Response to Reviewers

We thank the reviewers for their helpful comments. Our responses to the points raised and a description of the changes made accordingly are shown below. Comments are typed in bold and responses in regular typeface.

#Reviewer 1

This study is a well designed review, the authors concentrated on the diagnosis, staging, treatment of pCCC, which is a relatively advanced stage of CCC. They performed a systematic review of current literatures about the diagnosis and treatment of pCCC, and interestingly, they provide comprehensive substaging of pCCC.

However, there are still some small tips for authors. As we all konw, there is no standrad systematic chemotherapy for CCC, we recommed the authors providing more detail information about the chemotherapy or other adjuvant treatment for pCCC.

Thanks for your comments. The medical treatment for pCCC is the same for all CCC, irrespectively of site, both in the adjuvant and advanced stage. We reported the standard treatments for all settings. However, we added the recent results of the ABC-06 study, not published yet, because its results are important in order to define the standard for second line treatment (Page 17 Line 23-30 and Page 18 Line 1-16).

#Reviewer 2

This is an excellent work, which answered many of the clinical questions and compensate the current guidelines. However, there were several limitations in this review.

Major:

1. **In Line 15, Page 4, the author stated that "CCC accounts for 20% of primary liver tumors". However, primary liver cancer typically includes hepatocellular carcinoma and intrahepatocellular cholangiocarcinoma, but not CCC, which is also different from the depiction in the Abstract. In addition, the incidence of CCC seemed a little higher (at least compared with that in China), and data in the latest epidemiological investigation should be recommended.**

We modified the text and updated abstract and references. Thank you for the suggestion. (Page 2 line 4; Page 4, Line 15-16 and 19)

2. **In Line 3, Page 7, the author stated that "18-70% of patients have a resectable tumor at the time of diagnosis", which is inconsistent with the depiction of the following surgical treatment, and relevant references should be added.**

   Thank you for the suggestion. A review of the main contributions on this topic was performed and the statement modified. We also added relevant references. (Page 7, line 5)

3. **Molecularly targeted therapy and/or immunotherapy should be considered to be choices for patients with cholangiocarcinoma. but these treatments were not included in this study, please make a reasonable explanation.**

   As far as the aim of this work is to provide a pratical review especially to surgeons, we focused on the results of the main studies on the topic of medical treatment. Currently, immunotherapy does not find a place in the standard treatment of biliary tract cancers, evidence is poor and only early-phase studies have been performed so far.

   On the contrary, we added the results of the recent ClarIDHy phase III study of ivosidenib, the first molecular treatment with proven efficacy in the treatment of CCC (Page 18, Line 11).

4. **In figure 2, the therapeutic work-flow for pCCC not recommend surgery according patient stage. In addition, the flow not mentioned other treatments, please make a reasonable explanation**

   Figure 2 was drown only to underline the diagnostic work-flow and not to depict all treatment options according to pCCC stage. Through this figure, we would like to offer a simple and clear representation only of the diagnostic iter to underline its importance. In our opinion, if specific (per stage) treatment strategies are added, the figure could become too complicated. However, we implemented the figure adding the treatments dedicated to unserectable pCCC patients and referring to table 3 where non-resecability criteria are displayed.

5. **To drain or not to drain is a quite problem, and we are also concerned on it. In our**

previous meta-analysis, we found that the type of biliary drainage (BD), i.e percutaneous or ERCP, would affect the prognosis of cholangiocarcinoma, although the conclusion deserved further validation. But we quite disagree with the statement in Line 13, Page 10, the authors should re-reviewed the article of Farges's, and the association between BD and left- or right-hepatectomy should be furtherly studied.

Bile duct drainage before proper imaging/diagnosis and referral to tertiary Centres is a main problem in our geographical area. As you suggested, the statement in line 13 was confounding, as it was written. We reviewed Farges and colleagues paper and we better clarify the issue highlighted by the authors (Page 10, line 15-24). Thank you for the opportunity to review the paragraph.

Minor:

1. **spelling mirrors, such as "avoid" in L1, Page 12 should be "avoided", "hemorrage" in Table 2 be "hemorrhage", and "disconfort" in Table 2 be "discomfort".**

   All the suggested correction were done, sorry for the spelling errors.

2. **In Page 8, full name of "FNA" should appear firstly in line 20 not in Line 20.**

   We reviewed the abbreviation , thank you

3. **In Line 11, Page 18, "57% e 49%" should be "57% and 49%"**

   We correct the phrase, sorry for the mistake.