Response to Reviewers

Dear Editor,

We are thankful to the reviewers for their constructive comments. We have made amendments in response to them and improved the manuscript accordingly. Please find below a point-by-point response:

Reviewer #1:

1. In the baseline table, it is advisable for the authors to inclusively present the median number of dissected lymph nodes, along with the incidence rate of lymph node positivity.

This has now been added in Table 1 where available in the studies; please note only one study reported the median number of lymph nodes extracted and two the mean number of lymph nodes extracted.

2. Numerous contemporary studies advocate for a recommended threshold of lymph node dissections ≥ six. Thus, it becomes imperative to conduct a subgroup analysis pertaining to the number of LND.

This was already performed as a univariable meta-regression (see Figure 5). It is not possible to do a subgroup analysis on the percentage of patients with >6 nodes extracted in each study as this is a continuous variable rather than categoric.

3. The preoperative assessment of lymph node metastasis (LNM) plays a pivotal role in guiding the decision to undertake lymph node dissection. It is anticipated that the authors would undertake subgroup analyses stratified by the presence or absence of LNM, if feasible.

Again, as above this was performed as a univariable meta-regression rather than a sub-group analysis for the same reason above.

4. Safety stands as a pivotal factor in the deliberation over the implementation of LND. Consequently, the results should include safety indicators, comprising operative mortality, rates of postoperative complications, as well as incidences of intraoperative hemorrhage loss and blood transfusions.

Blood loss has been added to Table 1 and is discussed qualitatively in the results. Unfortunately, few studies have reported on complications in a systematic or consistent way to allow for meta-analysis or discussion.

Reviewer #2:

1. The guidelines and expert consensuses should be told. The International Liver Cancer Association (ILCA) strongly recommends LND for patients with iCCA, given the strong prognostic value of LN metastasis. The National Comprehensive Cancer Network (NCCN) clinical practice guidelines on hepatobiliary cancers (version 1.2023) recommend routine LND for accurate staging, but acknowledge that data in support of its therapeutic benefit are lacking. The American Hepato-Pancreato-Biliary Association (AHPBA) consensus meeting noted that routine LND is still controversial, especially in the West. The Liver Cancer Study Group of Japan recommends regional lymph node dissection of different lymph node basins depending on whether the iCCA tumor is located on the right or left side of the liver.

We thank the reviewer for this recommendation and have added the following paragraph based on guidelines from ILCA, NCCN, AHBPA and the Liver Cancer Study Group of Japan.

"In terms of consensus on performing LND, the international societies have expressed a range of perspectives. For example, the European Association for the Study of Liver (EASL) and the International Liver Cancer Association (ILCA) recommend that patients with ICCA that is amenable to surgical resection should have lymph node *sampling* performed for the purposes of pre-operative staging. For those that eventually undergo a resection, all should undergo an LND (of ≧6 nodes) for more precise disease staging and prognosis. Similarly, the National Comprehensive Cancer Network (NCCN) in the USA also recommends a regional lymphadenectomy be performed. However, they do not specify a minimum quantity of lymph nodes to harvest. This procedure is to be performed for more precise prognosis estimation. In the event of positive lymph node identification, those patients could be considered for adjuvant chemotherapy. Furthermore, the American Hepato-Pancreato-Biliary Association (AHPBA) recommends that a regional lymphadenectomy be *considered* rather than routinely performed. They also do not stipulate a minimum quantity of lymph nodes for harvest and consider the procedure to be useful for prognostication as well. Conversely, the Japanese Liver Cancer Study Group does not offer a definitive view on the role of LND. This is especially the case if no clear evidence of lymphatic disease is identified on pre-operative imaging or staging laparoscopy."

2. Some closed papers should be cited (doi: 10.1007/s11605-023-05696-8; 10.1007/s00268-022-06857-7; 10.3389/fonc.2022.957792).

Thank you for highlighting these papers. We have cited all 3 papers in our manuscript.

Our submission complies with the *Company editor-in-chief's* comments.

Yours sincerely,

Mr Vasileios Mavroeidis,
on behalf of the authors