

Format for ANSWERING REVIEWERS

March 12, 2015



Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 15634-edited manuscript.doc).

Title: Transarterial Radioembolization for Hepatocellular Carcinoma: an update and perspectives

Author: Rodolfo Sacco, Valeria Mismas, Sara Marceglia, Antonio Romano, Luca Giacomelli, Marco Bertini, Graziana Federici, Salvatore Metrangolo, Giuseppe Parisi, Emanuele Tumino, Giampaolo Bresci, Ambra Corti, Manuel Tredici, Michele Piccinno, Luigi Giorgi, Carlo Bartolozzi, Irene Bargellini

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The following authors have been added to the list of authors for their relevant contribution to the revision of the manuscript: Ambra Corti, Michele Piccinno, Manuel Tredici. The list of authors has been revised accordingly.

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

1 - Revision has been made according to the suggestions of reviewer #1

(1) In the description of Methods, more references are needed to support the criteria.

Thank you for your comment. We added a few references in the "Method" section, to better

support the criteria described in the paragraph.

- (2) It is recognized that treatment planning based on proper dosimeter is of vital importance for the optimization of the results of radioembolization. More information about individualized treatment planning, such as dose calculation, need to be explained in this review.

Thank you for your useful suggestion. We have expanded the topic of dose calculation, discussing the different methods available for a proper dosimetry and the importance of increasing the individualization of treatment for each patient

- (3) In the seventh line on page 9, after the number "11", I think there is a word missing.

Thank you for pointing out this typing error. The word "months" has been added after "11".

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

- (1) Even if in be beginning of development it was thought that glass and resin product were quite similar, there are more and more evidence that those 2 products have different radiobiological effects due to a highly difference of amount of radioactivity by microsphere (2500 Bq/ glass sphere as only 50 Bd/resin sphere). As main example the threshold tumoral dose allowing a response identified is between 205 (Garin et al. J Nucl Med 2012) and 257 Gy (Chiesa et al Q J nucl Med mol imaging 2011) and for resin microsphere the target tumoral dose is 120 Gy (Lau et al Int J Radiat Oncol Biol Phys. 2012). A recent simulation study highlights this difference (Warland et al J Nucl Med 2014). Resin is supposed to have a more embolic effect du to a larger number of sphere injected requiring slow injection with sequential angiographic control Difference in size, specific activities and so on have to be specified in the paper (may be in a small table).

A small paragraph dealing with those differences has to be inserted

Thank you for your interesting comment. We have added a section on the main different features of the two types of microspheres, such as differences in size, specific activity and embolic power; we have also included a Table where the main characteristics of glass and resin microspheres are summarized.

- (2) There is absolutely not data regarding dosimetric evaluation and it's impact despite

one hold but precept study (Ho and al. Eur J Nucl Med 1997) several recently published data (Chiesa et al. Q J Nucl Med Mol Imaging et al 2011, Garin et al J Nucl Med 2012 and Eur J Nucl Med 2013, Lam et al J Nucl Med 2013).

A paragraph dealing with this dosimetry, the clear dose/response relationship recognition and perspective with personalized dosimetry has to be inserted in this interesting paper has this open perspectives on a clear optimization of radioembolization in the future with improvement of efficacy.

Thank you for your valuable suggestion. A paragraph on the dosimetric evaluation has been added and relevant references have been included in the manuscript; please refer also to response n. 2 to reviewer 1.

- (3) The definition of radioembolization proposed by the authors (administration of microspheres loaded with Yttrium 90) is wrong and has to be modified : radioembolization is the administration of radioactive compound, microspheres loaded with Yttrium 90 is a kind of radioembolization and I agree the most used today. Lipiodol labelled with iodine 131 has been used for more than 20 years and lipiodol labelled with rhenium 188 is actually used in clinical trial. Please correct the definition.

Thank you for your suggestion. The definition of radioembolization has been corrected as suggested.

- (4) For patients with unilateral PVT (segmental or branch) the median OS is effectively 10-14 months but reaches 17 months for glass microsphere (Salem Gastroenterology 2010, Mazzaferro Hepatology 2013) and even 24 months while using personalized dosimetry (Garin Eur J Nucl Med Mol Imaging 2014), please correct.

Thank you for providing this useful information. The median overall survival in patients with unilateral PVT (segmental or branch) has been updated in line with the suggestion and relevant references have been added to the manuscript

3 References were corrected according to the new references added

Thank you again for considering our manuscript for publication in the *World Journal of Gastroenterology*.

Sincerely yours,

Rodolfo Sacco MD, PhD,

On behalf of all Authors.