Effects of different preoperative biliary drainage methods for resected malignant obstruction jaundice on the incidence rate of implantation metastasis: A meta-analysis

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Abstract. The aim of the present study was to compare the effects of percutaneous transhepatic biliary drainage (PTBD) and endoscopic biliary drainage (EBD) for resected malignant obstruction jaundice (MOJ) on the incidence rate of implantation metastasis. Databases including PubMed, EMBase, Web of Science and Cochrane Library were utilized. With reference to literature reported until January 2019, controlled clinical trials were designed to compare the effects of PTBD and EBD for MOJ on the incidence rate of implantation metastasis. Subsequently, odds ratio (OR) with 95% confidence interval (CI) was calculated with Review Manager 5.3.0 software. A total of 10 studies were enrolled in this meta-analysis, including 1,085 cases in the PTBD group and 1,379 cases in the EBD group. The results revealed that there was a significant difference in the incidence rate of implantation metastasis between the PTBD group and EBD group (OR=0.35, 95% CI: 0.23-0.53, P<0.00001). Subgroup analysis revealed that the incidence rates of both catheter-related implantation metastasis and peritoneal metastasis were lower in the EBD group (OR=0.23, 95% CI: 0.12-0.44, P<0.00001; OR=0.47, 95% CI: 0.31-0.74, P=0.0008, respectively), and the advantage of EBD was demonstrated in perihilar cholangiocarcinoma, distal cholangiocarcinoma and pancreatic carcinoma (OR=0.35, 95% CI: 0.17-0.74, P=0.006; OR=0.32, 95% CI: 0.17-0.60, P=0.0005; OR=0.27, 95% CI: 0.19-0.40, P=0.00001, respectively). In conclusion, this meta-analysis revealed the appropriate choice of preoperative biliary drainage for resected MOJ. The application of EBD reduced the incidence rate of implantation metastasis, however more evidence is required from future studies, to confirm the results.

Introduction

Malignant obstructive jaundice (MOJ) is caused by intrahepatic and extrahepatic bile duct obstruction due to malignant obstructive tumor invasion or oppression, which is mainly manifested by hyperbilirubinemia and scleral yellow staining (1). Obstruction can cause a series of pathophysiological disorders of the organism, including bile duct dilation, increased capillary bile duct permeability, the flowing of bile composition into blood and the reverse inflow of bile into the blood and lymph, which is the leading cause of death (2).

The main treatment for malignant biliary obstruction is resection and drainage (3). However, due to the malignancy of the tumor itself and its special anatomical structure, most patients have lost the opportunity of radical surgery at the time of diagnosis. Therefore, 90% of patients diagnosed with malignant biliary obstruction can only benefit from palliative resection (4). In addition, effective preoperative drainage can significantly improve the prognosis of patients undergoing radical surgery (4). The harm of malignant biliary obstruction is not only the tumor itself but also the organ damage caused by hyperbilirubinemia. Therefore, effective biliary drainage is an important treatment for patients in the advanced stage. Reducing jaundice can protect liver and kidney function, improve quality of life and prolong survival (5). Tibble et al (6), have revealed that due to the delayed diagnosis, the resectability of high biliary tract tumors is only 15-20%. Therefore, removing obstruction, unobstructed drainage and rapid and effective reduction of jaundice is the key to treatment. According to bile discharge methods, preoperative biliary drainage can be divided into internal drainage and external drainage, and based on the drainage pathway, it can be divided into percutaneous transhepatic biliary drainage (PTBD) and endoscopic biliary drainage (EBD) (7). However, the method of preoperative biliary drainage is still controversial. Some scholars believe that PTBD is prone to complications such as pancreatitis, cholangitis, biliary perforation, biliary bleeding and stent displacement (8). However, other studies have found...
that compared with EBD, PTBD causes less surgical trauma, fewer complications and faster bilirubin decrease (9).

At present, the specific selection of preoperative biliary drainage methods for malignant obstructive jaundice has not been determined. In this meta-analysis, therefore, the advantages and disadvantages of these two drainage methods were analyzed from the perspective of tumor implantation metastasis after drainage. In addition, all included controlled clinical trials were designed to compare the incidence rate of implantation metastasis between EBD and PTBD in preoperative biliary drainage of MOJ, in order to provide references for clinical application.

Materials and methods

Search strategy. PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=), Embase (https://www.embase.com/), Web of Science (www.isiknowledge.com/) and Cochrane Library (https://www.cochranelibrary.com/) were utilized. Literature published from the database establishment to January 2019 as well as similar literature and references attached to the search results were consulted. The retrieval strategy was ‘malignant obstruction jaundice’ (Title/Abstract) or ‘perihilar cholangiocarcinoma’ (Title/Abstract) or ‘distal cholangiocarcinoma’ (Title/Abstract) or ‘pancreatic cancer’ (Title/Abstract) and ‘preoperative biliary drainage’ (Title/Abstract) or ‘percutaneous transhepatic biliary drainage’ (Title/Abstract) or ‘endoscopic biliary drainage’ (Title/Abstract) and ‘seeding metastasis’ (Title/Abstract) or ‘peritoneal metastasis’ (Title/Abstract).

Inclusion and exclusion criteria. The inclusion criteria were as follows: i) Clinical study of preoperative biliary drainage in patients with MOJ; ii) EBD and PTBD were preoperative biliary drainage methods; iii) The incidence rate of implantation metastasis was the main objective of the study; iv) The methodology used in the study was reliable; and v) The data provided were complete and accurate. The exclusion criteria were as follows: i) Irrelevant or in vitro experiments; ii) Case report, review, letter or conference paper; or iii) Repeated reports. If the data of a center were published numerous times, the most recently published data would be selected. If a study was reported more than once, the data with the longest follow-up time would be used.

Data extraction and quality assessment. Two reviewers independently read the literature titles and abstracts according to the aforementioned inclusion and exclusion criteria and after excluding the studies that evidently did not meet the inclusion criteria, the full text of the remaining studies was read to determine whether they met the inclusion criteria and extract relevant data. In case of disagreement, inclusion was determined by a third reviewer. The extracted contents included: i) General information: Title, first author, publication date and literature source; ii) Research characteristics: Grouping methods and included cases of the subjects; iii) Outcome index (incidence rate of implantation metastasis); and iv) Information related to literature quality assessment.

Two reviewers evaluated the quality of the included studies according to the Newcastle Ottawa scale (NOS) (10) and the third reviewer evaluated the study when the scores were inconsistent. The full score of the NOS is 9 points, and the evaluation criteria include the selection, comparability and outcome of the cohort studies. Selection indicates the selection of cases and controls with a total score of 4, including the typicality of the exposed cohorts (1 score), non-exposed cohorts from the same community (1 score), reliable determination of exposure (1 score), and the presented outcomes at the beginning of the study (1 score). Comparability indicates the comparability of cases and control group with a total score of 2, including the control of the most important confounders (1 score) and the control of other confounders (1 score). Outcome indicates methods of investigation and assessment of exposure with a total score of 3, including independent blind evaluation (1 score), adequate follow-up time (1 score) and full follow-up of all subjects (1 score). The study with a score equal to or greater than 6 points is divided into a high-quality study.

Intervention measures and observed indicators. Intervention measures were as follows: PTBD, percutaneous transhepatic biliary drainage, including internal drainage and external drainage, EBD, endoscopic biliary drainage, including internal drainage and external drainage.

Observed indicators were as follows: Implantation metastasis, (a) The area through which the catheter passed, including the skin poke and the abdominal chest wall layer; (b) Right pleural implantation metastasis; (c) Peritoneal implantation metastasis; (d) Intrahepatic metastasis; and (e) Surgical success rate. Deaths in hospital and severe postoperative complications (such as infection) were considered surgical failures. Catheter-related implantation metastasis included (a) (b) (d).

Statistical analysis. Meta-analysis was performed using the RevMan5.3.0 software provided by the Cochrane Collaboration. Heterogeneity between studies was analyzed. P<0.05 or I²<50% indicated that there was a small possibility of heterogeneity among studies, and the fixed effect models were used. Conversely, P<0.05 or I²>50% indicated that there was heterogeneity among the studies, and the random effect models were used. Enumeration data were analyzed according to the odds ratio (OR), and the 95% confidence interval (95% CI) was calculated. The funnel plot was drawn by RevMan5.3.0 software to determine whether there were any publication biases.

Results

Study selection and study characteristics. Ten studies were included (9,11-19), including six for hilar cholangiocarcinoma, two for distal cholangiocarcinoma, and two for pancreatic carcinoma. The retrieval and screening processes are presented in Fig. 1. Baseline data of the included literature are presented in Table I. All the studies included PTBD and EBD schemes, all of which were retrospective cohort studies with NOS scores ranging from 7 to 8 points, as presented in Table II.

Comparison of the effects of EBD and PTBD on the overall incidence rate of implantation metastasis in resected MOJ. A total of ten studies reported the comparison of the incidence rate of implantation metastasis. The results of the heterogeneity
analysis ($I^2=53\%$, $P=0.02$) demonstrated that there was heterogeneity among the studies, and the random effect model was used for analysis. Meta-analysis results revealed that the overall incidence rate of implantation metastasis in the EBD and PTBD groups was 11.2% (1379/1230) and 21.2% (1085/1078), respectively, with statistically significant differences between the two groups ($OR=0.35$, 95% CI: 0.23-0.53, $P<0.00001$; Fig. 2).

Comparison of the effects of EBD and PTBD on the incidence rate of different types of implantation metastases in resected MOJ. Implantation metastases can be divided into peritoneal metastasis and catheter-related implantation metastasis. The subgroup analysis results revealed that the incidence rates of catheter-related implantation metastasis and peritoneal implantation metastasis in the EBD and PTBD groups were 2.1% (26/1230) vs. 6.4% (69/1078) and 10.5% (116/1101) vs. 19.3% (138/716), respectively, and the differences were statistically significant ($OR=0.23$, 95% CI: 0.12-0.44, $P<0.00001$; and $OR=0.47$, 95% CI: 0.31-0.74, $P=0.0008$; Fig. 3).
Comparison of the effects of EBD and PTBD on the surgical success rate in resected MOJ. A total of 5 studies reported the comparison of the surgical success rate. The heterogeneity analysis results ($I^2=43\%$, $P=0.14$) demonstrated that there was no obvious heterogeneity among the studies, and fixed effect model analysis was used. Meta-analysis results revealed that the surgical success rate of the EBD and the PTBD groups were 96.6\% (676/700) and 94.6\% (372/393), respectively, and there was no statistically significant difference between the two groups (OR=1.52, 95% CI: 0.82-2.82, $P=0.19$; Fig. 5).

Publication bias analysis. A funnel plot was used to analyze the incidence rate of implantation metastasis in the EBD and PTBD groups, and the results revealed that funnel plot was basically symmetrical, indicating that publication bias had little impact on meta-analysis results (Fig. 6).

Discussion

Implantation metastasis is an important metastatic route for abdominal malignancy and invasive procedures, while preoperative biliary drainage may directly or indirectly increase the risk of implantation metastasis (20). In this meta-analysis, the incidence rate of implantation metastasis in the application of two common preoperative biliary drainage methods was analyzed, and it was found that the incidence rate of implantation metastasis in EBD was lower than that in PTBD for resected MOJ.

Surgery remains the most effective treatment for resected hepatobiliary and pancreatic malignancies (21). For malignant hepatobiliary and pancreatic tumors with obstructive jaundice, how to effectively remove biliary obstruction and reduce hyperbilirubinemia is of great importance to improve the success rate of surgery. However, a growing body of studies have found that preoperative biliary drainage (PBD) cannot prolong the survival of MOJ patients, and it extends the length of hospital stay and increases the postoperative complications (22). Nevertheless, the US (23), European (24) and Japanese (25) guidelines recommend appropriate PBD for patients with MOJ. However, there remains controversy in the international hepatobiliary and pancreatic community about which drainage method to select: The European and American guidelines recommend PTBD, while the Japanese guidelines strongly recommend EBD. Compared with EBD, PTBD surgery is simple and easy to perform. The latest meta-analysis confirmed that PTBD was more effective in reducing postoperative complications than EBD (26.5\% vs. 44.3\%, $P=0.0009$) (26). As supporters of the EBD procedure, the Japanese consider implantation metastasis as the most important factor (27).

Implantation metastasis is one of the distant metastatic pathways of abdominal malignant tumors. It can be divided into direct dissemination and hematogenous or lymphatic dissemination according to the metastatic pathway, and into thoracoperitoneal implantation and body wall implantation according to implantable location. Hepatobiliary and
pancreatic malignancies, especially hilar cholangiocarcinoma, are more prone to implantation metastasis due to their unique anatomical location. A study found that implantation metastasis occurred in up to 15.9% of patients with MOJ, even without preoperative biliary drainage (11).

In this meta-analysis, the total implantation metastasis rate of preoperative biliary drainage was 13.6% (336/2464), with 9.6% (132/1379) and 18.8% (204/1085) in the EBD and PTBD groups, respectively, and the difference was statistically significant (P<0.00001). In addition, PTBD significantly increased

<table>
<thead>
<tr>
<th>Author (refs.)</th>
<th>Publication year</th>
<th>Selection</th>
<th>Comparability</th>
<th>Outcome</th>
<th>Total</th>
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<tbody>
<tr>
<td>Higuchi et al (11)</td>
<td>2017</td>
<td>4</td>
<td>1</td>
<td>2</td>
<td>7</td>
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<tr>
<td>Hirano et al (12)</td>
<td>2014</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Hwang et al (13)</td>
<td>2012</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Kawakami et al (14)</td>
<td>2011</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>8</td>
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<tr>
<td>Komaya et al (15)</td>
<td>2016</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>7</td>
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<td>2</td>
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<td>Miura et al (17)</td>
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<tr>
<td>Wiggers et al (9)</td>
<td>2015</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>8</td>
</tr>
</tbody>
</table>

*NOS was used to evaluate the quality of included cohort studies. The criteria for NOS scores include the following three aspects: Selection, selection of cases and controls (the total score is 4): A, the typicality of the exposed cohorts (1 score); b, non-exposed cohorts come from the same community (1 score); c, reliable determination of exposure (1 score); d, the outcomes at the beginning of the study were not presented (1 score). Comparability, comparability of cases and control group (the total score is 2): A, the most important confounders were controlled (1 score); b, other confounders were also controlled (1 score). Outcome, methods of investigation and assessment of exposure (the total score is 3): A, independent blind evaluation (1 score); b, adequate follow-up time (1 score); c, all subjects were followed-up completely (1 score). The study with a score equal to or greater than 6 was deemed a high-quality study. NOS, Newcastle Ottawa scale.

Figure 3. Forest plot of the incidence rate of different types of implantation metastases in resected MOJ.
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The risk of catheter-related implantation metastasis (4.3% vs. 0.6%, P<0.0001). In conclusion, the prevalence and poor prognosis of implantation metastasis after PTBD surgery indicates that attention must be paid to the problem of implantation metastasis after PBD surgery.

Although this meta-analysis studies the effect of drainage in MOJ, drainage is not necessary for MOJ in some cases. Some scholars theorize that pancreaticoduodenectomy can be performed without cholangitis in the presence of obstructive jaundice (28). All the ten studies included in this study were retrospective cohort studies that were clearly grouped, and no selective results were reported. Although literature retrieval and strict inclusion criteria were utilized in the present study, there are still limitations. In spite of the retrieval procedure adopted widely, some data such as supplements, conference papers, and certain grey literature were unavailable. Furthermore, as the original data of the included studies were not sufficient, the meta-analysis could only comment on relevant indicators, thus potential publication bias cannot be avoided. In addition, a large number of patients underwent preoperative biliary drainage in the studies included, and no control group was set up. Hence, the results of this study may have been influenced by the indication of preoperative biliary drainage, and the conclusion of this study may not be widely applicable to other cases.

### Table 1: Comparison of surgical success rates between EBD and PTBD

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>EBD</th>
<th>PTBD</th>
<th>Odds ratio (M-H, Random, 95% CI)</th>
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<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Total</td>
<td>M-H, Random, 95% CI</td>
</tr>
<tr>
<td></td>
<td>Events</td>
<td>Events</td>
<td>Weight</td>
</tr>
<tr>
<td>1.3.1 hilar cholangiocarcinoma</td>
<td>31</td>
<td>87</td>
<td>13.0%</td>
</tr>
<tr>
<td>Higuchi 2017</td>
<td>11</td>
<td>76</td>
<td>13.0%</td>
</tr>
<tr>
<td>Hirano 2014</td>
<td>3</td>
<td>74</td>
<td>7.4%</td>
</tr>
<tr>
<td>Kwak 2012</td>
<td>0</td>
<td>122</td>
<td>2.0%</td>
</tr>
<tr>
<td>Komaya 2017</td>
<td>25</td>
<td>150</td>
<td>16.6%</td>
</tr>
<tr>
<td>Wiggers 2015</td>
<td>25</td>
<td>147</td>
<td>13.9%</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>685</td>
<td>685</td>
<td>54.7%</td>
</tr>
<tr>
<td>Total events</td>
<td>64</td>
<td>120</td>
<td></td>
</tr>
</tbody>
</table>

### Figure 4: Forest plot of the incidence rate of implantation metastasis in different parts of resected MOJ.

### Figure 5: Forest plot of the surgical success rate in resected MOJ.

### Figure 6: Funnel plot for publication bias assessment.

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For more detailed analysis and results, please refer to the full text of the article.
of retrospective cohort studies were included in this study, lacking large sample, multi-center randomized controlled studies. There was no clear definition of MOJ implantation metastasis. Intrahepatic metastasis belongs to the implantation metastasis related to PBD of pancreatic carcinoma, but it is controversial for hilar cholangiocarcinoma and distal cholangiocarcinoma (29). The categories of implantable abdominal metastasis are different, and the definitions of abdominal invasion, abdominal dissemination and abdominal metastasis are confounding. The PBD schemes included in the studies were different, and the PBD including PTBD and EBD technologies used varied among hospitals, resulting in heterogeneity of the studies, which may affect the evidence strength and credibility of the results of this meta-analysis. In addition, there was no significant difference in the surgical success rate between the two groups. Due to the limitation of the original research, there is a lack of relevant research in western countries. Therefore, more studies in western countries are expected to be carried out to draw more convincing conclusions.

In conclusion, this meta-analysis indicated that the incidence rate of implantation metastasis in EBD was lower than that in PTBD for resected MOJ. However, it should be noted that at present, sufficient evidence-based medicine is still lacking. In view of the lack of multi-center randomized controlled studies with a large sample size and the limitations of the literature quality, the aforementioned results should be confirmed by future studies.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

GY, YX, JL and JS collected the data. TT, WL and GW analyzed the data. GY and JL prepared and wrote the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References


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