

## ANSWERING REVIEWERS

July 25, 2014



Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 11362-review.doc).

**Title: Radiofrequency ablation for hepatocellular carcinoma in difficult locations: 7 year outcomes in 382 patients**

**Author:** Wei Yang, Min-Hua Chen, Gong-Xiong Wu, Wei Wu, Ying Fu, Jung-chieh Lee, Zhong-Yi Zhang, Song Wang, Kun Yan

**Name of Journal:** World Journal of Gastroenterology

**ESPS Manuscript NO:** 11362

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.

1) To reviewer 1# (02530754)

**The manuscript by Wei et al evaluated 382 patients with HCC candidates to RFA in order to know whether a more complex technique influence outcome (tumour recurrence and survival). The strengths of this paper are the increased number of patients and the sufficient follow-up. However there are limitations, some of them important, that should be fully addressed:**

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-The English should be revised.**

**Reply:** We got the help to polish the English of this manuscript with a professional English language editing company. Please find out the recommendation letter provided by the English language editing company in attachment I.

**2- It is not appropriate to include descriptive values of the patients included in “Methods”. This pertains to baseline features of patients and tumour characteristics. These data should be transferred to the section “results”.**

**Reply:** Thank you. We agree with you. We have moved this part to “results” section. Please check it in page 13 in result section.

**3- “p” values should be expressed as an exact number (ie.  $p=0.64$ ). Intervals such as  $p>0.05$  or  $p<0.05$  provides inaccurate information and therefore should be changed. This affects either the text and tables/figures.**

**Reply:** Revised. We have provided an exact number for all P values in text and tables/figures.

**4- In the tables, percentages should be added to the absolute values for categorical variables.**

**Reply:** Revised. Percentages have been added to the absolute values for categorical variables. Please check it out in table 1,2,6.

**5- Several protocols and devices were used to perform RFA across the study period. An analysis comparing the outcome for such different schemes should be performed, and this variable controlled in the multivariate analysis (see comment below).**

**Reply:** Revised. According to your comment, we performed cox regression for overall survival. Multivariate analysis showed the independent risk factors included child-pugh classification, tumor number, serum liver function enzyme and tumor size. There was no significant difference among different RFA devices groups in overall survival. Please check it out in page 4, 12, 14, 17 and table 5.

**6- Details about the protocol of anesthesia used may not be necessary. Please consider removing this information.**

**Reply:** Revised. The protocol of anesthesia has been removed. Please check it in page 12.

**7- The main limitation of the study is the lack of control for potential confounding factors. Survival may be influenced by liver function, portal hypertension and tumour features, rather than the complexity of the RFA. The use of TACE after RFA may be also considered a potential confounding factor. I strongly recommend using multiple Cox’s regression to control for possible confounding factors. This analysis would reinforce the idea that RFA is also useful for difficult locations.**

**Reply:** Revised and added table 5. I agree with you. The limitation for our clinical study is lack of control for confounding factors, also it is hard to keep patients in one therapy group for cancer treatment during the long term period (7 years). According to your comment, we performed cox regression for overall survival. Multivariate analysis showed the independent risk factors included child-pugh classification, tumor number, serum liver function enzyme and tumor size. There was no

significant difference between difficult location group and control group in overall survival. This result would reinforce the idea that RFA is also useful for difficult location. Please check it out in page 4, 12, 14, 17 and table 5.

**8- Surgical resection is becoming an option even for patients with portal hypertension with excellent outcomes (Gianini Liver Int 2013 and Cuccetti Ann Surg 2009 among others). Furthermore a tumour >3 cm has an increased risk of HCC recurrence with RFA. The authors should further discuss the criteria for selecting patients for RFA, and why these patients were not considered for liver resection.**

**Reply:** I agree with you. The resection rate and outcome for surgery is improving as well as RFA does. In our group, patients were not suitable candidates for hepatectomy as a result of elder age, inadequate hepatic reserve related to intrinsic liver disease and/or lesion location, or limited cardiopulmonary function. Also a quite number of patients were preferred to undergo mini-invasive therapy even though they would have been eligible for hepatic resection.

Regarding to the tumour size criteria for RFA, I would like to further explain it. In previous series, technical success rates for larger HCCs (3-5 cm) after RFA seem unfavorable, ranging from 61.3% to 82.5%. However, higher-power RFA generators and modifications to the electrodes have enabled ablation sizes of up to 6–7 cm in diameter in animal models. Only lesions smaller than 3 cm were treatable with RFA in the past, whereas physicians can now ablate tumors of up to 5 cm [1,2,3]. These advances have opened the door to more patients who were previously considered untreatable and whose only options were palliation or chemotherapy. Clinicians are now commonly using RFA to treat hepatic tumors larger than 3.0 cm in size, with some even treating tumors greater than 5.0 cm with satisfactory results [4,5]. In the past 14 years, our team made great effort to improve the outcome of liver tumors larger than 3cm. We also published a treatment protocol for overlapping ablation of tumors sized 3-6cm based on mathematical model [6]. With skilled hand and optimized protocol, even >3cm tumors could be completely treated and achieve fairly good outcome.

1. Guglielmi A, Ruzzenente A, Valdegamberi A, Pachera S, Campagnaro T, D'Onofrio M et al. Radiofrequency ablation versus surgical resection for the treatment of hepatocellular carcinoma in cirrhosis. *J Gastrointest Surg* 2008; 12: 192–198.
2. Khan MR, Poon RT, Ng KK, Chan AC, Yuen J, Tung H et al. Comparison of percutaneous and surgical approaches for radiofrequency ablation of small and medium hepatocellular carcinoma. *Arch Surg* 2007; 142: 1136–1143.
3. Iannitti DA, Dupuy DE, Mayo-Smith WW, Murphy B. Hepatic radiofrequency ablation. *Arch Surg* 2002; 137: 422–426.
4. 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.
5. Gillams AR, Lees WR. Five-year survival in 309 patients with colorectal liver metastases treated with radiofrequency ablation. *Eur Radiol* 2009; 19: 1206–1213.

6. Chen MH, Yang W, Yan K, et al. Large liver tumors: protocol for radiofrequency ablation and its clinical application in 110 patients. Radiology 2004; 232:260–271.

**9- The discussion should be shortened. It includes too much information which difficult the reading.**

**Reply:** revised. The discussion section has been shortened. Please check it out from page 15 to page 20.

2) To reviewer 2 (02527808)

**The manuscript is very interesting presenting valuable practice in the field of intervention management of HCC showing excellent presentation & detailed description of the methods & techniques used. However some points must be considered:**

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

**1- The title of the paper focus on the comparison between radiofrequency in difficult HCC cases in comparison to the non difficult one, so other ttt options must be excluded from the study like TACE & surgical resection. When the patients characteristics were revised you observe some patients had past history of TACE or surgical resection while other patients were subjected to combined ttt at the same time. The percentage of those patients exceed 25% of total cases. These cases were better to be excluded to avoid bias of the results or change the title of the manuscript to include the comparison of all ttt options with each others and classify the patients into either isolated radiofrequency or radiofrequency with other options.**

**Reply:** Revised and added table 5. I agree with you. The limitation for general clinical study is lack of control for confounding factors, also it is hard to keep patients in one therapy group for cancer treatment during the long term period (7 years). To control the confounding factors for this cohort, we added multivariate analysis with cox regression for overall survival. Multivariate analysis showed the independent risk factors included child-pugh classification, number of tumors, serum liver function enzyme and tumor size. More importantly, there was no significant difference between difficult location group and control group in overall survival. This result would reinforce the idea that RFA is also useful for difficult location. We didn't change the title of paper because RFA was the main treatment modality and TACE was used as adjuvant measure in a limited number of patients in our study. Please check it out in page 4, 12, 14, 17 and table 5.

**2- The radiofrequency is not a good option for cases above 5 cm & at least microwave for example perform good ablation.**

**Reply:** Regarding to the tumour size criteria for RFA, I would like to further explain it. In previous series, technical success rates for larger HCCs (3-5 cm) after RFA seem unfavorable, ranging from 61.3% to 82.5%. However, intense research over the recent 10 years has produced impressive results. Only lesions smaller than 3 cm were treatable with RFA in the past, whereas physicians can

now ablate tumours of up to 5 cm<sup>[1-3]</sup>. In the past 14 years, our team made great effort to improve the outcome of liver tumors larger than 3cm. We also published a treatment protocol for overlapping ablation of tumor sized 3-6cm based on mathematical model<sup>[4]</sup>. With skilled hand and optimized protocol, even >3cm tumors could be completed treated and achieve fairly good outcome.

1. Guglielmi A, Ruzzenente A, Valdegamberi A, Pachera S, Campagnaro T, D'Onofrio M et al. Radiofrequency ablation versus surgical resection for the treatment of hepatocellular carcinoma in cirrhosis. J Gastrointest Surg 2008; 12: 192–198.
2. Khan MR, Poon RT, Ng KK, Chan AC, Yuen J, Tung H et al. Comparison of percutaneous and surgical approaches for radiofrequency ablation of small and medium hepatocellular carcinoma. Arch Surg 2007; 142: 1136–1143.
3. Iannitti DA, Dupuy DE, Mayo-Smith WW, Murphy B. Hepatic radiofrequency ablation. Arch Surg 2002; 137: 422–426.
4. Chen MH, Yang W, Yan K, et al. Large liver tumors: protocol for radiofrequency ablation and its clinical application in 110 patients. Radiology 2004; 232:260–271.

**3- A comparison must be made between different techniques of radiofrequency, also the number of sessions of radiofrequency must mentioned in results.**

**Reply:** Revised. We performed cox regression for overall survival to control confounding factors. Multivariate analysis showed the independent risk factors included child-pugh classification, number of tumors, serum liver function enzyme and tumor size. There was no significant difference between different RFA devices in overall survival. Please check it out in page 4, 12, 14, 17 and table 5. We added the number of sessions of RFA in result. Please check it out in page 14.

**4- This statements (There were no statistically significant differences in clinic pathological characteristics between the two groups.) must be mentioned in the results section & term (Clinic pathologic) is not appropriate.**

**Reply:** Thank you. revised. Please check it out in page 13, in result section.

**5- extensive language editing is needed.**

**Reply:** We have got the help to polish the English of this manuscript with a professional English language editing company. Please check the recommendation letter by the English language editing company in attachment I.

**6. the section of discussion must be brief without unnecessary details.**

**Reply:** revised. The discussion section has been shortened. Please check it out from page 15 to page 20.

**3) To reviewer 3# (02860590)**

**Article – Radiofrequency Ablation for Hepatocellular Carcinoma in Difficult Locations: 7 Year Outcomes in 382 Patients** The topic is of general interest because local ablation is considered the first line treatment option for patients at early stages not suitable for surgical therapies. My specific queries and comments are below:

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- Please, get a native English speaker to check the English used in the paper. Various sentences should be reviewed due to grammatical error.**

**Reply:** We have got the help to polish the English of this manuscript with a professional English language editing company. Please check the recommendation letter by the English language editing company in attachment I.

**2- Title: The title is so long. Can the authors please provide a title more centred on the objective of the article?**

**Reply:** revised. Please check the title page.

**3- Abstract: The characteristics of the two groups are not well described such as age, sex, severity of baseline disease and presence of other comorbidities. Furthermore, the text should be reviewed due to grammatical error.**

**Reply:** revised. This information has been added in abstract. Please check it in abstract.

**4-Introduction: The introduction is under-elaborated. There is limited information regarding a theoretical framework that grounds the research. ? Pg 5, lines 92-95: “The efficacy of individual RF strategies established considering tumour size, morphology, anatomic relations and other factors was explored to determine the value of RFA for the treatment of difficult tumors.” The objective should be rephrased; “other factors” should be determined.**

**Reply:** The objective has been rephrased. Our objective is to confirm the safety and effectiveness of the RFA procedure in problematically located HCC. Please check it out in page 5.

**5- Materials and methods: ? Pg 6, Inclusion Criteria and Definition: Can you clarify this part of the text? ?**

**Reply:** Thank you for pointing out this mistake for us. Revised. The subtitle of this part should be “Definition of difficult locations”. Please check it out in page 6.

**6-Pg 7, lines 140-142: The Materials and methods section and result section are conflated. ?**

**Reply:** Thank you. We agree with you. We have moved **baseline features of patients and tumour** part to “results” section. Please check it in page 13 in result section.

**7- Treatment strategy and procedure:** Please, this part should be rewritten and it is necessary to be more objective.

**Reply:** revised. Please check it out in page 7-11.

**8- Pg 8, lines 183-188:** Some patients were submitted to more than one modality of treatment. It could represent a bias. Please, clarification should be provided for this issue.

**Reply:** with the development of tumor ablation, more and more physicians would like to adopt more than one modality of treatment. RFA is the main treatment modality and TACE was used as adjuvant measure for large HCC and supplied by rich vessels. The percent of patients received previous TACE in difficult group was equal to the control group in the present study. Thus the use of TACE in some patients should not bias the analysis of the long-term outcomes between the two groups. This information has been discussed in discussion section. Please check it out in page 20.

**9-Results:** The result section is under-elaborated. The data should be analysed in profundity. The groups are heterogeneous. Some patients were submitted to more than one modality of treatment. On other hand, others patients were submitted to one modality of treatment, but more than one occasion. These particularities should be evaluated during the analysis of the data.

**Reply:** Revised. We performed cox regression for overall survival to control confounding factors. Multivariate analysis showed only number of tumors and tumor size (in tumor factors) was significantly associated with survival outcome, whereas tumor location was not a significant risk factor. This information suggests that RFA is also useful in high risk location as well as normal location. Please check it out in page 4, 12, 14, 17 and table 5.

**10-Discussion:** The discussion is so long. Can the authors please provide a discussion more centred on the results and their analysis.

**Reply:** revised. The discussion section has been shortened. Please check it out from page 15 to page 20.

4) to reviewer 4# (02860618)

**The manuscript by Yang Wei and co-workers aimed at evaluating HCC patients treated by RFA in order to investigate the long-term outcomes (tumour recurrence and survival) in normal or high risk HCC location groups.**

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

**1- This study is very similar to a previously published work (Teratami T, Hepatology, 2006).**

**Even though the Authors cite this manuscript. I consider that their paper can be published after major modifications that point out the differences with the previous work.**

**Reply:** Revised. **The previously published work** (Teratami T, Hepatology, 2006) reported 207 patients with 231 nodules in high-risk locations treated with percutaneous RFA, and showed no significant differences in the 3-year local progression rate. However, the outcome of RFA in difficult location still needs to be verified in a large series of patients with long time follow up. **Our study** has the longer time of outcomes (7 years) of RFA for tumors in high-risk locations. In addition, the differences between tumors in different difficult locations, such as abutting major vessels/bile duct, adjacent to extrahepatic organs, and subcapsular were further analyzed in our study. The long-term follow-up studies involving large samples with tumors in different locations, provided important evidence for extending the indications of RFA and confirmed its efficacy for difficult cases of HCC. Please check it out in page 16 in discussion section.

**2- Moreover, it needs a deep revision by an English native speaker.**

**Reply:** We got the help to polish the English of this manuscript with a professional English language editing company. Please check the recommendation letter by the English language editing company in attachment I.

3 References and typesetting were corrected

Yes. Some references don't have DOI number and we provided the copy of first page for them in attachment II.

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

Sincerely yours,

A handwritten signature in blue ink, appearing to read 'Min-Hua Chen'.

**Min-Hua Chen, MD.**

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## Attachment I



AMERICAN JOURNAL EXPERTS

# EDITORIAL CERTIFICATE

This document certifies that the manuscript listed below was edited for proper English language, grammar, punctuation, spelling, and overall style by one or more of the highly qualified native English speaking editors at American Journal Experts.

### Manuscript title:

Radiofrequency ablation of hepatocellular carcinoma in difficult locations: strategy and long-term outcomes

### Authors:

Wei Yang, Min-Hua Chen, Gong-Xiong Wu, Wei Wu, Ying Fu, Jung-chieh Lee, Zhong-Yi Zhang, Song Wang, Kun Yan

### Date Issued:

July 20, 2014

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• BRIEF REPORTS •

## Treatment efficacy of radiofrequency ablation of 338 patients with hepatic malignant tumor and the relevant complications

Min-Hua Chen, Wei Yang, Kun Yan, Wen Gao, Ying Dai, Yan-Bin Wang, Xiao-Peng Zhang, Shan-Shan Yin

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Received: 2004-12-31 Accepted: 2005-03-24

for the patients of hepatic malignant tumor, even of advanced liver tumor, tumor recurrence, and liver metastases. Knowledge about possible complications and their control may increase the treatment efficacy and help to promote the use of RFA technique.

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**Key words:** Radiofrequency ablation; Liver neoplasms; Survival; Complication; Ultrasonography

Chen MH, Yang W, Yan K, Gao W, Dai Y, Wang YB, Zhang XP, Yin SS. Treatment efficacy of radiofrequency ablation of 338 patients with hepatic tumor and the relevant complications. *World J Gastroenterol* 2005; 11(40):6395-6401

<http://www.wjgnet.com/1007-9327/11/6395.asp>

### Abstract

**AIM:** To investigate the treatment efficacy of radiofrequency ablation (RFA) of hepatic malignant tumor and the relevant complications.

**METHODS:** A total of 338 patients with 763 hepatic tumors underwent ultrasound-guided RFA (565 procedures). There were 204 cases of hepatic cellular carcinoma (HCC) with 430 tumors, the mean largest diameter was 4.0 cm. Of them, 48 patients (23.5%) were in stages I-II (UICC Systems) and 156 (76.5%) in stages III-IV. There were 134 cases of metastatic liver carcinoma (MLC), with 333 metastases in the liver, the mean diameter was 4.1 cm, the liver metastases of 96 patients (71.6%) came from gastrointestinal tract. Ninety-three percent of the 338 patients were treated using the relatively standard protocol. Crucial attention must be paid to monitor the abnormal changes in ultrasound images as well as the vital signs of the patients to find the possible hemorrhage and peripheral structures injury in time. The tumors were considered as ablated completely, if no viability was found on enhanced CT within 24 h or at 1 mo after RFA. These patients were followed up for 3-57 mo.

**RESULTS:** The ablation success rate was 93.3% (401/430 tumors) for HCC and was 96.7% (322/333 tumors) for MLC. The local recurrence rate for HCC and MLC was 7.9% (34/430 tumors) and 10.5% (35/333 tumors), respectively. A total of 137 patients (40.5%) underwent 2-11 times of repeated ablations because of tumor recurrence or metastasis. The 1<sup>st</sup>, 2<sup>nd</sup>, and 3<sup>rd</sup> year survival rate was 84.6%, 66.6%, and 63.1%, respectively; the survival rate from 48 patients of I-II stage HCC was 93.7%, 80.4%, and 80.4%, respectively. The major complication rate in this study was 2.5% (14 of 565 procedures), which consisted of 5 hemorrhages, 1 colon perforation, 5 injuries of adjacent structures, 2 bile leakages, and 1 skin burn.

**CONCLUSION:** RFA, as a minimally invasive local treatment, has become an effective and relatively safe alternative

### INTRODUCTION

The treatment efficacy of radiofrequency ablation (RFA) of liver tumors has been confirmed by sufficient quantity of clinical results<sup>[1-6]</sup>. With the improvement in both equipments and treatment skills, RFA has gradually been developed in China to treat large tumors<sup>[5,6]</sup>, and provided an efficient alternative for the tumors which were difficult to manage with conventional treatments. With the wide adoption of the RFA technique, the complications increased accordingly, which drew a very important clinical attention. Large tumor and advanced tumor were commonly seen in China. Taking into consideration the characteristics of the tumors of our country study, this research aimed to summarize the treatment efficacy of RFA in 338 malignant liver tumors and explore the effective measures for complications.

### MATERIALS AND METHODS

#### Patients

From 1999 to 2004, 338 patients with 763 hepatic tumors underwent 565 US-guided percutaneous RFA. All patients were diagnosed by biopsy at least on one lesion. Two hundred and forty-four patients were men (mean age, 59.1 years; age range, 24-87 years) and 94 were women (mean age, 58.6 years; age range, 32-86 years). Two hundred and four were hepatic cellular carcinoma (HCC) patients (430 tumors), with mean diameter of 4.0 cm (range, 1.2-10.8 cm). Of these 204 HCC patients, 96, 95, and 13 had Child-Pugh class A, B, and C cirrhosis, respectively. According to the UICC-TNM staging system, 48 patients (23.5%) were

## Original article

# Intraperitoneal hemorrhage during and after percutaneous radiofrequency ablation of hepatic tumors: reasons and management

CHEN Min-hua, DAI Ying, YAN Kun, YANG Wei, GAO Wen, WU Wei, LIAO Sheng-ri and HAO Chun-yi

**Keywords:** liver neoplasm • radiofrequency ablation • complication • intraperitoneal hemorrhage • ultrasound

**Background** Intraperitoneal hemorrhage is one of the most common complications of radiofrequency (RF) ablation of hepatic tumors. This study was designed to investigate the reason and management of intraperitoneal hemorrhage occurred during or after percutaneous RF ablation of hepatic tumors.

**Methods** Three hundred and fifty-six patients with hepatic tumors have been treated at 592 procedures of ultrasound guided RF ablation. Intraperitoneal hemorrhage occurred in 5 patients (0.8%). The reasons and management of intraperitoneal hemorrhage in these 5 cases were retrospectively analyzed.

**Results** Two patients with liver metastasis and one hepatocellular carcinoma (HCC) patient suffered from hemorrhage during the RF treatment. Two patients with recurrent HCC after surgery developed hemorrhage 20 minutes or 4 hours after RF treatment. One case of hemorrhage was due to the inappropriate electrode positioning induced liver laceration while treating a 1 cm liver metastasis near the liver capsule. One was due to the injury of a small vessel by the RF needle in another liver metastasis patient. Three cases were due to tumor rupture with two cases induced by cough or position change after treating large protruding HCC lesions. Four (80%) of the 5 cases of hemorrhage were rapidly identified by ultrasound. The causes and sites of bleeding during the RF treatment in three cases were confirmed through ultrasound, which were successfully treated using RF coagulation to achieve hemostasis of the bleeding site. Two patients with post-ablation hemorrhage recovered in one hour and 24 hours, respectively after given blood transfusion and other conservative measures. No surgical intervention was required. Two patients died of wide spread metastasis 23–36 months afterwards and the other three patients have lived for 18–25 months to date.

**Conclusions** It is important to perform close monitoring during and after RF ablation in order to identify intraperitoneal hemorrhage in time. RF ablation of the bleeding sites was a simple and effective management when the bleeding site could be confirmed by ultrasound. The hemorrhage due to the rupture of large and protruding liver tumors could be serious and should be considered as contraindication for RF treatment.

*Chin Med J 2005; 118(20):1682-1687*

Many studies have established the role of radiofrequency (RF) ablation as a minimally invasive treatment of hepatic neoplasms.<sup>1-6</sup> Good outcomes with low morbidity and mortality have been identified. Although relatively safe, a broad spectrum of complications, of which the hemorrhage is the most common, has been reported along with the increasing use of RF ablation.<sup>7-9</sup> Hence, it is absolutely essential to minimize complications and learn how to deal with them properly. The purpose of this study is to investigate the reason of the

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This study was supported by a grant from the Foundation of Capital Medicine Development (No. ZD199909).