

BMJ Open Endoscopic ultrasound versus endoscopic retrograde cholangiopancreatography-guided biliary drainage for primary decompression of malignant biliary obstruction: protocol for a systematic review and meta-analysis of randomised controlled trials

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ABSTRACT

Introduction Current evidence supporting the utility of endoscopic ultrasound-guided biliary drainage (EUS-BD) as a first-line treatment option for malignant biliary obstruction (MBO) is limited. We plan to provide a systematic review and meta-analysis to compare the performance of EUS-BD and endoscopic retrograde cholangiopancreatography-guided biliary drainage (ERCP-BD) as primary palliation of MBO.

Methods and analysis Randomised controlled trials evaluating EUS-BD versus ERCP-BD in primary drainage of MBO will be searched in MEDLINE, EMBASE, Web of Science, the Cochrane Library, ClinicalTrials.gov and Google Scholar, from database inception to 31 October 2018. Data on study design, participant characteristics, intervention details and outcomes will be extracted. Primary outcomes to be assessed are technical and clinical success. Secondary outcomes include adverse events, stent patency, stent dysfunction, reinterventions, procedure duration and overall survival. Study quality will be assessed using the Cochrane Risk of Bias Tool. Meta-analysis will be performed using RevMan V.5.3 statistical software. Data will be combined with a random effect model. The results will be presented as a risk ratio for dichotomous data, weighted mean difference for continuous data and HR for time-to-event data. Publication bias will be visualised using funnel plots.

Ethics and dissemination This study will not use primary data, and therefore, formal ethical approval is not required. The findings will be disseminated through peer-reviewed journals and committee conferences.

PROSPERO registration number CRD42018117040

INTRODUCTION

Not uncommonly, malignant biliary obstruction (MBO) is diagnosed at an advanced

Strengths and limitations of this study

- This is the first meta-analysis comparing endoscopic ultrasound-guided biliary drainage- with endoscopic retrograde cholangiopancreatography-guided biliary drainage for primary drainage of malignant biliary obstruction.
- The study selection, data extraction and quality assessment will be performed independently by two researchers.
- We will calculate time-to-event outcomes using HRs, in contrast to other meta-analyses using risk ratios or weighted mean differences.
- We will be able to comprehensively survey the literature and identify areas where further study may be required.
- A possible weakness may be the quality of the trials we include.

stage when treatment is mainly palliative. Endoscopic retrograde cholangiopancreatography-guided biliary drainage (ERCP-BD) has been the most commonly used technique for the palliation of MBO.¹ However, a wide range of postprocedure complications has continued to pose a serious challenge.² In addition, patients with MBO may be accompanied by duodenal invasion and altered anatomy from the previous surgeries, which could increase ERCP difficulty.³

Since first reported by Giovannini *et al*,⁴ endoscopic ultrasound-guided biliary drainage (EUS-BD) has emerged as an alternative procedure to percutaneous transhepatic biliary drainage (PTBD) after failed

ERCP.^{5–8} A recent meta-analysis evaluating EUS-BD reported cumulative technical success and adverse events of 94.71% and 23.32%, respectively.⁹ With increasing availability and familiarity with this procedure, several studies have compared EUS-BD versus ERCP-BD for primary biliary decompression for MBO.^{10–12} These studies have reported variable results and were limited because of small sample sizes. We had planned to conduct a meta-analysis to compare the performance of EUS-BD with ERCP-BD as primary treatment in relieving MBO.

METHODS

The review will be performed according to the recommendations specified in the Cochrane Handbook for Intervention Reviews.¹³ The reporting of the review will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.¹⁴

Criteria for considering studies for this review

Eligibility criteria are established in terms of the population, intervention, comparison, outcome, study design framework. Studies will be selected according to the following criteria:

Participants

Included studies will involve patients presenting with MBO and initially undergoing endoscopic drainage, with no age limitation. Both distal and hilum MBO will be included. There will be no restrictions on aetiology, which include, but are not limited to, pancreatic cancer, cholangiocarcinoma, gallbladder cancer, ampulla of Vater cancer and metastasis. Patients with benign biliary diseases, and those with EUS-BD performing as a salvage procedure for failed ERCP will be excluded.

Interventions/comparison

The intervention comparisons are EUS-BD versus ERCP-BD. EUS-BD can be performed in several ways, choledochoduodenostomy, hepaticogastrostomy, antegrade procedure and rendezvous technique.¹⁵ All these methods of EUS-BD will be included except for rendezvous technique. Because the rendezvous approach is a cross-over technique using EUS to pass a guidewire via the papilla to perform an ERCP. There will be no restrictions on stent type (metal/plastic stent), dilation device (dilation catheter/cystotome/balloon), and whether patient has an indwelling duodenal stent or not.

Outcomes

There are two primary outcomes for this study: technical success (defined as successful stent placement as determined endoscopically or radiographically) and clinical success (defined as reduction of total serum bilirubin levels to less than half of the preoperative level within 4 weeks).¹⁰

There are six secondary outcomes: (1) adverse events: total, pancreatitis, cholangitis, cholecystitis, bleeding and bile peritonitis; (2) stent patency (HR) for interval from

initial insertion to recurrence of obstruction); (3) stent dysfunction: stent occlusion, stent migration and tumour in/overgrowth; (4) reinterventions; (5) procedure duration and (6) overall survival (HR for death).

Study design

Only randomised controlled trials (RCTs) will be included. Unpublished trials and abstracts will be included if the methodology and data are accessible. We will only include studies that are presented in English language due to constraints in translational resources.

Exclusion criteria will be: (1) studies without a comparative arm of ERCP-BD; (2) observational studies, case reports, reviews, editorials and letters to editor; (3) duplicate studies, in vitro studies or animal studies and (4) no data on any of the primary or secondary outcomes.

Search methods for identification of studies

Electronic searches

Two investigators (ZJ and YW) will independently search MEDLINE, EMBASE, Web of Science, the Cochrane Library, ClinicalTrials.gov and Google Scholar, for all entries through 31 October 2018. The search strategies will be decided on after a discussion among all reviewers. The primary search strategy will be used for PubMed MEDLINE (online supplementary appendix I). Modifications to the search strategy will be made for other databases. We will assess eligibility of the retrieved articles by title and abstract using predetermined inclusion criteria. If this information is insufficient for eligibility assessment, we will review the full article. If any up-to-date evidence is published during the review period, we will evaluate the eligibility of each study and consider its addition to the analysis.

Searching other resources

To further increase the robustness of the literature search, a manual recursive search of the reference sections of the retrieved articles, as well as the related articles option in PubMed, will be carried out to identify other potentially relevant articles.

Data collection and analysis

Selection of studies

Decisions about study inclusion and exclusion will be made independently by two investigators (ZJ and YW). Disagreements will be resolved by consensus after a mutual discussion. The details of the study selection procedure are shown in a PRISMA flow chart. (figure 1)

Data extraction and management

Two investigators (YW and HL) will independently extract the appropriate data onto a data collection form (online supplementary appendix II). The following variables will be contained in the collection form: country and year of the study, study design, patient demographics and clinical characteristics, methods of EUS-BD, types of stents, technical success, clinical success, procedure duration, stent patency, stent dysfunction, reinterventions, adverse

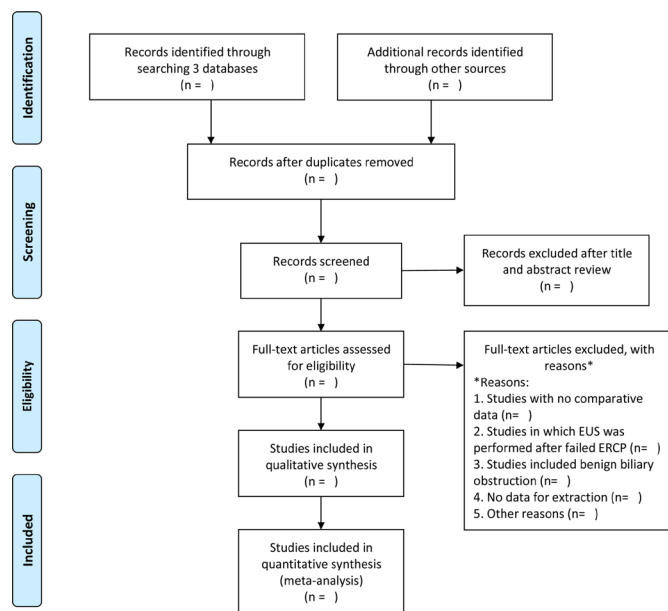


Figure 1 Flow diagram of the study selection process. ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound.

events, overall survival and follow-up information. When necessary data are not included in the published studies, the corresponding authors will be contacted for additional information. If there is no reply, we will analyse only the available data. If there are no data on any of the primary or secondary outcomes, those studies will be excluded from the meta-analyses.

Assessment of risk of bias in included studies

We will assign two independent investigators (YW and HL) to appraise methodological quality of the included trials with the Cochrane Collaboration's tool for assessing risk of bias.¹⁶ The tool appraises existence of selection bias by assessing methods of randomisation and allocation concealment, performance and detection of biases by checking blinding of personnel and outcome assessment, and attrition and reporting bias by evaluating incomplete and selective data reporting. Each of the items is assigned a judgement of high, low or unclear risk.

Data synthesis

The HRs for time-to-event outcomes (stent patency and overall survival) will be calculated using the Excel sheet published by Tierney *et al*,¹⁷ based on Parmar *et al*'s method of data extraction¹⁸ from Kaplan-Meier curves. Weighted mean differences (WMDs) will be calculated for continuous variables. Medians will be used if means are not available and SDs will be calculated or imputed when possible.¹⁹ Risk ratios (RRs) will be calculated for categorical variables. Owing to the assumption of inherently various study scenarios and study populations, a random effects model for all analyses will be assumed.¹³ Heterogeneity among studies will be assessed by calculating the I^2 statistics whereby $I^2 < 25\%$ indicates no heterogeneity, $25\% \leq I^2 < 50\%$ indicates mild heterogeneity, $50\% \leq$

$I^2 < 75\%$ indicates moderate heterogeneity and $I^2 \geq 75\%$ indicates strong heterogeneity.²⁰ We had planned that if sufficient studies (≥ 10) are included in the analysis of primary outcomes, we would construct funnel plots to evaluate publication bias,¹³ otherwise, Egger's test will be applied.²¹ All statistical analyses will be performed using Review Manager V.5.3 (Cochrane Collaboration, 2014).

Subgroup analyses

In the case of possible strong heterogeneity, we will explore the possible sources using subgroup and meta-regression analyses. Subgroup analyses will be carried out based on geographical location, publication form, study design, location of biliary obstruction, indwelling duodenal stent, EUS-BD technique, stent type and definitions of adverse event. For those subgroups with only one study included, subgroup analyses will not be performed.

Sensitivity analysis

We will carry out a sensitivity analysis by systematically removing every study and checking the pooled results for the remaining studies to see if there is any significant change in test performance.

Patient and public involvement

Because the collected data within this systematic review and meta-analysis originates from previously published studies, patients and the general public were not involved in the development of the research question or choice of outcome measures that we wanted to assess.

DISCUSSION

ERCP-BD has been a generally preferred treatment for inoperable MBO.²²⁻²⁴ Conventionally, when ERCP fails for achieving biliary drainage, patients undergo PTBD and EUS-BD.^{5 8 25} For primary drainage of MBO, several studies have investigated EUS-BD versus ERCP-BD showing different results.¹⁰⁻¹² A recent meta-analysis⁹ reported that EUS-BD may not be used as an initial modality for relieving biliary obstruction, however, none of the included studies were direct comparative. We, therefore, propose a meta-analysis to pool the evidence to evaluate the performance of EUS-BD versus ERCP-BD.

One strength of our meta-analysis will be that stent patency and overall survival will be calculated using HRs, in contrast to other meta-analyses using RRs or WMDs.²⁶ Because the included studies had various length of follow-up, and the events might not occur in some patients at the end of study. For these time-to-event outcomes, the most appropriate way of analysis is to use methods of survival analysis and express the intervention effect as an HR.¹³ This will be the first meta-analysis of RCTs comparing EUS-BD with ERCP-BD for primary drainage of MBO. The results of this study will influence decision-making for unresectable MBO, assist in future guideline development and guide future research endeavours.

DISSEMINATION

We will disseminate the findings of our work through conference presentations and a peer-reviewed publication.

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Contributors XZ is the guarantor. ZJ drafted the manuscript protocol. YW, HL and WL contributed to the development of the selection criteria, article screening strategy, risk of bias assessment strategy and data extraction criteria. ZJ developed the search strategy. HH provided statistical expertise. All authors read, provided feedback and approved the final protocol.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval Ethics approval will not be required because all analyses in the present study will be performed based on data from published studies.

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