

October 7, 2015

Dear Dr. Yu and Our Reviewers,

Thank you for your considerable time and effort reviewing our manuscript. We have attached a revised version of our manuscript with our changes highlighted in yellow. We have considered your thoughtful comments and suggestions and have adjusted our manuscript to address them. Below, we summarize our reviewers' comments as well as how we addressed them in our revision.

**Reviewer 1:** *The manuscript entitled, "Factors associated with increased incidence of severe toxicities following yttrium-90 resin microspheres" is a well-designed and well-written original article. However, it still needs some minor revisions: 1- The total number of treatments accepted for the data collection was given as 79 in 58 patients (page 7, line 1-3). The total number of excluded studies was given as 24. So, total number of treatments (79+24) does not match with the total treatment number during 2010-2014.*

**Response:** Thank you for pointing out a discrepancy in the treatment numbers. We had accidentally not mention 1 treatment excluded because it occurred in a lobe that had already been treated 2 years earlier and, as such, we could not exclude the influence of the first treatment on any toxicities that developed as a result of this repeat treatment. We have changed the first paragraph of the results section to include this.

**Reviewer 1:** *2- Please make some comments about the reason for the limited number (55) of follow-ups after treatment (page 7, last 2 lines).*

**Response:** Two of the primary reasons for the limited number of radiographic follow-ups were the death of patients prior to assessing their response and our institution's role as a tertiary referral center. We have included a statement in the "Radiographic Response and Overall Survival" subsection of our Results section.

**Reviewer 1:** *3- What is the treatment result for the rest of patients other than partial response (23.3%) and stable disease (33.3%)? (page 8, line 1-2)*

**Response:** All our patients who did not have a partial response or stable disease at either 3 or 6 months had progressive disease entailing either an increase in the size of treated lesions or the development of new lesions in the treated portion of the liver. We have included an explanation of this in our manuscript.

4- The sentence starting with "Among our patients, ...." should be re-writtten (page 8, line 9-11)

**Response:** We recognize the lack of clarity in this sentence at the end of the first paragraph of our discussion and have re-written it to hopefully provide greater clarity as to our meaning.

**Reviewer 1:** 5- Please explain the "MELD Score" and the calculation method in the introduction or discussion section.

**Response:** We used the Model for End-stage Liver Disease (MELD) score based on the modification of the original model by UNOS. We have added such a clarification and reference to its inclusion in our discussion section.

**Reviewer 1:** 6- I am a little confused about the data given in Table2. For example post-embolization syndrome: 11/86; emesis: 10/85; INR: 3/70; albumin 21/79; etc. Please clarify how you calculated the "n" for this table.

**Response:** The *n* for this table was calculated based on the number of our original treatments with any type of follow-up. We were able to analyze up to 86 patients for clinical toxicities and up to 79 patients for laboratory toxicities. Thus, the table should be read as: Of the 86 patients with clinical follow-up, 11 were recorded to have experienced the post-embolization syndrome; similarly, of the 70 patients with INR laboratory follow-up, 3 developed a toxicity. We have included a note on Table 2 to clarify and address this issue.

**Reviewer 2:** 1. Abstract: you studied toxicity events of grade 3 or more ("methods") but in "results" presented percents of both grade 2 and grade 3 or more toxicities. This can confuse readers. My advice is to keep these data in the main text of the article but to remove them from the abstract.

**Response:** Thank you for pointing out this potentially confusing aspect of our abstract. We have taken your advice and re-written the first sentence of the results section of the abstract while leaving such data in the main text of the article.

**Reviewer 2:** 2. Materials and methods, p.5, paragraph 12: as far as I know, when extrahepatic shunting is present, the dose of Y-90 should be increased. Why did you reduce the dose?

**Response:** The theory behind reducing the dose for hepatopulmonary shunts > 10% involves an increased risk of patients' developing radiation pneumonitis. These shunts are believed to reflect arteriovenous shunts within the neoplastic vasculature which allow for a percentage of the microspheres to avoid being embedded in arterioles and escape into the lung. Since the risk of radiation pneumonitis increases with doses > 30

Gy to the lung, hepatopulmonary shunts cause a decrease in the dose of yttrium-90 microspheres to avoid causing radiation pneumonitis. The method we employed for decreasing the dose is one that is adopted from the manufacturer's recommendations, both in their training manual and the package insert (see reference 12 in our manuscript). We have also provided greater explanation in our text to address this.

**Reviewer 2:** *3. Discussion, p.9, lines 2-4. This sentence contains 4 words that are "toxicity" and 3 words that are "clinical". Some language correction is desirable.*

**Response:** We thank you for pointing out the repetitive nature of this sentence and have re-written it to avoid such repetition.

**Reviewer 3:** *We need some more details: what is the total number of treatments considered for data collection?*

**Response:** Thank you for pointing out this lack of clarity in our wording. We considered all 104 treatments that occurred within our stated time frame for inclusion in our analysis with 25 treatments being excluded. We have clarified this statement in the first paragraph of the response.

**Reviewer 3:** *Why is the number of follow-up so limited? Death of patients? Other?*

**Response:** Please see our response to Reviewer 1's second point. We would be happy to provide more explanation if you would like.

**Reviewer 3:** *Please specify the MELD score.*

**Response:** Please see our response to Reviewer 1's fifth point. We have included a reference for where we derived our formula in our revised manuscript.

**Reviewer 3:** *Please rewrite Table 2 as it is not clear.*

**Response:** Please see our response to Reviewer 1's sixth point. We have included a note on table 2 to provide greater clarity.

**Reviewer 3:** *Why did you report toxicity events of grade 3 or more (in the methods) but then introduce percents of grade 2 and 3 toxicities in the results section? This is not clear and can create problems. Please take this data out of the abstract.*

**Response:** Thank you for pointing out this area of confusion. We defined two sets of patients in our manuscript: (1) those who developed any toxicity from the treatment (defined as grade  $\geq 2$ ) and (2) those who developed a severe toxicity (defined as grade  $\geq 3$ ). As well as changing the mention of grade 2 toxicities in the abstract, we have also

provided further clarification for how we defined these two sets of patients in the second paragraph of the “Data Collection and Endpoints” subsection of the Methods section.

**Reviewer 3:** *In Materials and methods, p.5, paragraph 12: when extrahepatic shunting is present, shouldn't the dose of Y-90 be increased? Why did you reduce the dose? For the risk of radiation pneumonitis? Please specify.*

**Response:** You are absolutely correct: the reason we reduced the dose of yttrium-90 with hepatopulmonary shunts > 10% involves the risk of radiation pneumonitis. We have attempted to clarify this in our Methods section. Also, please see our response to Reviewer 2's second point for a greater explanation.

Once again, we thank you all for your comments, questions, and concerns. We believe that they have been very beneficial in improving and clarifying our manuscript. Please let us know if you have any other questions or concerns.

Sincerely,