Digestive and Liver Disease 48 (2016) 717–725

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Review Article

Clinical prognostic significance of regional and extended lymphadenectomy for biliary cancer with para-aortic lymph node metastasis: A systematic review and meta-analysis

Jinyang Gu[a,1], Lei Xia[a,1], Biyun Xu[b], Tianfei Lu[a], Obulkasim Halmurat[c], Jun Wang[c], Jianjun Zhang[a], Yitao Ding[c], Qiang Xia[a,*]

[a] Department of Liver Surgery, Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China
[b] Department of Biostatistics, Affiliated DrumTower Hospital of Nanjing University Medical School, Nanjing, China
[c] Department of Hepatobiliary Surgery, Affiliated DrumTower Hospital of Nanjing University Medical School, Nanjing, China

ARTICLE INFO

Article history:
Received 21 August 2015
Accepted 29 March 2016
Available online 4 April 2016

Keywords:
Adjuvant therapy
Biliary cancer
Extended lymphadenectomy
Micrometastasis
Para-aortic lymph node metastasis

ABSTRACT

Background: The aim of our study was to evaluate clinical prognostic significance of regional and extended lymphadenectomy for biliary cancer with para-aortic lymph node metastasis.
Methods: A thorough literature search was performed in PubMed/Medline, Cochrane Central Register, Embase, ISI Web of Science and Google Scholar between January 1965 and May 2014 with restricted articles for the English language. Data were processed for a meta-analysis by RevMan 5 software.
Results: Altogether 10 retrospective studies were finally enrolled in our study. For positive para-aortic lymph node group irrespective of regional lymph node metastasis, the overall 1-, 3-, 5-yr pooled RR estimates of survival rates were 2.30, 1.70, and 1.42. There were significant differences between positive para-aortic lymph node group and negative group. For positive para-aortic lymph node group in the setting of regional lymph node metastasis, the overall 1-, 3-, 5-yr pooled RR estimates of survival rates were 1.57, 1.29, and 1.11, respectively. The long-term outcomes referred to 5-yr survival rate were similar between para-aortic lymph node metastasis and regional lymph node metastasis only.
Discussion: Radical resection with extended lymphadenectomy should be caution in terms of the results of an intraoperative sampling biopsy of para-aortic lymph node, which requires a well-designed, prospective controlled study in the future.

1. Introduction

Biliary cancer including intrahepatic cholangiocarcinoma (ICC), hilar cholangiocarcinoma (HC), gallbladder carcinoma, distal cholangiocarcinoma and ampullary carcinoma (AC), represents a prevalent and highly fatal malignancy of the whole biliary tract with dismal prognosis due to the absence of specific symptoms associated with cancer in early-stage patients [1]. Up to date, surgical approaches such as major hepatectomy, extrahepatic bile duct resection, pancreatoduodenectomy, vascular resection and reconstruction, as well as even liver transplantation with neoadjuvant radiochemotherapy remain the ideal alternative to achieve curative treatment for such population [2,3]. However, its preference for spreading into lymphatic vessels results in an unfavorable long-term outcome especially in patients with advanced biliary carcinomas [4]. Therefore, some experienced surgeons mainly from Japan recently advocate more aggressive surgical resection consisting of en bloc hepatopancreatoduodenectomy, and regional or extended lymph node dissection so as to obtain sufficient tumor-free surgical margins or R0 resection in spite of a relatively high surgical morbidity and mortality [5,6].

Theoretically, metastasis of para-aortic node as the final station in the abdominal lymphatic system is predictive of a very poor prognosis in patients with biliary cancer, which is regarded as a distant metastasis similar to hepatic or peritoneal involvement by many clinicians [7]. However, several recent pilot studies have explored this possibility with mixed results [8–10]. Murakami et al. reported a 64-year-old woman diagnosed as peripheral ICC underwent a left hemihepatectomy with wide lymph node dissection. Seven of 12 para-aortic lymph nodes metastasis was proved by biopsy and intraoperative pathologic examination. Surprisingly, the patient had survived for 7 years without evident recurrence [8]. Another two individual cases with ICC or gallbladder cancer (GBC) from

* Corresponding author. Tel.: +86 13661889035.
E-mail address: xiaqiang@medmail.com.cn (Q. Xia).
[1] These authors equally contributed to this work.

http://dx.doi.org/10.1016/j.dld.2016.03.019
1590-8658/

Japan both achieved a tumor-free long-term survival in the presence of positive para-aortic lymph node before surgery [9,10]. Since regional and para-aortic lymphadenectomy has not been routinely performed in almost all clinical centers, there is no consensus about the prognostic significance of regional and extended lymphadenectomy for biliary cancer with para-aortic lymph node metastasis. The purpose of our study was to conduct a meta-analysis of the published literature concerning the efficacy and safety of extended lymphadenectomy in patients with biliary cancer when para-aortic lymph node metastasis is confirmed.

2. Methods

This is a systematic review including a meta-analysis, which was performed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement [11] and the Cochrane Handbook for Systematic Reviews of Interventions [12].

2.1. Search strategy and selection criteria

Two authors (J.Y.G. and O.H.) independently searched the online databases of medical literature (PubMed/Medline, Cochrane Central Register, Embase, ISI Web of Science and Google Scholar) for all levels of evidence published in print or electronically in English from January 1965 to May 2014. A global literature search was undertaken by combinations of the following search terms: "cholangiocarcinoma" or "cholangiocellular carcinoma" or "bile duct cancer (BDC)" or "biliary cancer" or "gallbladder cancer" or "carcinoma of ampulla" or "ampullary carcinoma", and "para-aortic node" or "paraaortic node" for the purpose of the prognostic significance of regional and extended lymphadenectomy for biliary cancer with para-aortic lymph node metastasis. Further manual searches of reference lists from original and review articles were conducted for other potentially relevant citations. Three investigators (J.Y.G, J.W., and O.H.) reviewed the titles and abstracts of studies identified by the search strategy and discarded clearly irrelevant studies. Because of the limited number of related studies, retrospective investigations or observational studies for the purpose of the effectiveness and safety of para-aortic lymphadenectomy in the surgical treatment of diagnosed biliary malignancies were included in this meta-analysis with a minimum of 5 positive para-aortic lymph node patients in a single study. Conference abstracts, letters to the journal editors, and review articles were excluded because they contained limited data. When information in the abstract was not sufficient to determine eligibility, the full text of the article was reviewed. All studies that were potentially included should report 1-, 3-, or 5-yr survival rates. Overlapping reports such as duplicate data from a single study were identified based on matching study names, settings, and authors, which was followed by comparing sample sizes, years of data collection, and other study characteristics to select the most complete and informative report for our research question of interest. If reports came from the same study center, we only included data from the publication with the largest population. Discrepancies between the independent reviewers were resolved by means of mutual resolution.

The criteria for inclusion of trials in details were as follows: (1) only observational subjects with ICC, HC, GBC, BDC or AC excluding pancreatic head carcinoma were enrolled in this study; (2) to assure the quality of analysis, only clinical trials comparing the outcomes of para-aortic lymph node metastasis group with negative para-aortic lymph node group could be included in the study; (3) if multiple publications reported estimates based on the same study population, the largest or most recent sample was used; (4) studies must have reported patient long-term survival rates in relation to para-aortic lymph node metastasis; and (5) our search included only those original articles published in English.

2.2. Data extraction and outcome measures

Two investigators (J.Y.G. and O.H.) independently determined the eligibility of each publication for the systematic review and meta-analysis by filling in a Microsoft Excel spreadsheet and evaluating study quality, with disagreements resolved by a third reviewer (J.W.). Extracted data included general information (first author, year of publication, study center and period), baseline characteristics of participants (type of biliary cancer, gender ratio, mean age, operation procedures, number of vascular resection, in-hospital death, and adjuvant therapy), and patient survival rates from the texts, tables, and graphs of published eligible trial reports. Data summarized as total number and events for each group were extracted. Number of events was derived from the percentage reported, if possible. The risk of bias in eligible studies was assessed by a single reviewer (B.Y.X.) and checked by a second reviewer (J.Y.G.) in terms of the quality of selective outcomes. We determined whether groups were balanced at baseline and whether an intention to treat analysis was undertaken. Any disagreement was resolved by consensus.

2.3. Quality assessment

Two authors (J.Y.G. and J.W.) independently assessed the methodological quality of the included trials using the quality checklist recommended by the Cochrane Handbook [13]. The following domains on the risk of bias were assessed: randomization, patients blinded, concealment of treatment allocation, intention-to-treat analysis, and incomplete outcome. We resolved all disagreements by discussion and referral to a third author (L.X.) for adjudication.

2.4. Data synthesis and analysis

We processed data in accordance with the Cochrane Handbook for Systematic Reviews of Interventions [12]. Funnel plots and Egger's tests were created using standard techniques for detecting publication bias. For case control trials, outcome data were pooled using a random effect model weighted by the inverse variance. We calculated p values and 95% confidence intervals (CI) for each outcome. We explored heterogeneity among the included studies qualitatively (by comparing the characteristics of included studies) and quantitatively (using the χ^2 test of heterogeneity and I^2 statistic). When appropriate, we combined the results from included studies for each outcome to give an overall estimate of the treatment effect. We used a fixed effect model for meta-analysis, except where we identified statistical heterogeneity, when we used a random effect model instead. Heterogeneity between studies was considered present if the P value was less than 0.1 or I^2 was more than 50%. The meta-analyses results of continuous variables were expressed as mean differences and as risk ratios (RR) for binary outcomes with 95% CI. Meta-analyses of the binary variables were conducted on the log-odds ratios to satisfy the assumption of normality of effect sizes. Statistical analyses were performed using RevMan 5. Instead, we undertook specific stratified meta-analyses to examine the sensitivity of the findings of the review to key potential causes of heterogeneity.

2.5. Publication bias

We assessed the potential for publication bias through visual inspection of funnel plot asymmetry, and evaluated the statistical