

Answers to Reviewers:

Reviewer 1:

We thank the Reviewer for the time and the attention dedicated to our paper. We sincerely appreciated the suggestions made in order to improve the quality of the manuscript. We answered to the queries as follows and we hope the Reviewer will find our changes to be appropriate.

- 1) *In several points in manuscript (e.g., in the conclusion of abstract), the authors claimed that minimally invasive resection is safe for "selected cases", however, the definition of selected cases has never been described in the method or in discussion. The criteria for selection of ICC patients for minimally invasive resection should be provided according to what the original papers had described.*

Thank you for your advice. Since the selection criteria applied in the retrieved studies selected for the systematic review were different and not clearly stated by all the authors we used the expression "selected cases". Nevertheless, we agree with the reviewer that "selected cases" is a vague description. Therefore, after your suggestion, we looking for any selection criteria used for laparoscopic patients in analyzed studies. Haber et al. describes three different laparoscopic surgical techniques and indications was reported literally : "Indication for the specific surgical approach was given at the operating surgeon's discretion." (p. 1355 – surgical approach)

Kang et al. preferred laparoscopic surgery for patients having a localized tumor with no signs of invasions to the hilar area.

Kinoshita et al. assessed the safety of laparoscopic approach considered tumor diameter, location, proximity to major vessels and performance status. Moreover, after receiving information explaining that LLR for ICC was not a standardized procedure, patients who were deemed suitable for laparoscopic surgery were permitted to choose their preferred surgical approach (laparoscopic or open).

Martin and Lee selected patients for LLR of ICC based on the Louisville statement

Instead, for Ratti et al. treatment strategies were systematically evaluated at weekly multidisciplinary meetings, where liver surgeons, radiologists, hepatologists, and medical oncologists defined the indications for surgical procedures and both the type and the resection technique.

Wei et al. , Wu et al and Zhu et al. not clear specify how selected laparoscopic patients.

- 2) *In Materials and Methods, the information of how many papers were retrieved from each database should be provided.*

Thank you for your advice. We uploaded the missing PRISMA flowchart in which are reported the requested data.

- 3) *I cannot find figure 1 that referred from the results section. The authors need to provide a PRISMA flow diagram to show the searching and recruiting literature to study.*

We apologize, during the uploading process we missed to attach the PRISMA flowchart. We added Fig.1 which includes the PRISMA flowchart, also at the end of this file.

- 4) *The authors should provide more table to show the data of tumor characteristics, it would be easier to follow rather than only explain in the main text.*

Thank you for your advice. We added a new table (called table 3). We hope now will be easier follow our main text.

- 5) *The comparison and discussion on the rate to achieve R0 margin between open vs minimally invasive should be provided and emphasized. As this is one of the major prognostic markers for ICC patients after operation.*

Thank you for your suggestion. We agree with the Reviewer that radical resection is the main prognostic factor for patients resected for ICC. Data on the R0 versus R1 resection rate have been reported (when available from the retrieved studies) in Tab. 3. We now added in the text data on R0 vs R1 resection between the open and the laparoscopic groups in the Results section (pag. 8, lines 8-10) and discussed them in the Discussion section (pag. 11, lines 21-25).

- 6) *The limitations of this systematic review and suggestions for further study should be provided in Discussion. The authors may provide and suggest based on their own expertise what the direction of this topic will be in the next 5 years, in term of both treatment strategies and research field.*

Thank you for your advice. We modified the Discussion section providing the information required by the Reviewer. See Discussion section pag. 12, lines 8-16.

- 7) *The heading (name) of table 3 is needed. The abbreviations of overall survival and open surgery are the same word in table 3 which could confuse the readers. For statistical significance, it is better to indicate using the asterisk marked rather than a bold font.*

Thank you for your advice. We added the heading of Table 3 and we changed the abbreviation of overall survival and open surgery and changed bold font with asterisk to mark data with a significant p-value as suggested by the Reviewer.

- Minor points:

1. *The word "negative prognostic factors" should be replaced with the other terms as this is ambiguous. Using the word negative or positive in such of context can confuse the readers. The authors may consider words like; poor or good prognostic factor, or as such the other word that make clear to the point.*

Thank you for the suggestion. We made the requested change. See pag. 4, line 14

2. *The pattern of abbreviation should be consistent through the whole manuscript, e.g., CA19-9.*

Thank you for your advice. We have checked and modified the main text for all abbreviations in order to have a correct homologation. See pag. 8, line 18 and 22

We performed a grammatical and English review of our text. We hope result more readable in this version.

Reviewer 2:

We thank the Reviewer for the time and the attention dedicated to our paper. We sincerely appreciated the suggestions made in order to improve the quality of the manuscript. We answered to the queries as follows and we hope the Reviewer will find our changes to be appropriate.

1. *This manuscript still has critical points needing to be edited (Page 21, please add the title of table 3).*

Thank you for your advice. We added the title of Table 3.

2. *In result part.*

- In study inclusion, you mention that 2 studies selected after full-text analysis were then excluded because more recent studies from the same authors presented more updated data. Please clarify this point because these publications studied same population group

Thank you for the opportunity to clarify the point. This two studies by Cho and Ratti (Uy BJ, Han HS, Yoon YS, Cho JY. Laparoscopic liver resection for intrahepatic cholangiocarcinom J Laparoendosc Adv Surg Tech A. 2015 Apr;25(4):272-7. doi: 10.1089/lap.2014.0233. Epub 2015 Mar 19. PMID: 25789408) (Ratti F, Cipriani F, Ariotti R, Gagliano A, Paganelli M, Catena M et al. Safety and feasibility of laparoscopic liver resection with associated lymphadenectomy for intrahepatic cholangiocarcinoma: a propensity score-based case-matched analysis from a single institution. Surg Endosc 30(5):1999–2010.

<https://doi.org/10.1007/s00464-015-4430-4>) used the same population group of the two studies selected for analysis made by the same authors. In the most recent article, Authors, expand the follow-up and the number of patients but

more of them are the same of the previous study. For this reason we not select this two work so from reduce overlaps of data.

- In geographical distribution of selected pater in this study including Italy and UK, USA, Germany, Japan, Korea and China; how about in other country such as Thailand because high prevalence of CCA in this country.

The authors agree with the Reviewer that in Thailand there is a high prevalence of ICC and a wide experience in the surgical treatment of ICC has been developed in that country. Nevertheless, in the current systematic review we only analyzed English language papers fulfilling the selection criteria applied for the search and comparing open and minimally invasive approach for the surgical resection of ICC. Unfortunately we did not retrieve any paper from Thailand fulfilling the selection criteria. If we missed some paper from Thailand fulfilling the selection criteria we would be happy to add it.

- In tumor characteristic, why you mention only 7 publications.

We are sorry, maybe we are not clear in our exposition. We analyze all manuscript and we mentioned all. However not all papers reported all variable. Nevertheless we changed our sentences in way to have a better exposure.

3. *In discussion part.*

-You mention that, 4 studies reported a lower intraoperative blood loss associated to the minimally invasive approach even when dealing with radical lymph nodes clearance. However, Kang et al. reported that the blood loss in laparoscopic surgery higher than open surgery, please clarify.

We thank the Reviewer for his comment.

Among the analyzed studies, as we mentioned in the text, 4 of them reported a statistically significant lower intraoperative blood loss in the laparoscopic group. As regards the study by Kang et al., as correctly highlighted by the Reviewer, a trend towards a higher intraoperative blood loss was reported for the laparoscopic group (this has been reported in Tab. 2). Nevertheless, this trend

was not statistically significant ($p=0.393$). Anyway to better clarify the point for the readers we added this information also in the text (pag. 10 , line 8-10)

-Please clarify why the number of patients for 90-day motility in laparoscopic surgery lower than open surgery in Wu et al., and Ratti et al.

We thank the Reviewer for his comment.

We cannot answer to this since unfortunately no data were reported in the manuscript by Ratti et al. and Wu al. about the causes of death. Therefore, we are not able to motivate the 90-day mortality rate (which was anyway not statistically significant between the open and the laparoscopic groups).

-Please state why the histopathological margin (R0) in laparoscopic surgery higher than open surgery.

Thank you for this comment. No statistical difference was reported about R0 margin between open and laparoscopic approach. Nevertheless we add at pag. 8, lines 8-10 and at pag. 11, lines 21-25 some discussion about. We hope that, in this way, manuscript will be clearer than previous version

Fig. 1 Prisma Flow-Chart

