

Format for ANSWERING REVIEWERS

September 26, 2014

Dear Editor,



Please find enclosed the edited manuscript in Word format (ESPS Manuscript NO: 13364).

Title: Radioembolization with ⁹⁰Yttrium Microspheres in hepatocellular carcinoma: role and perspectives

Author: Cristina Mosconi, Alberta Cappelli, Cinzia Pettinato, Rita Golfieri

Name of Journal: *World Journal of Hepatology*

ESPS Manuscript NO: 13364

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

Reviewer 1

No answer

Reviewer 2

1) I think the authors need to add a little bit more after the following: "Albeit a systematic review by Llovet et al.⁶ has reported an increased survival rate in patients treated with TACE; its low efficacy has however been demonstrated in large (> 5cm) and in multinodular tumors.^{7,8,9,10}" It would be good if the authors even give some statistics after this statement to give a sense of the improved survival.

RE: Revision has been made according to the suggestions of the reviewer :

" A multicentric Japanese¹¹ study showed a significant decrease in 3-year survival after superselective TACE for lesions >5 cm and multiple lesions (four or more) and an inverse correlation between survival and tumor size and number; in fact they obtained, in group of Child-Pugh A, the highest 3-year survival (80%) in patients with single lesion ≤2 cm and the lowest 3-year survival (30%) in patients with more than 4 lesions ≥5.1 cm and, in the group of Child-Pugh B, highest 3-year survival (65%) in patients with 2 lesions ≤2 cm, and the lowest (0%) in patients with three lesions ≥5.1 cm."

2) The authors might want to consider the section starting " The lung shunt fraction is obtained by planar ^{99m}Tc-MAA imaging as follows...". The authors might want to include some values for the lung shunt fraction (LSF) if they are available from the literature.

RE: Revision has been made according to the suggestions of the reviewer :

"A radiation absorbed dose limit of 30 Gy per radioembolization treatment session is recommended³³. The published upper limit for hepatopulmonary shunt fraction is 20% for resin-based microspheres³⁴."

3) It would be nice if the authors could add a little bit more after the portion, "An important limitation of TARE is the dose to the normal liver because an excessive dose to the normal parenchyma could induce radiation hepatitis and liver failure." A reference regarding radiation hepatitis would be good.

RE: Revision has been made according to the suggestions of the reviewer and the reference was added.

4) For the calculated variable A(GBq) is the 90Y injected activity, it might be good if the authors gave common expected values.

RE: Activity values are strongly related to many factors like tumor volume, volume involved BSA of the patient and fractional uptake of the lesions. Common values are not predictable but values lower than 3 GBq are usually found for resin microspheres treatment when the BSA formula is used, while glass microspheres are more related to target volume and the range of values is quite wide.

5) In the sentence "Table 3 summarizes the largest and the most significant series reported in the literature.", it might be good if the authors used a word other than "significant" since "significant" might imply a statistical relationship. Another possible word might be "noteworthy".

RE: Revision has been made according to the suggestions of the reviewer :

"Table 3 summarizes the largest and the most noteworthy series reported in the literature."

6) In their discussion of TARE and sorafenib, it might be good if the authors discuss the combined use of TARE and sorafenib if that data is available.

RE: Up to now data about the combined use of TARE and sorafenib is not available in literature; the only paper about this combination concerns safety and toxicity but not efficacy. (Ricke J1, Bulla K, Kolligs F, Peck-Radosavljevic M, Reimer P, Sangro B, Schott E, Schütte K, Verslype C, Walecki J, Malfertheiner P; the SORAMIC study group. Safety and toxicity of radioembolization plus Sorafenib in advanced hepatocellular carcinoma: analysis of the European multicentre trial SORAMIC. *Liver Int.* 2014 Jun 14. doi: 10.1111)

7) Regarding their discussion of Radioembolization-induced liver disease (RILD), is any data available in which there have been biopsies of this disease.

RE: Revision has been made according to the suggestions of the reviewer :

"Radioembolization-induced liver disease (RILD) is described as a form of sinusoidal obstruction syndrome which usually occurs 4-8 weeks after TARE³⁴; Sangro et al.³⁴ who described RILD for the first time, performing the liver biopsy of some patients, showed extensive sinusoidal congestion affecting perivenular areas with focal hepatic atrophy, areas of necrosis around central veins with fresh thrombosis, and some cholestasis in periportal areas. These findings were consistent with hepatic veno-occlusive disease (VOD)."

8) Regarding the statement "Other side effects to be expected after treatment are a transient elevation in liver function tests, specifically in alkaline phosphatase, bilirubin and alanine transferase levels.", Is this the so-called "radiation hepatitis" mentioned earlier?

RE: No, we mentioned Radioembolization-induced liver disease (RILD) that is a well defined liver disease characterized by presence of jaundice, mild ascites, a marked increase in bilirubin and alkaline phosphatase, no change in transaminase levels and LFTs and it occurs 4-8 weeks after TARE; "transient elevation in liver function tests, specifically in alkaline phosphatase, bilirubin and alanine transferase levels" are only signs of transient liver metabolic alterations (without the described above morphologic damage characteristics of RILD).

9) In the last paragraph of the body of the paper, I think "demostrated" should be "demonstrated". The heading "Bibliografia" should be "Bibliography".

RE: Revision has been made according to the suggestions of the reviewer .

10) In reference 89, I think that "wath" should be "what".

RE: Revision has been made according to the suggestions of the reviewer .

11) In Table 2, I think some explanation of the Okuda system should be provided; or the authors could provide a pertinent reference.

RE: Revision has been made according to the suggestions of the reviewer; pertinent reference was added .

12) In the footer of Table 4, I think that "Critera" should be "Criteria".

RE: Revision has been made according to the suggestions of the reviewer .

13) In Figure 1's legend, I think that "corrisponding" should be "corresponding".

RE: Revision has been made according to the suggestions of the reviewer .

References and typesetting were corrected.

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

Sincerely yours,

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