Peer Review File

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Reviewer A

The retrospective cohort study identified pre-transplant characteristics associated with oligorecurrence and polyrecurrence amongst patients with recurrent hepatocellular carcinoma post-liver transplantation and provide evidence that receipt of metastasis-directed therapy to all sites of recurrence (MDT-All) may improve overall survival for oligorecurrence patients. We thank all the authors for their efforts. However, this article also needs to be further modified in the following aspects.

1. Participants included in the retrospective study are critical to the establishment and conclusion of the study. However, in this article, the inclusion and exclusion criteria are not stated. In addition, the method of selecting these patients is not clear. Is there selection bias in this study?

> **Reply 1**: Thank you for raising this excellent point. Three hundred ninety-seven patients who underwent liver transplantation for HCC were reviewed for subsequent radiographic or biopsy-proven recurrence from 2005-2022, of whom 43 were found to have recurrence and were included in this study. There were no other inclusion or exclusion criteria. There was no known selection bias in this study.
>
> **Changes in the text:** Line 164-165 of Results were changed to include the total number of patients with HCC who underwent liver transplantation at our institution.

2. Please elucidate if the blinding is used.

> **Reply 2:** We thank the reviewer for this point. There was no blinding to the therapy (MDT vs no MDT). This is a limitation of retrospective analyses.
>
> **Changes in the text:** We have included this limitation in the Discussion, lines page 10, lines 311-312.

3. In the section of Effect of MDT on outcomes in patients with initial oligoM1 disease, Line 177, 3/27 is best changed to 3.

> **Reply 3:** We thank the reviewer for this helpful suggestion and have made the change as suggested.
>
> **Changes in the text**: We have modified our text as advised (see page 8, line 222).

4. The transplant waiting time in polyM1 group (266 days) was longer than that in oligoM1 group (199 days), but the difference was not statistically significant. Waiting too long for transplantation may promote HCC progression and lead to multiple relapses. Please explain whether this difference between the two groups would affect the accuracy of the final conclusions.

> **Reply 4**: We thank the reviewer for making this insightful point. It is true that time to time transplant may increase the likelihood of HCC progression in general. Perhaps longer time to transplant increases the likelihood of micro-metastatic disease that is not detectable on imaging prior to transplantation. In this study, we focused on the effect of metastasis-directed therapy in patients with oligorecurrent disease, a subgroup that is less likely to have undetected micro-metastatic disease that would not have been

addressed with metastasis-directed therapy, a local treatment. The findings of this study suggest that in patients with oligorecurrent disease, metastasis-directed therapy to all sites of disease may prolong survival.

Changes in the text: Not applicable.

5. There are several articles relevant to your research, please add 2 references from the list below.

Impact of body mass index on hepatocellular carcinoma recurrence after liver transplantation through long-term follow-up. (doi: 10.21037/hbsn.2020.04.01)

Microvascular invasion of hepatocellular carcinoma predicts microvascular invasion of its recurrence: potential implications for salvage liver transplantation? (doi: 10.21037/hbsn-21-346)

Hepatocellular carcinoma recurrence after direct-acting antiviral therapy: an individual patient data meta-analysis. (doi: 10.1136/gutjnl-2020-323663)

Reply 5: We thank the author for these helpful suggestions. We have incorporated the second and third references ((doi: 10.21037/hbsn-21-346 and doi: 10.1136/gutjnl-2020-323663) into the discussion of risk factors for recurrence, including MVI and pre-transplant AFP.

Changes in the text: The Discussion (pages 9-10, lines 293-301) has been expanded to reflect the changes discussed, and we have added the references mentioned in our Reply.

Reviewer B

The authors reported the patterns and kinetics of HCC recurrence after liver transplantation, depending on the pattern whether it was oligorecurrence or not. They concluded that metastasis-directed therapy to all sites of disease was associated with improved OS for oligorecurrence. As the authors also pointed out, the treatment of recurrent HCC after LT might be difficult due to various coexist clinical item, especially immunosuppression, so that standard therapy for primary HCC might not be adopted in such situation. I am interested in the topic, and the paper is generally well written and easy to read. My specific comments and questions are as follows.

1. What is the author's basic policy of LT for HCC? Do they follow the Milan criteria?

Reply: Thank you for this question, yes, we follow the Milan criteria to determine transplant eligibility.

Changes in text: In the Methods on page 5, line 112, we now specify that Milan criteria were followed to determine transplant eligibility.

2. The authors should show their way of posttransplant follow-up, including the modalities and interval of imaging studies.

Reply: Thank you for this comment, we agree that specifying our follow-up schedule would be of value to the reader. Our follow-up schedule post-transplant involved surveillance imaging scans and labs every 3 months for 2 years, then every 6 months. Imaging typically involved MRI or CT Abdomen/Pelvis, with CT Chest every 6 months.

Changes in text: We now include our surveillance strategy in the methods, page 5, line 112-115.

3. The authors should show the actual indication of MDT.

Reply: We thank the reviewer for this useful suggestion. As is defined in the Methods, page 6, lines 133-137, MDT was by definition therapeutic (i.e. to definitively treat or resect any evident disease). In some cases, MDT was also delivered for symptom palliation. For instance, two of 15 patients with oligorecurrence underwent MDT-All consisting of surgical resection. One patient underwent Whipple resection for a mass causing extrinsic compression of the common bile duct, with negative margins, and did not have a subsequent local recurrence, though did have distant recurrence elsewhere. The second patient presented with a humeral head fracture and underwent radical resection of the metastasis with placement of a humeral head prosthesis, and had durable local control, with subsequent progression owing to skull metastases which were treated with stereotactic radiation therapy.

Changes in text: We have clarified in the Methods, page 6, line 137-138, that MDT could have both a therapeutic and palliative rationale. We have added additional discussion of the two patients who underwent surgical resection as MDT-All in the Results, page 8, Lines 228-236.

4. In page 6, line 142, 19 patients received MDT, while in page 7, line 177, 18 patients received MDT (15 with MDT-All, 3 with MDT to at least 1 metastasis). Was it duplicated in 1 patient? If so, please show it in detail.

Reply 1: Thank you for raising this insightful question. First, there was a typographical error, as there were in fact 20 patients who received MDT, not 19. This has now been corrected in the manuscript, and we apologize for the oversight. With this in mind, the apparent discrepancy can be attributed to the fact that 2 patients with poly-metastatic recurrence underwent MDT. Of the 43 patients in the overall study cohort, 20 patients received MDT, of whom 18 had oligorecurrence and 2 had polyrecurrence. Of the 18 with oligorecurrence, 15 received MDT-All and 3 patients received MDT to less than all sites of disease. The breakdown amongst the oligorecurrent cohort is reported on lines 221-223.

Changes in text: At line 180, there was a typographical error which has been corrected to report that 18/20 patients (not 18/19, as was erroneously reported previously) who received MDT had oligoM1 disease at the time of recurrence.

Reviewer C

Postoperative recurrence of HCC after LT is still the important issue to secure long-term prognosis of LT patients. The authors have demonstrated that receipt of MDT to all sites of disease was associated with improved overall survival in patients with limited HCC disease recurrence following LT. Please refer my comments and revise your article.

1. How about R0 achievement rate and the impact of R0 for these patients?

Reply: We thank the reviewer for this very insightful comment. We agree that the margin-negative resection rate may impact subsequent recurrence. Two patients underwent surgery as part of MDT-All in our cohort. One patient underwent a Whipple

resection in the setting of a mass causing extrinsic compression of the common bile duct, with negative margins; this patient subsequently developed polymetastatic recurrence however maintained local control at the resection site. The second patient had a humeral metastasis causing pathological fracture and underwent radical resection with placement of a humeral head prosthesis, followed by post-operative palliative radiation therapy at an outside facility. The patient maintained local control but subsequently was found to have bone metastases of the skull which were treated with stereotactic radiation therapy.

Changes in text: We have added a description of these two patients to the Results, page 8, lines 228-236.

2. If possible, not only MIlano criteria, 5-5-500 criteria should be also used for statistical analyses.

Reply: We thank the reviewer for this insightful suggestion. We reviewed numerous clinical and pathological variables in our statistical analysis of recurrence. In the interest of avoiding collinearity, we have not included 5-5-500 criteria in the analysis shown in Table 3. Upon further review of the Tables we have also added clarification to the variable of "downstage status," which is more aptly described as "Baseline HCC within Milan Criteria" (Yes vs No). This has resulted in a slight modification to the values related to this variable in tables 2 and 3, however has not changed the overall statistical non-significance for the p-values for this variable in Table 2 and Table 3, and did not impact any of the major results of the study.

Changes in text: Not applicable. Tables updated as noted.

3. The duration of Kaplan-Meier curve is too long to visualize a significant difference. I think that narrower duration can emphasize the results.

Reply: We thank the author for this useful suggestion. Our intention in showing the entire follow-up periods in the Kaplan-Meier curves of Figures 1 and 2 was to demonstrate that the addition of metastasis-directed therapy may result in long-term survival in selected patients. While the difference in survival would be visually accentuated by focusing on the early follow-up period, we would lose the ability to demonstrate long-term survival.

Changes in text: Not applicable

Reviewer D

The manuscript is clear and well-structured. Methods and results are reported in a rational manner. The authors drew attention to the limitation of the retrospective nature and small sample size.

Points for revision:

I would suggest describing the surveillance schedule after liver transplantation (imaging at regular intervals versus at symptoms onset) at the center. Also, I would suggest adding the total number of liver transplants performed in other countries to clarify the overall recurrence rate.

Reply: Thank you for this comment, we agree that specifying our follow-up schedule would be of value to the reader. Our follow-up schedule post-transplant involved

surveillance imaging scans and labs every 3 months for 2 years, then every 6 months. Imaging typically involved MRI or CT Abdomen/Pelvis, with CT Chest every 6 months. All liver transplants reviewed (397 in total) were performed at our institution, and the crude overall recurrence rate is 11%.

Changes in text: We now include our surveillance strategy in the methods, page 5, line 112-115. We have included the crude overall recurrence rate in the Results, page 6, line 165.