3	220	1.03 (0.94; 1.12)	0.70	0		
▪ Excluding Paik et al.	2	95	1.05 (0.94; 1.16)	0.61	0		
▪ Compared to percutaneous	2	91	0.99 (0.88; 1.12)	0.82	0		
Procedure duration[2]	2	95	3.73 (–4.10; 11.55)	0.26	23	–	
▪ Only fully published	2	95	3.73 (–4.10; 11.55)	0.26	23		
▪ Continuity correction	2	95	3.73 (–4.10; 11.55)	0.26	23		
▪ Fixed effects model	2	95	2.80 (–2.44; 8.04)	0.26	23		
▪ Compared to ERCP	2	95	2.80 (–2.44; 8.04)	0.26	23		
▪ Excluding Paik et al.	2	95	2.80 (–2.44; 8.04)	0.26	23		
▪ Compared to percutaneous	0						
Adverse events	6	352	0.56 (0.34; 0.94)	0.15	40	*P* = 0.26	*P* = 0.66
▪ Only fully published	5	311	0.55 (0.25; 1.22)	0.16	42		
▪ Continuity correction	5	311	0.50 (0.22; 1.14)	0.25	25		
▪ Fixed effects model	5	311	0.53 (0.30; 0.94)	0.16	42		
▪ Compared to ERCP	3	220	0.67 (0.16; 2.79)	0.06	71		
▪ Excluding Paik et al.	2[1]	95	1.44 (0.51; 4.09)	–	–		
▪ Compared to percutaneous	3	132	0.59 (0.39, 0.87)	0.16	42		

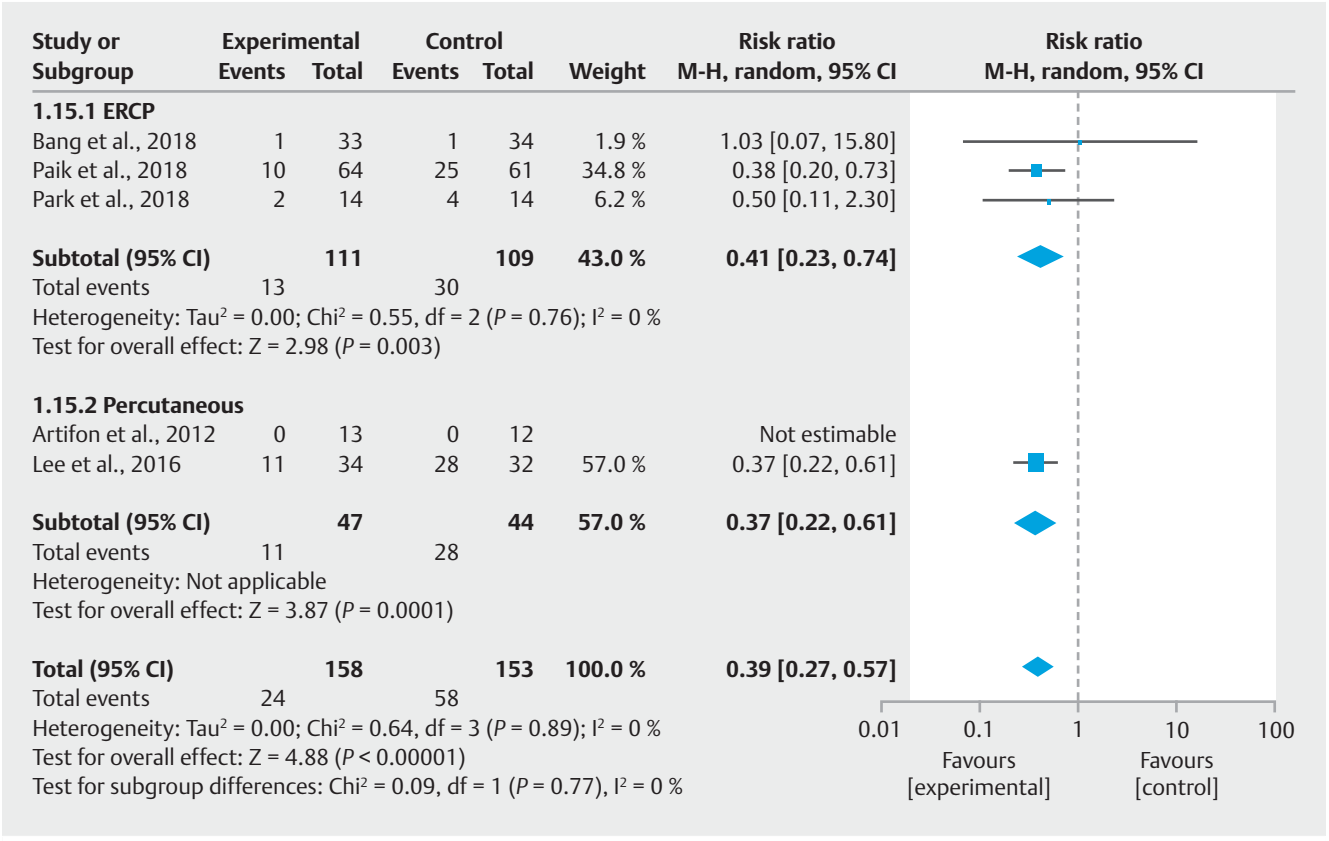
▶ **Table 2** (Continuation)

	Studies, n	Patients, n	RR (95 %CI)	Heterogeneity		Egger	Beggs
				P value	I^2 (%)		
Post-procedure pancreatitis	5	311	0.34 (0.03; 3.65)	0.16	46	*P* = 0.46	*P* = 0.34
▪ Only fully published	5	311	0.34 (0.03; 3.65)	0.16	46		
▪ Continuity correction	5	311	0.43 (0.08; 2.16)	0.34	12		
▪ Fixed effects model	5	311	0.21 (0.05; 0.81)	0.16	46		
▪ Compared to ERCP	3	220	0.12 (0.01; 0.97)	0.35	0		
▪ Excluding Paik et al.	2[1]	95	0.34 (0.01; 8.13)	–	–		
▪ Compared to percutaneous	2[1]	91	2.83 (0.12; 67.01)	–	–		
Tumor in/overgrowth	3	219	0.18 (0.06; 0.62)	0.92	0	*P* = 1.00	*P* = 0.53
▪ Only fully published	3	219	0.18 (0.06; 0.62)	0.92	0		
▪ Continuity correction	3	219	0.18 (0.06; 0.62)	0.92	0		
▪ Fixed effects model	3	219	0.18 (0.05; 0.60)	0.92	0		
▪ Compared to ERCP	2	153	0.18 (0.05; 0.69)	0.69	0		
▪ Excluding Paik et al.	1	28	0.11 (0.01; 1.89)	–	–		
▪ Compared to percutaneous	1	33	0.19 (0.01; 3.78)	–	–		
Stent clogging	3	219	1.20 (0.25; 5.64)	0.07	63	*P* = 1.00	*P* = 0.28
▪ Only fully published	3	219	1.20 (0.25; 5.64)	0.07	63		
▪ Continuity correction	3	219	1.20 (0.25; 5.64)	0.07	63		
▪ Compared to ERCP	2	153	0.96 (0.09; 10.10)	0.11	62		
▪ Excluding Paik et al.	1	28	5.00 (0.26; 95.61)	–	–		
▪ Compared to percutaneous	1	33	2.35 (0.49; 11.28)	–	–		
Stent migration	3	219	1.46 (0.45; 4.74)	0.59	0	*P* = 0.30	*P* = 0.09
▪ Only fully published	3	219	1.46 (0.45; 4.74)	0.59	0		
▪ Continuity correction	3	219	1.46 (0.45; 4.74)	0.59	0		
▪ Fixed effects model	3	219	1.60 (0.52; 4.92)	0.59	0		
▪ Compared to ERCP	2	153	2.78 (0.44; 17.71)	0.62	0		
▪ Excluding Paik et al.	1	28	5.00 (0.26; 95.61)	–	–		
▪ Compared to percutaneous	1	33	0.94 (0.50; 4.33)	–	–		

CI, confidence interval; ERCP, endoscopic retrograde cholangiopancreatography; RR, risk ratio.
[1] Includes one double-zero event study.
[2] Effect estimate given as weighted mean difference in minutes.

tion of this modality in clinical practice [30]. Our meta-analysis, however, demonstrates that EUS-BD is comparable to ERCP and superior to PTBD in terms of minimizing adverse events, at least in the expert hands of operators participating in the RCTs. Regarding the notorious complication of post-procedure pancreatitis, we observe an 88 % relative risk reduction compared to ERCP. In terms of technical feasibility, EUS-BD is indeed labor-intensive and technically difficult at the present time; however, emerging dedicated biliary stents for EUS such as the one-step tapered tip stent available in Korea (DEUS, Standard Sci Tech Inc., Seoul, South Korea) and the electrocautery-enhanced lumen apposing metal stent (LAMS) (Hot AXIOS, Boston Scientific Corporation, Marlborough, Massachusetts, United States) will likely facilitate the procedure and increase its implementation outside of expert centers. In fact, recent retrospective data with EUS-BD using LAMS show excellent technical success, clinical success, and safety with a low rate of stent dysfunction [31]. Our group is currently coordinating a multicenter, prospective, randomized trial to further evaluate EUS-BD with LAMS (clinical trial registration number: NCT03870386).

In terms of the two transmural approaches for EUS-BD, choledochoduodenostomy (CDS) and hepatogastrostomy (HGS),



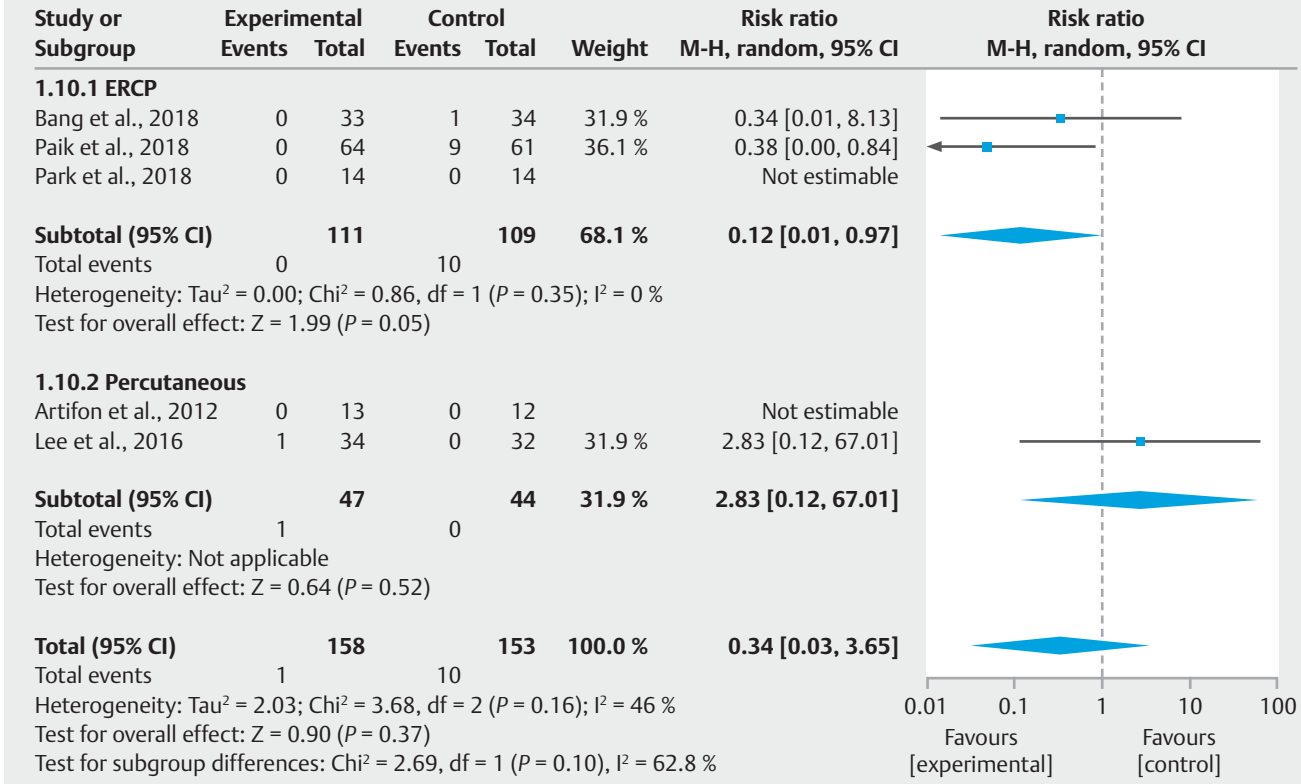
▶ **Fig. 2** Forest plot of stent dysfunction requiring biliary reintervention. CI, confidence interval; ERCP, endoscopic retrograde cholangiopancreatography; M-H, Mantel–Haenszel.

there is no clearly superior technique. Although two retrospective studies suggested a possible advantage in stent patency associated with HGS [32, 33], and one suggested a decreased risk of late adverse events [33], no significant differences in efficacy or safety outcomes were found in a meta-analysis of 10 studies [34]. Indeed, in the only randomized trial to compare the two approaches head-to-head, there were no significant differences found in any outcomes including technical success, clinical success, adverse events, mortality, and quality of life [35]. In our analysis, only two studies reported on outcomes within the individual techniques. One found no difference in clinical success and one reported no differences in several outcomes including reintervention rate, technical success, clinical success, and adverse events. At this point, the decision on which approach to use should be decided based on local experience and patient-specific anatomy considerations.

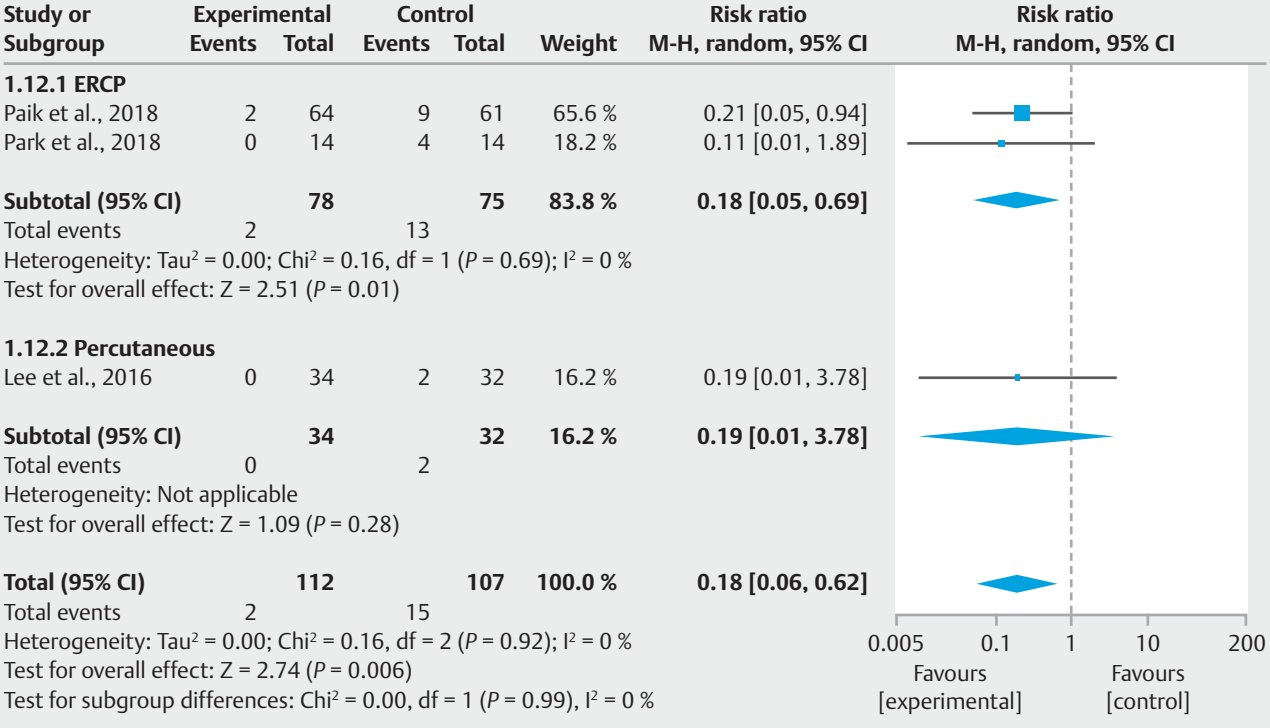
Our study has a few important limitations. The first is the relatively small number of reported RCTs and included patients. To that end, the more conservative random effects model was used to estimate effect sizes. The fact that differences in outcomes were no longer observed with removal of the largest study in a sensitivity analysis of the ERCP comparison subgroup reflects a lack of robustness and our study should be repeated once more randomized data are available. The small number of studies also limits the use of a prediction interval to further ascertain heterogeneity in a random effects model, given that such statistical methods have been shown to be inaccurate and potentially misleading in small meta-analyses [36, 37]. Second, the use of different devices in the individual studies creates clinical heterogeneity. Again, sensitivity analysis was performed removing the study with a dedicated device only available in Korea. Third, the per-patient event rate was frequently not reported in studies; therefore, an overall event rate was used. Finally, the performance of EUS-BD only within expert centers limits generalizability to other settings.

Some key strengths of this study are the inclusion of only randomized data, the lack of statistical heterogeneity, and the novelty in that it is the first meta-analysis to compare EUS-BD to ERCP for the primary treatment of malignant biliary obstruction.

In conclusion, the present systematic review and meta-analysis of RCTs demonstrates that EUS-BD is effective and safe when compared overall to a combination of standard therapies for distal malignant biliary obstruction with decreased stent/catheter dysfunction requiring reintervention, tumor in/overgrowth and adverse events as well as similar technical and clinical success. As second-line therapy after failed ERCP, it is favorable to PTBD with regard to stent/catheter dysfunction and adverse events. Compared to ERCP as primary therapy, EUS-BD is associated with decreased stent dysfunction requiring reintervention, tumor in/overgrowth, and post-procedure pancreatitis, suggesting a promising role as an alternative first-line mod-



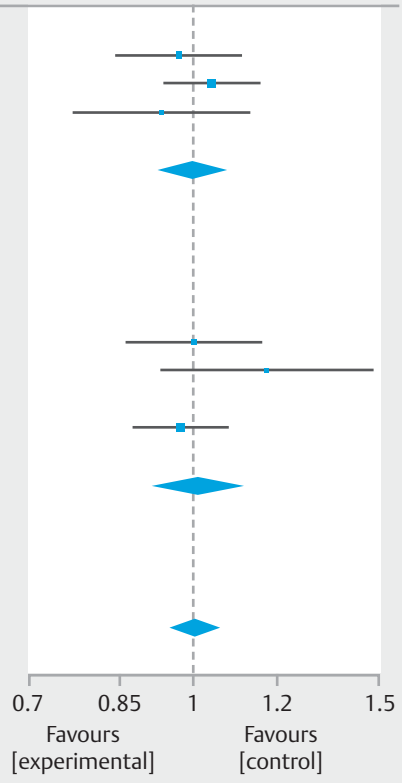
a



b

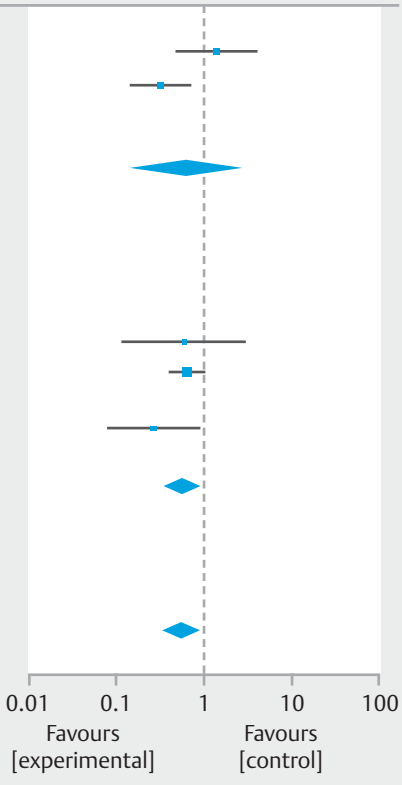
▶ **Fig. 3** Forest plot: **a** post-procedure pancreatitis; **b** tumor in/overgrowth. CI, confidence interval; ERCP, endoscopic retrograde cholangiopancreatography; M-H, Mantel – Haenszel.

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk ratio M-H, random, 95% CI
1.2.1 ERCP						
Bang et al., 2018	30	33	32	34	16.3 %	0.97 [0.84, 1.11]
Paik et al., 2018	60	64	55	61	28.0 %	1.04 [0.94, 1.15]
Park et al., 2018	13	14	14	14	8.2 %	0.93 [0.77, 1.13]
Subtotal (95% CI)		**111**		**109**	**52.2 %**	**1.00 [0.93, 1.08]**
Total events	103		101			
Heterogeneity: Tau² = 0.00; Chi² = 1.31, df = 2 (*P* = 0.52); I² = 0 %						
Test for overall effect: Z = 0.03 (*P* = 0.98)						
1.2.2 Percutaneous						
Artifon et al., 2012	13	13	12	12	13.9 %	1.00 [0.86, 1.16]
Giovanni et al. 2015 – abstract	19	20	17	21	5.7 %	1.17 [0.93, 1.48]
Lee et al., 2016	32	34	31	32	27.9 %	0.97 [0.88, 1.08]
Subtotal (95% CI)		**67**		**65**	**47.5 %**	**1.01 [0.92, 1.11]**
Total events	64		60			
Heterogeneity: Tau² = 0.00; Chi² = 3.65, df = 2 (*P* = 0.27); I² = 24 %						
Test for overall effect: Z = 0.21 (*P* = 0.84)						
Total (95% CI)		**178**		**174**	**100.0 %**	**1.00 [0.95, 1.06]**
Total events	167		161			
Heterogeneity: Tau² = 0.00; Chi² = 3.65, df = 5 (*P* = 0.60); I² = 0 %						
Test for overall effect: Z = 0.02 (*P* = 0.98)						
Test for subgroup differences: Chi² = 0.03, df = 1 (*P* = 0.86), I² = 0 %						



a

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk ratio M-H, random, 95% CI
1.7.1 ERCP						
Bang et al., 2018	7	33	5	34	16.5 %	1.44 [0.51, 4.09]
Paik et al., 2018	7	64	20	61	23.4 %	0.33 [0.15, 0.73]
Park et al., 2018	0	14	0	14		Not estimable
Subtotal (95% CI)		**111**		**109**	**39.9 %**	**0.67 [0.16, 2.79]**
Total events	14		25			
Heterogeneity: Tau² = 0.85; Chi² = 4.84, df = 1 (*P* = 0.03); I² = 79 %						
Test for overall effect: Z = 0.56 (*P* = 0.58)						
1.7.2 Percutaneous						
Artifon et al., 2012	2	13	3	12	8.5 %	0.62 [0.12, 3.07]
Giovanni et al. 2015 – abstract	11	20	18	21	38.0 %	0.64 [0.42, 0.99]
Lee et al., 2016	3	34	10	32	13.6 %	0.28 [0.09, 0.93]
Subtotal (95% CI)		**67**		**65**	**60.1 %**	**0.59 [0.39, 0.87]**
Total events	16		31			
Heterogeneity: Tau² = 0.00; Chi² = 1.95, df = 2 (*P* = 0.38); I² = 0 %						
Test for overall effect: Z = 2.66 (*P* = 0.008)						
Total (95% CI)		**178**		**174**	**100.0 %**	**0.56 [0.34, 0.94]**
Total events	30		56			
Heterogeneity: Tau² = 0.13; Chi² = 6.69, df = 4 (*P* = 0.15); I² = 40 %						
Test for overall effect: Z = 2.21 (*P* = 0.03)						
Test for subgroup differences: Chi² = 0.03, df = 1 (*P* = 0.87), I² = 0 %						



b

▶ **Fig. 4** Forest plot: **a** technical success; **b** adverse events. CI, confidence interval; ERCP, endoscopic retrograde cholangiopancreatography; M-H, Mantel–Haenszel.

ality for the treatment of distal malignant biliary obstruction in centers where the expertise is available. Our results should be validated with the emergence of dedicated EUS therapeutic devices and as more randomized data become available.

Competing interests

Alan N. Barkun is a consultant for Pendopharm Inc., Boston Scientific Inc., Olympus Inc., and Cook Inc. He has also received "at arms-length" grant funding from Cook Inc. Yen-I Chen is a consultant for Boston Scientific Inc. The remaining authors disclose no conflicts.

References

[1] Boulay BR, Birg A. Malignant biliary obstruction: From palliation to treatment. World J Gastrointest Oncol 2016; 8: 498 – 508

[2] Eloubeidi MA, Decker GA, Chandrasekhara V et al. The role of endoscopy in the evaluation and management of patients with solid pancreatic neoplasia. Gastrointest Endosc 2016; 83: 17 – 28

[3] Freeman ML, Nelson DB, Sherman S et al. Complications of endoscopic biliary sphincterotomy. NEJM 1996; 335: 909 – 918

[4] Kochar B, Akshintala VS, Afghani E et al. Incidence, severity, and mortality of post-ERCP pancreatitis: a systematic review by using randomized, controlled trials. Gastrointest Endosc 2015; 81: 143 – 149 e149

[5] Moss AC, Morris E, Mac Mathuna P. Palliative biliary stents for obstructing pancreatic carcinoma. Cochrane Database Syst Rev 2006: CD004200

[6] Barkun AN, Adam V, Martel M et al. Partially covered self-expandable metal stents versus polyethylene stents for malignant biliary obstruction: a cost-effectiveness analysis. Can J Gastroenterol Hepatol 2015; 29: 377 – 383

[7] Giovannini M, Moutardier V, Pesenti C et al. Endoscopic ultrasound-guided bilioduodenal anastomosis: a new technique for biliary drainage. Endoscopy 2001; 33: 898 – 900

[8] 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 – 496

[9] Sharaiha RZ, Khan MA, Kamal F et al. Efficacy and safety of EUS-guided biliary drainage in comparison with percutaneous biliary drainage when ERCP fails: a systematic review and meta-analysis. Gastrointest Endosc 2017; 85: 904 – 914

[10] Bang JY, Navaneethan U, Hasan M et al. Stent placement by EUS or ERCP for primary biliary decompression in pancreatic cancer: a randomized trial (with videos). Gastrointest Endosc 2018; 88: 9 – 17

[11] Paik WH, Lee TH, Park DH et al. EUS-guided biliary drainage versus ERCP for the primary palliation of malignant biliary obstruction: A multicenter randomized clinical trial. Am J Gastroenterol 2018; 113: 987 – 997

[12] Park JK, Woo YS, Noh DH et al. Efficacy of EUS-guided and ERCP-guided biliary drainage for malignant biliary obstruction: prospective randomized controlled study. Gastrointest Endosc 2018; 88: 277 – 282

[13] 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

[14] Moher D, Liberati A, Tetzlaff J et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009; 151: 264 – 269, W64

[15] Cotton PB, Eisen GM, Aabakken L et al. A lexicon for endoscopic adverse events: report of an ASGE workshop. Gastrointest Endosc 2010; 71: 446 – 454

[16] Trotti A, Colevas AD, Setser A et al. CTCAE v3. 0: development of a comprehensive grading system for the adverse effects of cancer treatment. Semin Radiat Oncol 2003; 13: 176 – 181

[17] DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986; 7: 177 – 188

[18] Hardy RJ, Thompson SG. Detecting and describing heterogeneity in meta-analysis. Stat Med 1998; 17: 841 – 856

[19] Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002; 21: 1539 – 1558

[20] Sweeting MJ, Sutton AJ, Lambert PC. What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data Stat Med 2004; 23: 1351 – 1375

[21] Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994; 50: 1088 – 1101

[22] Egger M, Davey Smith G, Schneider M et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315: 629 – 634

[23] Artifon EL, Aparicio D, Paione JB et al. Biliary drainage in patients with unresectable, malignant obstruction where ERCP fails: endoscopic ultrasonography-guided choledochoduodenostomy versus percutaneous drainage. J Clin Gastroenterol 2012; 46: 768 – 774

[24] 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 – 1019 e1013

[25] Giovannini M, Bories E, Napoleon B et al. 855 Multicenter randomized phase II Study: Percutaneous biliary drainage vs EUS guided biliary drainage: Results of the intermediate analysis. Gastrointest Endosc 2015; 81: AB174

[26] Conroy T, Desseigne F, Ychou M et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. NEJM 2011; 364: 1817 – 1825

[27] Conroy T, Hammel P, Hebbar M et al. FOLFIRINOX or gemcitabine as adjuvant therapy for pancreatic cancer. NEJM 2018; 379: 2395 – 2406

[28] Kindler HL. A glimmer of hope for pancreatic cancer. NEJM 2018; 379: 2463 – 2464

[29] Dhir M, Malhotra GK, Sohal DPS et al. Neoadjuvant treatment of pancreatic adenocarcinoma: a systematic review and meta-analysis of 5520 patients. World J Surg Oncol 2017; 15: 183

[30] Varadarajulu S, Hawes RH. EUS-guided biliary drainage: taxing and not ready. Gastrointest Endosc 2013; 78: 742 – 743

[31] Kunda R, Perez-Miranda M, Will U et al. EUS-guided choledochoduodenostomy for malignant distal biliary obstruction using a lumen-apposing fully covered metal stent after failed ERCP. Surg Endosc 2016; 30: 5002 – 5008

[32] Khashab MA, Messallam AA, Penas I et al. International multicenter comparative trial of transluminal EUS-guided biliary drainage via hepatogastrostomy vs. choledochoduodenostomy approaches. Endosc Int Open 2016; 4: E175 – 181

[33] Ogura T, Chiba Y, Masuda D et al. Comparison of the clinical impact of endoscopic ultrasound-guided choledochoduodenostomy and hepaticogastrostomy for bile duct obstruction with duodenal obstruction. Endoscopy 2016; 48: 156 – 163

[34] 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 – 1227

[35] Artifon EL, Marson FP, Gaidhane M et al. Hepaticogastrostomy or choledochoduodenostomy for distal malignant biliary obstruction

after failed ERCP: Is there any difference?. Gastrointest Endosc 2015; 81: 950 – 959

[36] Higgins JP, Thompson SG, Spiegelhalter DJ. A re-evaluation of random-effects meta-analysis. J R Stat Soc Ser A Stat Soc 2009; 172: 137 – 159

[37] Nagashima K, Noma H, Furukawa TA. Prediction intervals for random-effects meta-analysis: A confidence distribution approach. Stat Methods Med Res 2019; 28: 1689 – 1702

[38] Paik WH, Lee TH, Park DH et al. Correction: EUS-guided biliary drainage versus ERCP for the primary palliation of malignant biliary obstruction: A multicenter randomized clinical trial. Am J Gastroenterol 2018; 113: 1566