

26/July/2017

Prof. Damian Garcia-Olmo

Editor-in-Chief

World Journal of Gastroenterology

Dear Dr. Garcia-Olmo:

Subject: Evaluation of the Relationship Between Hepatocellular Carcinoma Location and Transarterial Chemoembolization Efficacy [34902]

Thank you for your email July 17, 2017, regarding our manuscript, "Evaluation of the Relationship Between Hepatocellular Carcinoma Location and Transarterial Chemoembolization Efficacy", and the valuable comments of the three reviewers. We have carefully reviewed the comments and have revised the manuscript accordingly. Our responses are given in a point-by-point manner below.

We hope the revised version is now suitable for publication and look forward to hearing from you in due course.

Thank you in advance for your kind consideration of this paper.

Sincerely,

Satoru Murata, MD, PhD

Department of Radiology, Center of Advanced Medicine

Nippon Medical School

1-1-5, Sendagi, Bunkyo-ku, Tokyo 113-8603, Japan

TEL: +81-358146240

FAX: +81-35685-1795

E-mail: genji@nms.ac.jp

Response to Reivewer 1:

Thank you for your review of our paper. We have answered your points below.

Comment 1: *There were very few HCC nodules in the caudate lobe in the study, it need further supplemental data and compare the location of HCC and efficacy of TACE in the caudate lobe. I suggest that the manuscript can be published in the form of retrospective study in World Journal of Gastroenterogy after data are supplemented.*

Response: We appreciate the Reviewer's comment. If there were more cases of HCC in the caudate lobe, future studies could evaluate the difference in the efficacy of TACE in each lobe or segment in detail. However, because there were very few cases of HCC nodules in the caudate lobe within the research institution, we were unable to supply the sufficient additional data in the caudate lobe.

Reponse to Reviewer 2:

Thank you for your comments. Our answers to your points are as follows.

Comment 1: *The main defect is the small number of cases in the subgroups below statistical significance as in table 2.*

Response: Even though there were small numbers of cases in the subgroups, we were able to perform all the statistical analyses.

Comment 2: *Language editing is needed as spacing between words need revision e.g group,with no significant difference in the lateral segment.*

Response: We are uncertain as to the meaning of the reviewer's comment. If more space is needed in front of the subgroup, we have changed Tables 2 and 3.

Response to Reviewer 3:

We wish to express our appreciation to the Reviewer for his or her insightful comments, which have helped us to significantly improve the paper.

Comment 1: *Please clarify whether the concept of “HCC location ratio” is empirically proposed by the authors, or has been validated in previous studies. In the latter scenario, please provide references.*

Response 1: “HCC location ratio” is empirically proposed.

Comment 2: *Conventionally, p values <0.001 are presented as such. Please avoid expressions like “ 7.5×10^{-5} ” (see for instance line 13 in the abstract).*

Response 2: We have corrected the denotation of p values in the manuscript and the accompanying figures and tables.

Comment 3: *Among the inclusion criteria, the following can be read: ““MDCT or MRI performed before TACE and at least 6 months after TACE”. Does it mean that the interval between TACE and evaluation of radiological response varied among the included patients?*

Response 3: This does not mean that the interval between TACE and evaluation of radiological response varied among the included patients. We determined the location of the HCC using MDCT or MRI performed before TACE and evaluated the effect of TACE using MDCT or MRI at least 6 months after TACE.

Comment 4: *The authors state that “the median recurrence time was 2 months”, but evaluation of radiological response was performed from 6 months onwards. If a radiological surveillance was protocolized earlier after TACE, it should be described in methods.*

Response 4: We evaluated the effect of TACE 6 months after on a per nodule basis according to the mRECIST. The median recurrence time was 2 months for the non-CR (PR, SD, and PD) groups 6 months after TACE.

Comment 5: *Some demographic features are displayed in methods. Please, move this information to the results' section.*

Response 5: Accordingly, we have moved some demographic features displayed in the Methods to the Results section.

We have changed the following text from (p.8, line 10- line 14):

“Overall, 115 patients (88 men and 27 women; median age, 73 years; range, 49–92 years) with 127 HCC nodules were included in our study. The tumor size ranged from 5.0 mm to 56.7 mm (mean \pm standard deviation: 14.00 \pm 10.30) (Table 1). Other patient characteristics are presented in Table 1.”

to

“Overall, 115 patients with 127 HCC nodules were included in our study.”

We have added the following text to the beginning of the Results section (p.10, line 18-21):

“The median patient age was 73 years (range, 49–92 years; 88 men and 27 women). The tumor size ranged from 5.0 mm to 56.7 mm (mean \pm standard deviation: 14.00 \pm 10.30) (Table 1). Other patient characteristics are presented in Table 1.”

Comment 6: *The term “ratio” in epidemiology is a time-dependent concept, which may be cause misunderstanding in the present paper. I would recommend using “location coefficient” instead of “location ratio”.*

Response 6: The suggested key terms have been used throughout the manuscript.

Comments 7: *Although the reader may be able to infer that an increased location ratio actually refer to a more peripheral nodule, I would recommend to specify this information in methods to avoid confusion.*

Response 7: We agree that this point requires clarification, and we have added the following text (p. 9, line 26-27):

“An increased location coefficient indicates a more peripheral nodule.”

Comments 8: *The potential role of HCC imaging and histological features as potential confounding factors in the present study is unclear. Are those tumors with increased location coefficient also more advanced, less differentiated or associate microvascular invasion more frequently? In order to clarify this important caveat, I would recommend the authors to run a multivariate logistic regression analysis including tumor features, location coefficient and Child-Pugh status. These new results would greatly increase the strength of the evidence.*

Response 8: We appreciate the reviewer’s concerns on this point. However, we find that it is difficult to clarify histological features of tumors that were treated by TACE because very few patients underwent surgery. Thus, we would like to retain the original text.

Comments 9: *The manuscript would benefit from minor English polishing.*

Response 9: The paper has been edited and rewritten by an experienced scientific editor, who has improved the grammar and stylistic expression of the paper.

Comments 10: *In table 3, please provide standard deviations for location coefficient values. In addition, p values should be corrected as stated above in comment number 2.*

Response 10: We appreciate the reviewer's concerns on this point. However, we consider standard deviations unnecessary because we indicated median location coefficients, not means. Thus, we would like to retain the original text.

We have corrected the denotation of p values in the manuscript and in the accompanying figures and tables.

Thank you again for your comments on our paper. I trust that the revised manuscript is suitable for publication.