



## PEER-REVIEW REPORT

**Name of journal:** World Journal of Gastroenterology

**Manuscript NO:** 61373

**Title:** High rate of complete histopathological response in HCC patients after combined TACE and SBRT

**Reviewer's code:** 05221455

**Position:** Editorial Board

**Academic degree:** MD, PhD

**Professional title:** Assistant Professor, Professor

**Reviewer's Country/Territory:** South Korea

**Author's Country/Territory:** Germany

**Manuscript submission date:** 2021-02-05

**Reviewer chosen by:** AI Technique

**Reviewer accepted review:** 2021-02-07 23:12

**Reviewer performed review:** 2021-02-08 07:41

**Review time:** 8 Hours

<b>Scientific quality</b>	<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 Grade E: Do not publish
<b>Language quality</b>	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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## **SPECIFIC COMMENTS TO AUTHORS**

Although this study is a retrospective study conducted on a small sample size, it is thought that it will be helpful for future treatment policies and research by analyzing the effectiveness of combination therapy of TACE and SBRT, which is suggested as an alternative loco-regional modality of bridging therapy in HCC treatment, in terms of pathologic complete response. As suggested below, however, further explanation or discussion is needed in several aspects.

**major points**

1. If there is a reason for not analyzing the case of bridging therapy with RFA or MWA, it is better to present it briefly in methods or discussion section.
2. As suggested by the authors, the most commonly used bridging therapy is TACE in these situation. The TACE case presented in the presnt study seems to be relatively small, and it is necessary to provide a reason for this.
3. Was radiologic response evaluation conducted before LT? If so, it would be helpful to present comparison results for radiologic and pathologic responses.
4. It is known that obtaing of CR after SBRT varies significantly according to the interval between SBRT and response evaluation. It would be helpful to present the timeline of SBRT and LT in all patients received SBRT as a figure.

**minor points**

When abbreviation used, the authors are to be defined where first used. Correctly present the BED fomula using a formula function of MS WORD.



### PEER-REVIEW REPORT

**Name of journal:** World Journal of Gastroenterology

**Manuscript NO:** 61373

**Title:** High rate of complete histopathological response in HCC patients after combined TACE and SBRT

**Reviewer's code:** 03742333

**Position:** Editorial Board

**Academic degree:** MD, PhD

**Professional title:** Doctor, Full Professor, Professor, Surgeon

**Reviewer's Country/Territory:** Brazil

**Author's Country/Territory:** Germany

**Manuscript submission date:** 2021-02-05

**Reviewer chosen by:** Ya-Juan Ma

**Reviewer accepted review:** 2021-02-10 10:13

**Reviewer performed review:** 2021-02-16 01:16

**Review time:** 5 Days and 15 Hours

<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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#### **SPECIFIC COMMENTS TO AUTHORS**

I have read with great interest the manuscript entitled 'High rate of complete histopathological response in HCC patients after combined TACE and SBRT', submitted to the World Journal of Gastroenterology. In this multicentre retrospective study, the combination of TACE and SBRT as a bridging therapy for HCC prior to transplantation increased the rate of complete histopathological response compared to each method alone. While the article suggests the benefit of the combination, it acknowledges in the discussion of the manuscript their limitations. The manuscript is written well, and the topic is relevant. **MAJOR COMMENTS** - While the manuscript properly acknowledges its limitations in the Discussion, it would be necessary to also include these comments in the Abstract. This is because the influence of several confounders cannot be excluded. The large duration of study recruitment and treatment performed at different centres may bias the results, albeit the distribution of procedures per centre is not clear. In addition, differences in the number of lesions between the groups (most of the two lesions cases were in the TACE group).



## PEER-REVIEW REPORT

**Name of journal:** World Journal of Gastroenterology

**Manuscript NO:** 61373

**Title:** High rate of complete histopathological response in HCC patients after combined TACE and SBRT

**Reviewer's code:** 05105325

**Position:** Editorial Board

**Academic degree:** MD

**Professional title:** Professor, Surgeon

**Reviewer's Country/Territory:** China

**Author's Country/Territory:** Germany

**Manuscript submission date:** 2021-02-05

**Reviewer chosen by:** Ya-Juan Ma

**Reviewer accepted review:** 2021-02-18 12:27

**Reviewer performed review:** 2021-02-18 12:58

**Review time:** 1 Hour

<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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#### **SPECIFIC COMMENTS TO AUTHORS**

the combination of Transarterial chemoembolization (TACE) and less commonly stereotactic body radiation therapy (SBRT) was not a common treatment of hepatocellular carcinoma.the results of the uncommon combination were surprising.I hope to see whether the combination of TACE and SBRT can lead to the same surprising tumor-free survival.



## PEER-REVIEW REPORT

**Name of journal:** World Journal of Gastroenterology

**Manuscript NO:** 61373

**Title:** High rate of complete histopathological response in HCC patients after combined TACE and SBRT

**Reviewer's code:** 00730738

**Position:** Editorial Board

**Academic degree:** MD, PhD

**Professional title:** Assistant Professor

**Reviewer's Country/Territory:** Slovenia

**Author's Country/Territory:** Germany

**Manuscript submission date:** 2021-02-05

**Reviewer chosen by:** AI Technique

**Reviewer accepted review:** 2021-02-05 21:37

**Reviewer performed review:** 2021-02-21 11:32

**Review time:** 15 Days and 13 Hours

<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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## **SPECIFIC COMMENTS TO AUTHORS**

This is an interesting paper that looks at the treatment response to combined TACE and SRB therapy in patients with hepatocellular carcinoma prior to transplantation, who could not be treated with surgical resection or ablation. The results are promising as they suggest that a combination of TACE and SBRT increases the rate of complete histopathological response compared to TACE or SBRT alone. The manuscript is well written, with the title, key words, as well as the abstract reflecting the main conclusions that could be drawn from the results. Nevertheless, I have several suggestions on how to improve the manuscript. The introduction is extensive and the significance of the study well presented; however, some of its parts do repeat in the discussion. I believe that the manuscript could be shortened in the introduction or discussion part or both. In the Materials and Methods section the part about post-transplant analysis of the presence of vital tumour tissue is not clearly presented. Specifically: there is a mention that "Size and number of tumour nodules were determined"; however, in the Results section there is no mention about the post-treatment size and number of the tumours. Then there is a mention of "grading of any remaining tumour tissue", where there are just actually two categories - that is the presence or the absence of vital tumour tissue. It would be interesting to know the percentage of vital tumour tissue in those without complete response, as this could be anything from 5 to 100%. In the discussion there is a term "partial histopathological response" that is not explained in the Methods section (anything from 0 to 99% tumour necrosis?). It would be interesting to specify a partial response at least for the one patient with good outcome despite high AFP. The Discussion is extensive and informative; however, it does not focus enough on the main topic of the study, that is the histological evaluation. The authors cite appropriately the latest, important and authoritative references. As the authors have pointed out, there



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have already been several publications regarding the combination therapy for HCC. Have they also analysed histological treatment response and what were their results? What is the advantage of this study compared to previous studies? The Discussion needs to be considerably improved with higher focus on histology. The terminology regarding no vital tumour should be unified and the term “no detectable tumour burden” replaced with more suitable term. The first sentence in the third paragraph of the Results section is redundant as HCC within MC was an inclusion criteria. The figures could be sharper. Figures 2 B and D do not have a scale bar. It seems that Figure 2b is a higher magnification. In the legend the statement “no vital tumour cells could be detected in the TACE + SBRT group” is not completely true for the group, although it is correct for 89% of cases including the one depicted in the figure. The quality of the Supplemental figures is not good enough to evaluate, at least in the World file. They do not provide much additional information. In addition the Legends are confusing: There are two pictures in the Supplemental Figure 1, however the legend does not reflect that. Is there a difference between TACE without SBRT (Supp. Figure 1) and TACE only (Supp Figure 2)? There is no scale bar in the Supplemental Figure 2. In the legend to Table 2 there is an explanation for c and d, however, the letters do not appear on the table. To summarize: I find this work to be interesting and important, but the manuscript does require quite a few finishing touches and optimisations so that the results can be clear and without any doubts or major open issues.



## RE-REVIEW REPORT OF REVISED MANUSCRIPT

**Name of journal:** World Journal of Gastroenterology

**Manuscript NO:** 61373

**Title:** High rate of complete histopathological response in HCC patients after combined TACE and SBRT

**Reviewer's code:** 03742333

**Position:** Editorial Board

**Academic degree:** MD, PhD

**Professional title:** Doctor, Full Professor, Professor, Surgeon

**Reviewer's Country/Territory:** Brazil

**Author's Country/Territory:** Germany

**Manuscript submission date:** 2021-02-05

**Reviewer chosen by:** Man Liu

**Reviewer accepted review:** 2021-03-22 13:26

**Reviewer performed review:** 2021-03-23 17:07

**Review time:** 1 Day and 3 Hours

<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input checked="" type="checkbox"/> 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
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Peer-reviewer statements</b>	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



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I have re-reviewed the manuscript entitled 'High rate of complete histopathological response in HCC patients after combined TACE and SBRT' submitted to the World Journal of Gastroenterology. The authors have appropriately addressed all my major comments. Of note, the revised version of the manuscript reads better and, also, the scientific quality of the paper has improved significantly. My only minor comment is regarding the amendment made in the abstract. I would strongly advice discussing the study's limitations in the Conclusion section and not in the Results. All the considerations correctly inserted must be used to balance the Conclusion of the paper – they are not the results of any analysis.



## RE-REVIEW REPORT OF REVISED MANUSCRIPT

**Name of journal:** World Journal of Gastroenterology

**Manuscript NO:** 61373

**Title:** High rate of complete histopathological response in HCC patients after combined TACE and SBRT

**Reviewer's code:** 00730738

**Position:** Editorial Board

**Academic degree:** MD, PhD

**Professional title:** Assistant Professor

**Reviewer's Country/Territory:** Slovenia

**Author's Country/Territory:** Germany

**Manuscript submission date:** 2021-02-05

**Reviewer chosen by:** Man Liu

**Reviewer accepted review:** 2021-03-22 10:52

**Reviewer performed review:** 2021-04-06 07:18

**Review time:** 14 Days and 20 Hours

<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input checked="" type="checkbox"/> 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
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Peer-reviewer statements</b>	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



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The authors have appropriately addressed all my comments and I find the manuscript acceptable for publication. There are still some typos: - page 6: The sentence "SBRT is therefore mainly performed as an" .... has no ending - page 7, last sentence: "aimed TO analyse" - page 8: "Additionally, with data showing excellent response ..." - omit with - page 12, the end of first paragraph - omit in - page 12: response to TACE alone is found IN less than 35% - page 16: ... and 25% OF the SBRT