ANSWERING REVIEWERS

Nov 13, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 22520-Revised manuscript.doc).

Title: Ten Years Survival of Radiofrequency Ablation in Hepatocellular Carcinoma as a First Line Treatment

Author: Yang Wei, Yan Kun, Goldberg S. Nahum, Ahmed Muneeb, Lee Jung-Chieh, Wu Wei, Zhang Zhong-Yi, Wang Song, Chen Min-Hua

Name of Journal: World Journal of Gastroenterology

ESPS Manuscript NO: 22520

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

1 Format has been updated

Yes.

2 Revision has been made according to the suggestions of the reviewer.

Yes. Revision has been made according to the suggestions of the reviewer and was highlighted with underline.

To editor

Please notice that one of the foreigner author's name is "S. Nahum Goldberg" not "Nahum S. Goldberg" on the old version. Please check the page 1.

1) The title must be informative, specific, and brief (Title should be no more than 10~12 words/60 bytes. Please revise it). Words should be chosen carefully for retrieval purposes. All nonfunctional words should be deleted, such as 'the', 'studies on', 'observations of', and 'roles of', *etc*.

Reply: the title has been revised. Please check the page 1.

2) Please add these content, which must be provided, otherwise the manuscript will be unaccepted finally.

Reply: Institutional review board statement, Informed consent statement, Conflict-of-interest statement, Data sharing statement have been added. Please check the page 2.

3) Telephone and fax should consist of +, country number, district number and telephone or fax number, e.g. Telephone: +86-10-59080039, Fax: +86-10-59080039.

Reply: these information has been added. Please check the page 2.

4) An informative, structured abstract of no less than 246 words should accompany each original article. The Abstract will be structured into the following sections and adhering to the word count thresholds indicated in parentheses: AIM (no more than 20 words): The purpose of the study should be stated clearly and with no or minimal background information, following the format of: "To investigate/study/determine…" METHODS (no less than 80 words): You should present the materials and methods used for all of the data presented in the proceeding Results section of the abstract. RESULTS (no less than 120 words): You should present *P* values where appropriate. You must provide relevant data to illustrate how the statistical values were obtained, e.g. 6.92 ± 3.86 *vs* 3.61 ± 1.67, *P* < 0.001. CONCLUSION (no more than 26 words): You should present your findings and implications that are within the scope of the data you have presented in the preceding Results section. The conclusion should

be written in the present tense.

Reply: these parts have been revised. Please check page 4.

5) Please read the core tip then provide the audio core tip: Acceptable file formats: .mp3, .wav, or .aiff Maximum file size: 10 MB To achieve the best quality, don't allow to have the noise.

Reply: the audio core tip was provided with mp3 file.

6) The format should be like this. Please revise others.

Reply: the format of reference cites has been revised in all of the paper.

7) COMMENTS

Background

To concisely and accurately summarize the related background of the article and to enable the readers to gain some basic knowledge relevant to the article, thus helping them better understand the significance of the article.

Research frontiers

To briefly introduce the hotspots or important areas in the research field related to the article.

Innovations and breakthroughs

To summarize and emphasize the differences, particularly the advances, achievements, innovations and breakthroughs, from the other related or similar articles so as to allow the readers to catch up the major points of the article.

Applications

To summarize the actual application values, the implications for further application and modification, or the perspectives of future application of the article.

Terminology

To concisely and accurately describe, define or explain the specific, unique terms that are not familiar to majority of the readers, but are essential for the readers to understand the article.

Peer- review

To provide the comments from peer reviewers that most represent the characteristics, values and

significance of the article, and allow the readers to have an objective point of view toward the article.

Reply: these contents have been added. Please check them at page 15-17.

8) For the figures, the fonts and lines can be edited or moved. It can be made by ppt.

Reply: For the figure 1-2, we provided with PPT. For the rest figures, we provided with TIFF.

To reviewer 1# (00182114)

Ethanol injection was formerly the standard procedure among the various percutaneous ablation techniques for HCC. Randomized controlled trials, however, have demonstrated that radiofrequency ablation (RFA) has a more reliable local antitumor effect, leading to a lower local tumor progression risk and higher survival rates. RFA has largely replaced ethanol injection. This is very interesting paper about author's experience of RFA for HCC for the past fourteen years.

Reply: Thank you for reviewing my paper and I really appreciate your wonderful comments. I tried to give you a reasonable answer for each question and revised my paper according to your recommendations.

1. **Minami and Kudo (Radiofrequency Ablation of Hepatocellular Carcinoma: A Literature Review International Journal of Hepatology 2011)report an accurate evaluation of treatment response is very important to secure successful RFA therapy since a sufficient safety margin (at least 0.5?cm) can prevent local tumor recurrence. What kinds of treatment do you perform the case which you can not get safety margin 0.5cm in RFA for HCC?**

Reply: we agree with you that safety margin (at least 0.5cm) is very important for successful local ablation. In our study, for tumors in risky location such as adjacent to diaphragm, bowel, gallbladder, we performed artificial ascites to separate the liver and nearby structure, and then extend the safe margin as much as we can. Treatment strategies for HCC in risky locations were described in our previous papers. There was no significant difference in long-term overall survival between the two groups even though the local progression rate was higher in the difficult group in our data. In the revised paper, we added this reference (Yang W, et al. World Journal of Gastroenterology 2015; 21: 1554-1566.) in the text. Please check up page 7/ line 21-23.

2. **In your paper, tumor size did not significantly impact overall survival. Recently, higher-powered RFA generators and modifications to the electrodes have enabled ablation sizes increase. But Shiina et al (RFA for HCC 10 years outcome and prognostic factor. American College of Gastroenterology 2011) report TAE was combined with RFA in**

patients with one tumor >3cm in diameter. Please tell me the detail RFA procedure for HCC tumor >3-5cm in diameter.

Reply: Thank you for this comment. We agree with you that large size of HCC was a factor for lower disease-free survival. The combination therapy of RFA and TACE play more and more important role in large HCC. This part was emphasized in discussion section. Please check this in the revised manuscript (page 13/line 16-18).

However, even with RFA alone, the outcome of 3-5cm HCC was not bad. We had the experience in RFA of >3cm liver tumors for more than 10 years and we published the first related paper in 2004. The indication for RFA of liver tumors has been changed to "tumor size ≤ 5cm" in the guideline for diagnosis and treatment of HCC in China. Also there were several clinical studies which reported the satisfactory outcome of RFA of 3-5cm or even larger than 5cm HCCs as follows.

- N' Kontchou G, et al. Radiofrequency ablation of hepatocellular carcinoma: long-term results and prognostic factors in 235 Western patients with cirrhosis. Hepatology 2009; 50: 1475 -1483.
- Yin XY, Xie XY, Lu MD, Xu HX, Xu ZF, Kuang M, Liu GJ, Liang JY, Lau WY. Percutaneous thermal ablation of medium and large hepatocellular carcinoma: long-term outcome and prognostic factors. Cancer. 2009;115(9):1914-23.
- Lupo L, Panzera P, Giannelli G, Memeo M, Gentile A, Memeo V. Single hepatocellular carcinoma ranging from 3 to 5 cm: radiofrequency ablation or resection? HPB (Oxford) 2007; 9:429-434.
- Seror O, et al. Large (>5.0-cm) HCCs: Multipolar RF Ablation with Three Internally Cooled Bipolar Electrodes—Initial Experience in 26 Patients. Radiology;2008: 248(1):288-296.
- Iannitti DA, Dupuy DE, Mayo-Smith WW, Murphy B. Hepatic radiofrequency ablation. Arch Surg 2002; 137: 422–426.
- Zhang YJ, Liang HH, Chen MS, Guo RP, Li JQ, Zheng Y et al. Hepatocellular carcinoma treated with radiofrequency ablation with or without ethanol injection: a prospective randomized trial. Radiology 2007; 244: 599–607.

3. Most of Authors report Child A and B is suitable liver function data for RFA. In your paper, you performed Child C HCC patients for RFA. Please tell me the condition of Child C patients. Could you perform RFA for the HCC patients with ascites in Child C. Please tell me the detail RFA procedure for HCC tumor with ascites in Child C.

Reply: We agree with you. Child-Pugh class C is a comparative contraindication for RFA but not an absolute contraindication. The RFA treatment was still considered for Child-Pugh class C patients whose liver function was improved after liver protection therapy and tumor was smaller than 3cm, also had no obvious ascites in front of puncture site of liver. This information has been added in text. Please check this in the revised manuscript (page 6/line 8-10).

There were several studies reported the role of RFA in HCC patients with Child-Pugh class C liver function as follows:

- Hsieh CB, Chang HM, Chen TW, Chen CJ, Chan DC, YC, Liu Y, Chang TM, Shen KL. Comparison of transcatheter arterial chemoembolization, laparoscopic radiofrequency ablation, and conservative treatment for decompensated cirrhotic patients with hepatocellular carcinoma. World J Gastroenterol 2004; 10(4):505-508.
- Kim YK, Kim CS, Chung GH, Han YM, Lee SY, Jin GY, Lee JM. Radiofrequency Ablation of Hepatocellular Carcinoma in Patients with Decompensated Cirrhosis: Evaluation of Therapeutic Efficacy and Safety. AJR 2006; 186:S261–S268.
- Wu JY, Yang W, Cui M, Yin SS, Gao W, Wu W, Yan K, Chen MH. Efficacy and feasibility of radiofrequency ablation for decompensated cirrhotic patients with hepatocellular carcinoma. Chinese Medical Journal 2010;123(15):1967-1972.

To reviewer 2 (01804246)

This is an interesting paper. This monocentric large experience shows us that RFA is a good first treatment option in HCC patients. The analysis of prognostic factors is also important. In conclusion the paper is good and can be published after minor corrections.

Reply: Thank for your careful review of my paper. We have revised the whole paper according to your comments.

Some corrections are necessary:

1-Child-Pugh not child-pugh, CEUS not CUES.

Reply: these words have been revised. Please check up at page 4/line 25, page 5/line 7, page 6/line 8, page 15/line 7; Page 10/line 19.

2-Please give more explanations how CEUS before RFA can increase the results? (Detecting local metastasis?)

Reply: Unenhanced US is commonly used to guide ablation because it is easy to use and widely available. However, CEUS can provide more important information and plays a more significant role in ablation therapy. We had added more explanation about the role of CEUS before RFA in treatment. Please check it at page 14 /line 13-16, and reference 37.

And the detailed information was as follows:

1). Choose indications according to number and size of lesions: CEUS is sensitive to detect small lesions which are invisible on unenhanced US or CT, even satellite lesions of 3-5mm, providing evidence for choosing indication. Usage of CEUS to choose indications can reduce recurrence rate and prolong survival time [Chen MH, JUM 2007].

2). Measurement of tumor size: CEUS can accurately show the dimensions of tumors. The assessment of size must include the perilesional hypervascular halo or area which must be included in the treatment volume. When unenhanced US cannot detect all the lesions visualized by CECT or CEMRI, real-time CT/MRI–US fusion imaging helps define the location, characteristics, and the size of the sonographically undetectable lesions.

3). Definition of tumor margins: CEUS can depict the infiltrating margin and the invasiveness of

tumors better than unenhanced US [Chen MH, Clinical Radiology, 2007]. Precise depiction of the tumor margins by CEUS allows better definition of its relationships with surrounding structures, such as the intestines, diaphragm and gallbladder, thus helping develop appropriate treatment strategies and reducing the risks of complications [Chen MH, JVIR 2006; Chen MH, JUM 2007]. This is especially important for subcapsular and exophytic tumors.

4). Assessment of degree of enhancement and homogeneity of vascularity and presence of necrosis to direct ablation therapy: For liver metastases, in substance phase CEUS can be more sensitive to display small washout lesions invisible on CECT or CEMRI, which should be positively treated by ablation. In addition, CEUS can accurately guide electrode placement.

5). Identification of blockage of tumor feeding vessels: when these are detected with CEUS, the region where they enter the tumor should be ablated first because a larger treatment volume can be achieved once the main blood supply has been blocked. Subsequently, a secondary CEUS evaluates the effect of blocking tumor feeding vessels to guide ablation, which can increase the effective inactivation rate [Hou YB, WJG 2009].

3-The paper seems to be a little too long, especially the discussion section.

Reply: the paper has been shorten, especially the discussion section.

To reviewer 3# (02860590)

The authors have brought their retrospective experience on the use of RFA in a large group of patients with HCC during a significant long -term follow-up. This is an important experience in this filed of HCC therapy.

Reply: Thank you for your comments. I tried to give you a reasonable answer for each question and revised my paper according to your recommendations.

I suggest the authors have to add two more informations:

1) **-how many patients were receiving antiviral treatment and what was the status of response to therapy.**

Reply: this is a very good suggestion. We agree antiviral therapy is very important factor for the prognosis of patients with HCC. And we have recorded the related information about anti-virus therapy in HBV associated HCC patients before and after RFA treatment in recently years. However, the condition for anti-virus B treatment was complicate in China in the last 15 years. Although the incidence of hepatitis virus B was very high in China but the anti-virus therapy was not paid enough attention around 5 years ago. Also the main kind of anti-virus B drug such as Lamivudine and entecavir were expensive and were not covered by medical insurance around 5 years ago.

In this retrospective cohort study, the patients who enrolled in this prognostic analysis had received RFA treatment as early as 15 years ago. So far we do not have enough data of anti-virus therapy to cover the whole study period (2000-2013) for the prognostic analysis. We have added this limitation in the discussion section and we would like to further evaluate the role of anti-virus therapy in the next study. Please check this in the revised manuscript (page 15/line 2-4).

2) **- Comparison between the different periods of enrollment. for example they could divide enrollment period into two blocks of seven Years and then compare the results on survival curves**

Reply: Thank you for your good suggestion. We had added this data in text. Please check this in the revised manuscript (page 10/line 9-12).

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

Sincerely yours,

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