Comparison of long-term efficacy between endoscopic and percutaneous biliary drainage for resectable extrahepatic cholangiocarcinoma with biliary obstruction: A systematic review and meta-analysis

Lei Wang1,2, Nanping Lin1,2,3,4, Fuli Xin1,2,3,4, Yongyi Zeng3,4, Jingfeng Liu2,4

1Department of Radiation Oncology, Mengchao Hepatobiliary Hospital of Fujian Medical University, 2The United Innovation of Mengchao Hepatobiliary Technology Key Laboratory of Fujian Province, Mengchao Hepatobiliary Hospital of Fujian Medical University, 3Department of Hepatopancreatobiliary Surgery, Mengchao Hepatobiliary Hospital of Fujian Medical University, 4Liver Diseases Center, The First Affiliated Hospital of Fujian Medical University, Fuzhou, Fujian, China

†These authors contributed equally as first authors

Abstract

Background/Aim: For resectable extrahepatic cholangiocarcinoma with biliary obstruction, it remains a controversy whether to choose percutaneous transhepatic biliary drainage (PTBD) or endoscopic biliary drainage (EBD). A systematic review was conducted to compare the long-term efficacy between the two techniques.

Materials and Methods: Eligible studies were searched from January 1990 to May 2018, comparing the long-term efficacy between EBD and PTBD for extrahepatic cholangiocarcinoma. Primary end point was overall survival (OS) rate, and secondary end points included postoperative severe complications and seeding metastasis. Effect size on outcomes was calculated using a fixed- or random-effect model, accompanied with hazard ratio (HR) and 95% confidence interval (CI).

Result: Six studies were included in this meta-analysis. Meta-analysis showed that EBD was superior to PTBD in OS (HR = 0.70, 95% CI 0.59–0.84, P = 0.0002). But subgroup results showed that the superiority disappeared in distal cholangiocarcinoma (HR = 0.76, 95% CI 0.56–1.01, P = 0.06). Other prognostic factors such as intraoperative blood transfusion, lymphatic metastasis and seeding metastasis, were inconsistent between groups. In addition, regional disparity was obviously apparent between Japanese and non-Japanese studies.

Conclusion: The conclusion that EBD was superior to PTBD in OS for resectable extrahepatic cholangiocarcinoma with biliary obstruction is less convincing, and more trials need to be conducted in future.

Keywords: Endoscope biliary drainage, extrahepatic cholangiocarcinoma, meta-analysis, overall survival, percutaneous biliary drainage, preoperative biliary drainage
INTRODUCTION

Extrahepatic cholangiocarcinoma is still the most common of cholangiocarcinoma, though the incidence remains stable (annual percentage change, 0.14%).[1] Extrahepatic cholangiocarcinoma is generally divided into perihilar cholangiocarcinoma (PHC) arising at or near the junction of the right and left hepatic ducts, and distal cholangiocarcinoma (DCC) occurring in the extrahepatic bile ducts above the ampulla of Vater.[2] Complete resection is the only potentially curative strategy for extrahepatic cholangiocarcinoma, and the 5-year survival rates following radical surgery were reported to be in the range of 20–42% for PHC and 16–52% for DCC, respectively.[3]

Extrahepatic cholangiocarcinoma is typically present with biliary obstruction, which is one of the most important risk factors for perioperative mortality and morbidity.[4] Palliative biliary drainage was strongly recommended for unresectable or metastatic extrahepatic cholangiocarcinoma,[5,6] whereas it remains controversial for resectable extrahepatic cholangiocarcinoma.[7] However, appropriate biliary drainage had brought more chances for surgery, as well as decreased perioperative mortality and morbidity.[8,9]

Endoscopic or percutaneous biliary drainage has been applied clinically worldwide for biliary obstruction[10] but to choose between one or the other is still a matter of debate. With the development of endoscopy, endoscopic biliary drainage (EBD) was recommended clinically,[11,12] although recent meta-analyses showed that percutaneous biliary drainage (PTBD) was superior, or at least not inferior, to EBD in therapeutic success[13] and was comparable in complications.[10,13,14] However, long-term efficacy is rarely systematically reported. Hence, a systematic review and meta-analysis was performed to evaluate the long-term efficacy of the two biliary drainages for resectable extrahepatic cholangiocarcinoma with biliary obstruction.

MATERIALS AND METHODS

Literature search
A comprehensive literature search was conducted by two independent researchers to clarify all the published researches of preoperative biliary drainage (PBD) for resectable extrahepatic cholangiocarcinoma with biliary obstruction. Both English electronic databases such as PubMed, Medline, the Cochrane Library and Web of Knowledge were used to seek literature, from 1st January 1990 to 31st May 2018. Search terms included “percutaneous transhepatic biliary drainage” and “EBD” combined with at least one of the following terms “extrahepatic cholangiocarcinoma,” “perihilar cholangiocarcinoma carcinoma,” and “distal cholangiocarcinoma carcinoma.” All the terms were searched as medical subject headings and free-text terms. Furthermore, additional citations fulfilling the inclusion criteria were searched manually from review articles, editorials and original studies.

Selection criteria

**Inclusion criteria:** (1) Cohort studies and randomized controlled trials were both considered; (2) extrahepatic cholangiocarcinoma including at least one of the two tumors, PHC and DCC; (3) PBD including both PTBD and EBD; (4) long-term efficacy including overall survival (OS) and recurrence-free survival (RFS) was the primary end point; and (5) sufficient data such as the baseline of characteristic were depicted.

**Exclusion criteria:** (1) In vitro or animal studies; (2) case reports, letters, reviews, and conference reports; (3) studies based on overlapping cohorts derived from the same center; (4) sample size was not more than 20; and (5) data including disease-free survival or RFS only.

Data extraction

Data were extracted including all of the following: (1) general data, such as title, first author, publication data and literature source; (2) baseline characteristics, such as sex, gender, tumor stage, lymphatic metastasis, surgical margin, adjuvant chemotherapy, intraoperative blood transfusion and so on; (3) primary end point, OS rate; and (4) secondary end points including postoperative severe complications and seeding metastasis.

All data were extracted and assessed by two independent investigators with predefined forms such as baseline characteristics and outcomes from each study. In case of disagreement, a third investigator intervened for a conclusion. Hazard ratios (HRs) and its 95% confidence interval (CI) were extracted from original studies or calculated by Engauge Digitizer 4.1 according to Kaplan–Meier curve.[15]

**Intervention and outcome definition**

PTBD: Including external drainage and internal drainage (percutaneous transhepatic biliary stent, PTBS).

EBD: Including external drainage such as endoscopic nasobiliary drainage and internal drainage (endoscopic biliary stent). Usually, PTBD was available when EBD failed.
Tumor stage was evaluated according to AJCC staging system (7th edition).

Of note, seeding metastasis was extracted according to the original studies, including at least one of the followings: (1) PTBD catheter tract recurrence, (2) pleural dissemination on the right side alone, and (3) peritoneal dissemination.

Postoperative severe complication was defined as Grade III–V according to Clavien–Dindo classification.

Quality assessment
Cohort studies were assessed by Newcastle–Ottawa Scale (NOS), and studies scored as ≥6 were considered of high quality.

Statistical analysis
The systematic review and meta-analysis was registered at http://www.researchregistry.com and performed using RevMan Version 5.3 and Stata 14. The $\chi^2$ test and $I^2$ statistics were used to assess heterogeneity; $P < 0.10$ or $I^2 > 50\%$ were considered as significant heterogeneity. When the hypothesis of homogeneity was not rejected, the fixed-effects model was used to estimate the case with homogeneity, and the random-effects model was used for the cases with significant heterogeneity.\cite{15,16} HRs were evaluated for the OS,\cite{15} and odd ratios (ORs) were for other prognostic factors, followed with 95% confidence intervals (CI).\cite{16} Publication bias was evaluated by visually assessing the asymmetry of an inverted funnel plot and then was supported quantitatively by Begg's and Egger’s tests.\cite{15}

RESULTS
Base characteristic of the included studies
Initially, 617 reports were identified initially by two independent reviewers. A total of 29 articles were excluded for duplication by NoteExpress 3.1. After browsing titles and abstracts, 582 records were excluded, among which 179 articles were not for malignant obstruction, 96 articles were concurrent with gastrointestinal obstruction, 215 articles for palliative treatment, 26 articles for case reports, 3 articles for pancreatic carcinoma, 36 articles for lack of OS and 27 articles for being reviews. Of note, OS was the only primary end point, because there was only one study that focused on RFS.\cite{17} Finally, six reports were included for analysis, including four studies of PHC\cite{18–21} and two of DCC\cite{22,23} [Figure 1]. In total, 1260 patients were enrolled in this meta-analysis, with 665 cases in the EBD group and 595 cases in the PTBD group.

The characteristic and quality of the included trials are shown in Table 1. All the studies included in this meta-analysis were nonrandomized studies and were assessed by NOS. The scores ranged from 7 to 8, indicating that all the studies were of high quality [Table 1].

Comparison of OS rate between EBD and PTBD
There were six studies\cite{18–21} evaluating the OS rate between EBD and PTBD. Significant heterogeneities were not observed among the studies ($I^2 = 30\%, P = 0.21$), and therefore fixed-effects model was adopted. Compared with PTBD, EBD yields a significant benefit to OS (HR = 0.70, 95% CI 0.59–0.84, $P = 0.0002$, Figure 2).

Analysis of OS-related factors between EBD and PTBD
Other prognostic factors were further analyzed, and the results are shown in Table 2.

Subgroup analysis of OS rate between EBD and PTBD
Extrahaepatic cholangiocarcinoma was divided into PHC and DCC. Subgroup results showed that EBD was also superior to PTBD in PHC\cite{18–21} (HR = 0.67, 95% CI 0.53–0.85, $P = 0.0008$, Figure 3), but there were no significant differences between PTBD and EBD in DCC\cite{22,23} (HR = 0.76, 95% CI 0.56–1.01, $P = 0.06$, Figure 3).

Regional disparity among different studies
In this meta-analysis, four of the six included studies\cite{22,23} were from Japan and regional disparity was analyzed between Japanese and non-Japanese studies. Subgroup

---

**Figure 1:** Flowchart of study selection process for meta-analysis

---

**Table 1:** Characteristics and quality of the included trials

---

**Table 2:** Analysis of OS-related factors between EBD and PTBD

---
results showed that EBD was superior to PTBD in Japanese studies\(^{[22,23]}\) (HR = 0.68, 95% CI 0.56–0.83, \(P = 0.0001\), Figure 4) without significant heterogeneity (\(I^2 = 41\%\), \(P = 0.17\)), while the superiority disappeared in non-Japanese studies\(^{[22,23]}\) (HR = 0.85, 95% CI 0.54–1.35, \(P = 0.50\), Figure 4) without significant heterogeneity (\(I^2 = 22\%\), \(P = 0.26\)).

In this meta-analysis, seeding metastasis was reported in all of the six studies\(^{[22,23]}\). Subgroup results showed that the incidence of seeding metastasis was lower in EBD in Japanese studies\(^{[22,23]}\) (OR = 0.39, 95% CI 0.28–0.55, \(P < 0.00001\), Figure 5) without significant heterogeneity (\(I^2 = 0\%\), \(P = 0.48\)), whereas there was significant difference between the two groups in non-Japanese studies\(^{[22,23]}\) (OR = 0.97, 95% CI 0.49–1.92, \(P = 0.93\), Figure 5) without significant heterogeneity (\(I^2 = 0\%\), \(P = 0.39\)).

**Publication bias**

Funnel plot and Begg’s and Egger’s tests were used to detect the publication bias of our meta-analysis. A total of six included studies exhibited a basically symmetrical funnel plot (Figure 6a) and yielded a Begg’s and Egger’s test score of \(P = 0.707\) and \(P = 0.542\), respectively (Figure 6b and c).

**DISCUSSION**

In this meta-analysis, EBD was confirmed to be superior to PTBD in the OS rate of resectable extrahepatic cholangiocarcinoma with biliary obstruction as a whole. However, further analysis found that there were significant differences in other prognostic factors between the two groups. And, regional disparity among different studies was significantly apparent. Hence, in our opinion, the conclusion that EBD was superior to PTBD in the long-term efficacy was far from being reached.

The conclusion was coincident with Komaya’s two reports\(^{[20,22]}\), which adopted propensity score matching. But many more potential confounding factors, such as tumor stage\(^{[24,25]}\), surgical margin\(^{[26]}\), lymphatic metastasis\(^{[27]}\), intraoperative blood transfusion\(^{[28]}\) and so on, were rarely matched in both two studies. In this meta-analysis, all the potential confounding factors were evaluated. The results showed that the percentage of intraoperative blood transfusion, the rate of lymphatic metastasis and the incidence of seeding metastasis were found to be inconsistent between the two groups, which weaken the conclusion at length.

PHC and DCC share a single Tumor-Node-Metastasis (TNM) staging system, but have been separated independently since the 7th edition of AJCC staging system\(^{[27]}\) because of...
Wang, et al.: PTBD or EBD for extrahepatic cholangiocarcinoma

Table 2: Analysis of OS-related factors

<table>
<thead>
<tr>
<th>Factor</th>
<th>Included studies</th>
<th>EBD (%)</th>
<th>PTBD (%)</th>
<th>OR (95% CI)</th>
<th>P</th>
<th>Heterogeneity test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood transfusion</td>
<td>2</td>
<td>37/137</td>
<td>41/92</td>
<td>0.23 (0.11, 0.46)</td>
<td>&lt;0.0001</td>
<td>0.99</td>
</tr>
<tr>
<td>Adjuvant chemotherapy</td>
<td>3</td>
<td>129/402</td>
<td>72/382</td>
<td>1.63 (0.85, 3.13)</td>
<td>0.14</td>
<td>0.05</td>
</tr>
<tr>
<td>Postoperative severe complication</td>
<td>3</td>
<td>83/259</td>
<td>103/255</td>
<td>0.74 (0.51, 1.09)</td>
<td>0.13</td>
<td>0.42</td>
</tr>
<tr>
<td>Seeding metastasis</td>
<td>6</td>
<td>89/665</td>
<td>138/595</td>
<td>0.47 (0.35, 0.63)</td>
<td>&lt;0.0001</td>
<td>0.12</td>
</tr>
<tr>
<td>Positive surgical margin</td>
<td>4</td>
<td>139/462</td>
<td>93/406</td>
<td>1.03 (0.54, 1.98)</td>
<td>0.93</td>
<td>0.09</td>
</tr>
<tr>
<td>Lymph node metastasis</td>
<td>5</td>
<td>215/633</td>
<td>219/537</td>
<td>0.78 (0.61, 1.00)</td>
<td>0.05</td>
<td>0.13</td>
</tr>
<tr>
<td>Moderately or poorly differentiated</td>
<td>3</td>
<td>268/402</td>
<td>252/382</td>
<td>1.13 (0.83, 1.53)</td>
<td>0.44</td>
<td>0.95</td>
</tr>
<tr>
<td>AJCC T stage T3 or T4</td>
<td>5</td>
<td>285/633</td>
<td>317/537</td>
<td>0.64 (0.40, 1.02)</td>
<td>0.06</td>
<td>0.01</td>
</tr>
</tbody>
</table>

EBD = Endoscopic biliary drainage, PTBD = Percutaneous biliary drainage, OR = odd ratio, AJCC = American Joint Committee Cancer (7th edition)

Figure 2: Forest plots of OS rate between EBD and PTBD for resectable extrahepatic cholangiocarcinoma with biliary obstruction

Figure 3: Subgroup analysis of OS rate between EBD and PTBD for biliary obstruction derived from different extrahepatic cholangiocarcinoma

Figure 4: Subgroup analysis of OS between Japanese and non-Japanese studies
Wang, et al.: PTBD or EBD for extrahepatic cholangiocarcinoma

Different clinicopathological characteristic and prognosis.[11] Recent meta-analysis showed that PTBD has a lower rate of complications than EBD as the initial procedure for resectable PHC.[14] However, in this meta-analysis, PTBD was confirmed to be inferior to EBD in the long-term efficacy for PHC other than DCC. It indicated that the short-term advantage did not convert into long-term efficacy, the reasons for which need to be further explored.

The most puzzling finding in this meta-analysis was its regional disparity. In this meta-analysis, EBD was confirmed to be superior to PTBD in the long-term efficacy for extrahepatic cholangiocarcinoma in the studies derived from Japan, whereas the superiority disappeared in the non-Japanese studies. Such a trend happened on seeding metastasis, which was reported to be an important prognostic factor for extrahepatic cholangiocarcinoma following preoperative biliary drainage.[22,23] The reasons for this disparity remain unknown, and regional disparity should be taken into consideration for future clinical trials.

Apart from OS, quality of life after PBD is also a crucial factor to consider. PTBD, as an external drainage is considered troublesome when compared with internal drainage.[10] However, quality of life after PTBD is better than EBD at 3 months, according to World Health Organization Quality of Life physical and psychological scores, though the result did not reach statistical significance. But environmental functioning scores in the EBD were higher than those in PTBD.[29] Hence, more factors related to long-term efficacy should be taken into consideration in future clinical trials.

There were several limitations in this meta-analysis. First, none of the studies included in this meta-analysis were RCTs, and selection bias is inherent in retrospective studies. Second, heterogeneity was unavoidable due to diverse array of tumors and their location as mentioned above, although $I^2 < 50\%$, $P > 0.1$. Third, publication bias might be a factor, owing to inclusion of studies only written only in English, and inclusion of studies concerning positive results. Fourth, the initial level of bilirubin varied among the studies, and the threshold for surgery was different from each center.[18,19,22,23] Fifth, the level of endoscopic technique varied among different centers. Finally, indicators
of long-term efficacy, such as quality of life, cost–benefit analysis, were not evaluated in this meta-analysis due to sporadic data available from individual studies.

CONCLUSION

With the current data, we believe that the conclusion that EBD is superior to EBD for resectable extrahepatic cholangiocarcinoma with biliary obstruction is less convincing. Multidisciplinary team settings including gastroenterologists and surgeons should be undertaken with regards to the optimal form of PBD, especially for those who are potentially for surgery. In future, multiregional randomized controlled trials need to be conducted, and more factors, including both short-term and long-term efficacy, should be evaluated.

Acknowledgment

Nil.

Financial support and sponsorship

This study was supported by Wu Jieping Medical Foundation (LDWJPMF-102-17007).

Conflicts of interest

There are no conflicts of interest.

REFERENCES

Wang, et al.: PTBD or EBD for extrahepatic cholangiocarcinoma

