ANSWERING REVIEWERS

Reviewer 1

1.**Was sample size calculated?**

A: At the time we began this study (2011), there were no articles in the literature using drug eluting bead and imaging response predictors to support the sample calculation. However, with our collected sample we were able to determine the prevalence of complete or partial response (objective response) with 95% confidence and 6.1% accuracy.

2.**Was there a limit / maximal dose of Drug used?**

A: Yes. The maximum dose administered was 50mg doxorubicin and 1 vial of drug eluting bead microsphere, making up the standard solution. Only 1 patient received 2 vials of drug eluting bead microspheres and 100mg doxorubicin because the availability of the vial on this date was already prepared for use in another patient who did not attend to perform the procedure.

3.**What were the profile of adverse effects / events?**

A: One patient presented respiratory failure after anesthetic sedation, but before the chemoembolization began. The procedure was suspended and the patient was excluded from the analysis.

Regarding the patients who underwent chemoembolization, there were no adverse events classified as Grade 4 and 5.[1] It was observed the occurrence of adverse effects grade 1, 2 and 3.[1] However, they were not evaluated because the purpose of this study was to analyze only the predictors of radiological response after chemoembolization.

4.**Was calculation of cost benefit analysis included in the study?**

A: No. The purpose of this study was to analyze only the predictor of radiological response after chemoembolization.

5.**Was a comparative intervention/group considered to establish superiority of the described procedure?**

A: Our study was performed exclusively using the standard drug-eluting bead technique (DEB-TACE). Thus, there is no control group of patients treated with conventional TACE.

6.**How reliable is using 'pseudocapsule', a histological entity for a study based on imaging? Is that not a limitation of the study?**

A: It is reliable and not a limitation of the study, since according to data reported in reference 20 of the paper, there is correlation between the

radiological findings of the pseudocapsule and histopathological analysis. Furthermore, the radiological pseudocapsule sign is widely used term, easily identifiable and fundamental for the diagnosis of hepatocellular carcinoma, according to the main current non-invasive diagnosis of hepatocellular carcinoma (LIRADS)[2].

Reviewer 2

1. Well written and documented paper.

A: Thank you for the very appropriate considerations.

2. In should be usefull inserting the role of pseudocapsule in the tittle.

A: Thanks again for the suggestion, however, adding pseudocapsule to the title would also imply adding the chemoembolic dose, as they are the two main predictors of response found in this study, a fact that would disfigure the general purpose of the current title.

3. ... and knowing if there have been undesirable side effects with increasing drug dose.

A: The undesirable side effects were not evaluated because the purpose of this study was to analyze only the predictors of radiological response after chemoembolization.

Reviewer 3

1. Dear Authors my comment as below: Some terminological corrections are needed. Both odds ratio and objective response words are presented as OR. This leads to serious complexity. In my opinion, ''Objective Response'' should be written directly without any abbreviation.

A: We appreciate the remark. We removed the abbreviation OR for the term Odds Ratio. Now, all text abbreviations and tables refer to the term objective response.

2. Please do not use the term "Ortotopic". Because Heterotopic liver transplantation is extremely rare.

A: We removed the term Orthotopic Liver Transplant (OLT) and replaced it with the term Liver Transplant (LT).

3. Authors should specify which parameters are included in the multivariate analysis model. That is, the p values obtained from univariate analysis were taken into the multivariate analysis model.

A: Yes, the univariate analysis values were considered to take part in the multivariate analysis. However, only significant values were retained in the final model, based on the Stepwise Backward selection method. Based on your assessment, we added this information more clearly in the "statistical analysis" session in the paper.

4. "Flowchart" may be more appropriate instead of "Fluxogram"

A: The term Fluxogram has been removed and replaced by flowchart.

5. I don't understand what '' r = '' is. If the expression r r 'is related to correlation analysis, it should be stated in the statistical analysis method. And also if this is a correlation term, the correlation you found in the study is very low.

A: We added the term "r" to the Pearson's correlation in Table 6 footnote and added in the statistical methodology session the missing analysis. Although the correlation between the dose and the percentage of necrosis is low, it was only one of the few parameters that influenced this finding. Other parameters not evaluated in this study might contribute to explain better the percentage of necrosis. Nevertheless, the chemoembolic agent dose must still be considered as a radiological response predictor.

6. There is no information in the article on what are Tables 6 and 7. Please explain them.

A: Thanks to the reviewer since the table numbering was inadequate. Correction of the number of Tables was performed, as well as inclusion of their correct reference in the results.

7. Figure-5 shows that the cutt of value is calculated for the objective response. But there is no statement what this is. So if the objective response is a quantitative value, it needs to be explained.

A: Objective response is a complete or partial response category pre-specified by mRECIST, presented in the article methodology.

8. It is very difficult to make an inference from this article. In summary, this article should definitely be reviewed.

A: We understand that prior to our review and appropriate corrections, the article had confusing passages. Correction of the language of the text was performed, as directed by the Non-Native Speakers of English Editing Certificate. We appreciate all the important advice from reviewers and hope to have resolved these issues.

References:

1. Quality Improvement Guidelines for Transarterial Chemoembolization and Embolization of Hepatic Malignancy. Gaba RC, Lokken RP, Hickey RM, Lipnik AJ, Lewandowski RJ, Salem R, Brown DB, Walker TG, Silberzweig JE, Baerlocher MO, Echenique AM, Midia M, Mitchell JW, Padia SA, Ganguli S, Ward TJ, Weinstein JL, Nikolic B, Dariushnia SR; Society of Interventional Radiology Standards of Practice Committee.J Vasc Interv Radiol. 2017 Sep;28(9):1210-1223.e3.
   DOI: 10.1016/j.jvir.2017.04.025. Epub 2017 Jun 29. PMID:28669744.
2. Tang A, Bashir MR, Corwin MT, Cruite I, Dietrich CF, Do RK, et al.; LI-RADS Evidence Working Group. Evidence supporting LI-RADS major features for CT- and MR imaging–based diagnosis of hepatocellular carcinoma: a systematic review. Radiology.2018;286(1):29-48.
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