INPLASY PROTOCOL

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Review Stage at time of this submission: **Preliminary searches.**

Conflicts of interest:
None declared.

Photodynamic therapy with or without systemic chemotherapy for unresectable extrahepatic cholangiocarcinoma: protocol for a systematic review and meta-analysis

Wang, YY[1]; Wang, N[2]; Wang, BF[3]; Ma, CH[4]; Yu, R[5]; Wang, XY[6]; Yu, Y[7]; Chen, H[8].

Review question / Objective: **This study will evaluate all studies on the results of photodynamic therapy(PDT) alone, synergized with chemotherapy and chemotherapy alone on unresectable extrahepatic cholangiocarcinoma(ECC), aiming to clarify the significance of PDT in improving the outcomes of ECC patients.**
Information sources: **We will search the PubMed, Cochrane Library, Embase, Web of science, CBM, CNKI, and Wanfang Data. All searches on these databases will be conducted from their inception to July 2022. We will also perform a manual search using the Google scholar and track the bibliographies of potentially included article to retrieve relevant gray literatures.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 21 June 2022 and was last updated on 21 June 2022 (registration number INPLASY202260086).

INTRODUCTION

Review question / Objective: **This study will evaluate all studies on the results of photodynamic therapy(PDT) alone, synergized with chemotherapy and chemotherapy alone on unresectable extrahepatic cholangiocarcinoma(ECC), aiming to clarify the significance of PDT in improving the outcomes of ECC patients.**

Condition being studied: **Unresectable extrahepatic cholangiocarcinoma.**

METHODS

Search strategy: A combination of subject terms with free-text terms will be used to conduct these searches. The following terms will be selected and adapted for search in the corresponding databases: “Cholangiocarcinoma”, “Cholangiocellular Carcinoma”, “Bile Duct Neoplasm”, “Bile Duct Cancer”, “Bile Duct Carcinoma”, “Photochemotherapy”, “Photodynamic”, “Phototherapy”, “PDT” in English databases and “胆管上皮癌”, “胆管细胞癌”, “胆管肿瘤”, “胆管癌”, “胆道肿瘤”, “胆道癌”, “胆总管肿瘤”, “光化学”, “光动力”, “PDT” in Chinese databases. These terms will also combined for Google scholar search and the top 200 most relevant items of the results will be screened to identify potential additional studies.

Participant or population: Patients who are diagnosed as ECC by pathological examination or reliable radiologic imaging will be included. Both of hilar or distalcholangiocarcinoma will be eligible. All patients should be unresectable according to an acceptable criterion. There are no restrictions on patients’ age, sex, race, or place of residence. Patients will be exclude if they meets the following criteria: 1)receiving a curative surgery; 2)concurrence of other local therapy for tumor control in addition to PDT, such asradiation therapy and transcatheter arterial chemoembolisation; 3) incomplete data present; 4) without enough follow-up time.

Intervention: PDT combined with chemotherapy. PDT should be performed by endoscopic retrograde cholangiography or percutaneous transhepatic choledochoscopy. The intraoperative PDT are not eligible. Bile duct stents may be utilized as an adjuvant. There are not limitations on the protocol of PDT procedure, including the type of photosensitizer and optical fiber, illuminatedparameters, and period and course of PDT. Chemotherapy are the routine regimens recommended by ECC guidelines. The specific chemotherapy drugs can be selected by the overall consideration of drug accessibility and patient condition. Both first-line chemotherapy or later lines will be included. For patientstreated with PDT plus chemotherapy, they should receive both PDT and chemotherapy no matter which is applied first.

Comparator: PDT alone or chemotherapy alone. PDT should be performed by endoscopic retrograde cholangiography or percutaneous transhepatic choledochoscopy. The intraoperative PDT are not eligible. Bile duct stents may be utilized as an adjuvant. There are not limitations on the protocol of PDT procedure, including the type of photosensitizer and optical fiber, illuminated parameters, and period and course of PDT. Chemotherapy are the routine regimens recommended by ECC guidelines. The specific chemotherapy drugs can be selected by the overall consideration of drug accessibility and patient condition. Both first-line chemotherapy or later lines will be included.

Study designs to be included: All randomized controlled trials (RCTs) or retrospective controlled study published in Chinese or English will be considered. Studies without available full text will be excluded.

Eligibility criteria: Reported in P.I.C.O.S. items. None additional.

Information sources: We will search the PubMed, Cochrane Library, Embase, Web of science, CBM, CNKI, and Wanfang Data. All searches on these databases will be conducted from their inception to July 2022. We will also perform a manual search using the Google scholar and track the bibliographies of potentially included article to retrieve relevant gray literatures.

Main outcome(s): The primary outcomes are efficacy-related, including overall survival (OS) and treatment response. OS is defined as the time from PDT initiation to death of any cause or the censored date

during follow up. Treatment response is evaluated based on the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. Safety will be assessed as the secondary outcome. For safety assessment, any adverse events with their severity should be recorded.

Data management: All study records will be processed through EndNote X9, which can identify and remove duplicates. All extracted data will be stored in a Microsoft Excel spreadsheet. According to the established inclusion and exclusion criteria, two researchers will independently screen the titles and abstracts of records identified in the initial search and will subsequently check the full texts of the selected studies. Disagreements will be resolved by face-to-face discussion or consultation for a third researcher. A pre-designed form will be used by two independent researchers to collect the data of included studies and consensus will be reached by discussion during the data extract. During the data extract, we will include the bibliographic information (i.e., the title, author's name, publicationyear, country, and type of study), the patient's general characteristics (i.e., sample size, patient age, sex, location of tumor, TNM stage, pathological information, Bismuth classification, and comorbidity), intervention information (i.e., methods of PDT surgery, PDT protocol, usage of stents, chemotherapy regimens, lines of chemotherapy, details of PDT chemotherapy strategy, and other combined treatments), and outcome indicators (i.e., survival and safety-related statistical indicators).

Quality assessment / Risk of bias analysis: Two researchers will independently assess the quality of each included non-RCT using the tool of Newcastle-Ottawa Scale (NOS score). Scores of the NOS are split into three aspects: object selection, inter-group comparability and outcome measurement. It is generally considered that an article with a score 0–5 point(s) is of low quality, and an article with a score >6 is of high quality. For RCTs, the Cochrane Collaboration Risk of Bias tool will be used for quality assessment from the following seven fields: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias. Each field will be judged as low, high, or unclear risks based on the defined standard.

Strategy of data synthesis: All statistical analysis will be conducted by the R software (version 4.0.2). Comparison between two groups will be performed for benefits analysis. HR value with 95%CI will be pooled for each comparison to determine the survival difference in patients treated with different interventions. OR with 95%CI will be used for adverse events evaluation by collecting the number of corresponding events from different intervention groups. HR and 95%CI will be first obtained from the reported data of the included studies. If the required HR and 95%CI is not reported, they will be extracted from the survival curves by using the Engauge Digitizer software (version 4.1). ln (HR) and SEln (HR) will be calculated for survival data as the generic inverse variance method is used during data combination. The fixed-effect model will be used if the combined data are homogenous, otherwise, the random effect model will be used. The heterogeneity will be assessed qualitatively by $\chi 2$ test and quantitatively by I^2 statistic. $\chi 2$ p values 50% are defined as substantial heterogeneity. The reporting bias will be assessed graphically by a funnel plot, and statistically using Egger's testify 10 or more studies are available. A p value<0.05 will be considered having potential publication biases.

Subgroup analysis: Subgroup will be performed when appropriate to explore the sources of heterogeneity. All tests are two-side tests, and a p value< 0.05 will be considered statistically significant.

Sensitivity analysis: Sensitivity analysis will be performed when appropriate to explore the sources of heterogeneity. All tests are

two-side tests, and a p value< 0.05 will be considered statistically significant.

Country(ies) involved: China.

Other relevant information: The Grading of Recommendation, Assessment, Development and Evaluation method will be applied to assess the level of evidence obtained from this systematic review.

Keywords: protocol, extrahepatic cholangiocarcinoma, photodynamic therapy, chemotherapy, systematic review, meta-analysis.

Dissemination plans: The results will be sought for publication in a peer-reviewed journal and all data will be deposited in public databases.

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