Peer Review File

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Reviewer A

General comments
- Structure is poor, methods and results are mixed.
- Methodology poorly described.
- Novelty of data missing.
- Discussion too limited, only on PFS/OS and Bolondi.

Reply: All these comments are expanded below
Changes in Text: As noted below across all comments.

REVIEWER A responses
Abstract
No comment

Introduction
No comments

Methods
Comment 1: - How did you address missing data?

Reply 1: Tables 2-4 include a column with the number of patients for each measure so the reader can identify what is available. This is addressed in the weaknesses paragraph in the discussion
Changes in Text: We have added a statement calling out the available data column to the weaknesses paragraph: Page 12, lines 490-491.

Comment 2: - For clarity add that patient with PVT were excluded

Reply 2: The presence of PVT would mean that a patient would be BCLC C, not BCLC B.
Changes in Text: We have clarified this on page 8, lines 286-287. This issue is also addressed in Table 1.

Comment 3: - Demographics part already includes results of de data presented, this should be placed in the results section. Only description of the data parameters collected here! Same goes for the following subsections (size of lesions included, is already a result of your registry).

Reply 3: We have reformatted the manuscript.
Changes in text:
Page 5, line 163
Page 5, line 186-page 6, line 192
Demographics moved to Page 7, lines 258-271
Baseline Imaging moved to Page 7-8, line 273-287
Delivered Activity moved to Page 8, line 289-297.

Comment 4: - Section dosimetry isn't dosimetry, just a summary of activities and treatment approaches. Again, results section. But this section should mention how patients were dosed!? BSA-method, modified BSA? Monocompartment model? Multicomparment model? Any real dosimetry done?

Reply 4: This section has been re-titled "Delivered Activity". Dosimetry details have also been added to Table 4
Changes in Text: Title altered, page 8, line 289. Information added to Table 4

Comment 5: - How was PFS defined? RECIST 1.1, mRECIST? EASL?

Reply: mRECIST was used. We apologize for leaving this out.
Changes in text: Addressed, page 6, line 198-200 and 203.

Comment 6: - Was there structured follow-up? CT of MR? Mixed? Every 3 months?

Reply: The use of local guidelines for follow-up is in the methods, page 5, lines 185-186.
Changes in text: None

Comment 7: - Who did the reading? Central reading or local? IR or body radiologist? Experience?

Reply: Imaging was interpreted by abdominal imagers.
Changes in text: Addressed, page 5, lines 186-187.

Comment 8: - Definition of OS? OS reporting is useless, if you don't report subsequent treatments

Reply: OS is defined in the Data Analysis section, page 6, line 198-200. We have included PFS as well as OS. We have reviewed 2 other recent prospective studies and found our reporting methods to be consistent with those.

1. IMBRAVE 150: Cheng AL, et al J Hepatol 2022, PMID: 34902530
2. LAUNCH: Peng Z, et al. J Clin Oncol 2022, in press PMID: 35921605

Changes to Text: None. While some trials report post PFS treatment, this is not universal.

Comment 9: - How many missing data?? Lost-to-follow-up??

Reply: Missing data is addressed in comment 1. We have added the reasons for going off study in the methods and results. Table 5 has also been added.
Changes to Text: Page 6, lines 204-206, Page 9, lines 327-332 and Table 5

Comment 10: - Collinearity between tumor size and Bolondi, so why is Bolondi usefull? No persuading argument given.

Reply: Bolondi incorporates tumor size as well as Child Pugh score. This is addressed in existing text, page 4, lines 135-137.
Changes to Text: Further clarified, page 4, lines 145-146 and page 10, lines 347-351.

Comment 11: All non-PVT..?

Reply: As addressed in comment 2, the presence of PVT would define the criteria for BCLC C, not BCLC B HCC.
Changes in text: Added to Table 1 as noted in the reply to comment 2.

Results:
Comment 12: - OS PFS part, missing definitions here

Reply: OS and PFS are defined in the Data Analysis section
Changes in text: mRECIST used for PFS definition as in Comment 5, page 6, lines 198-200.

Comment 13: - Progression section; how defined, by whom?

Reply: this is addressed in the responses to comments 5, 7 and 12.
Changes in text: In addition to mRECIST for PFS in Comment 5, image interpretation by abdominal imagers is addressed in Comment 7.

Comment 14: - "with isolated intrahepatic progression, 52 (36%) were in an area of previous treatment.", your methods section said nothing on analyzing this. Add it.

Reply: This is added as suggested
Change to text: Page 6, line 206

Comment 15: - Extrahepatic disease on CT or other modality?

Reply: This has been added
Change to text: Page 6, line 200.

Comment 16: - Tox data; **no missings**? You've gathered grade 1-5 9methods section), why only report grade 3 and 4? Show the data in table 5.

Reply: This was an error on our part. We tracked Grade 3 or higher toxicities for constitutional events and for liver functions. All reported toxicities are presented in Table 5.
Changes in Text: The Data Analysis section has been edited to reflect the above, Page 6, lines 207-208.

Discussion
Comment 17- Missing any limitation regarding true dosimetry. DOSISPHERE-1, LEGACY, etc.

Reply: Reference to DosiSphere added.
Changes in Text: Page 11, lines 419-422.

Comment 18: - Here you report less than 100% entry… how much was it really???

Reply: We have addressed this above, in comment 1.
Changes in Text: We have added a statement calling out the available data column to the weaknesses paragraph: Page 12, lines 490-491.

Comment 19: - This study has many more limitations.

Reply: We are responding to all specific comments.
Changes in Text: None

Comment 20: Table 1; not a real representation of Bolondi, correct

Reply: The Tumor burden and Child-Pugh scores are accurate and match p356 in Reference 12, which is the source material.
Changes in Text: We have added the absence of portal vein thrombosis to Table 1, which also addresses comments 1 and 11 above.

Table 2;
Comment 21: - Bilirubin and albumin correlated with bolondi… correlated/collinearity seems logical

Reply: We address in the discussion as per Comment 10
Changes in Text: As per comment 10.

Comment 22: - In all groups patients with hepatic encephalopathy were treated.. why? Poor patient selection? What grades at baseline?
Reply: 10/11 patients were grade 1 at baseline. Added to text. Patient selection addressed in

Registry/Patients section.
Changes in Text: Page 7, lines 266-271.

Comment 23: Table 3 no comment

Reply: No changes needed
Changes in Text: None

Comment 24: Table 4; can be put in table 2 of main text.

Reply: This table reflects treatment rather than demographic findings. We are going to explore the toxicities in more depth and would prefer to keep this portion separate.
Changes in Text: None.

Comment 25: Table 5. Missing grade 1-2 tox.

Reply: This was addressed in Comment 16. We did not include toxicities less than Grade 3.
Changes in Text: The Data Analysis section has been edited to reflect the above, Page 6, lines 207-208.

Comment 26: Figures no comment

Reply: No changes needed
Changes in Text: None

Reviewer B

Radioembolization with 90Y-microspheres has been a treatment option for inoperable patients. In this manuscript, the authors reported that the Bolondi subgroup classification may help physicians exclude patients with unfavorable treatment outcomes. This manuscript could represent a background for future studies in this field. However, a few questions/comments should be addressed or answered before publication.

Major
Comment 1: The authors should address the Bolondi subgroup classification in more detail in either the INTRODUCTION or DISCUSSION section.

Reply: This has been addressed in both sections.
Changes in Text: Page 4, lines 145-146 and Page 10, lines 356-360

Comment 2: The authors should provide the details about the site of 90Y-microspheres application, i.e. monolobar, or bilobar selective.

Reply: Prescribed activity by site has been added
Changes in Text: Page 8, lines 292-297. Table 8 also provides comparison of toxicities by infusion location.

Comment 3: How many patients with cirrhosis were in this study? Is cirrhosis a risk factor for a poor outcome?

Reply: The presence of cirrhosis has been added to Table 2. There was a difference between groups, however some patients may have been cirrhotic without the diagnosis being officially in the medical record.
Changes in Text: Added to Table 2 and page 7, lines 260-262.

Minor
Comment 4: Please unify the expression of RESiN throughout the manuscript.

Reply: Thank you. We have changed the title to reflect the text.
Changes in Text: Title changed to “RESiN” from “RESIN”

2. Proofreading the article for English style, and misprints are necessary before further evaluation, as some mistakes are notable:

Comment 5: Line 192: “Overall (OS)”

Reply: Changed
Changes in text: As requested on page 6, line 198

Comment 6:
(b) Line 249: “Giannini, et al” should be “Giannini et al.”
(c) Line 257: “Kim, et al” should be “Kim et al.”
(d) Line 268: “Nouso, et al” should be “Nouso et al.”

Reply: This has been edited for these points and throughout the discussion.
Changes in text:
B: Page 11, line 424
C. Page 11, line 429
D. Page 12, line 478
D. Page 12, line 456

Reviewer C

This study is an important contribution towards better patient selection for TARE/SIRT in HCC patients.

In the recent years dosimetry became a crucial part of treatment planning and improved therapy outcome. Therefore, my main comment is on dosimetry.

Dosimetry:
In SIRT/TARE achieved tumor dose has a significant impact on treatment response. Therefore, it would be necessary to state the dosimetry method used and – if available – the relevant dosage information for tumor and normal liver tissue.

Comment 1: If dosimetry followed only a general approach (BSA model), one reason for the poor outcome of subgroup 3 might be a non-sufficient tumor dose. As HCC diameter where higher in this subgroup, the expected tumor dose would likely be lower if not corrected by personalised dosimetry approaches like partition model.

Reply 1: Dosimetry methods have been added to Table 4
Changes in Text: Table 4 has been edited. Addressed, pages 11, lines 419-422

Comment 2: Furthermore, it would be interesting if those 52 patients who developed isolated intrahepatic progression within the previous treatment area did receive a sufficient tumor dose according to actual treatment recommendations.

In the case that accurate dosimetry information is not available or cannot be retrieved retrospectively, differences in PFS and OS cannot be associated purely to different BCLC B subgroups, which should be mentioned as a limitation of the study.

Reply: We have expanded the description of intrahepatic progression to report this outcome more thoroughly. The weaknesses/limitations paragraph has been expanded to include that absence of personalized dosimetry, which was first reported at the very end of enrollment in RESiN.
Changes in Text: Page 9, lines 316-322 and Page 12-13, lines 491-499.

Comment 3: Apart from this, toxicity is likely associated with the applied dose to the non-tumor liver tissue. If available, I recommend investigating toxicity not only in relationship to the different BCLC B subgroups but also to the achieved liver dosage.
As the treatment zones are known, toxicity should be analysed as well in relationship to whole liver, lobar or segmental treatment.

Reply: Given the predominance of body surface area measurements, assessing hepatic dose isn't feasible with our data set. The toxicity paragraph has been revised. Since the article was written there was an update in toxicities which accounts for the higher values seen now than in the original submission. We have completed an evaluation of toxicities by infusion zone.
Changes in text: The toxicity paragraph has been revised, page 10, lines 341-352.
Additionally, Tables 7 and 8 have been added, providing details on the hepatic function toxicities by Bolondi Group and infusion zone.

Further comments:
Comment 4: Line 127: The quoted EASL guidelines are from 2012, whereby treatment recommendations have changed in the past 10 years. Although the actual EASL HCC guideline from 2018 quotes TACE still as first line therapy in BCLC B HCC, there are newer guidelines like the ESMO HCC guideline from 2021 (Updated treatment recommendations for hepatocellular carcinoma (HCC) from the ESMO Clinical Practice Guidelines) where SIRT/TARE is listed as an alternative treatment option in BCLC B. Furthermore, the EASL 2022 update (BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update) divides BCLC B already in 3 subgroups and recommends TACE only for well defined nodules, preserved portal flow and HCC with selective access. For different BCLC B situations, either liver transplantation or systemic therapy is recommended.

Reply: References have been updated.
Changes to Text: References **6, 7, 15,** added. These include DosiSphere, the updated BCLC guidelines and also the ESMO guidelines.

Comment 5: Please clarify if for patients of all your 4 BCLC B subgroups local therapy would still be recommended according to the updated recommendations or if some patients would rather receive different treatment options (and how many if applicable).

Reply: Addressed in discussion
Changes to Text: Page 12, lines 475-477.

Comment 6: Line 104-108: Although all included patients where in BCLC B stage, you refer to a "BCLC B subgroup" next to the subgroups 1-4 you divided according to tumor burden and liver function, which is confusing. Please clarify when you are referring to the whole study cohort and when to the defined subgroups.

Reply: This has been edited as suggested throughout the manuscript.
Changes to text: The entire manuscript was searched to specifically refer to individual subgroups as subgroups and to the entire cohort as a cohort, rather than a group.

Reviewer D

In the present study, the authors try to determine the efficacy and safety of 90Y-radioembolization in patients with BCLC B depending on the Bolondi subgroup classification. Surprisingly, OS and PFS were worse for group 3, although (as expected) the most severe toxicity occurred in the most advanced group (group 4). However, some questions arise after reading the manuscript and also some clarifications should be made by the authors.

Comment 1: Did the authors find more toxicity within subgroup 4 in patients treated in a whole liver fashion, or in those with worse functional status (bilirubin >2 ng/ml or ascites) or who received higher 90Y activity? The subgroup 4 is very heterogeneous in terms of amount of liver treated, tumor burden and functional status, and being able to determine more precisely in those patients in whom there is a greater probability of toxicity (or vice versa, those with better responses) would be of great help to select best candidates for this therapy.

Reply: Tables 7 and 8 (addressed above for reviewer C, comment 3) address toxicity by subgroup and infusion zone. We believe it will be hard to subdivide this group down further. However, we address the risk of subgroup 4 treatment in the discussion along with the desirability to treat that group with segmental treatment if feasible.
Changes in Text: Page 12, lines 475-477

Comment 2: Was the absorbed dose by tumor and healthy liver collected in the RESIN registry? Because these data, which may be of great importance for efficacy and toxicity, are missing. In this regard, if absorbed dose data are not to be included, the word "dosimetry" should be removed from the heading, since 90Y activity by itself is not dosimetry. Dosimetry is referred to a dose (absorbed radiation energy measured in gray (Gy) or the equivalent dose measured in sieverts (Sv)). Likewise, the calculation method (BSA or partition) used to calculate the activity should be specified.

Reply, Edited as suggested. The prescribed activity methods have also been added to Table 4, per reviewer C, comment 1.
Changes in Text: Page 6, line 191, Table 4

Comment 3: At what time did a greater number of toxicities occur: immediate after RE, at 1 month, 3 months?

Reply: Most toxicities evolved more than a month after treatment.
Changes in text: Addressed page 10, lines 341-352. Additionally, Table 6 reviews the 1 month vs later toxicities. Of note as above, this paragraph was edited to reflect updated toxicities.

Comment 4: In Table 2 there are errors in the percentage of patients with and without ascites (17 vs 120%). Also, in the Child-Pugh classification, the numbers in parentheses are not explained.

Reply: Thank you for picking up on these errors. The percentage in the ascites portion has been corrected and the Child-Pugh numbers have been as well. The percentages and raw numbers were inverted.
Changes in Text: Ascites and Child Pugh Class in Table 2.

Comment 5: The current study provides evidence that the more advanced the disease in BCLC B, the worse the response and toxicity after RE. In my opinion, it would improve its value if the authors could more specifically determine which is the profile of the patient within subgroup 4 that benefits most from this therapy (greater efficacy and less toxicity)
Reply: Addressed in discussion (also in keeping with reviewer C, comment 5).
Changes in Text: Page 12, lines 475-477.