

A meta-analysis and systematic review: Success of endoscopic ultrasound guided biliary stenting in patients with inoperable malignant biliary strictures and a failed ERCP

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Abstract

Background: In patients with inoperable malignant biliary strictures, endoscopic retrograde cholangiopancreatography (ERCP) guided biliary stenting fails in 5% to 10% patients due to difficult anatomy/inability to cannulate the papilla. Recently, endoscopic ultrasound guided biliary drainage (EUS-BD) has been described.

Primary outcomes were to evaluate the biliary drainage success rates with EUS and compare it to percutaneous transhepatic biliary drainage (PTBD). Secondary outcomes were to evaluate overall procedure related complications.

Methods: Study selection criteria: Studies evaluating the efficacy of EUS-BD and comparing EUS-BD versus PTBD in inoperable malignant biliary stricture patients with a failed ERCP were included in this analysis.

Data collection and extraction: Articles were searched in Medline, PubMed, and Ovid journals. Two authors independently searched and extracted data. The study design was written in accordance to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement. Subgroup analyses of prospective studies and EUS-BD versus PTBD were performed.

Statistical method: Pooled proportions were calculated using fixed and random effects model. I^2 statistic was used to assess heterogeneity among studies.

Results: Initial search identified 846 reference articles, of which 124 were selected and reviewed. Sixteen studies (N=528) that met the inclusion criteria were included in this analysis. In the pooled patient population, the percentage of patients that had a successful biliary drainage with EUS was 90.91% (95% CI=88.10–93.38). The proportion of patients that had overall procedure related complications with EUS-PD was 16.46% (95% CI=13.20–20.01). The pooled odds ratio for successful biliary drainage in EUS-PD versus PTBD group was 3.06 (95% CI=1.11–8.43). The risk difference for overall procedure related complications in EUS-PD versus PTBD group was –0.21 (95% CI=–0.35 to –0.06). Relative risk for infectious complications and bile leak in EUS-BD versus PTBD was 0.25 (95% CI=0.07–0.94) and 0.33 (95% CI=0.12–0.87), respectively.

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Key Points: In patients with inoperable malignant biliary strictures, endoscopic retrograde cholangiopancreatography (ERCP) guided biliary stenting is the standard management for palliation; it fails in 5% to 10% patients due to difficult anatomy/inability to cannulate the papilla.

Percutaneous transhepatic biliary drainage (PTBD) or surgical bypass are well-established alternatives in these patients, however associated with increased morbidity, longer length of hospital stay, and higher patient discomfort.

Endoscopic ultrasound guided biliary drainage (EUS-BD) seems to be an excellent management option with higher successful biliary drainage rates and relatively fewer complications in this patient population.

In patients with failed ERCP guided biliary stenting, EUS-BD seems to be significantly superior to percutaneous transhepatic biliary drainage (PTBD) with higher successful drainage rates and fewer complications.

In patients with a known altered biliary tree and duodenal anatomy (likely due to metastasized cancer), ampulla covered with an enteral stent, and diagnostic imaging that shows periampullary malignancy with duodenal invasion, it would be reasonable to consider EUS-BD as the primary biliary drainage approach at the time of initial ERCP.

Operator expertise and availability of specific tools should be a guide in selecting one technique over the other.

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Conclusions: In patients with inoperable malignant biliary strictures who failed an ERCP guided biliary stenting, EUS-BD seems to be an excellent management option and superior to PTBD with higher successful biliary drainage rates and relatively fewer complications.

Abbreviations: ERCP = endoscopic retrograde cholangiopancreatography, ERCP-BS = ERCP guided biliary stenting, EUS-AT = EUS guided antegrade transpapillary biliary stenting, EUS-BD = endoscopic ultrasound guided biliary drainage, EUS-REN = EUS guided Rendezvous technique, EUS-TL = EUS guided transluminal stenting technique, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, PTBD = percutaneous transhepatic biliary drainage, RCT = randomized controlled trial.

Keywords: endoscopic ultrasound guided biliary drainage, inoperable malignant biliary strictures, meta-analysis and systematic review, percutaneous transhepatic biliary drainage

1. Introduction

Malignant biliary obstruction occurs as a result of primary neoplasms of pancreato-biliary tract and other local cancers (gall bladder and liver malignancies) that can compress the biliary tract. These tumors manifest as strictures occluding the biliary tract.^[1] The 5-year survival rate of most of these malignancies is less than 5%.^[2] These malignancies are often unresectable at the time of presentation, thus making palliation with biliary drainage a widely accepted management option.^[3–6] Biliary obstruction causes jaundice, malabsorption, pruritus, anorexia, or cholangitis.^[4,5] In this patient population, nonsurgical drainage has shown to be safe, effective, and is currently the standard of care.^[7–11] Palliation via biliary drainage is most commonly achieved using Endoscopic retrograde cholangiopancreatography guided biliary stenting (ERCP-BS).

ERCP-BS fails in 5% to 10% patients due to difficult anatomy/inability to cannulate the papilla.^[12] Advanced malignancies often infiltrate the gastric outlet/duodenum and biliary tree, thereby creating an altered anatomy and difficulty performing ERCP-BS. Percutaneous transhepatic biliary drainage (PTBD) or surgical bypass are well-established alternatives in these patients, however associated with increased morbidity, longer length of hospital stay, and higher patient discomfort.^[13] A more recent, relatively less invasive alternative after an unsuccessful biliary cannulation is endoscopic ultrasound guided biliary drainage (EUS-BD). EUS provides better visualization of the biliary obstruction and facilitates direct access to the biliary tree via gastrointestinal lumen. This was first described in 2001 by Giovannini et al.^[14] Since then, multiple studies have been published describing the techniques, indications, safety, and efficacy of EUS-BD.

EUS-BD can be achieved using 3 different techniques: Transluminal stenting technique (EUS-TL) usually uses a transgastric (choledochogastrostomy) or transduodenal (choledochoduodenostomy) approach. A stent is placed from the gastrointestinal lumen into the bile duct without accessing the papilla. In Rendezvous technique (EUS-REN) a guide wire is inserted into an extrahepatic or intrahepatic bile duct. The guide wire is then advanced via the papilla, and retrieved using an endoscope for interventions such as stent placement.^[15,16] A less common approach is antegrade transpapillary biliary stenting (EUS-AT).^[17] After transluminal puncture, a guide wire is passed from intrahepatic bile ducts via the papilla into the duodenum. A stent is then placed anterograde fashion across the biliary stricture after appropriate dilatation.

Individual studies have demonstrated high success rates with the use of EUS-BD.^[17–32] Due to the sparse data available, mixed results in individual studies, and smaller size of the individual studies, overall efficacy, and adverse events profile of EUS-BD is currently not clear. There have been only 3 studies that compared EUS PD with PTBD.^[30–32] The results of these studies have never

been pooled so far. In this meta-analysis we aim to pool the evidence for EUS-BD in managing malignant biliary strictures.

2. Methods

2.1. Aims

The aims of this meta-analysis are to pool the evidence for EUS-BD in managing malignant biliary strictures. Primary outcomes were to evaluate the biliary drainage success rates with EUS and compare the drainage success in EUS-BD group versus PTBD group. Secondary outcomes were to evaluate the overall procedure related complications (bleeding, biloma, bile leak, infections, and pancreatitis) in both groups. A subgroup meta-analysis was performed on prospective studies only, evaluating the same variables.

2.2. Study selection criteria

2.2.1. Inclusion criteria. Studies evaluating patients with advanced malignant biliary strictures requiring biliary drainage and at-least 1 failed ERCP-BS. Studies must have included patients that underwent 1 of the 3 variants of EUS-BD. Studies should have evaluated the biliary drainage success rates with EUS-BS and/or PTBD. Studies should have evaluated the procedure related adverse event rates with EUS-BS and/or PTBD. In Khashab et al,^[30] initial EUS-BD was attempted using EUS-REN; EUS-TL was used only in patients who failed EUS-REN.^[33] Before all procedures, patients were administered a prophylactic dose of a second-generation cephalosporin or a fluoroquinolone. Patient with both metal and/or plastic stents were included in this analysis.

2.2.2. Exclusion criteria. Studies that included patients undergoing EUS-BD without a prior failed ERCP were excluded from this analysis. Patients undergoing biliary drainage via rendezvous procedure (EUS-BD or PTBD) were excluded from Bapaye et al.^[31]

2.3. Data collection and extraction

The study design was written in accordance to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement. Ethical approval was not necessary as the study is a systematic review and meta-analysis. Articles were systematically searched in Medline, PubMed, Ovid journals, EMABSE, Cumulative Index for Nursing & Allied Health Literature, ACP journal club, DARE, International Pharmaceutical Abstracts, old Medline, Medline nonindexed citations, OVID Healthstar, and Cochrane Central Register of Controlled Trials (CENTRAL). The search was performed for the years 1966 to January 2016. Abstracts were manually searched in the major gastroenterology journals (Gastroenterology, Gut, American Journal of Gastroenterology and Gastrointestinal Endoscopy) for

the past 3 years. Study authors for the abstracts included in this analysis were contacted when the required data for the outcome measures could not be determined from the publications. Search was limited to English articles. The MeSH search headings used were “endoscopic ultrasound guided biliary drainage,” “percutaneous transhepatic biliary drainage,” “malignant biliary obstruction,” “failed ERCP.” The reference lists of the included studies were manually searched for any relevant publications. Two authors (HM and SRP) independently searched and extracted the data into an abstraction form. Any differences were resolved by mutual agreement. If the disagreement persisted, the final decision was made by a third author (DF) after reviewing the relevant information. The agreement between reviewers for the collected data was quantified using the Cohen κ .^[34] Data were extracted from the selected studies and entered into a standardized data collection form. The following variables were recorded: name and year of study; type of study; age; male/female distribution; total number of patient included; number of patient that underwent EUS-BD; number of patients that underwent PTBD; number of patients with successful biliary drainage in EUS-BD group; and PTBD group; overall complications in EUS-BD group; and PTBD group; postprocedural bleeding in both groups; postprocedural biloma in both groups; postprocedural bile leak in both groups; postprocedural infection (hepatic abscess/cholangitis/perihepatic abscess/drain site infection) in both groups; pre- and postprocedural bilirubin levels in both groups; pre- and postprocedural quality of life in both groups.

2.4. Definitions

Successful biliary drainage was defined as a reduction in serum total bilirubin $>50\%$ at 2 weeks and to a value <3.0 mg/dL at 4 weeks follow up. Technical success was defined as successfully placed stent in the appropriate location, confirmed radiographically and/or endoscopically. Stent patency is defined as time interval between biliary stent insertion and the need for an unanticipated reinterventions.

2.5. Quality of studies

Clinical trials designed with a control and treatment arms can be assessed for quality of the study. A number of criteria have been used to assess this quality of a study (e.g., randomization, selection bias of the arms in the study, concealment of allocation, and blinding of outcome). Jadad score was used to evaluate the quality of randomized studies. Cochrane Collaborations and the Quality of Reporting of Meta-analysis guidelines were followed to assess the quality of studies.^[35,36]

2.6. Statistical methods

This meta-analysis was performed by calculating pooled proportions. First the individual study proportion of pain control, ductal clearance, quality of life, etc., was transformed into a quantity using Freeman–Tukey variant of the arcsine square root transformed proportion. The pooled proportion is calculated as the back-transform of the weighted mean of the transformed proportions, using inverse arcsine variance weights for the fixed effects model and DerSimonian–Laird weights for the random effects model.^[37,38] Forest plots were drawn to show the point estimates in each study in relation to the summary pooled estimate. The width of the point estimates in the Forest plots indicates the assigned weight to that study. The

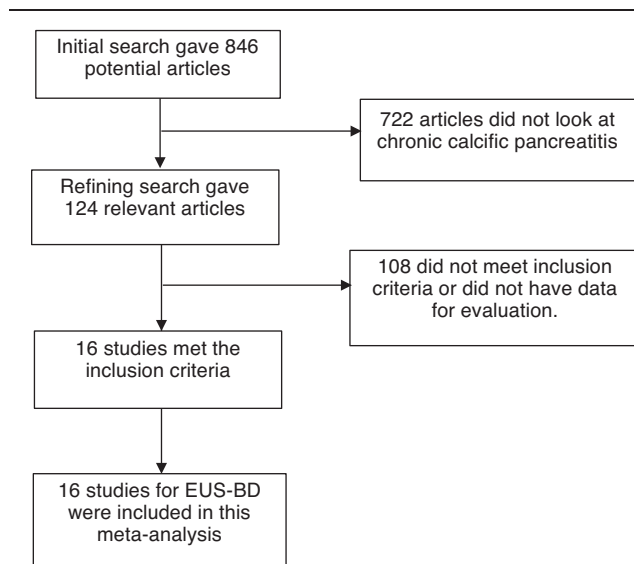


Figure 1. Flow diagram: Search results.

heterogeneity among studies was tested using I^2 statistic and Cochran Q test based upon inverse variance weights.^[39] I^2 of 0% to 39% was considered as nonsignificant heterogeneity, 40% to 75% as moderate heterogeneity, and 76% to 100% as considerable heterogeneity. If P -value is >0.10 , it rejects the null hypothesis that the studies are heterogeneous. The effect of publication and selection bias on the summary estimates was tested by both Harbord–Egger bias indicator^[40] and Begg–Mazumdar bias indicator.^[41] Also, funnel plots were constructed to evaluate potential publication bias.^[42,43] Microsoft Excel 2013 software was used to perform statistics for this meta-analysis. Subgroup analysis was performed on 2 subgroups—studies comparing EUD-BD versus PTBD; and only prospective studies evaluating the clinical outcomes with EUS-BD.

3. Results

Initial search identified 846 reference articles, in which 124 articles were selected and reviewed. Data were extracted from 16 studies^[17–32] ($N=528$) that evaluated the efficacy of EUS-BD, which met the inclusion criterion. All the studies are published as full text articles. Figure 1 shows the flow diagram of search results. All the pooled estimates given are estimates calculated by the fixed effect model. Fixed effect model was preferred to random effects model for better accuracy based on the nature of individual study characteristics and heterogeneity. Among the 16 studies included in this analysis, only 3 studies compared EUS-BD to PTBD.^[30–32] We were able to perform comparative analysis on these 3 studies, to evaluate if 1 is superior to the other. More than 1 EUS-BD technique was used for biliary drainage in most of the studies. Due to the nature of data available from individual studies, we were not able to analyze and compare the different techniques separately. Six studies out of the 16 studies were retrospective studies.^[21,26,27,29–31] Subgroup analysis was performed on all prospective trials.^[17–20,22–25,28,32]

The total number of patients included in this meta-analysis is 528, with a predominantly male population (65%). Median age of the patients was 66 years. Table 1 shows the baseline characteristics of the studies. The P for Chi-squared heterogeneity for all the pooled accuracy estimates was $>.10$. The agreement

Table 1
Basic characteristics of the included studies.

No.	Study	Type	N	N-EUS	N-PTBD	EUS-BD	PTBD
1	Artifon et al ^[32]	RCT	25	13	12	13	12
2	Bapaye et al ^[31]	R	51	25	26	23	12
3	Khashab et al ^[30]	R	73	22	51	19	47
4	Poincloux et al ^[29]	R	101	101	0	93	0
5	Will et al ^[28]	P	95	95	0	93	0
6	Nicholson et al ^[27]	R	5	5	0	5	0
7	Iwashita et al ^[26]	R	40	40	0	29	0
8	Park et al ^[25]	P	57	57	0	49	0
9	Ramirez-Luna et al ^[24]	P	11	11	0	9	0
10	Hara et al ^[23]	P	17	17	0	17	0
11	Siddiqui et al ^[22]	P	8	8	0	8	0
12	Kim et al ^[21]	R	15	15	0	12	0
13	Park et al ^[20]	P	5	5	0	5	0
14	Nguyen-Tang et al ^[17]	P	5	5	0	5	0
15	Bories et al ^[19]	P	11	11	0	10	0
16	Will et al ^[18]	P	9	9	0	8	0

EUS-BD=no. of patients with successful EUS guided biliary drainage, N=total number of patients in each study, N-EUS=total number of patients in EUS biliary drainage wing, N-PTBD=total number of patients in percutaneous biliary drainage wing, P=prospective study, PTBD=no. of patients with successful percutaneous biliary drainage, R=retrospective study, RCT=randomized controlled trial.

between reviewers for the collected data gave a Cohen κ value of 1.0.

3.1. Efficacy and morbidity with EUS-BD

In the pooled patient population, the percentage of patients that had a successful biliary drainage with EUS was 90.91% (95% CI=88.10–93.38). Bias indicators for this variable were:

Begg–Mazumdar: Kendall tau $b = -0.06, P = 0.79$; Egger: bias = -0.78 (95% CI = $-1.81-0.25$), $P = 0.13$. Heterogeneity for this variable was assessed using I^2 (inconsistency) = 50.6% (95% CI = 0–70.9). Figure 2 is a forest plot representing the pooled and individual rates of successful biliary drainage with EUS-BD. Figure 3 is a funnel plot assessing the publication bias for same variable.

Proportion meta-analysis plot [fixed effects]

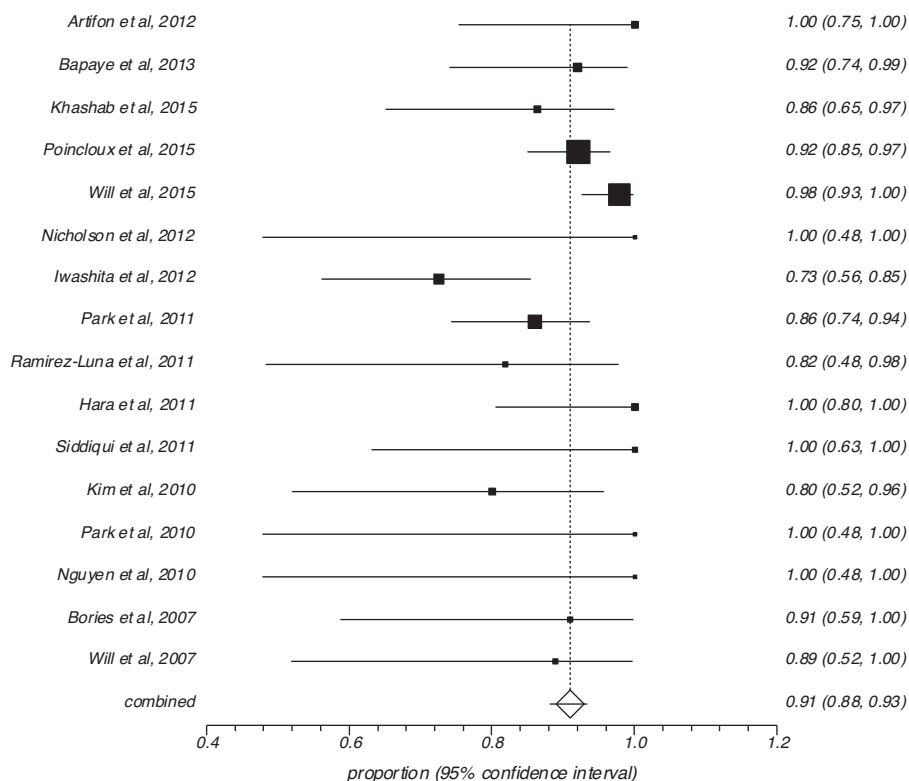


Figure 2. Forest plot—Individual study proportions and the pooled estimate for patients with successful EUS-BD (fixed effects).

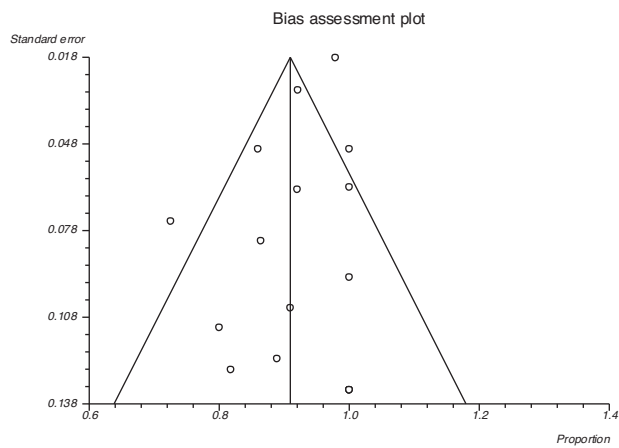


Figure 3. Funnel plot assessing for publication bias (for successful EUS-BD).

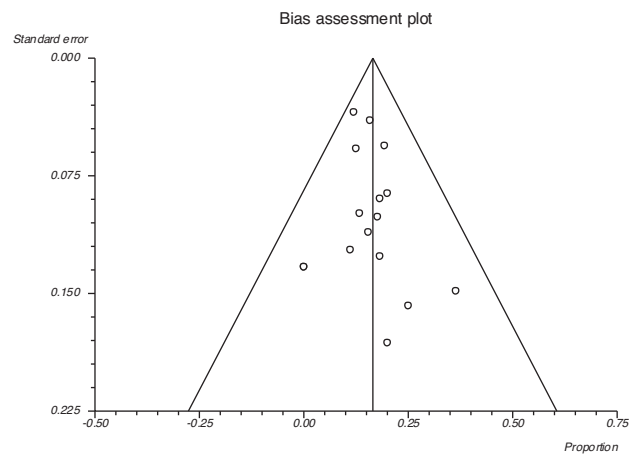


Figure 5. Funnel plot assessing for publication bias (for adverse events in EUS-BD group).

The proportion of patients that had overall procedure related complications (bleeding, biloma, bile leak, infections, and pancreatitis) with EUS-PD was 16.46% (95% CI= 13.20–20.01). Bias indicators for this variable are as follows: Begg–Mazumdar: Kendall tau b=0.03, $P=0.93$; Egger: bias= 0.28 (95% CI=−0.50 to 1.06), $P=0.46$; Harbord: bias=0.21 (92.5% CI=−0.58 to 1.00), $P=0.61$. Figure 4 is a forest plot representing the pooled and individual adverse events with EUS-BD. Figure 5 is a funnel plot assessing the publication bias for

same variable. Due to the paucity of data and variable follow up periods (1 day to 6 months) in the individual studies, we were unable to evaluate mortality and quality of life related outcomes.

3.2. Subgroup analysis of prospective studies

Subgroup analysis was performed on all prospective trials.^[17–20,22–25,28,32] Ten studies were included in this analysis. The total number of patients included in this subgroup was 243,

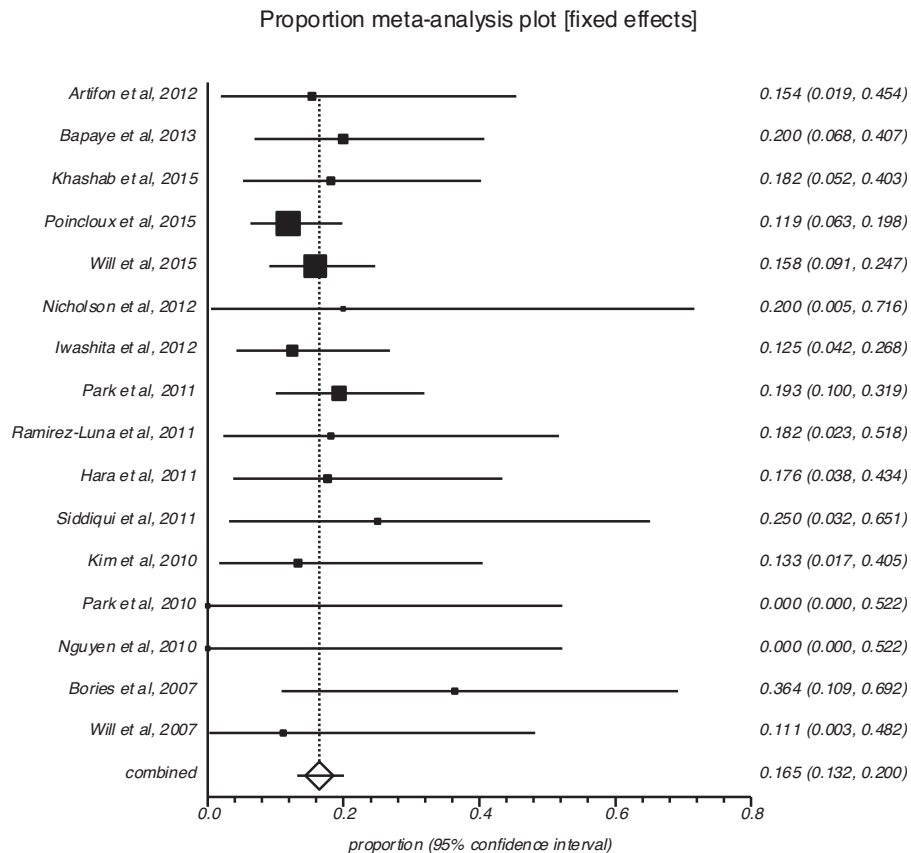


Figure 4. Forest plot—Individual study proportions and the pooled estimate for adverse events in EUS-BD group (fixed effects).

with a predominantly male population (65%). Median age of the patients was 65 years. In the subgroup analysis of prospective studies, successful biliary drainage was achieved in 93.88% (95% CI=90.52–96.55) and overall procedure related complications were present in 18.04% (95% CI=13.46–23.14) of the pooled patient population. Heterogeneity of the studies was assessed using I^2 (inconsistency)=34.6% (95% CI=0–67.7). Bias indicators for this subgroup are as follows: Egger: bias=−0.46 (95% CI=−1.53 to 0.62), $P=0.35$; Harbord: bias=0.07 (92.5% CI=−1.77 to 1.90), $P=0.94$.

3.3. EUS-BD versus PTBD

As mentioned earlier, only 3 studies compared EUS-BD and PTBD. These 3 studies^[30–32] were included in this subgroup analysis. The total number of patients included in this subgroup was 149, with a predominantly male population (65%). Median age of the patients was 66 years. The pooled odds ratio for successful biliary drainage in EUS-PD versus PTBD group was 3.06 (95% CI=1.11–8.43). The risk difference for overall procedure related complications in EUS-PD versus PTBD group was −0.21 (95% CI=−0.35 to −0.06). Relative risk for infectious complications (hepatic abscess/cholangitis/perihepatic abscess/drain site infection) and bile leak in EUS-BD versus PTBD was 0.25 (95% CI=0.07–0.94) and 0.33 (95% CI=0.12–0.87), respectively. Bias indicator for this subgroup: Horbold–Egger: bias=−1.73 (92.5% CI=−2.41 to −1.06), $P=0.03$.

4. Discussion

In patients with inoperable malignant biliary obstruction and a failed ERCP, recent studies have shown that EUS-BD could be an alternate option to PTBD. However, outcomes of the individual studies have been variable. In this meta-analysis we have attempted to pool this information from individual studies to look at the overall outcomes of EUS-BD compared to PTBD. There are only 3 studies that compared the outcomes of EUS-BD to PTBD.^[30–32] In Khashab et al,^[30] EUS-BD was compared to PTBD in patients with only distal biliary strictures. EUS-REN was used as the first option, however, EUS-TL was used when EUS-REN technique failed. They noted that successful biliary drainage was comparable in EUS-BD and PTBD (86.4% vs 92.2%, $P=0.40$). However, EUS-BD was associated with lower adverse event rates compared to PTBD (15.7% vs 80.4%). Healthcare costs for PTBD were twice that of EUS-BD group, primarily due to high reintervention rates (EUS-BD, 15.8% vs PTBD, 45.1%; $P=0.02$) in PTBD group.

Bapaye et al^[31] was a retrospective study done in patients in inoperable malignant biliary obstruction who failed an ERCP due to inaccessible papilla. Patient that underwent EUS-REN were excluded from this study. Their study showed higher rates of successful biliary drainage with EUS-BD compared to PTBD (92% vs 46%, $P<0.05$) and lower rates of adverse events in EUS-BD group versus PTBD group (20% vs 46%, $P<0.05$).

Artifon et al^[32] is the only randomized controlled trial (RCT) done to compare EUS-BD and PTBD in patients with inoperable malignant biliary obstruction. This study used only 1 technique (EUS-TL) for EUS-BD. It was a small size study with 13 patients in EUS-BD wing and 12 patients in PTBD wing. This study showed that EUS-BD and PTBD are comparable in terms of cost (EUS-BD, \$5673 vs PTBD, \$7570; $P=0.39$), adverse events (15.3% vs 25%; $P=0.44$), and clinical significant improvement

in bilirubin levels (EUS-CD, 16.4–3.3; $P=0.01$ and PTBD, 17.2–3.8; $P=0.01$).

Advantages of EUS-BD:

1. Higher rates of successful biliary drainage and lower reintervention rates compared to PTBD.^[30,31]
2. EUS-BD offers multiple routes of access to the biliary tree, which is especially helpful in patients with abnormal anatomy (duodenal obstruction/bypass procedures). These techniques have been briefly discussed in the introduction. EUS-TL (this includes choledochoduodenostomy and choledochogastrotomy), EUS-REN, and EUS-AT are the most commonly used techniques.^[30]
3. EUS-BD can be performed in patients with liver metastasis and ascites.
4. Patients with EUS-BD would not have an external catheter. This is more pleasing to the patients, lower chances of biliary leak and skin irritation. Patient usually perceives this as being a less invasive procedure compared to PTBD. Patient end up having an external drain with PTBD. This could cause discomfort to patients and is not cosmetically pleasing. Healthcare providers should change the external drainage bags frequently which could be cumbersome.^[30]
5. After a failed ERCP, EUS-BD can be performed in the same session, if the operator and infrastructural expertise is available. This would prevent a separate procedure at a later date, hence facilitating timely intervention for biliary drainage and quicker decrease in bilirubin levels.^[44,45]
6. EUS-BD facilitates internal biliary drainage. The bile is drained into gastrointestinal tract and hence is more physiologic than PTBD. Bile promotes nutrient absorption and digestion of food.

Key limitations for EUS-BD are:

1. Operational expertise required for EUS-BD is available in very few hospitals. On contrary, there is a lot of experience and expertise in PTBD in most of the hospitals. Interventional radiologists have been well trained and equipped with performing PTBD.^[30,32]
2. Currently, there are limited tools and devices (stents, guide wires) available for EUS-BD. Most of the tools used are borrowed from the ERCP equipment. Due to lack of dedicated tools, the procedure can be technically challenging in many patients. There are many dedicated tools and accessories designed specifically for PTBD, which would make the procedure less challenging.^[30,32]

Results from our meta-analysis show that EUS-BD is associated with high rates of successful biliary drainage (93.88% with 95% CI=90.52–96.55) and acceptable procedure related adverse event profile (18.04% with 95% CI=13.46–23.14). These results consolidate all the available evidence regarding the successful application of EUS-BD. Furthermore, this meta-analysis also compared EUS-BD and PTBD. Results showed that EUS-BD is significantly superior to PTBD in patients with inoperable biliary obstruction with a failed ERCP. EUS-BD had higher odds of successful biliary drainage compared to PTBD group with an odds ratio of 3.06 (95% CI=1.11–8.43) and lower risk for procedure related adverse effects (risk difference was −0.21 with 95% CI=−0.35 to −0.06) and infectious complications (relative risk was 0.25 with 95% CI=0.07–0.94). Number of patients with bile leak was lower in EUS-BD group compared to PTBD group (relative risk was 0.33 with 95% CI=0.12–0.87).

Strengths of this meta-analysis include the high quality methodology of statistical analysis, high quality methodology used in individual studies, relatively large number of studies that met the inclusion criteria, and total number of patients included in this analysis (N=528). This is the first meta-analysis to pool the evidence for EUS-BD and compare it to PTBD.

Limitations of this study are: we were unable to perform cost-benefit analysis due to the lack of data from individual studies. Local expertise plays a key role in the outcomes of EUS-BD. Since the studies were performed in different countries, using different endoscope equipment, used by different operators with varying skill sets, this variable should be considered while try to analyze the final outcomes. Thirteen studies included in this analysis had only 1 arm (EUS-BD), there was no control arm. All 3 variants of EUS-BD have been included in this meta-analysis. Due to the nature of data available from individual studies, we were not able to analyze and compare EUS-TL, EUS-REN, and EUS-AT separately. There were a few retrospective studies included in this meta-analysis. In order to mitigate this issue, we have performed a subgroup analysis on prospective studies only. The individual studies included in this meta-analysis were performed in highly specialized and famous worldwide centers, and maybe this is the reason for higher success and lower complication rates of EUS-BD in comparison to PTBD.

Granted there is availability of operator expertise and infrastructure availability, we believe that EUS-BD is an excellent option for biliary drainage. It should be indicated in the following clinical situations:

1. In patients with failed ERCP-BS, patient would benefit more from EUS-BD compared to PTBD.
2. In patients with a known altered biliary tree and duodenal anatomy (likely due to metastasized cancer), ampulla covered with an enteral stent, and diagnostic imaging that shows periampullary malignancy with duodenal invasion, it would be reasonable to consider EUS-BD as the primary biliary drainage approach at the time of initial ERCP.

Among the various EUS-BD techniques available, there are no head to head comparison studies to show that one is beneficial than the other. Operator expertise and availability of specific tools should be a guide in selecting 1 technique over the other. Currently, EUS-BD is restricted to specialized centers and not widely available. EUS training should be spread and opened to more endoscopists. Ongoing research on developing dedicated devices and tools for EUS-BD would likely improved outcomes of this procedure.^[46] The manufacturing industry and the endoscopists should continue to work in a close fashion to promote the designing of appropriate accessories. Further studies looking at quality of life and cost-benefit analysis would provide us more insight into the efficacy of EUS-BD compared to PTBD.

Studies with statistically significant positive results tend to be published and cited. Additionally, smaller studies may show larger treatment effects compared to larger studies. This publication and selection bias may affect the summary estimates. The bias can be estimated using Egger bias indicators and the construction of funnel plots, whose shape can be affected by bias. In the present meta-analysis and systematic review, bias calculations both Egger^[40] and Begg-Mazumdar^[41] bias indicators showed no statistically significant bias. Furthermore, analysis using funnel plots showed no significant publication bias among the studies included in the present analysis.

5. Conclusions

In patients with inoperable malignant biliary strictures who failed an ERCP guided biliary stenting, EUS-BD seems to be an excellent management option with higher successful biliary drainage rates and relatively fewer complications. EUS-BD seems to be significantly superior to PTBD with higher successful drainage rates and fewer complications. In patients with failed ERCP and altered biliary and duodenal anatomy, EUS-BD should be preferred to PTBD when appropriate operator expertise and infrastructure is available.

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