May 5, 2019

Re: Manuscript NO: 47519

Dear Editor,

Thank you for your careful review of our invited manuscript, "Neoadjuvant and Adjuvant Treatment Strategies for Hepatocellular Carcinoma." We appreciate the time and effort of the reviewers and editorial board in reviewing our manuscript and providing valuable feedback.

We have carefully considered this feedback and have modified the manuscript based on their insightful comments. We have addended citations as suggested and rewritten the various sections for better clarity. It is our hope that the reviewer comments have been fully addressed.

We greatly appreciate the opportunity to submit a revised version of the manuscript, and we look forward to hearing your response.

Please find detailed responses to individual reviewer comments included below.

Sincerely,

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Referee comments are listed in ***bolded italics*** and the authors' responses are listed below the comments.

Reviewer 1:

1. ***In the neoadjuvant strategies for HCC section, the part of "Transarterial Radioembolization", the references are required in the sentences "In 2016, they reported on another group of 10 patients with HCC and insufficient or borderline FLR who underwent Y-90 RL prior to resection. Following RL, the median FLR increased from about 33% (pre-RL) to about 43% (post-RL). Additionally, they reported >50% necrosis in greater than 92% of the resected tumors."and "In a previously reported non-randomized trial comparing TARE to TACE, TARE resulted in a better response than TACE (61% vs. 37% partial response) and resulted in more patients being downstaged from UNOS T3 to T2, which could be critical for patients awaiting transplantation."***

These references have been added.

2. ***In the adjuvant strategies for HCC section, the part of "Antiviral therapy", the authors described direct-acting antiviral therapy, but not the outcomes (overall survival and recurrence) after curative therapies including resection or ablation. For example, J Hepatol. 2019 Apr 5. pii: S0168-8278(19)30221-1.; Gastroenterology. 2019 May;156(6):1683-1692.e1.***

We thank the reviewer to bringing this to our attention. Given the limited availability of RCTs and/or large scale trials investigating the use of direct-acting antiviral therapies in patients who undergo curative resection, as well as the controversy surrounding the possibility of increase recurrence, we had opted not to explore this topic in depth. . However, in doing so we inadvertently left out key findings from these studies, which could potentially help inform the reader on the subject matter. In response to the reviewer's suggestion, we have revised this section to include the outcomes from these pivotal studies.

3. ***In the adjuvant strategies for HCC section, the part of "Systemic Therapy", the references are wrong in the sentences "While early studies suggested that the adjuvant use of sorafenib might be associated with decreased recurrence and prolonged RFS, other studies have found no benefit[89-91]. In contrast, some studies have shown that the use of adjuvant sorafenib may be associated with worse outcomes[90, 92].". These references (89-92) are not associated with the use of adjuvant sorafenib.***

We sincerely thank the reviewer for identifying these incorrect citations. The references have since been updated and the text revised to more accurately reflect the cited studies and intended message.

4. ***As the authors mentioned ablation in the adjuvant strategies for HCC section, ablation is used as a bridging therapy to LT. Is "ablation" also included in the neoadjuvant strategies for HCC?***

We apologize for this confusion. While ablation is often used in the neoadjuvant setting as a bridging therapy to transplantation, the goal of our review was to address neoadjuvant and adjuvant therapies to curative resection. While ablation is occasionally used following or at the same time as curative intent resection, we are unaware of research using ablative techniques in the preoperative time period. Thus, we opted to focus on the role of ablation as adjuvant therapy to curative resection.

5. ***In Table 1, reference 153 is a RCT of postoperative adjuvant IFN therapy after resection of HBV-related HCC. Therefore, this reference should be removed in this table.***

This is reference has been removed.

Reviewer #2:

1. ***Residual and/or recurrent cancer cells after surgical resection of hepatocellular carcinoma develop through either way of multicentric carcinogenesis or intrahepatic metastasis. Because the prognosis of patients with hepatocellular carcinoma is defined within a trade-off between anatomical cancer extent and functional hepatic reserve, the impact of locoregional treatments on patients' prognosis largely depends on whether the target cancer cells developed through which way. The efficacy of adjuvant and neoadjuvant therapies, therefore, should be discussed in the context of the process through which recurrent diseases developed. Otherwise, the discussion becomes a simple accumulation of controversial results.***

The reviewer raises an excellent point regarding the role of neoadjuvant and adjuvant therapy in the management of HCC. We agree with the reviewer that various neoadjuvant and adjuvant strategies target these different etiologies of HCC tumorigenesis and recurrence. We have revised the discussion/conclusion section of the manuscript based on this insightful comment.

2. ***Stereotactic radiotherapy including heavy particle radiation therapy is another valuable locoregional treatment option for hepatocellular carcinoma.***

We agree with the reviewer that radiation represents an important locoregional therapy for HCC. Although there is limited literature on the subject of neoadjuvant or adjuvant radiation, based on the reviewer's suggestion, a paragraph on adjuvant radiation has been added to the manuscript.

3. ***In a randomized study, in which a patient was stratified into a TACE or surveillance group, will a patient in the TACE group take the treatment at a scheduled time point without surveillance?***

The reviewer brings up an important point, which unfortunately remains a challenge in the use of TACE and in designing trials involving TACE. Overall, surveillance typically follows the EASL-EORTC guidelines, which recommend surveillance imaging at usually 4 weeks after initial treatment, and assessment of response using the modified RECIST (mRECIST) criteria.