

PEER-REVIEW REPORT

Name of journal: *World Journal of Gastrointestinal Oncology*

Manuscript NO: 79806

Title: Combining local regional therapy and systemic therapy: Expected changes in the treatment landscape of recurrent hepatocellular carcinoma

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 02543955

Position: Peer Reviewer

Academic degree: FEBS, MD

Professional title: Associate Professor, Senior Researcher, Surgical Oncologist

Reviewer's Country/Territory: Germany

Author's Country/Territory: China

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Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-09-29 08:08

Reviewer performed review: 2022-10-06 21:27

Review time: 7 Days and 13 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Judgment by peer reviewers	Does this manuscript meet the code of ethics standards? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No Does this manuscript have important novelty? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No Does this manuscript have important creativity or innovation?

	<input type="checkbox"/> [J31] Yes <input type="checkbox"/> [J30] No Does this manuscript use reliable research methods? <input type="checkbox"/> [J41] Yes <input type="checkbox"/> [J40] No Are the manuscript-accompanying data and figures authentic? <input type="checkbox"/> [J51] Yes <input type="checkbox"/> [J50] No Does this manuscript make scientifically significant conclusions? <input type="checkbox"/> [J61] Yes <input type="checkbox"/> [J60] No
Language quality	<input checked="" type="checkbox"/> [Y] Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> [Y] Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> [Y] Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> [Y] Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> [Y] No

SPECIFIC COMMENTS TO AUTHORS

The manuscript by Liang et al. summarizes the available data about the combination of local and systemic therapy for recurrent hepatocellular carcinoma (HCC). In general, the manuscript is well written and addresses an important issue. However, some points should be addressed: 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. 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 trials 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. 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? 4. A possible combination of local and systemic treatment is also the re-resection combined with adjuvant therapy. Is there any data on this? 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. 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? 3. Page 7, last paragraph: ".....divided into radical treatment and palliative treatment". I'd rather recommend the division into "curative and palliative treatment". 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. 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. 6. Page 13, 1st paragraph: I don't understand the sentence: "Compared with an initial diagnosis of HCC, recurrent HCC at any stage



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involves tumor recurrence[91]". Could you please explain?

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	<input type="checkbox"/> [31] Yes <input type="checkbox"/> [30] No Does this manuscript use reliable research methods? <input type="checkbox"/> [41] Yes <input type="checkbox"/> [40] No Are the manuscript-accompanying data and figures authentic? <input type="checkbox"/> [51] Yes <input type="checkbox"/> [50] No Does this manuscript make scientifically significant conclusions? <input type="checkbox"/> [61] Yes <input type="checkbox"/> [60] No
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Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

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?