**Format for ANSWERING REVIEWERS**

April 17, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 2464-review.doc).

**Title:** Can Imaging Patterns of Neuroendocrine Hepatic Metastases Predict Response Yttruim-90 Radioembolotherapy?

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Szklaruk, MD, PhD

**Name of Journal:** *World Journal of Radiology*

**ESPS Manuscript NO:** 2464

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

Reviewer 1.

1. The abstract was modified to include the number of patients :
   1. 65 lesions in 17 patients met study criteria and formed the cohort. Statistically significant response was found for lesions <5 cm versus those >5 cm with RECIST (*p* = 0.04), WHO (*p* = 0.002) and combined Choi criteria (*p* = 0.02).
2. The treatment modalities now lists others chemotherapeutic agents.
   1. Treatment modalities for NETLM include medical (somatostatin analogues octreotide (Sandostatin; Novartis Pharmaceuticals, East Hanover, NJ) streptozocin (Zanosar; Sicor Pharmaceuticals, Irvine, CA), doxorubicin (Pharmacia & Upjohn), fluorouracil (5-FU; Adrucil; Teva Parenteral Medicines, Irvine, CA) cisplatin (Baxter) Mitomycin C (Ben Venue Laboratories, Bedford, OH), and bevacizumab (Avastin; Genetech, South San Francisco, CA)),
3. Authors. There are 5 Authors. : Julia Neperud, MD; Armeen Mahvash, MD; Naveen Garg, MD; Ravi Murthy, MD; Janio Szklaruk, MD, PhD . All authors were involved in the study design. All authors were involved in image evaluation. Not sure why only one author was listed in the original submission.
4. Figure Legends.
   1. Figure legends have been added.
   2. Figure 1: 61 y.o. female with metastatic islet cell carcinoma.Transverse LAVA images of the abdomen following Gd contrast administration. The

lesions in the liver (arrow) are hyperenhancing lesions relative to the liver.

Figure 2: 61 y.o. female with metastatic islet cell carcinoma CT image of the abdomen following IV contrast. The lesions in the liver are hypoenhancing relative to the liver (arrow).

* 1. Figure 3: 56 year old male with islet cell cancer. CT image of the abdomen following IV contrast. The lesion in the liver is iso enhancing relative to the liver (arrow).
  2. Figure 4. 58 year old male with islet cell cancer. CT image of the abdomen following IV contrast. The lesions in the liver are less than 50% necrosis and hyper enhancing relative to the liver.
  3. Figure 5. 77 year old male with islet cell cancer. CT image of the abdomen following IV contrast. The lesion in the liver is more than 50% necrosis.
  4. Figure 6. 58 year old male with islet cell cancer. (a)\_CT image of the abdomen following IV contrast. The lesion in the liver is less than 50% necrosis in the pre-treatment (b) CT image of the abdomen following IV contrast. The lesion in the liver demonstrates necrosis on the post-treatment images

1. Linguistic Changes.
   1. Our goal is to evaluate if there are specific imaging features of NETLM at presentation for 90Y therapy that may predict response to treatment.
   2. The most common site of metastatic of disease of NET to the liver;
   3. Patients that had have been on several different chemotherapeutic regimens or have participated in…
   4. Each metastatic lesion was evaluated on the pre-therapy imaging study and was placed into five separate categories:

Reviewer 2.

1. Small size.
   1. We agree that a small number of patients limit the conclusion of our results. And a larger number would have made the conclusions more substantive.
2. Tumor burden
   1. The tumor burden of the liver was assessed with CT or MR. The SPECT was used to evaluate the distribution of Y90 distribution.
3. Figure Legends.
   1. See reply to Reviewer 1.

Reviewer 3.

1. Scope of the article.
2. We agree that in retrospect with knowledge of the results, the article scope may be re-written as Correlation between radiologic findings pre-Y90 RE and response to therapy instead of radiologic findings as selection criteria for Y90. However, if the results of our analysis would have been overwhelming and havepredicted that certain imaging pattern would have benefit from y90 compare this would have met our initial goal. We were true to our original design that was to use imaging as a predictor of response to Y90 treatment.
3. At presentation
   1. The term “at presentation”, is now follow by the phrase for y90 treatment. We did not exclude the patients based on prior treatment.
4. Clinical and Pathological Findings.
   1. We agree that there are likely contributions to response based on pathological and clinical findings. Our goal was to evaluate the imaging findings as a predictor independent of these other parameters. Our goal was not find the parameters that may predict response to treatment. We may review in the future and include these parameters as predictors of response. We had a very narrow goal in the evaluation of imaging patterns prior to Y90 treatment.
5. Symptomatology
   1. .Introduction has been edited: Patients with neuroendocrine tumors (NET) often have clinical symptomatology that is most commonly due to hormone secretion by the tumor
6. Liver
   1. Introduction has been edited 30% to 85% of patients with NET from pancreatic or gastrointestinal origin have liver metastases
7. Resectable.
   1. The treatment of neuroendocrine tumor liver metastases (NETLM) is aimed at alleviating clinical symptoms in patients with non-resectable tumors.
8. Results.
   1. We have originally drafted the document with an extended RESULTS section. This would have added at least 6 more pages and make the text repetitious. We defer to the editorial board to decide if this is to be modified (Please see attached file- RESULTS SECTION).
9. Discussion
   1. Our goal was to only evaluate the imaging patterns of the tumor burden prior to Y90. Our goal was to search for an imaging pattern that may predict better response. Our goal was not evaluate all the clinical and pathological variables that may predict response. This is beyond the scope of our project. We agree that at this time, imaging findings are not used a selection criteria. However, we believe this is an area of research that has not been fully explored.

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Radiology*

Sincerely yours,

Janio Szklaruk

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