

RESPONSES TO EDITORS

We sincerely thank editors for their insightful and constructive suggestions. Please find enclosed a point-by-point response to all issues raised by the editors.

Reviewer#1

1. *Several sections of the manuscript have very little references e.g. the first part of pathological factors has zero references*

Answer: Thank you so much for your positive comments and suggestions for improvement. In this revision, we have revised the manuscript accordingly.

2. *Kindly run Grammarly, a free tool, prior to resubmission in order to ensure the minor mistakes present are corrected.*

Answer: Thank you so much for your positive comments and suggestions for improvement. We have used the software to touch up the manuscript

3. *Consider explaining the current prediction models for predicting HCC recurrence. A newly published one is <https://www.diagnosticimaging.com/view/machine-learning-mri-model-may-help-predict-recurrence-of-hepatocellular-carcinoma>.*

Answer: Thank you so much for your positive comments and suggestions for improvement. We have revised the section on surveillance of recurrent hepatocellular carcinoma and added a paragraph describing the current predictive model used to predict HCC recurrence.

4. *Role of MRI has not been discussed. Please incorporate data on MRI and recurrent HCC. Min JH, Kim YK, Choi SY, et al. Detection of recurrent hepatocellular carcinoma after surgical resection: Non-contrast liver MR imaging with diffusion-weighted imaging versus gadoxetic acid-enhanced MR imaging. Br J Radiol. 2018;91(1090):20180177. doi:10.1259/bjr.20180177 Lee MW, Lim HK. Management of sub-centimeter recurrent hepatocellular carcinoma after curative treatment: Current*

status and future. World J Gastroenterol. 2018;24(46):5215-5222. doi:10.3748/wjg.v24.i46.5215

Answer: We have modified the section on surveillance of recurrent hepatocellular carcinoma and described the role of MRI in the last paragraph of the section

5. Please provide a simplified management protocol as a figure as well. This will considerably enhance value of your manuscript.

Answer: Thank you so much for your positive comments and suggestions for improvement. We have added the proposed flow chart for the management of recurrence of hepatocellular carcinoma in the manuscript.

6. Please remove the section of Other Therapies. This section strongly decreases the scientific trustworthiness of your manuscript.

Answer: Thank you so much for your positive comments and suggestions for improvement. We have removed that part of the content.

7. Please spend more time discussing actual clinical data rather than just describing basic sciences or describing that this tool may be useful - let the reader make the judgement. Several key studies on RFA, MWA have not been discussed.

Answer: Thank you so much for your positive comments and suggestions for improvement. We have revised the manuscript accordingly

Reviewer#2

1. The authors list the different treatments for HCC but not resection and transplantation in the first section.

Answer: Thank you so much for your positive comments and suggestions for improvement. In the first section, we focused on describing the various adjuvant treatment options for liver cancer, while resection and transplantation

are not generally viewed as adjuvant treatments. We have revised the title of Part I to make its expression clear.

2. The authors may want to consider presenting an algorithm regarding the use of the different therapies

Answer: Thank you so much for your positive comments and suggestions for improvement. We have added a flow chart for the management of recurrent liver cancer that can be used to demonstrate the process of using different therapies.

Revision reviewer

1. Authors should upload a file that has tracked changes so that the reviewer can review the changes they have made.

Answer: Thank you so much for your positive comments and suggestions for improvement. We describe our changes in detail in the current document.

2. I advise authors to print the manuscript and have it read slowly to identify glaring errors. E.g. "Similarly, with the demarcation line being set at 2 years, HCC recurrence after liver transplantation can be divided into early and recurrence." This sentence is missing the word "LATE"

Answer: Thank you so much for your positive comments and suggestions for improvement. We have fixed the error here and re-checked the original.

3. Significant advances have been made in adjuvant chemotherapy including several major results presented at ASCO in 2022, 2021 and 2020. Please incorporate data from these trials and discuss specific agents.

Answer: Thank you so much for your positive comments and suggestions for improvement. The discussion is as follows:

The drug combinations for HAIC are also being continuously explored by scholars in various countries. A Japanese HAIC study^[1] compared the outcomes of 476 patients with HCC who received HAIC (5-fluorouracil and

cisplatin) with 1466 patients who did not receive active treatment and showed that the median survival time was longer in patients who received chemotherapy (14.0 months) than in those who did not receive active treatment (5.2 months, $P < 0.0001$). However, several cisplatin (DDP)-based HAIC regimens are dose limited by renal, neurological, and gastrointestinal toxicity, making it difficult to achieve the desired outcomes^[2]. In contrast, with the publication of the EACH study^[3], oxaliplatin is coming into the limelight as a systemic chemotherapeutic agent. The study explored whether FOLFOX4 (infusional fluorouracil, leucovorin, and oxaliplatin) as palliative chemotherapy for patients with advanced HCC provides survival benefit and efficacy compared to doxorubicin, and found that this regimen may offer some benefit to Asian patients^[3]. Subsequently, Chinese scholars modified and applied the FOLFOX regimen to HAIC and achieved stunning results. In the ASCO 2021 meeting, Rongping Guo's team firstly explored the efficacy of comparing neoadjuvant HAIC (FOLFOX regimen) (NT group) with direct surgery (OP group) in patients with HCC with ultra-Milan standard BCLC stage A/B and found that the ORR in the NT group reached 63.6% and DCR reached 96.0%^[4]. Furthermore, the team found that this protocol was also effective in HCC patients with microvascular invasion. The study showed that patients who received one or two cycles of postoperative adjuvant arterial perfusion chemotherapy had significantly better OS and DFS compared to patients without any adjuvant therapy (97.7% vs. 78.5%; 58.7% vs. 38.6%; $P = 0.037$ and 0.023)^[5]. Thus, HAIC based on the FOLFOX regimen is gaining more and more attention in the academic community for its high ORR and surgical conversion rate.

- 1 **NOUSO K, MIYAHARA K, UCHIDA D, et al.** Effect of hepatic arterial infusion chemotherapy of 5-fluorouracil and cisplatin for advanced hepatocellular carcinoma in the Nationwide Survey of Primary Liver Cancer in Japan [J]. *Br J Cancer*, 2013, 109(7): 1904-7. [PMID: 24008659 DOI: 10.1038/bjc.2013.542]

- 2 **OSAKI A**, SUDA T, KAMIMURA K, et al. A safe and effective dose of cisplatin in hepatic arterial infusion chemotherapy for hepatocellular carcinoma [J]. *Cancer Med*, 2013, 2(1): 86-98. [PMID: 24133631doi:<https://doi.org/10.1002/cam4.55>]
- 3 **QIN S**, BAI Y, LIM H Y, et al. Randomized, multicenter, open-label study of oxaliplatin plus fluorouracil/leucovorin versus doxorubicin as palliative chemotherapy in patients with advanced hepatocellular carcinoma from Asia [J]. *J Clin Oncol*, 2013, 31(28): 3501-8. [PMID: 23980077 DOI: 10.1200/jco.2012.44.5643]
- 4 **LI S**, ZHONG C, LI Q, et al. Neoadjuvant transarterial infusion chemotherapy with FOLFOX could improve outcomes of resectable BCLC stage A/B hepatocellular carcinoma patients beyond Milan criteria: An interim analysis of a multi-center, phase 3, randomized, controlled clinical trial [J]. *Journal of clinical oncology*, 2021, 39(15_suppl): 4008-. [DOI: 0.1200/JCO.2021.39.15_suppl.4008]
- 5 **LI S**, MEI J, WANG Q, et al. Postoperative Adjuvant Transarterial Infusion Chemotherapy with FOLFOX Could Improve Outcomes of Hepatocellular Carcinoma Patients with Microvascular Invasion: A Preliminary Report of a Phase III, Randomized Controlled Clinical Trial [J]. *Annals of surgical oncology*, 2020, 27(13): 5183-90. [DOI: 10.1245/s10434-020-08601-8]