Peer Review File

Article Information: https://dx.doi.org/10.21037/jgo-23-890

Reviewer A

General:
Significantly more detail on how the images were processed is needed, this is a vital aspect of the study that is almost glossed over.

Abstract:
1) Please give the actual data for the last statement of the results.

In the revised manuscript, we added the mean and SD of the underestimation, as follows, "PET/MR underestimated tumor dose at both low (<1 GBq) and high (>3 GBq) injected activity levels ($p<0.001$) by -22.3 (SD=13.5) and -24.3 (SDS=18.7), respectively.

2) No data to support the statement "Intermodality differences were more pronounced at low and high injected doses" is given, please remove or add to the abstract.

In the revised results section of the abstract, we added the mean and SD of the underestimation, along with the p-value for the non-linear relationship.

Introduction:
1) The majority of the first paragraph should be deleted, you can assume that the readers understand the basics of y90 and it's use in humans.

Thanks for the feedback. The first paragraph has been significantly revised to shorten the section.

2) The reporting in accordance with TREND should be in the materials and methods, not the introduction.

Thanks for the feedback. Per the JGO instructions for authors, the reporting guideline adherence should be reported at the end of the introduction section.

Methods:
1) Was no advanced dosimetry used in the glass cohort?

Thanks for your comment. We do not routinely performed advanced dosimetry at our institution. We are aware of the recent advances in personalized dosimetry but it was not used during the study period.

2) How did the authors determine the perfused volume? Was this done anatomically, using intra-procedural CBCT, etc?

Thanks for the feedback. The liver and tumor volumes were delineated on MR images using MIM software. A short description was added.

3) In general further data is needed on imaging analysis, this is essentially the crux of the study and errors here will determine outcomes. Please provide greater detail.

Thanks for the comment. The imaging analysis section has been significantly revised. However, it should be emphasized that most of the imaging analysis process was automated using the MIM software. The software algorithm was FDA approved and has been used in prior studies.

4) How was the normal tissue dose calculated, considered only the dose to the normal liver within the perfused volume, assumed equal distribution among the entirety of the normal liver for the non-tumoral radiation?

Thanks for the comment. Similar to the last question, the dosimetry calculation was performed automatically by the software. A discussion of the particular mathematical formula (including local deposition method) is beyond the scope of the article but can be referenced in the MIM white paper (referenced in the article).

Results:
1) Other important factors should probably be evaluated such as particle load per volume and specific activity in the analysis that attempts to identify factors leading to intermodality differences.

Thanks for the feedback. In our discussion, we explored the potential factors that could have predisposed the study to differences in dosimetry between modalities. These included possible differences in ROI tracing, uptake time bias, and MR attenuation correction errors. These factors were discussed under the Discussion section. Unfortunately, because the number of patients were small, we did not perform sub-group analysis to elucidate potential factors that lead to intermodality differences.

Discussion:
1) Please avoid overly enthusiastic adjectives like "exquisite".

Thanks for the feedback. The discussion section has been significantly modified per other reviewer's comments.

2) A number of other dosing algorithms are employed in modern dosing and BSA method is consider by many to be borderline malpractice, please revise accordingly.

Thanks for the feedback. As discussed in the manuscript, there are currently three methods for Y-90 dosimetry including BSA, MIRD and partition models. We felt that a detailed discussion of each model was beyond the scope of this article. However, we agree with the reviewer that these dosimetry models had significant limitations and therefore a brief discussion of the limitations was included under the Discussion section.

3) While accurate, I'm not sure what paragraph 3 adds to the paper, would remove it.

Thanks for the feedback. The discussion section has been significantly modified per other reviewer's comments.

4) Some discussion of the spatial resolution difficulties of PET and the fact that it is not know how accurate PET/CT really is at determining dose distribution (although it is the gold standard) is probably warranted.

Thanks for the feedback. A very brief discussion of PET spatial resolution limitation was included under the Discussion section.

5) The conclusion should be shortened to give a 1-2 sentence summary of findings, not a summary of the entire paper (aka delete first sentence shorten most of the others, things such as reminding readers about trial design is un-needed and laborious as is repeating reported outcomes).

Thanks for your comments. The conclusion has been significantly modified to shorten the paragraph and to make the points more concise.

Reviewer B

Introduction:
1) Line 64: The authors mention: "Given the small size of these radioembolic …." This statement is wrong. Sir-sphere has embolic effect and the reason TheraSphere does not seem to be an embolic agent is not due to the small size of the microsphere but due to the fact that a smaller number of embolic agents are injected and there is a tendency for them to clump. So I would recommend deleting this sentence. The sentence doesn't add anything to the articles aim and background anyway.

Thanks for the feedback. Per the other reviewer's comments, the Introduction has been significantly shortened.

2) Line 70: "A variety of post-treatment imaging…" Please include a reference.

Thanks for the feedback. Relevant references on bSPECT and PET have been updated.

Method:

3) Line 107: "How many IRs and how many years of training. Please provide a range i.e. > 5 years of experience.

Thanks for your comment. The missing detail has since been added to the manuscript.

Discussion:
4) Needs to be re-written. Some parts of it belong to introduction and should be moved to that section i.e. line 200. The entire paragraph belongs to introduction.
The entire first paragraph is repeating the results. I suggest incorporating each component individually at the start of paragraphs, followed by an analysis of pertinent articles.

Thanks for the feedback. The discussion section has been re-written to reflect your comments. In particular, some of the background information (such as paragraph 2 as suggested) have been moved to the Introduction section. Relevant information pertinent to the Discussion section were retained but updated.

Reviewer C

Abstract
1) No comments.

Introduction
2) No comments.

Materials and Methods
3) Page 4 line 99 – why were these exclusion criteria chosen? An explanation and citation of the reasons for the readership would be beneficial.

Thanks for the feedback. A brief discussion was included. It should be mentioned that there is no definitive literature support for the time cut off but these time points are chosen to ensure optimal study quality based on the physical property of the radioembolization microspheres.

4) Page 4 line 111 – why wasn't partition/multicompartment/personalized dosimetry used for all dosing?

Thanks for the feedback. As answered previously, partition or personalized dosimetry was not routinely performed at our institution during the study period.

5) Page 5 line 127 – are there PET/MR systems available commercially that do offer TOF imaging?

Thanks for your question. To our knowledge, GE Signa PET/MR has TOF capability

but the Siemens Biograph PET/MR does not (the one used in the study). The old Phillips PET/MR did have TOF but is no longer available.

6) Page 5 line 131 – Are there PET/MR systems available commercially that do offer larger than 60cm bores?

Thanks for your question. To our knowledge, no commercial PET/MR system offers larger than 60 cm bores. It has been added to the manuscript.

7) Page 5 line 146 – transferred to the CT from the PET/CT?

Thanks for the feedback. Correct, the CT referred to the CT portion of the PET/CT.

8) Page 6 line 149 – how was contouring confirmed with cbct? Fused via mim?

Thanks for the feedback. A brief discussion is now included.

9) Page 6 line 154 – if multiple tumors were present, were they combined into a single compartment or separated into multiple?

Thanks for your comment. If multiple tumors were present, they were seperated into multiple compartments.

10) Page 6 line 157 – was MAA spect dosimetry performed, why or why not, was this compared to post y90 delivery pet dosimetry?

Thanks for the comment. MAA SPECT dosimetry was not performed other than lung shunt fraction calculation. MAA SPECT dosimetry was not a routine practice at our institution. However, we do have an ongoing project comparing MAA dosimetry to post-Y90 dosimetry.

Results

11) Page 6 line 167 – volume values are in mL?

Correct. Liver and tumor volumes were in mL.

12) Page 6 line 168 – a better explanation of patient demographics is warranted. Disease burden, BCLC, liver function/CP/ALBI, functional status, etc.

Thanks for the comment. Since this study was only intended as a feasibility study to assess the dosimetry methods, we did not feel that it was necessary to include patient demographic data and therefore not collected for this study.

Discussion

13) Page 7 line 219 – dosing thresholds for HCC are now established. Would

recommend adding to the discussion. The 3 citations (29-31) are all older and updated literature should be cited here.

Thanks for the feedback. The discussion section has been significantly changed. Updated citations were provided.

Conclusion
14) No comments.

References
15) No comments.

Figures and Tables
16) Figure 3 – there is discordance in the location of the second lesion in the legend, please fix. Adding timepoints to the imaging would be helpful for the readership. How is image C different from image D? It is unclear how PET/MR was beneficial here over PET/CT?

Thanks for the feedback. It should have been a segment "II" lesion. It has been corrected. Imagine C and D are two sequential images of the same PET/MR to demonstrate the lack of adequate coverage. The goal was not to demonstrate PET/MR was more beneficial than PET/CT but rather it was applicable for dosimetry purposes.

17) Figure 4 and 6 – please provide more explanation of the figure in the legend.

In the revised manuscript, we provided additional explanation in the legends, as follows: Figure 4 (A) The intermodality difference in liver dose (diffliver) was plotted against the mean liver dose measurements (meanliver). There was significant underestimation of liver dose with positron emission tomography (PET)/magnetic resonance (MR) **but no significant trend between the underestimation and the magnitude of the liver dose (p=0.338). The mean underestimation was -3.1 (SD=5.9), with 95% CI of [-0.35, -5.8].** (B) The intermodality difference in tumor dose (difftumor) was plotted against the mean tumor dose measurements (meantumor). There was significant underestimation of tumor dose with PET/MR **but no significant trend between the underestimation and the magnitude of the tumor dose (p=0.502). The mean underestimation was -9.4 (SD=24.1), with 95% CI of [-18.8, -0.34].**

Figure 6 Intermodality differences in tumor dose measurements were plotted against the injected activity levels. There was significant underestimation of tumor dose with positron emission tomography/magnetic resonance at both low (<1 GBq) and high (>3 GBq) levels **and little bias between 2 and 3 GBq (p<0.001 for nonlinear relationship), suggesting that the magnitude of underestimation depends on the injected activity level.**