Dear Editor:

On behalf of my coauthors, thank you very much for your positive comments and valuable suggestions concerning our manuscript entitled ”Combining local regional therapy and systemic therapy: Expected changes in the treatment landscape of recurrent **hepatocellular carcinoma**" (NO79806). Based on your suggestions, we have made corrections that we hope will be met with your approval. The revised portions are marked in red in the manuscript.

Response to Reviewer #1

This is an interesting article, and it adds more to the field of hepatology, especially HCC. Are there any studies that discuss the issue of rebiopsy after recurrence, and what about the pathology compared to the previous one? Also, what about liquid biopsy as a marker after primary treatment to guide prognosis?

Response: Thank you very much for your comment and valuable suggestions for this article. Unfortunately, we found no literature on rebiopsy of recurrent HCC. We did find a small number of studies on liquid biopsy in recurrent HCC and added relevant content (Page 7, 2nd paragraph). Thank you again for your very meaningful advice.

Response to Reviewer #2

Major issues:

1. The manuscript recapitulates the data for recurrent HCC. However, the authors always refer to “liver cancer”. This is misleading throughout the manuscript but particularly in the title. To me, “liver cancer“at least includes cholangiocarcinoma as the other primary liver cancer besides HCC. This should be changed.

Response: Thank you for this important suggestion. It is true that most of the literature we referred to was for hepatocellular carcinoma; thus, it is not accurate to use the term “liver cancer”. Therefore, we changed “liver cancer” to hepatocellular carcinoma in the title and throughout the entire manuscript.

2. The main issue of the manuscript is the data about combination of local and systemic therapy in HCC. Therefore, I recommend to include a paragraph regarding the results from trails investigating the combination of local and systemic therapy in primary HCC, e.g. for TACE + sorafenib or local ablation

and systemic treatment. This might give a better basis for the understanding of the problems and opportunities for recurrent HCC.

Response: Thank you for this good suggestion. We have added these data to the manuscript (Page 16, 2nd paragraph).

3 I don't agree completely with your conclusion. Shouldn't patients with recurrent HCC undergo resection if the tumor is resectable and liver function is sufficient?

Response: We propose that combining local therapy with systemic therapy has value but do not deny the importance of resection. We very much agree with you, so we have added a corresponding statement to the manuscript (Page 9, 3rd paragraph and conclusion).

4 A possible combination of local and systemic treatment is also the re-resection combined with adjuvant therapy. Is there any data on this?

Response: We consider the combination of adjuvant therapy with repeat hepatectomy a meaningful strategy, and in section 5, we mentioned the possible benefit of combined systemic therapy in patients at high risk of recurrence after resection; however, we did not find relevant data. Clinical studies on immunotherapy to prevent recurrence after primary hepatectomy are ongoing, but no relevant literature was found for recurrent HCC.

Minor points:

1. Page 3, introduction section, 2nd paragraph: "Systemic therapy refers to antitumor therapy represented by molecular targeted drugs, immunotherapy, and chemotherapy and has become an emerging adjuvant therapy." As correctly mentioned later in the manuscript, adjuvant therapy is currently not recommended in HCC. Therefore, this sentence should be explained.

Response: We are very sorry for this inaccuracy and have revised it (Page 4, 3rd paragraph).

2 Page 6, 2nd paragraph: "…..TILs were significantly associated with a high recurrence rate and poor OS in patients with HBV-associated HCC and HCC patients not associated with HBV and HCV." This sentence seems to be somehow confusing to me. Who suffers from higher recurrence rates and poor OS? Those with HBV and those without? In conclusion, all patients?

Response: We revisited the study and modified the text accordingly. TILs

were significantly associated with a high recurrence rate and poor OS in all study patients, including HBV-associated and non-B non-C HCC patients (Page 7, the last line - page 8, the first line).

3. Page 7, last paragraph: "…..divided into radical treatment and palliative treatment". I'd rather recommend the division into "curative and palliative treatment".

Response: Thank you for your suggestion; the text has been modified.

4. Page 8, 1st paragraph: "…..postoperative complications and the length of hospital stays, but the survival time is still similar to that of hepatectomy, with no significant improvement in the overall prognosis of recurrent liver cancer patients." I recommend to include the term "open hepatectomy" instead of hepatectomy only to pronounce the meaning of minial-invasive surgery in this issue.

Response: Thank you very much for this good advice; the text has been modified.

5 Page 9, 2nd paragraph: "….because of limited liver function after liver surgery , TACE…". Why should the liver function be impaired after liver surgery? Usually, surgery is performed in the case of sufficient liver remnant and the liver function recovers soon after resection. Otherwise the decision to go for resection is probably wrong. This should be clarified.

Response: We agree that this sentence was incorrect and have removed it.

6. Page 13, 1st paragraph: I don't understand the sentence: "Compared with an initial diagnosis of HCC, recurrent HCC at any stage involves tumor recurrence[91]". Could you please explain?

Response: We apologize for our unclear presentation, and we have revised the sentence. The risk of tumor recurrence is higher for recurrent HCC than for the original tumor (Page 14, 3rd paragraph).