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Title: Importance of surgical margin in the outcomes of hepatocholangiocarcinoma

Reviewer 02945170: Ma. KW et al. had retrospective evaluated the risk factors associated with the improved survival outcome in patients with hepatocholangiocarcinoma (HCC-CC). They found that resection margin of 1 cm or above was associated with improved survived outcome in patients with multifocal HCC-CC. This finding is importance to clinic practice to the HCC-CC patients .Although, the statistic methods is satisfactory, there are some points needed to illustrate: 1) statistic methods: a) the study design is a retrospective analysis, the sample size of the patients with HCC-CC are needed to amplified, although patients with the HCC-CC are rare. b) the risk factors included in COX regression analysis such as CTP grade, Albumin levels, platelet counts, PT, and total bilirubin were duplication. What were the results if used only CTP grade. 2) In analysis factors associated with overall survive, what the role is to the different pathogen stage for HCC-CC patients.

Response from Authors

Dear reviewer,

Thank you very much for your expert comments, which are most helpful in refining our manuscript. Here is our response:

1a) In fact, this 20-years series consisting of 42 hepato-cholangiocarcionoma patients together with survival comparison with over 1500 hepatocellular carcinoma and 100 intrahepatic cholangiocarcinoma patients represented a relatively reasonable sample size compared with some other published series. The author totally agrees that the sample size of the current study is limited by its rarity; factors such as lymph node status, resection margin, tumour size, and adjuvant therapy might be significant but missed due to type 2 error. This concern is stressed in the discussion part of the manuscript.

1b) Since albumin, total bilirubin and PT each had been shown to be an important factors associated with outcomes in the management of other cancers such as HCC, the influence of each of this factor might be masked if they are analysed as a combined factor (i.e. CTP). To address this concern, we have repeated the regression analysis by using CTP score instead of albumin, total bilirubin and PT. However, this did not lead to a different result. In order to avoid duplicate, we have removed CTP from our analysis.

2) Since the pathological staging of HCC-CC depends on various parameters, namely

tumour multifocality, vascular invasion and involvement of lymph node, performing cox regression analysis for pathological stage using these factors would be redundant, and analysing the effect of each of these components would be more specific. Furthermore, pathological staging, nodal status and microvascular invasion are only known after operation and therefore they do not guide the preoperative surgical planning. Yet pathological staging (UICC 7th edition) does affect long term oncological outcomes if analysed individually. We have added microvascular invasion and nodal metastasis to the Cox regression analysis, and the results are added to Table 3.

Reviewer 03471188: In this retrospective study entitled “Importance of Surgical Margin in the Outcomes of Hepatocholangiocarcinoma”, Drs. Ma and Ho reported the information of a rare liver tumor – HCC-CC – in their hospital, in which they found that a clear resection margin of at least 1 cm could improve 1-year disease-free survival from 0% to 40%. In general, this article is important for clinical management of HCC-CC, with well-designed analysis and trustable conclusions. Following points are suggested to revise: 1. Page 4, 2nd paragraph of the INTRODUCTION, the authors should describe more about the importance of the width of resection margin for the hepatectomy for HCC and ICC. This will help readers to understand the study background better; 2. Possible reasons or mechanisms responsible for the importance of resection margin (> 1 cm) for HCC-CC could be discussed (in the DISCUSSION part).

Response from Authors

Dear reviewer,

Thank you very much for your expert comments, which are most helpful in refining our manuscript. Here is our response:

Revision 1: Description on how resection margin could influence oncological outcomes in the context of HCC and ICC are added to the last paragraph in the Introduction.

Revision 2: The possible mechanism of resection margin (>1cm) leading to improved HCC-CC outcomes are added to the Discussion (the second last paragraph in the manuscript).