

Lian-Sheng Ma
Editor in Chief
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Dear Dr. Ma,

Please find enclosed the edited manuscript in Word format (file name: ESPS Manuscript NO. 4436.doc).

Title: Radiofrequency ablation of hepatocellular carcinoma tumors sized >3 and ≤ 5 cm: is ablative margin of more than 1 cm justified?

Authors: Shan Ke, Xue-Mei Ding, Xiao-Jun Qian, Yi-Ming Zhou, Bao-Xin Cao, Kun Gao, Wen-Bing Sun

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The manuscript has been improved according to the suggestions of reviewers, including changes in

1. Formatting,
2. References,
3. Typesetting, and
4. Objects of reviewers' specific points, which are each addressed on the following pages.

We hope our manuscript is now suitable for publication in the *World Journal of Gastroenterology*. Thank you again for allowing us this opportunity.

Sincerely yours,

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Reviewer 1

#1: The median diameter of the HCC nodules was 4.2 ± 0.4 cm (range: 3.1-5.0). Median value should be not reported with standard deviation. Please remove SD or alternatively, report mean and SD, and median and range in parenthesis.

Answer: This has been corrected as suggested in the revised manuscript.

#2: If a randomization was not performed in this study what was the basis of the choice for 0.5 or 1.0cm AM target? Presence of vessels? Radiologist/ hepatologist in charge? Please describe better your approach.

Answer: As described in the Methods section, three-dimensional reconstructions of CT images were made before and after RF ablation (Figure 2). To define the AM as accurate as possible, we performed qualitative side-by-side comparison of CT scans obtained before and after RF ablation. Two radiologists who were blind to the results of quantitative analysis assessed in consensus whether an AM 0.5–1.0 cm or >1.0 cm was achieved. For this analysis, the adjacent hepatic vessels or the hepatic capsule were used to facilitate comparison.

#3: The distinction if group A and B is confusive. There are only two groups and it is not necessary to re-nominate them. Please use 0.5-1.0cm and >1cm as group names.

Answer: Thank you for your comments. It has been changed as suggested in the revised manuscript.

#4: In the title of the paragraph "Evaluation of AM" the abbreviation AM should be reported for its entire meaning.

Answer: This has been corrected as suggested in the revised manuscript.

#5: Continuous data were expressed as mean \pm SD and were compared using Mann-Whitney U test. However, Mann-Whitney U test is a non-parametric analysis, and this is in contrast with the choice to report data as mean and SD. If authors checked their data for normality they should use student t-test, alternatively, please report continuous data in median and

range. Of note that AFP, reported as mean and SD, evidently has a non-normal distribution.

This feature supports the need to completely change table 1 reporting medians and ranges.

Answer: Many thanks. This has been corrected as suggested in the revised manuscript.

Continuous data are expressed as median and range, and comparisons are made using the Mann-Whitney U test.

#6: Please explain better if TACE was performed (in all patients) with the aim of radiological assessment of AM or for oncological purposes.

Answer: In the study, the TACE was performed in all patients, *both* for radiological assessment of AM and for oncological purposes.

#7: Results: (44.7%) of 123 patients in the group B ($P = 0.000$). P-value is not correct; please change it in $P < 0.001$. The same must be done with the other $P = 0.000$ in the manuscript.

Answer: This has been corrected as suggested in the revised manuscript.

#8: In table 1, please report percentages for categorical variables.

Answer: It has been added as suggested in the revised manuscript.

#9: Please clarify why you use chi-square with Yates correction or Fisher for 2x2 tables.

Fisher's exact test is a more accurate test, which directly calculates the probability of the distribution of the sample appearing in the table by chance. I suggest using Fisher in all cases, for large sample sizes Fisher and Chi-square will produce very similar results.

Answer: Your suggestion is very helpful. We have used Fisher's test in all cases in the revised manuscript.

#10: In table 3, please add in the footnote the analysis that provided p-values (Cox regression as reported in methods)

Answer: Use of Cox regression analysis to provide *P*-values has been noted in the footnotes of Table 3 in the revised manuscript.

#11: Kaplan - Meier curves should be reported together with a footnote reporting patients at risk for specific time points.

Answer: Thank you for your comments. The footnotes have been added as suggested.

#12: In the discussion section, the statement “Extensive clinical studies support RF ablation as an efficient, less invasive, and well preferred treatment for early HCC patients with tumor diameters ≤ 5.0 cm” is not supported by any international guideline; conversely RFA can be a preferred treatment for very early HCC [EASL and AASLD guidelines]. This statement needs to be changed.

Answer: The statement has been changed in the revised manuscript as suggested.

Reviewer 2

#please explain the abbreviation TAE; I suppose is Trans-Arterial Embolization, however, if was used in the text, it should be explained (page 11 of the manuscript, bottom of page).

Answer: The explanation of TAE has been added in the revised manuscript as suggested.

Reviewer 3

#1: "The diagnosis of HCC was established on the basis of compatible radiological features with HCC in contrast-enhanced multiphase helical CT scan and dynamic contrast-enhanced MRI (n = 155) and histological confirmation (n = 126)." Please elaborate it.

Answer: In 126 of 281 patients, preoperative diagnosis of HCC was histologically confirmed by needle biopsy under CT guidance. In the remaining 155 patients, HCC was established on the basis of compatible radiological features in contrast-enhanced multi-phase helical CT scan and dynamic contrast-enhanced MRI. This explanation has been added to the Patients subsection of the Methods section.

#2: "The aim of this study was explained to all of the approved patients in advance, a safe AM of > 1.0 cm was tried in all the patients although an AM of ≥ 0.5 cm was routinely considered enough. On the basis of the AM, we categorized patients into group A (AM of 0.5-1.0 cm) and group B (AM > 1.0 cm). " How do you define the AM > 1.0 cm or not? Please make it clear.

Answer: As we described in the Methods section, three-dimensional reconstruction of CT images was made before and after RF ablation (Figure 2). To ascertain whether the AM > 1.0 cm or not as accurately as possible, we performed qualitative side-by-side comparison of CT scans obtained before and after RF ablation. Two radiologists who were blind to the results of quantitative analysis assessed in consensus whether an AM > 1.0 cm was achieved. For this analysis, the adjacent hepatic vessels or the hepatic capsule were used to facilitate comparison.

#3: "TACE was performed 2-3 weeks before RF ablation ". In my understanding, TACE was performed in all the cases. So the title should be revised to include TACE.

Answer: Thank you for your suggestion. However, in this article, we mainly focused on the relationship between the width of AM and the oncological results. The TACE was performed in all patients for radiological assessment of AM and oncological purposes. So we did not think the TACE should be necessarily added to the title.

#4:"RF generator (RITA 1500, RITA Medical Systems Inc, Manchester, GA, USA) or (Covidien Healthcare, Ireland) was used according to the manufacturer's protocol, respectively." Please describe the procedures in detail.

Answer: The procedures have been described in detail as suggested in the revised manuscript.

#5:"In the evaluation, the AM was defined as the narrowest width of the area of low density outside the iodine stain " This may have bias if the iodine stain in the tumor is not uniform or the tumor is hypovascular. Please discuss it.

Answer: This is a very good question. When the iodine stain in the tumor was not uniform or the tumor was hypovascular, measuring AM was a real problem. In such instances, if we were not in accordance with the iodine stain boundary to measure AM, we compared carefully the imaging data before and after RF ablation, and outlined the contours of the tumor in this area and measured AM according to the tumor contour rather than the edge of the iodine stain. We have added this information to the revised manuscript.

#6:Results " During the follow-up, LTP was found in 112 (70.9%) of 158 patients in the group A and in 55 (44.7%) of 123 patients in the group B ($P = 0.000$) (Table 2). The rates of LTP only and total LTP in the group A were significantly higher than these in the group B (46.8% and 70.9% vs. 31.7% and 44.7%, $P = 0.010$, 0.000 respectively). The 1-, 2-, 3-, 4-, and 5-year LTP-free survival rate was 91.3%, 78.4%, 49.5%, 27.8%, and 12.8% in the group A and 97.5%, 86.3%, 73.6%, 49.5% and 26.4% in the group B, respectively (Fig. 3), with statistical difference between the two groups ($P = 0.001$). "The LTP is substantially high, which lead to uncertainty about the author's skill. On the other hand, the LTP-free survival rate is very high. It seems incompatible. Please explain it.

Answer: The data came from 7-year follow-up exams. The author has been using RF ablation to treat HCC patients for more than 10 years and has rich experience in this field. We rechecked the data and confirmed that they were accurate.

#7:"liver unrelated diseases in 4 (5.1%), and undetermined in 6 (7.7%) "Please elaborate it.

Answer: The 4 patients who died of causes unrelated to liver diseases include 3 who died of cardiovascular disease and 1 who died of cerebral hemorrhage. The 6 patients who died of

undetermined causes did so in emergency situations in other hospitals without definite diagnoses related to death.

#8: The following articles might be useful for the authors to make revision: Zheng SG, Xu HX, Lu MD, Xie XY, Xu ZF, Liu GJ, Liu LN. The role of contrast-enhanced ultrasound in follow-up assessment after percutaneous ablation therapy for hepatocellular carcinoma. *World J Gastroenterol*, 2013 Feb 14;19(6):855-65. Liu LN, Xu HX, Zhang YF, Xu JM. Hepatocellular carcinoma after ablation: the imaging follow-up scheme. *World J Gastroenterol*, 2013 Feb 14;19(6):797-801. Xu HX, Lu MD, Liu LN, Guo LH. Magnetic navigation in ultrasound-guided interventional radiology procedures. *Clin Radiol*. 2012;67(5):447-54. Xu HX, Wang Y, Lu MD, Liu LN. Percutaneous ultrasound-guided thermal ablation for intrahepatic cholangiocarcinoma. *Br J Radiol*. 2012 Aug;85(1016):1078-84. Xu HX, Lu MD, Xie XH, Xie XY, Kuang M, Xu ZF, Liu GJ, Wang Z, Chen LD, Lin MX. Treatment response evaluation with three-dimensional contrast-enhanced ultrasound for liver cancer after local therapies. *Eur J Radiol*. 2010 Oct;76(1):81-8.

Answer: Many thanks. The authors of these articles have performed very fruitful work and we do enjoy these articles. However, after carefully reading these articles, we found that they did not directly relate to our paper. We therefore thought quoting one or more of them would not be quite suitable.