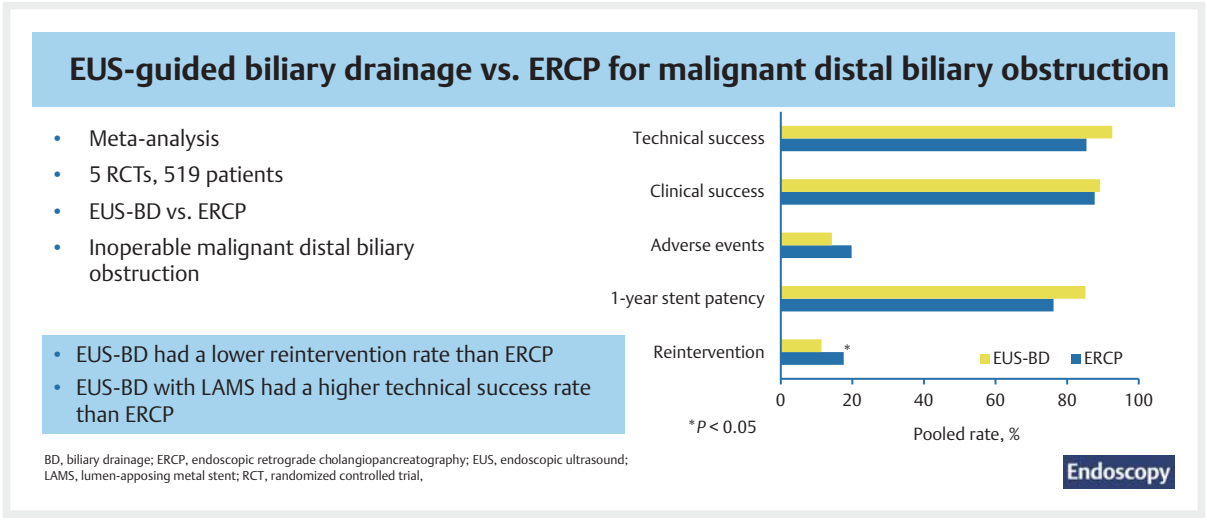
Endoscopic ultrasound- versus ERCP-guided primary drainage of inoperable malignant distal biliary obstruction: systematic review and meta-analysis of randomized controlled trials

GRAPHICAL ABSTRACT



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submitted 18.1.2024
accepted after revision 6.6.2024
accepted manuscript online 6.6.2024
published online 2024

Bibliography
Endoscopy
DOI 10.1055/a-2340-0697
ISSN 0013-726X

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

Supplementary Material
Supplementary Material is available at https://doi.org/10.1055/a-2340-0697

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ABSTRACT

Background We assessed efficacy and safety of endoscopic ultrasound-guided biliary drainage (EUS-BD) vs. endoscopic retrograde cholangiopancreatography (ERCP) as first-line intervention in malignant distal biliary obstruction (MDBO).

Methods PubMed/Medline, Embase, and Cochrane databases were searched until 01/12/2023 for randomized controlled trials of EUS-BD vs. ERCP for primary biliary drainage in patients with inoperable MDBO. The primary outcome was technical success. Secondary outcomes were clinical success, adverse events, mean procedure time, 1-year stent patency, and overall survival. Relative risk (RR) with 95 %CI were calculated using a random effects model.

Results Five studies (519 patients) were included. RR (95 % CI) for EUS-BD was 1.06 (0.96 to 1.17; P = 0.27) for pooled technical success and 1.02 (0.97 to 1.08; P = 0.45) for clinical success. 1-year stent patency was similar between the groups (RR 1.15, 0.94 to 1.42; P = 0.17), with lower reintervention with EUS-BD (RR 0.58, 0.37 to 0.9; P = 0.01). The RR was 0.85 (0.49 to 1.46; P = 0.55) for adverse events and 0.97 (0.10 to 0.17; P = 0.98) for severe adverse events. On subgroup analysis, EUS-guided placement of lumen-apposing metal stent (LAMS) outperformed ERCP in terms of technical success (RR 1.17, 1.01 to 1.35; P = 0.03). Procedure time was lower with EUS-BD (standardized mean difference –2.36 minutes [–2.68 to –2.05; P < 0.001]).

Conclusions EUS-BD showed a statistically significant lower reintervention rate than ERCP, but with similar technical success, stent patency, clinical success, and safety. Technical success of EUS-BD with LAMS was better than ERCP.

Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) with stent placement is the gold standard approach for primary drainage in nonsurgical patients with malignant distal biliary obstruction (MDBO) [1].

Percutaneous transhepatic biliary drainage and, more recently, endoscopic ultrasound-guided biliary drainage (EUS-BD) have been demonstrated as conservative "rescue" options in cases of failed or impossible ERCP, especially in patients with metastatic or locally advanced diseases [2]. In the past decade, high quality evidence has been published suggesting that EUS-BD should be preferred over percutaneous transhepatic biliary drainage for MDBO in cases of ERCP failure owing to higher rates of clinical success and a better safety profile [3, 4].

EUS-BD has also been advocated as a possible primary biliary drainage approach for MDBO because of several potential advantages over ERCP, such as reduction of tumor ingrowth, reduction of adverse events, mostly post-ERCP pancreatitis, and improved technical success, especially in cases where difficult ERCP can be anticipated (i. e. tumor invading the papilla or concomitant gastric outlet obstruction). Several studies [5–7] and two meta-analyses [8, 9] have assessed the outcomes of EUS-BD compared with the gold standard approach for primary biliary drainage in MDBO, with conflicting results. In detail, a meta-analysis [8] reported similar performance of ERCP and EUS-BD in terms of technical success rate, clinical success rate, and incidence of adverse events when EUS-BD with self-expandable metal stent (SEMS) placement was taken into account. Therefore, recent guidelines suggest the use of EUS-BD as primary intervention only in cases of unresectable disease in high volume centers [2].

Owing to the pivotal technological innovations represented by the advent of electrocautery-enhanced lumen-apposing metal stent (LAMS) delivery systems, two large randomized controlled trials (RCTs) have been conducted to assess EUS-guided choledochoduodenostomy (EUS-CDS) with LAMS placement compared with ERCP with SEMS placement as the primary approach in locally advanced or metastatic MDBO [10, 11].

The aim of our study was to assess the performance of EUS-BD compared with ERCP as the primary options for biliary drainage for MDBO. The primary objective was to compare the technical success rate of the two procedures, while the comparison of clinical success rate, incidence of adverse events, stent patency, and need for biliary reinterventions were secondary objectives. Finally, a subgroup analysis according to stent type used for EUS-BD (LAMS vs. SEMS) was planned.

Methods

This systematic review and meta-analysis is reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (see **Table 1 s** in the online-only Supplementary material) [12].

Selection criteria

Studies included in this meta-analysis were RCTs that met the following inclusion criteria. 1) Patients: adult patients with MDBO; 2) Intervention: EUS-BD as first-line approach; 3) Comparator: ERCP with SEMS placement; and 4) Outcomes: primary outcome was technical success, and secondary outcomes were clinical success, incidence of adverse events, incidence of severe adverse events, mean procedure time, 1-year stent patency, reintervention rate, and mean overall survival. We excluded: 1) studies conducted with a design other than RCT; 2) studies not reporting the primary outcome; 3) studies reporting outcomes of EUS-BD after failed ERCP.

Search strategy

A search of PubMed/Medline, Embase, and Cochrane bibliographic databases was conducted up until 01/12/2023, with studies limited to the English language and published up until

the end of November 2023. The search was conducted by two authors (A.L., T.K.) independently using the following search string: "("EUS" OR "EUS-guided" OR "Endosonography" [Mesh] OR "Endoscopic ultrasound") AND (Choledocho-duodenostomy OR Lumen apposing metal stent OR Hot Axios OR Spaxus OR Hot-Spaxus) AND (Endoscopic retrograde cholangiopancreatography (ERCP) OR biliary stenting OR metallic biliary stent)" AND (malignant distal biliary obstruction OR MDBO). An additional database search of Google Scholar and a check of the reference lists of all relevant studies on this topic were also conducted. Only randomized, controlled, head-to-head trials were considered. In cases of overlapping publications from the same population, the most recent reference was included.

Quality assessment

Study quality was evaluated using the revised Cochrane risk-of-bias tool for randomized trials (RoB2 tool, version 22 August 2019), reporting domains such as randomization process, assignment to intervention, missing outcome data, measurement of outcome, and selection of the reported result. The RoB2 tool finally categorized RCTs to low ("some concerns") or high risk of bias [13]. Each study was evaluated and classified by three independent investigators (T.K., W.S., G.M.). Discrepancies among reviewers about qualitative and quantitative data collection were infrequent (overall interobserver variation < 10 %) and were resolved through discussion and, if necessary, arbitration by a third reviewer (A.L.).

Data extraction

The following data were collected for each included study: first author's name, year of publication, journal of publication, study population size, cause of distal biliary obstruction; diameter of common bile duct (CBD), tumor size, type of stent used, mean procedure duration, technical success, clinical success, 1-year patency rate, reintervention rate, time to reintervention, incidence and severity of adverse events, procedure-related mortality, overall survival.

Outcome definitions

The primary outcome was technical success, defined as the complete and accurate deployment of either the LAMS or SEMS within the CBD. We defined our primary outcome as technical success because we considered this outcome to be the most important among the many other outcomes that were assessed in our study.

Secondary outcomes were: 1) clinical success, defined as improvement of cholangitis after deployment and/or a decrease in serum total bilirubin by 50 % or a decrease to < 3 mg/dL within 2 weeks; 2) incidence of adverse events (graded according to the American Society for Gastrointestinal Endoscopy lexicon [14]), calculated as the rate of adverse events/number of patients who underwent EUS-BD or ERCP (severe adverse events defined as unplanned admission or prolongation for > 10 nights, intensive care unit admission for > 1 night, surgery for an adverse event, and permanent disability); 3) stent patency, defined as the period until reintervention was required due to cholangitis and jaundice (cases that resulted in death without causing stent occlusion were counted as patent); 4) reintervention, defined as an endoscopic procedure or percutaneous transhepatic biliary drainage performed due to cholangitis and/or jaundice; 5) mean procedure time; 6) mean overall survival. The secondary outcomes were chosen as they were all related to the success of the primary outcome and were monitored to help interpret the results of the primary outcome.

Statistical analysis

Pooled performance of EUS-BD and ERCP were assessed and reported as relative risk (RR) with 95 %CI for dichotomous variables, and as mean difference for continuous variables. Moreover, risk difference analysis was conducted. Meta-analysis was performed using a DerSimonian and Laird random effects model. Heterogeneity was assessed through I^2 tests: $I^2 < 30\,\%$ was considered as a low level of heterogeneity, I^2 of 30 %–60 % as moderate heterogeneity, and $I^2 > 60\,\%$ was interpreted as a high level of heterogeneity. Any potential publication bias was verified through visual assessment of funnel plots and using the Egger's test.

The following subgroup analyses were performed: 1) study population > 100 patients; 2) single-center vs. multicenter studies; 3) publication year (before and after 2020); 4) CBD diameter (< 16 mm or ≥ 16 mm); 5) use of EUS-CDS as the only method for EUS-BD. Despite the small number of included studies, a subgroup analysis was planned according to stent type used for EUS-BD (either LAMS or SEMS). Moreover, despite structuring outcomes as primary and secondary, the statistical analysis does not address multiplicity issues.

Statistical analysis was performed with MedCalc Statistical Software version 20.115 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2022). Two-tailed P value of < 0.05 was considered statistically significant. All authors had access to the study data and reviewed and approved the final manuscript.

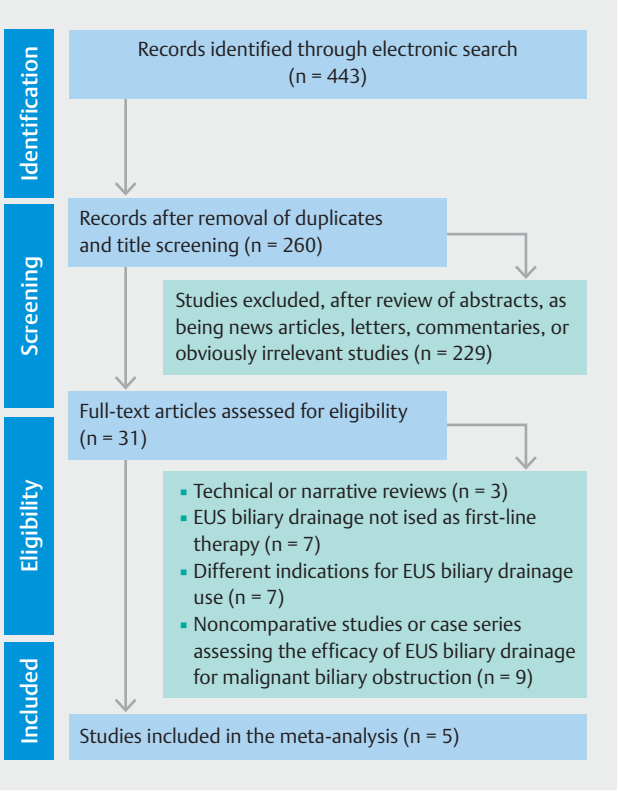
Results

Literature search and study characteristics

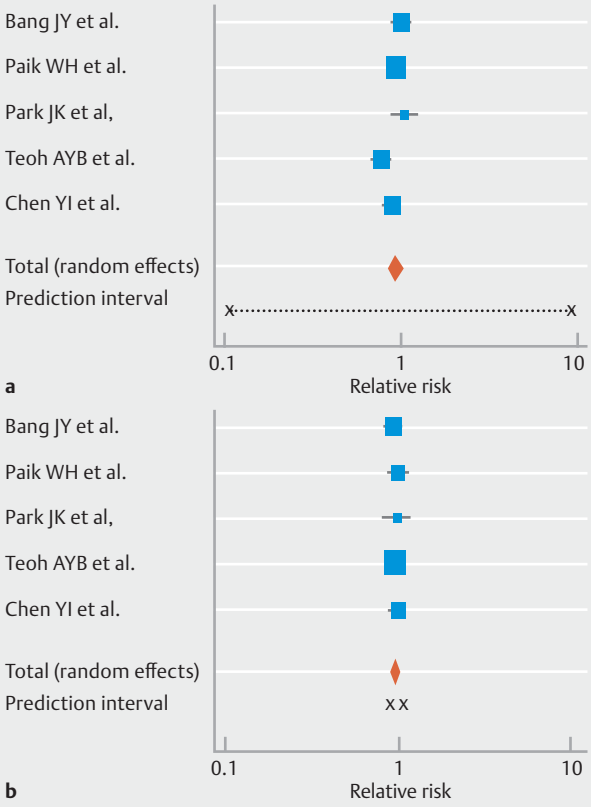
▶ **Fig. 1** summarizes the literature search according to the PRISMA reporting form. Overall, the literature search yielded 443 potentially relevant studies. After preliminary screening of titles and abstracts, 31 publications were fully reviewed. Five RCTs were finally included in the meta-analysis [5–7, 10, 11]. Studies characteristics are summarized in ▶ **Table 1**.

Quality assessment

Table 2 s summarizes the methodological quality evaluation of the studies included. According to the RoB2 tool, all studies included were of high methodological quality except for one study [6], which raised some concerns about the randomization process domain due to the absence of information on the blinding of patients, operators, and outcome assessors.



▶ **Fig. 1** PRISMA flow diagram of the study. EUS, endoscopic ultrasound.



▶ **Fig. 2** Forrest plots of endoscopic ultrasound-guided biliary drainage versus endoscopic retrograde cholangiopancreatography. **a** Technical success rate. **b** Clinical success rate.

Pooled technical success rate

The pooled RR for technical success with EUS-BD compared with ERCP was 1.06 (95 %CI 0.96 to 1.17; $P = 0.27$; prediction interval 0.11–9.82), with risk difference of + 4.58 % (95 %CI −4.8 to 13.9; prediction interval −2.4 to 2.3) (▶ **Fig. 2a**) and high heterogeneity (I^2 64.2 %, 95 %CI 5.86 to 86.40; $P = 0.02$) (▶ **Table 2**). In detail, the technical success rate was 92.6 % (95 %CI 88.8 to 95.4) in the EUS-BD arm (five studies; 263 patients) compared with 85.4 % (95 %CI 80.5 to 89.5) in the ERCP arm (five studies; 256 patients). No publication bias was observed (Egger's test 0.66, 95 %CI −15.87 to 11.69).

Subgroup analysis for the primary outcome (technical success) showed a higher technical success rate with EUS-BD compared with ERCP in large studies (> 100 patients, RR 1.12, 95 %CI 1.00 to 1.26), multicenter studies (RR 1.12, 95 %CI 1.00 to 1.26), studies published after 2020 (RR 1.17, 95 %CI 1.01 to 1.35), and CBD diameter ≥ 16 mm (RR 1.17, 95 %CI 1.01 to 1.35) (**Table 3 s**).

Pooled clinical success rate

The pooled RR for clinical success rate with EUS-BD compared with ERCP was 1.02 (95 %CI 0.97 to 1.08; $P = 0.45$; prediction interval 0.92 to 1.03), with risk difference of + 1.9 % (95 %CI −3.2 to 7; prediction interval −0.07 to 0.03) and no heterogeneity (I^2 0.0 %, 95 %CI 0.0 to 23.1; $P = 0.91$) (▶ **Table 2**, ▶ **Fig. 2b**). In detail, pooled clinical success rate was 89.2 % (95 %CI 84.8 to 92.6) in the EUS-BD treatment arm (five studies; 263 patients) and 87.7 % (95 %CI 83.1 to 91.4) in the ERCP treatment arm (five studies; 256 patients). No publication bias was observed (Egger's test 0.37, 95 %CI −1.78 to 3.56). Of note, the success rates were similar between the two groups because the failed ERCP cases were treated efficiently by EUS-BD and then were considered as ERCP success.

Pooled 1-year stent patency rate

The pooled 1-year stent patency rate was reported in four studies [5, 6, 10, 11] (EUS-BD 230 patients, ERCP 222 patients) and was 85.1 % (95 %CI 79.9 to 89.4) vs. 76.2 % (95 %CI 70.1 to 81.6), respectively (RR 1.15, 95 %CI 0.94 to 1.42; $P = 0.17$; prediction interval 0.05 to 15.13), with risk difference of 10.5 % (95 %CI −3.8 to 24.8; prediction interval −2.89 to 2.68) and a high level of heterogeneity (I^2 80.4 %, 95 %CI 48.3 to 92.6; $P = 0.002$) (▶ **Table 2**, ▶ **Fig. 3a**). No publication bias was observed (Egger's test 0.17, 95 %CI −8.28 to 2.81).

Pooled reintervention rate

The pooled RR for biliary reintervention with EUS-BD compared with ERCP was 0.58 (95 %CI 0.37 to 0.9; $P = 0.01$; prediction interval 0.95 to 3.13) (▶ **Fig. 3b**), with risk difference of −6.5 % (95 %CI −16.6 to 3.5; prediction interval −2.27 to 2.4) and a low level of heterogeneity (I^2 2.15 %, 95 %CI 0.0 to 80.8; $P = 0.39$) (▶ **Table 2**). In detail, the reintervention rate was 11.4 %

▶ **Table 1** Baseline study characteristics.

	Bang et al. [7]	Paik et al. [5]	Park et al. [6]	Teoh et al. [10]	Chen et al. [11]
Journal, year published	Gastrointest Endosc 2018	Am J Gastroenterol 2018	Gastrointest Endosc 2018	Gastroenterology 2023	Gastroenterology 2023
Type of study	RCT	RCT	RCT	RCT	RCT
Design	Single center	Multicenter	Single center	Multicenter	Multicenter
Cause of biliary obstruction	Pancreatic cancer	Pancreatic cancer Cholangiocarcinoma Gallbladder cancer Ampullary cancer	Pancreatic cancer	Pancreatic cancer Cholangiocarcinoma	Pancreatic cancer Cholangiocarcinoma Ampullary cancer
Patients, n	67	125	30	155	144
▪ EUS-BD	33	64	15	79	73
▪ ERCP	34	61	15	76	71
Type of EUS-BD	EUS-CDS	EUS-CDS/EUS-HGS	EUS-CDS	EUS-CDS	EUS-CDS
Stent used for EUS-BD	SEMS	SEMS	SEMS	LAMS	LAMS
CBD width, mean, mm					
▪ EUS-BD	13.3	15.7	NR	15.9	17.7
▪ ERCP	12.5	15	NR	16.8	18
Tumors size, mean, cm					
▪ EUS-BD	3.1	NR	NR	3.6	3.4
▪ ERCP	2.9	NR	NR	3.6	3.5
Procedure time, mean, minutes					
▪ EUS-BD	24.2	6.2	43	10	14
▪ ERCP	22.4	11.7	31	25	23.1
Overall survival, days					
▪ EUS-BD	190	178	188	232.2	118.1
▪ ERCP	174	144	197	202.6	145

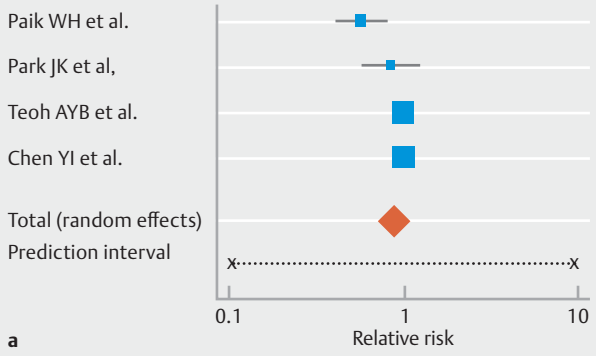
CBD, common bile duct; ERCP, endoscopic retrograde cholangiopancreatography; EUS-BD, endoscopic ultrasound-guided biliary drainage; EUS-CDS, EUS-guided choledochoduodenostomy; EUS-HGS, EUS-guided hepaticogastrostomy; LAMS, lumen-apposing metal stent; NR, not reported; RCT, randomized controlled trial; SEMS, self-expandable metal stent.

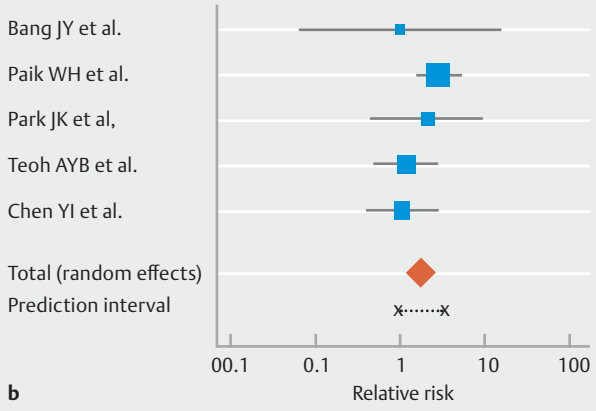
(95 %CI 7.9 to 15.8) in the EUS-BD treatment arm (five studies; 263 patients) and 17.6 % (95 %CI 13.1 to 22.7] in the ERCP treatment arm (five studies; 256 patients). No publication bias was observed (Egger's test 0.45, 95 %CI –4.74 to 2.71).

Safety profile

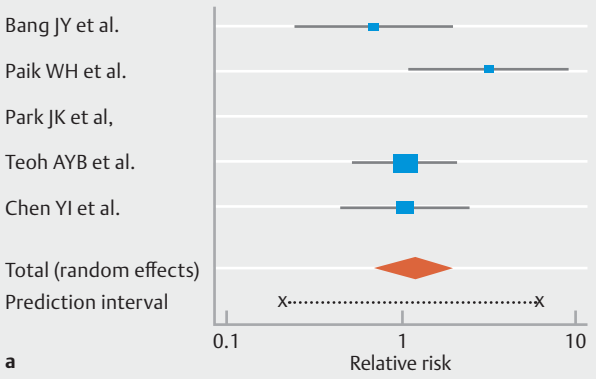
The RR for overall adverse event rate for EUS-BD compared with ERCP was RR 0.85 (95 %CI 0.49 to 1.46; $P = 0.55$; prediction interval 0.22 to 6.33) (▶ **Fig. 4a**), with risk difference of –3.1 % (95 %CI –10.8 to 4.67; prediction interval –1.82 to 1.88) and moderate heterogeneity (I^2 32.6 %, 95 %CI 0.0 to 76; $P = 0.22$) (▶ **Table 2**). Pooled incidence of adverse events was 14.3 % (95 %CI 10.3 to 19.1) in patients who underwent EUS-BD (five studies; 263 patients) and 19.8 % (95 %CI 15.1 to 25.1) in patients who underwent ERCP (five studies; 256 patients). No publication bias was observed (Egger's test 0.64, 95 %CI –14.92 to 19.23).

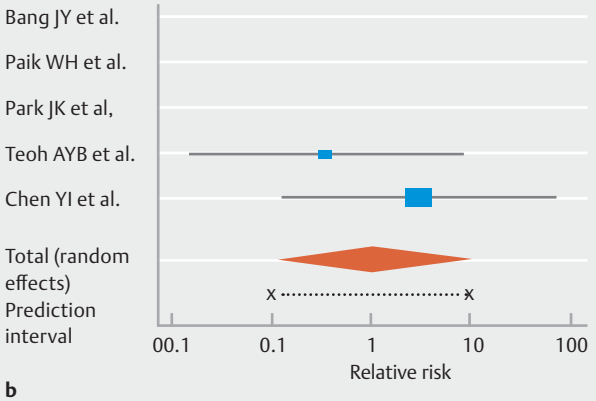
The pooled RR of severe adverse events (five studies) was 0.97 (95 %CI 0.10 to 9.17; $P = 0.98$; prediction interval 0.11 to 9.82) (▶ **Fig. 4b**), with no heterogeneity (I^2 0.0 %, 95 %CI 0.0 to 0.0; $P = 0.34$) (▶ **Table 2**). In detail, patients who underwent EUS-BD (n = 263) had a pooled incidence of severe adverse events of 0.8 % (95 %CI 0.1 to 2.8) compared with patients who underwent ERCP (n = 256) who had a 0.8 % incidence. A potential publication bias was noted (Egger's test < 0.0001). The pooled RR incidence of procedure-related mortality was 0.59 (95 %CI 0.19 to 1.84; $P = 0.36$; prediction interval 0.54 to 5.34) (▶ **Fig. 4c**), with no heterogeneity (I^2 0.0 %, 95 %CI 0.0 to 0.0; $P = 0.69$) (▶ **Table 2**). A potential publication bias was noted (Egger's test < 0.001).

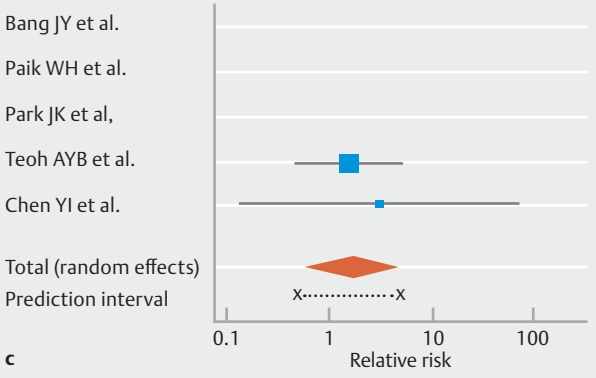




▶ **Fig. 3** Forrest plots of endoscopic ultrasound-guided biliary drainage versus endoscopic retrograde cholangiopancreatography. **a** 1-year stent patency. **b** Reintervention rate.







▶ **Fig. 4** Forrest plots of endoscopic ultrasound-guided biliary drainage versus endoscopic retrograde cholangiopancreatography. **a** Overall adverse event rate. **b** Severe adverse event rate. **c** Fatal adverse event rate.

Procedure time

Mean procedure time (five studies) for EUS-BD compared with ERCP was −2.36 minutes (standardized mean difference) (95 % CI −2.68 to −2.05; $P<0.001$), with high heterogeneity (I^2 99.2 %, 95 %CI 98.9 to 99.4; $P<0.001$) (▶ **Table 2**). No publication bias was observed.

Mean overall survival

Five studies reported results on patients' overall survival. Patients allocated to EUS-BD treatment arms showed a standardized mean difference of 17.5 days (95 %CI 0.37 to 0.78; $P<0.001$) compared with the ERCP arms, with high heterogeneity (I^2 98.4 %, 95 %CI 97.6 to 99.0; $P<0.001$) (▶ **Table 2**). No publication bias was observed.

Subgroup analysis according to type of stent used for EUS-BD

The results of the subgroup analysis are reported in **Table 4 s**. In detail, the technical success rate, clinical success rate, 1-year patency rate, reintervention rate, and adverse event rate were 92.7 %, 89.2 %, 73.0 %, 11.7 %, and 9.9 %, respectively, in the SEMS group, and 93.4 %, 89.5 %, 90.8 %, 10.5 %, and 14.5 %, respectively, in the LAMS group. EUS-BD with LAMS outperformed ERCP in terms of technical success (RR 1.17, 95 %CI 1.01 to 1.35; $P=0.03$), whereas the RR of technical success for the SEMS group compared with ERCP was 1.00 (95 %CI 0.93 to 1.08; $P=0.97$). The three studies conducted with SEMS accounted for a trend toward a higher 1-year stent patency rate compared with ERCP, with RR of 1.48 (95 %CI 0.97 to 2.24; $P=0.06$), whereas it was 1.02 (95 %CI 0.94 to 1.10) for LAMS vs. ERCP ($P=0.47$).

Similarly, the RR reintervention rate was 0.40 (95 %CI 0.23 to 0.71; $P=0.002$) for SEMS and 0.91 (95 %CI 0.48 to 1.73; $P=0.77$) for LAMS compared with ERCP. The RR of adverse events was 0.64 (95 %CI 0.16 to 2.50; $P=0.52$) for SEMS and 0.97 (95 %

▶ **Table 2** Pooled estimates with heterogeneity.

Outcomes[1]	RR/mean difference (95 %CI)[2]	*P*	Heterogeneity, I^2, %	Risk difference, % (95 %CI)	*P*	Heterogeneity, I^2, %
Technical success	1.06 (0.96 to 1.17)	0.27	64.2	+4.58 (–4.8 to 13.9)	0.34	70.8
Clinical success	1.02 (0.97 to 1.08)	0.45	0.0	+1.9 (–3.2 to 7)	0.46	0.0
1-year stent patency	1.15 (0.94 to 1.42)	0.17	80.4	+10.5 (–3.8 to 24.8)	0.15	76.2
Reintervention	0.58 (0.37 to 0.9)	0.01	2.2	–6.5 (–16.6 to 3.5)	0.20	70.5
Adverse events	0.85 (0.49 to 1.46)	0.55	32.6	–3.1 (–10.8 to 4.7)	0.43	33.8
Severe adverse events	0.97 (0.10 to 9.17)	0.98	0.0	–	–	–
Fatal adverse events	0.59 (0.19 to 1.84)	0.36	0.0	–	–	–
Procedure time	–2.36 (–2.68 to –2.05)	<0.001	99.2	–	–	–
Overall survival	17.5 (0.37 to 0.78)	<0.001	98.4	–	–	–

EUS-BD, endoscopic ultrasound-guided biliary drainage; ERCP, endoscopic retrograde cholangiopancreatography; RR, relative risk.
[1]All outcomes included 5 studies of EUS-BD (n = 263) vs. ERCP (n = 256), except for 1-year stent patency (4 studies; EUS-BD [n = 230] vs. ERCP [n = 222]).
[2]RR for technical success, clinical success, 1-year stent patency, reintervention, and adverse event rates; mean difference for mean procedure time (minutes) and overall survival (days).
[1] All outcomes included 5 studies of EUS-BD (n = 263) vs. ERCP (n = 256), except for 1-year stent patency (4 studies; EUS-BD [n = 230] vs. ERCP [n = 222]).
[2] RR for technical success, clinical success, 1-year stent patency, reintervention, and adverse event rates; mean difference for mean procedure time (minutes) and overall survival (days).

CI 0.56 to 1.67; $P = 0.90$) for LAMS. The studies conducted with LAMS accounted for the reduced mean procedure time.

Discussion

This systematic review included five RCTs reporting the performance of EUS-BD compared with ERCP as primary biliary drainage options in 519 patients with inoperable MDBO due to locally advanced or metastatic diseases. The results of the quantitative analysis showed that there was no statistically significant difference between EUS-BD and ERCP groups in terms of technical success, clinical success, and long-term stent patency, with similar adverse event and severe adverse event rates. Conversely, EUS-BD was associated with a lower need for biliary reintervention, and lower mean procedure time of 2.36 minutes compared with the ERCP group.

The results of this meta-analysis present several innovative details, potentially reflecting the technical and technological innovations in the field of EUS intervention. In fact, a previous meta-analysis [8] in this field comparing the pooled performance of EUS-BD with SEMS placement with that of ERCP reported similar technical and clinical success rates, with a trend toward a reduced risk of pancreatitis. Therefore, the positive results reported in the present study could be explained by the inclusion of studies in which both SEMS and LAMS have been used for EUS-BD. Moreover, our meta-analysis provides a higher level of evidence as only high quality RCTs were included, whereas previous meta-analyses also included nonrandomized studies [8, 9].

The main result of the present study was the demonstration that the reintervention rate with EUS-BD was lower than with ERCP (RR 0.58, 95 %CI 0.37 to 0.9; $P = 0.01$); in detail, the reintervention rate was 11.4 % (95 %CI 7.9 to 15.8) in the EUS-BD treatment arm and 17.6 % (95 %CI 13.1 to 22.7) in the ERCP treatment arm. We postulated that this statistically significant difference might be related to the duodenal bulb site of LAMS insertion, which avoids the bile duct and subsequently decreases the risk of stent involvement by the tumor. The subgroup analysis conducted on this outcome suggested that studies conducted after 2020, multicenter studies, and large studies (> 100 patients) accounted for the higher technical success rate observed compared with ERCP. This is probably due to the increased experience with EUS-BD.

This study confirms previous observations of short-term outcomes, such as similar clinical success rates and incidence of adverse events obtained with the two approaches; however, the present meta-analysis also demonstrates long-term outcomes in terms of 1-year stent patency for patients undergoing EUS-BD. There was no statistically significant difference in the 1-year stent patency rate observed in our meta-analysis: 85.1 % (95 %CI 79.9 to 89.4) in the EUS-BD group vs. 76.2 % (95 %CI 70.1 to 81.6) in the ERCP group; this could be attributed to LAMS occlusion by food impaction [10].

Despite the small number of included studies in this systematic review, we planned a subgroup analysis comparing the performance of biliary drainage according to the type of stent used for EUS-BD (LAMS vs. SEMS). This subgroup analysis, reported in **Table 4s**, provides some insightful observations. First, the use of LAMS for EUS-BD allowed more rapid and highly technically effective drainage [10, 11] compared with ERCP, whereas there was no statistically significant difference in technical success with EUS-BD using SEMS compared with ERCP. However, it is interesting to observe that there was a trend for a higher 1-year stent patency rate obtained by the studies conducted with SEMS [5–7]. Finally, it was surprising to observe that only studies conducted with SEMS showed a lower reinter-

vention rate compared with ERCP [5–7], whereas there was no statistically significant difference in the rate among the EUS-LAMS arm compared with ERCP. We speculate that the longer stent length of EUS-SEMS could better protect from tumor ingrowth. Moreover, there was no clinically relevant difference in the rate of adverse events among EUS-LAMS and EUS-SEMS compared with ERCP, thus further confirming the safety profile of EUS-BD. **Table 5 s** demonstrates the rates of procedure-related adverse events, stent dysfunction, and food impaction with EUS-BD. Of note, there was a potential publication bias for severe and fatal adverse events; this finding could be explained by failure to publish data showing negative and unfavorable results in EUS-BD, thus leading to publication bias, which might affect the outcomes assessed.

Our meta-analysis has several limitations. First, all studies enrolled patients with unresectable conditions and dilated CBD; therefore, the results of this meta-analysis of RCTs could be translated only in this specific setting and the technical success rate of EUS-BD will be dramatically lower. Moreover, all studies lacked operator blindness; together with the lack of a clear definition for ERCP failure, this limitation could account for the low (<80 %) technical success rate reported in some studies. Moreover, in several studies, EUS-BD was also the "rescue" strategy for cases of ERCP failure. Despite evidence-based clinical management, this issue represents a methodological weakness. Other limitations are that the cause of MDBO among the included studies was variable, and therefore might affect the study outcomes, and that the study by Paik et al. reported EUS-guided hepaticogastrostomy (EUS-HGS) in 32 patients, whereas the remaining included studies reported EUS-CDS using SEMS. Although this might impact the study conclusion, given the small number undergoing EUS-HGS in our study, and the fact that the rates of clinical success, adverse events, reintervention, stent patency, and overall survival in the study by Paik et al. were similar between EUS-CDS and EUS-HGS, the predicted bias would be marginal.

While the "comparator" is an established and substantially unmodified procedure, EUS-BD changed during the small timeframe (5 years) in which the included studies were published; in detail, the use of LAMS changed both the procedure and the outcomes. We tried to overcome these limitations by planning both a sensitivity analysis including the publication year and a subgroup analysis according to the type of stent used for EUS-BD. Finally, two RCTs had a very small sample size; the assessment of the main outcome in these two studies failed to identify any advantage of EUS-BD over ERCP.

The strength of our meta-analysis was the inclusion of RCTs with well-defined outcomes. Moreover, all included studies were classified with high methodological quality, except for one [6], which raised some minor concerns about the randomization process.

In conclusion, the results of this meta-analysis of RCTs demonstrated that EUS-BD outperformed ERCP for primary biliary drainage of MDBO in terms of lower reintervention rate, with similar technical and clinical success rates, while in the subgroup analysis, technical success of EUS-BD with LAMS was better than that of ERCP. Thus, EUS-BD can be considered a safe and effective option for the treatment of MDBO in patients with dilated CBD. We acknowledge that this consideration should be limited to patients with inoperable disease, due to either tumor extent or patients' underlying conditions. The use of EUS-BD as primary drainage in cases of operable MDBO is not yet supported by strong evidence.

Conflict of Interests

B. Napoléon has delivered a teaching session for Taewoong and is a consultant for Boston Scientific. A. Lisotti, P. Fusaroli, and F. Fumex are consultants for Boston Scientific. A.Y.B. Teoh is a consultant for Boston Scientific, Cook, Taewoong, Microtech, and MI Tech Medical. T. Khoury, W. Sbeit, G. Marasco, L.H. Eusebi, S.M. Chan, A. Shahin, M. Basheer, R. Gincul, S. Leblanc, and J. Jacques declare that they have no conflict of interest.

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