Peer Review File

Article Information: *https://dx.doi.org/10.21037/jgo-20-435*

Review Comments:

Comment 1: The title seems not consistent with the work done by the authors, i.e., prognosis and prognostic factors of patients with unresectable HCC treated with Y90 SIRT.

Reply 1: Thank you for this observation. We agree and we have changed the title to better reflect the findings of our study.

Changes in text: The title has been changed to "Prognostic Factors of Unresectable Hepatocellular Carcinoma Treated with Yttrium-90 Radioembolization: Results from a Large Cohort Over 13 Years at a Single Center."

Comment 2: Abstract. Methods, please write this part according to the PICOS criteria. The current description is very simple, details of subjects, measures, and follow up are not available. Line 76, the upper limit of the 95%CI is lacking. Line 80, please provide corresponding % of 75 and 13. Line 96, multivariable is different from multivariate. Please consider which one is correct here.

Reply 2: Thank you for your comment. We have modified the abstract to include the information requested. Please see pages 4–5, lines 65–83.

The upper limit of the 95% CI was not reached; therefore, it was not included in the manuscript. The upper limit of the 95% CI has been replaced with "not reached" in the abstract, in the main body of the manuscript, and in Table S1.

Following the reviewer's recommendation, the corresponding % have been included in the abstract for adverse events and grade 4 bilirubin values.

Multivariable Cox proportional hazards analyses were conducted for this manuscript, where multiple predictor variables were included on the right side of the equation. The manuscript only highlights multivariable analyses. Multivariate Cox proportional hazards analyses were not conducted for this manuscript. We have used "multivariable" throughout the manuscript.

Changes in text: We added "not reached" to the 95% CI in the abstract, main text, and the first row of Table S1, as follows:

Abstract: *Median OS was 16.6 months (95% CI, 13.1-not reached).*

Manuscript: *Median OS for all patients was 16.6 months (95% CI, 13.1-NR) (Table S1).*

The percentage of patients with adverse events were added to the last sentence of the Results section of the Abstract, where they are mentioned. The revised manuscript shows the following:

Abstract: *Of the 186 patients with adverse events data, 75 (40.3%) patients reported an event and, of these, 13 (17.3%) patients had grade 4 bilirubin values.*

Comment 3: Introduction. The authors talked a lot on the epidemiology of HCC. I suggest the write this part in a concise way, since this is not very related to the research topic. Because the focus of this study is the prognosis and prognostic factors of patients with unresectable HCC treated with Y90 SIRT, I

suggest the authors to review more on prognosis and prognostic factors of patients with unresectable HCC. The current literature review is inadequate.

Reply 3: We thank the reviewer for this suggestion, which we believe has helped us improved the manuscript. We have modified the introduction by shortening the overview of epidemiology and approved treatments for HCC, removing incidence information and focusing on prognosis. We have also discussed in more detail the current knowledge of prognostic factors in patients with HCC treated with SIRT. Please see pages 6–8, lines 100–140.

Changes in text: The first paragraph includes now information on prognostic factors of HCC. We have summarized most of the previous literature into the second and third paragraph. The fourth paragraph of the Introduction provides now an overview of other studies using SIRT and evaluating prognostic factors. Additionally, following the literature review carried out to expand the Introduction, we have added a brief note in the third paragraph of the Discussion.

Comment 4: Methodology. Please indicate the clinical research design in the beginning of this part. It is also necessary to provide the details of follow up. For the inclusion of patients, please use a flowchart to show its process.

Reply 4: Thank you for pointing out this information was missing. We have expanded the Methods to include this. We have also created a flowchart of patient inclusion, referenced under "Patients" in the Results section of the manuscript (Figure 1). Please see page 8, lines 154–157.

Changes in text: The Methods section has been modified to include the follow-up time and the cohort aspect of the retrospective study:

The study population for this retrospective cohort included all patients with unresectable HCC who were treated with Y90 SIRT at Methodist Dallas Medical Center from April 2004 through March 2017. Patients were followed-up for a median of 12.2 months (95% CI, 0.0–62.6).

We have added Figure 1 to the Results section of the manuscript.

Comment 5: Statistics. Subjects with too many missing data were excluded. The authors should consider to use multiple imputation to handle missing data and analyze the influence of such exclusion on the study findings. The term "multivariable" is problematic, please consider this. Line 236, "2-sample t tests" is not accurate and is not suitable for all continuous variables. "1-sample t tests" is also not accurate.

Reply 5: Thank you for this observation. Below, please find our response to this, subdivided into 4 responses:

Reply 5.1. Regarding the missing data: in the multivariable model of 226 subjects, missing data accounted for 'alcohol etiology' (2 subjects), 'bilobar disease' (5 subjects), 'radiation dose (mCi) of first SIRT treatment' (4 subjects), and prior Nexavar (Sorafenib) treatment (47 subjects). ALBI score and transplant status had no missing data. Analysis of the multivariable model did not exclude any subjects with missing data. Categories for the missing data were created, and the hazard ratios of the response variables compared to the reference were presented.

Based on the reviewer's recommendation for multiple imputation methods to handle missing data, a multiple imputation procedure was implemented involving 100 complete datasets of size 226 subjects. The impact of missing data is addressed by comparison of the original multivariable estimates to the estimates from the multiple imputation sensitivity analysis. Results are as follows:

Overall Survival Multivariable Cox Proportional Hazards Model with Transplant as Time-Dependent Covariate — Sensitivity Analysis on Impact of Missing Data by Multiple Imputation

	Original Results				Multiple Imputation Results			
Parameter	Hazard Ratio	HR Lower 95% CI	HR Upper 95% CI	P-Value	Hazard Ratio	HR Lower 95% CI	HR Upper 95% CI	P-Value
Sorafenib (Nexavar)	2.09	1.35	3.23	<0.001*	2.05	1.32	3.17	0.001*
Transplant	0.07	0.02	0.20	<0.001*	0.05	0.02	0.15	<0.001*
Bilobar Disease	1.97	1.38	2.82	<0.001*	1.91	1.33	2.75	<0.001*
Alcohol Etiology	1.84	1.22	2.79	0.004*	1.99	1.33	3.03	0.001*
Dose (mCi)	1.01	1.00	1.03	0.036*	1.01	1.00	1.02	0.105
ALBI score	2.20	1.62	2.98	<0.001*	2.17	1.60	2.94	<0.001*

*p<0.05

Please note that we have updated Figure 3 (Figure 2 in previous version of the manuscript) with the dose data presented in this table.

The sensitivity analysis by multiple imputation demonstrates the robustness of study findings to missing data.

Reply 5.2. Multivariable Cox proportional hazards analyses were conducted for this manuscript, where multiple predictor variables were included on the right side of the equation. The manuscript only highlights multivariable analyses. Multivariate Cox proportional hazards analyses were not conducted for this manuscript.

Reply 5.3. Regarding your comment on "2 sample t-tests", we confirm that two sample t-tests were conducted for:

A. Tumor burden at baseline by prior treatment received vs not
B. MELD score by prior treatment received vs not

Clarifications have been made in the statistical analysis portion of the manuscript to clearly indicate this, shown below in the "changes in the text" section of this response.

Reply 5.4. We have rephrased the Methods and replaced "1-sample t-test" with 'paired t-test' for changes from baseline. Additionally, the footnote for Table 4 has been changed to show "paired t-test" instead of "one-sample t-test".

Changes in text: We have modified the Methods section of the manuscript to add details on the

sensitivity analysis. Please see page 12, lines 233–235, 238–241.
“As a sensitivity analysis, a multiple imputation procedure was implemented involving 100 complete datasets of 226 subjects to address the influence of missing data.”

We have also modified the section that regarded the 2-sample t-test carried out and replaced “1-sample t-test” with ‘paired t-test’ for changes from baseline:
“For the secondary outcomes, the relationship of dose to baseline MELD score and dose to ALBI score was analyzed with the Pearson correlation coefficient, tumor burden at baseline by prior treatment received vs not was analyzed with a 2-sample t-test, MELD score by prior treatment received vs not was analyzed with a 2-sample t-test, and changes in laboratory variables from baseline were tested with a paired t-test.”