

Systematic Review and Meta-analysis of Surgery for Hilar Cholangiocarcinoma With Arterial Resection

Artur Rebelo

Universitätsklinikum Halle: Universitätsklinikum Halle <https://orcid.org/0000-0002-5267-079X>

Jörg Ukkat

Universitätsklinikum Halle: Universitätsklinikum Halle

Johannes Klose

Universitätsklinikum Halle: Universitätsklinikum Halle

Ulrich Ronellenfitsch

Universitätsklinikum Halle: Universitätsklinikum Halle

Jörg Kleeff (✉ joerg.kleeff@uk-halle.de)

Professor of Surgery and Chairman Department of Visceral, Vascular and Endocrine Surgery, University Hospital Halle (Saale) Martin-Luther-University Halle-Wittenberg Ernst-Grube-Str. 40, 06120 Halle (Saale), Germany

Protocol

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Abstract

Objective: With the advances in multimodality treatment in the recent years, an analysis of the outcome of vascular resections in surgery of hilar cholangiocarcinoma is lacking. The aim of this meta-analysis was to summarize the currently available evidence on outcomes of patients undergoing arterial resection for the treatment of hilar cholangiocarcinoma.

Methods: A systematic literature search from PubMed/Medline, Cochrane Library, Cinahl, ClinicalTrials.gov (clinical trials registry) and WHO ICTRP (clinical trials registry,) databases will be carried out. PRISMA guidelines will be followed. Pre-defined outcomes are mortality (100-day and in-hospital), morbidity (Clavien-Dindo classification, any type of complication, surgical and medical), vascular complications (thrombosis of the portal vein or hepatic artery, stenosis of these vessels, and pseudoaneurysms), liver failure, postoperative bleeding, duration of surgery, reoperation rate, length of hospital stay, survival time, actuarial survival (2-, 3- and 5-year survival), R0/R1/R2 resection rates, proportion of patients with no resection during surgery, rate of histologic arterial invasion and lymph node positivity (number of positive lymph nodes and lymph node ratio).

Discussion: Our findings will enable us to present the current evidence on feasibility, safety and oncological effectiveness of surgery for hilar cholangiocarcinoma with arterial resection. These data will support healthcare professionals in their clinical decision-making.

Systematic review registration: PROSPERO ID 223396

Background

Cholangiocarcinoma has an estimated incidence of 1-2 per 100,000 persons per year [1] and constitutes the second most common primary hepatic malignancy [2]. The effect of systemic treatment is limited in the majority of patients and surgery with complete removal of the tumor is the only option offering a chance of cure or at least of long-term freedom from tumor with 20-30% 5-year overall survival [3] [4]. Most cholangiocarcinomas arise in the area of the bile duct bifurcation. They are commonly referred to as hilar cholangiocarcinoma or Klatskin tumor [5]. Due to the proximity of vascular structures to the bile duct bifurcation, tumor invasion of the portal vein, the proper hepatic artery or the contralateral hepatic artery (i.e. a tumor arising from the left bile duct invading the right hepatic artery) occur in a relevant proportion of cases.

Vascular and especially arterial resection and reconstruction during surgical removal of hilar cholangiocarcinoma is a debated issue. Although it is the only way of facilitating complete resection if the vessels are invaded, there are concerns of high postoperative morbidity and mortality following vascular reconstruction, including hemorrhage and liver failure, which might offset the survival advantage gained from complete removal of the tumor. However, thanks to technical improvements in microvascular anastomoses and to a growing experience with liver transplants in many centers, the surgical approaches for hilar cholangiocarcinoma have generally become more aggressive in recent

years and concurrently the number of studies assessing feasibility, safety and oncological effectiveness of arterial resection and reconstruction has been growing [6] [7] [8] [9] [10].

In order to summarize the currently available evidence on the topic, we plan to conduct a systematic review with meta-analysis.

Methods

The literature search and data analysis will be conducted in accordance with the PRISMA guidelines [11]. The study has been registered in the PROSPERO database [12].

Search Strategy

The PubMed/Medline, Cochrane Library, Cinahl, ClinicalTrials.gov (clinical trials registry) and Web of Science Core Collection databases will be searched for this study through their respective online search engines. The search will be performed on studies published between database inception and a defined search date. The search strategies used in the single databases are displayed in the support material 1. Furthermore, the reference lists of the included studies will be manually searched to find relevant articles. Abstracts and full-text reviews will be evaluated independently in an unblinded standardized manner by two authors in order to assess eligibility for inclusion or exclusion. Disagreements between reviewers will be resolved by consensus; if no agreement could be reached, a third reviewer will decide whether to include the respective study.

Inclusion and Exclusion Criteria

Articles in English, German, Spanish, Portuguese and Italian language will be considered. Studies reporting resection of cholangiocarcinoma, both primary and secondary, in curative intent including resection of a segment of the hepatic artery with a control group of patients undergoing resection without arterial resection will be included. Studies with an irrelevant abstract or title will be excluded, as will be reviews, case reports, case series with less than five patients, comments and letters. Details of the study selection process will be summarized in a flowchart.

Data collection

Studies will be analyzed, and data will be extracted separately by two authors and presented in a tabular fashion. The following descriptive data will be documented for each selected study: first author, year of publication, inclusion period, country where the study was conducted, sample size and median follow up time. Patient and operation characteristics will be documented: age, gender, ASA classification, ECOG performance status, preoperative chemotherapy, type of operation, type of vessel resection and reconstruction, duration of surgery and blood loss. The following predefined outcomes will be also extracted:

- Mortality (100-day and in-hospital)

- Morbidity (Clavien-Dindo classification [8], any type of complication, surgical and medical)

- Vascular complications (thrombosis of the portal vein or hepatic artery, stenosis of these vessels, and formation of pseudoaneurysms)

- Liver failure (as defined in the included studies)

- Postoperative bleeding, survival time, actuarial survival (2-, 3- and 5-year survival), R0/R1/R2 resection rate, proportion of patients with no resection during surgery, rate of histologic arterial invasion and lymph node positivity (number of positive lymph nodes and lymph node ratio)

- Reoperation rate

- Length of hospital stay

- Survival time

- Actuarial survival (2-, 3- and 5-year survival)

- R0/R1/R2 resection rates

- Proportion of patients with no resection during surgery

- Rate of histologic arterial invasion

- Lymph node positivity (number of positive lymph nodes and lymph node ratio)

Risk of bias will be assessed using the ROBINS-I tool (risk of bias in non-randomized studies of interventions) [8].

Statistical analysis

A meta-analysis will be performed with:

- Mortality (100-day and in-hospital)

- Morbidity (Clavien-Dindo classification [13], any type of complication, surgical and medical)

- Vascular complications (thrombosis of the portal vein or hepatic artery, stenosis of these vessels, and formation of pseudoaneurysms)

- Liver failure (as defined in the included studies)

- Postoperative bleeding, survival time, actuarial survival (2-, 3- and 5-year survival), R0/R1/R2 resection rate, proportion of patients with no resection during surgery, rate of histologic arterial invasion and lymph node positivity (number of positive lymph nodes and lymph node ratio)

- Reoperation rate

- Length of hospital stay

- Survival time

- Actuarial survival (2-, 3- and 5-year survival)

- R0/R1/R2 resection rates

- Proportion of patients with no resection during surgery

- Rate of histologic arterial invasion

- Lymph node positivity (number of positive lymph nodes and lymph node ratio)

The Review Manager (RevMan) software, version 5.3 (Cochrane Collaboration, Oxford, UK) will be used. The magnitude of the effect estimate will be visualized by forest plots. An odds ratio (OR) will be calculated for binary data and the weighted mean difference for continuous data. The 95% confidence interval (CI), heterogeneity and statistical significance will be reported for each outcome. The X^2 and the Kruskal-Wallis tests will be used for the evaluation of statistical significance. $P < 0.05$ will be considered to be statistically significant. When the studies do not report mean and standard deviation, these will be calculated using the methods described by the guidelines of the Cochrane Collaboration [14] and Hozo et al. [15]. As not all studies report individual patient data or hazard ratios, the survival analysis will be performed with weighted rates. Subgroup analysis for patients with portal vein resection and patients who had undergone neoadjuvant chemotherapy prior to resection will be performed.

Discussion

This systematic review with meta-analysis will summarize the available evidence on feasibility, safety and oncological effectiveness of arterial resection and reconstruction during surgical removal of hilar cholangiocarcinoma. It will be conducted according to a defined protocol following the recommendations stipulated in the PRISMA statement [6]. The expected results will support healthcare professionals in their clinical decision-making

Abbreviations

ASA: American Society of Anesthesiologists

CI: Confidence Interval

ECOG: Eastern Cooperative Oncology Group

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

RevMan: Review Manager

ROBINS-I tool: Risk of bias in non-randomized studies of interventions

OR: Odds Ratio

WHO ICTRP: World Health Organisation International Clinical Trials Registry Platform

Declarations

Ethics approval and consent to participate - Not applicable

Consent for publication - Not applicable

Availability of data and materials - Not applicable

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

AR outlined, wrote and drafted the manuscript. All authors critically revised the manuscript and read and approved the final version of the manuscript.

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References

[1] Young, A. L., Prasad, K. R., Toogood, G. J., & Lodge, J. P. (2010). Surgical treatment of hilar cholangiocarcinoma in a new era: comparison among leading Eastern and Western centers, Leeds. *J Hepatobiliary Pancreat Sci*, 17(4), 497–504. <https://doi.org/10.1007/s00534-009-0203-6>

- [2] Khan, S. A., Thomas, H. C., Davidson, B. R., & Taylor-Robinson, S. D. (2005). Cholangiocarcinoma. *Lancet* (London, England), 366(9493), 1303–1314. [https://doi.org/10.1016/S0140-6736\(05\)67530-7](https://doi.org/10.1016/S0140-6736(05)67530-7)
- [3] Ito, F., Cho, C. S., Rikkers, L. F., & Weber, S. M. (2009). Hilar cholangiocarcinoma: current management. *Ann Surg*, 250(2), 210–218. <https://doi.org/10.1097/SLA.0b013e3181afe0ab>
- [4] Hidalgo, E., Asthana, S., Nishio, H., Wyatt, J., Toogood, G. J., Prasad, K. R., & Lodge, J. P. (2008). Surgery for hilar cholangiocarcinoma: the Leeds experience. *Eur J Surg Oncol*, 34(7), 787–794. <https://doi.org/10.1016/j.ejso.2007.10.005>
- [5] Klatskin, G. (1965). Adenocarcinoma of the hepatic duct at its bifurcation within the porta hepatis. An unusual tumor with distinctive clinical and pathological features. *The american journal of medicine*, 38, 241–256. [https://doi.org/10.1016/0002-9343\(65\)90178-6](https://doi.org/10.1016/0002-9343(65)90178-6)
- [6] She, W. H., Cheung, T. T., Ma, K. W., Tsang, S. H. Y., Dai, W. C., Chan, A. C. Y., & Lo, C. M. (2020). Vascular resection and reconstruction in hilar cholangiocarcinoma. *ANZ J Surg*, 90(9), 1653–1659. <https://doi.org/10.1111/ans.15969>
- [7] Matsuyama R, Mori R, Ota Y, Homma Y, Kumamoto T, Takeda K, Morioka D, Maegawa J, Endo I. Significance of Vascular Resection and Reconstruction in Surgery for Hilar Cholangiocarcinoma: With Special Reference to Hepatic Arterial Resection and Reconstruction. *Ann Surg Oncol*. 2016 Aug;23(Suppl 4):475-484. doi: 10.1245/s10434-016-5381-2. Epub 2016 Jul 7. PMID: 27387681.
- [8] Heinrich S, Baumgart J, Mittler J, Lang H. Gefäßrekonstruktionen in der Leberchirurgie [Vascular reconstruction in hepatic surgery]. *Chirurg*. 2016 Feb;87(2):100-7. German. doi: 10.1007/s00104-015-0144-3. PMID: 26787168.
- [9] Mizuno T, Ebata T, Yokoyama Y, Igami T, Yamaguchi J, Onoe S, Watanabe N, Kamei Y, Nagino M. Combined Vascular Resection for Locally Advanced Perihilar Cholangiocarcinoma. *Ann Surg*. 2020 Sep 24. doi: 10.1097/SLA.0000000000004322. Epub ahead of print. PMID: 32976284.
- [10] Govil S, Reddy MS, Rela M. Surgical resection techniques for locally advanced hilar cholangiocarcinoma. *Langenbecks Arch Surg*. 2014 Aug;399(6):707-16. doi: 10.1007/s00423-014-1216-4. Epub 2014 Jun 4. PMID: 24893723.
- [11] Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., Altman, D., Antes, G., ... Tugwell, P. (2009). Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Medicine*, 6(7). <https://doi.org/10.1371/journal.pmed.1000097>
- [12] <https://www.crd.york.ac.uk/prospero/>
- [13] Dindo, D., Demartines, N., & Clavien, P.-A. (2004). Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Annals of Surgery*, 240(2), 205–213. <https://doi.org/10.1097/01.sla.0000133083.54934.ae>

[14] Green S, Higgins J, Alderson P, Clarke M, Mulrow C, Oxman A (2008) Cochrane handbook for systematic reviews of interventions. John Wiley & Sons Ltd., West Sussex, England

[15] Hozo, S. P., Djulbegovic, B., & Hozo, I. (2005). Estimating the mean and variance from the median, range, and the size of a sample. BMC Medical Research Methodology, 5, 13.

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