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Klinik und Poliklinik für Innere Medizin II

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Revision letter: manuscript 61373

Dear Mr. Lian-Sheng Ma,
dear Mrs. Ya-Juan Ma,
dear Reviewers,

Thank you for your first decision regarding our manuscript entitled *"High rate of complete histopathological response in HCC patients after combined TACE and SBRT"*.

We greatly appreciate the constructive comments of the editorial team and the reviewers. We have now addressed these comments as outlined below and believe this has strengthened the paper. On the following pages, we outline the responses point by point to the comments of the editors and reviewers.

We hope our revised version will be fit for publication and look forward to hearing from you in the near future. We remain at your disposal for any further information.

Yours sincerely,

Ursula Ehmer

Comments from the Reviewers:

Reviewer #1:

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.

We thank the reviewer for her/his comments on the manuscript and shortened the text in both the introduction and discussion and removed redundant content.

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.

We apologize for not adding this data to the manuscript. We now added new Fig. 3 that show changes in size from before treatment to tumour size in explant livers. Additionally, we removed “grading of any remaining tumour tissue” from the Methods section as we did not analyze differences in tumour grading separately.

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 thank the reviewer for this important comment. In our cohort, the percentage of vital tumour tissue varied widely, ranging from 20 to >90% in those cases where the percentage was reported. Unfortunately, in most of our explant histology reports, the proportion of tumour necrosis was not precisely described. This might be due to sample preparation or the fact that it is difficult to determine

the exact percentage of residual tumor tissue throughout the tumor nodule. For the patient with high AFP and good outcome, however, data was available (20 percent). We now describe this part in the manuscript.

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 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.
We agree with the reviewer that the analysis of histopathology is highly important, however there are few studies analyzing treatment response by histology. Most of these studies use explant histology, but focus on more established treatment modalities such as TACE and SIRT (1, 2). In contrast, TACE + SBRT is not considered a standard treatment approach in international guidelines and randomized trials in comparison to TACE are ongoing. If used in HCC, then mainly as a palliative treatment approach with no resection or transplantation after treatment and therefore no histology available. Most of the studies assess tumor response by radiology (via RECIST). Therefore, data on the efficiency of this combination therapy – especially in early stage HCC – remains scarce. One study analyzing treatment response to different bridging therapies included only 2 tumors with TACE + SBRT combination therapy these tumors showed less than 80% of residual tumor, but not data on tumor size, AFP or time between treatment and transplant were given (3). Hence, the advantage of this study is the histopathological analysis a well-defined group of patients in the unique context liver transplantation. Even with a lack of supporting data, we assume that the assessment of tumor response by histopathology is more accurate than by radiology and might therefore better correlate with important clinical marker such as tumor recurrence. We now describe available data on TACE + SBRT as well as single treatment modalities in more detail the introduction and discussion.

The terminology regarding no vital tumour should be unified and the term “no detectable tumour burden” replaced with more suitable term.
As suggested, we unified terminology and used “no vitual tumor” where applicable.

“The first sentence in the third paragraph of the Results section is redundant as HCC within MC was an inclusion criteria”
We deleted the sentence to avoid redundancy.

The figures could be sharper.

We apologize for low providing low resolution figures. For revision purposes the figures were embedded into the manuscript file which unfortunately decreased image quality. We now provide original figures with better resolution.

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.
Thank you for pointing this out. We added scale bars in Figure 2B and D and changed the legend accordingly.

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.
As we inserted the Figures in the Word file, quality was not optimal. We know created a pdf file with improved resolution. Though we agree that limited information is obtained from additional low magnification pictures, we decided to add these pictures to give a better impression of the histopathological appearance of tumor lesions in explant livers.

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)?
We apologize for wrongly labeling Supplemental Fig. 2, which is from a patient after TACE + SBRT. We now combined Supplemental Fig. 1 and 2 into one new Supplemental Fig. 2.

There is no scale bar in the Supplemental Figure 2.
We now added scale bars to all histology pictures.

In the legend to Table 2 there is an explanation for c and d, however, the letters do not appear on the table.
We apologize for this error and edited Table 2 accordingly.

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.
We thank the review very much for his/her detailed comments and believe that we were able to address all comments to the reviewer’s satisfaction.

Reviewer #2:

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"

We thank the reviewer for this positive view of our manuscript.

Reviewer #3:

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.

We appreciate this concern and have now included the limitations of our study in the Abstract. We agree that differences in TACE procedures (DEB-TACE, different chemotherapeutic agents) in different centers may bias the results. However, the limited number of patients precludes any subgroup analysis. We now added the distribution of procedures per center to the Methods section.

In addition, differences in the number of lesions between the groups (most of the two lesions cases were in the TACE group).

We thank the reviewer for pointing this out. We now mention this potential bias in the discussion.

Reviewer #4:

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 briding

therapy in HCC treatment, in terms of pathologic complete response. As suggested below, however, further explanation or discussion is needed in several aspects.
We thank the reviewer for these useful comments on our manuscript and modified the manuscript to answer the reviewer's concerns.

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.
Ablation presents a standard bridging therapy that leads to a complete response by radiology and histopathology in the majority of cases (4, 5). Generally, ablation therapies such as RFA or MWA are considered as curative treatment approaches by aiming to achieve complete necrosis of treated tumor tissue. Though we know that complete response is not achieved in all tumors treated and recurrence at the border of ablated tumors does occur in a number of cases, we felt that ablation therapies are already well studied. We therefore decided to focus on the less established – though apparently highly effective – combination therapy of TACE and SBRT and added response to treatment with a single modality as comparison. We have addressed this comment by presenting the reasons for not analyzing these cases in Methods 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.
We agree that TACE is the most commonly used bridging therapy. However, many of the patients in our centres undergo multimodal therapy and ablation is used wherever possible. Therefore, the cohort of patients with TACE and without any additional local therapies (mostly ablation) was relatively small. Additionally, one center only screened for patients that received SBRT or TACE + SBRT. The distribution of procedures per center is now included in the manuscript.

3. Was radiologic response evaluation conducted before LT? If so, it would be helpful to present comparison results for radiologic and pathologic responses.
This point is indeed highly interesting. For several reasons, we decided not to include radiologic response into our paper due to limitations based on the retrospective design of our study. All patients had radiological assessments every three months prior to LT. However, imaging modalities differed over the time of the study with tumor response assessed by CT scans, and more recently by MRI scans. Additionally, data for tumor response by imaging was not reported in a standardized fashion in earlier reports, requiring detailed re-analysis of imaging data from different centers for each patient to take into account loss of arterial hyperperfusion as a criteria for response. As the main focus of our

manuscript is the analysis of histopathological response, we decided to include only data from diagnosis of HCC before treatment and aim to analyze radiologic treatment response in a future study.

4. It is known that obtaining 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.
This is a very good point, especially since non-responders in the SBRT group mostly had a short interval between SBRT and LT. We added new Supplemental Figure 1 showing time intervals for all TACE+SBRT and SBRT patients together with the pathological response. Additionally, ee clarified this concern in the discussion.

minor points: When abbreviation used, the authors are to be defined where first used. Correctly present the BED formula using a formula function of MS WORD”
We edited the paper to eliminate all such errors and presented the BED formula using a formula function (only possible in original word file, not in automatically generated document).

Comments from the Editorial Team:

Science editor:

Issues raised:

"(1) The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor"

We prepared the figures using PowerPoint and can provide original histology pictures on request (in case a higher resolution will be required).

"(2) The "Article Highlights" section is missing. Please add the "Article Highlights" section at the end of the main text"

As requested we added the "Article Highlights" section at the end of the main text.

Company editor-in-chief:

The title of the manuscript is too long and must be shortened to meet the requirement of the journal (Title: The title should be no more than 18 words).

The title consists of 14 words: "*High rate of complete histopathological response in HCC patients after combined TACE and SBRT"*

References:

1. Zhang W, Xu AH, Wang W, Wu YH, Sun QL, Shu C. Radiological appearance of hepatocellular carcinoma predicts the response to trans-arterial chemoembolization in patients undergoing liver transplantation. BMC Cancer 2019;19:1041.
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3. Rubinstein MM, Kaubisch A, Kinkhabwala M, Reinus J, Liu Q, Chuy JW. Bridging therapy effectiveness in the treatment of hepatocellular carcinoma prior to orthotopic liver transplantation. J Gastrointest Oncol 2017;8:1051-1055.
4. Lee MW, Raman SS, Asvadi NH, Siripongsakun S, Hicks RM, Chen J, Worakitsitisatorn A, et al. Radiofrequency ablation of hepatocellular carcinoma as bridge therapy to liver transplantation: A 10-year intention-to-treat analysis. Hepatology 2017;65:1979-1990.
5. Bale R, Schullian P, Eberle G, Putzer D, Zoller H, Schneeberger S, Manzl C, et al. Stereotactic Radiofrequency Ablation of Hepatocellular Carcinoma: a Histopathological Study in Explanted Livers. Hepatology 2019;70:840-850.