

Amsterdam, July 17th 2020

Dear dr. Lian-Sheng Ma,

Thank you for considering our manuscript for publication in *World Journal of Clinical Cases*. We hereby submit our revised manuscript.

We would like to thank the reviewers for their intensive reading and constructive comments regarding our manuscript, which helped us to make substantial improvements to our paper.

Please find our point-by-point reply to all comments of the reviewers below.

We hope this revised version of our manuscript sufficiently addresses the comments of the reviewers and we would be grateful to hear your response.

Yours sincerely,

Dr. L.C. Franken
Prof. T.M. van Gulik

Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: Authors evaluated the occurrence of seeding metastases in resectable perihilar cholangiocarcinoma and the role of low-dose radiotherapy to prevent this event. A total of 171 patients underwent resection of perihilar cholangiocarcinoma, 145 patients underwent preoperative biliary drainage and 111 patients underwent preoperative radiotherapy. The incidence of seeding metastases was very low: two patients (1.2%) showed metastases in the laparotomy scar 21 and 17 months after surgery. So, radiotherapy was discontinued in after January 2018. The main limitation of this study is its retrospective nature and the poor evidence of conclusions since this procedure was done only in the Authors' Institution. On the other hand, the topic is interesting and the number of patients included is consistent. Minor points:

1-Biliary drainage was performed in 145 patients but only 111 patients underwent preoperative radiotherapy. The reason to exclude the remaining patients is lacking.

Authors' response: We would like to thank the reviewer for his/her extensive read of the manuscript and this important suggestion. The main reason for these patients not to receive radiotherapy was mainly for logistic reasons; the protocol required patients to undergo three radiotherapy sessions on three

consecutive days preoperatively which was not always feasible. Also, the retrospective nature of this study precluded exact information for not performing radiotherapy in these 34 patients.

2- improvement in the incidence of seeding metastases from 20% to 1.2% is impressive. How the authors may explain this result since radiotherapy has been excluded?

As mentioned in the discussion of our manuscript, we cannot fully exclude the possibility of a positive effect of radiotherapy on reducing the occurrence of seeding metastases. However, after treating patients with radiotherapy for so many years, we were unable to prove such an effect. Occurrence of seeding metastases has decreased over time in all centers that have reported on the occurrence of seeding metastases in patients with PHC in literature. Additionally, a large study comparing our results to another large center (MSKCC in New York) that did not treat patients with preoperative radiotherapy, revealed no statistically significant difference in the proportion of patients developing seeding metastases. Taken together, this supported our hypothesis that the role of radiotherapy in preventing seeding metastases was limited.

3- The reason to perform postoperative radiotherapy in 13 patients should be reported.

PHC patients were treated with postoperative radiotherapy as part of a study conducted between 1983 and 1998. Citation: Gerhards MF, van Gulik TM, González González D, Rauws EA, Gouma DJ. Results of postoperative radiotherapy for resectable hilar cholangiocarcinoma. World J Surg. 2003;27(2):173-179. doi:10.1007/s00268-002-6434-1

Reviewer #2:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: Important manuscript but few evidence

Step 6: Editorial Office's comments

The author must revise the manuscript according to the Editorial Office's comments and suggestions, which listed below:

(1) *Science Editor*: 1 Scientific quality: The manuscript describes an observational study of the preventive radiotherapy for PHC. The topic is within the scope of the WJG. (1) Classification: Grade C and Grade C;

(2) Summary of the Peer-Review Report: The topic is interesting, and the number of patients included is consistent. The main limitation of this study is its retrospective nature and the poor evidence of conclusions since this procedure was done only in the authors' institution. The author should illustrate the reason to exclude the remaining patients. The authors need to explain the result that incidence of seeding metastases from 20% to 1.2% is impressive and the reason to perform postoperative radiotherapy in 13 patients. The questions raised by the reviewers should be answered;

Authors' response: We thank the editor for this suggestion and have answered all questions raised by the reviewer (see point-to-point answers above).

(3) Format: There are 2 tables and 1 figure. A total of 14 references are cited, without references published in the last 3 years. The authors need to update the references. There are no self-citations.

Authors' response: We agree with the editor that most references used in this study are slightly outdated. Unfortunately, recently no articles have been published on this specific topic. We have now added two recent references on the potential to treat patients with stereotactic radiotherapy on page 9/10 (Discussion, ref 14 and 15).

2 Language evaluation: Classification: Grade B and Grade B. No language editing certificate was provided.

3 Academic norms and rules: The authors provided the Biostatistics Review Certificate, the signed Conflict-of-Interest Disclosure Form and Copyright License Agreement, and the Institutional Review Board Approval Form. Written informed consent was waived. The authors need to fill out the STROBE checklist with page numbers.

Authors' response: We have added page numbers to the STROBE checklist.

No academic misconduct was found in the CrossCheck detection and Bing search.

4 Supplementary comments: This is an unsolicited manuscript. The study is without financial support. The topic has not previously been published in the WJG. The corresponding author has not published articles in the BPG.

5 Issues raised:

(1) I found no "Author contribution" section. Please provide the author contributions;

Authors' response: We have added author contributions (page 13).

(2) I found the authors did not provide the original figures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor;

Authors' response: We have submitted the original figures.

(3) I found the authors did not add the PMID and DOI in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout;

Authors' response: We have edited the reference list.

(4) I found the authors did not write the "article highlight" section. Please write the "article highlights" section at the end of the main text; and

Authors' response: We have added an article highlight section (page 2).

(5) the author should number the references in Arabic numerals according to the citation order in the text. The reference numbers will be superscripted in square brackets at the end of the sentence with the citation content or after the cited author's name, with no spaces.

Authors' response: We have edited the reference list.

6 Re-Review: Not required.

7 Recommendation: Conditionally accepted. (Man Liu)

(2) Editorial Office Director: I have checked the comments written by the science editor.

(3) Company Editor-in-Chief: I recommend the manuscript to be published in the World Journal of Clinical Cases.