

Dear Editor,

Thank you very much for an opportunity to revise our article. We revise our article as good as possible according to your and reviewers' kind suggestions. We are sure that our article is considerably improved with this major revision and now deserves publication in your journal.

Please find enclosed the edited manuscript in Word format

Title: Radiofrequency ablation as treatment for pulmonary metastasis of colorectal cancer

Author: Takao Hiraki; Hideo Gohara; Toshihiro Iguchi; Hiroyasu Fujiwara; Yusuke Matsui; Susumu Kanazawa,

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 5598

1 Format has been updated.

2 The manuscript has been improved with revision according to the suggestions **(a)-(e)** of the reviewer #02526287

(a) A prospective multicenter clinical trial showed that treatment was successfully completed in 99% (105/106) of patients. We add this datum. (Principle and techniques of lung RFA, last paragraph, lines 7-9)

(b) As you suggest, contrast CT would be helpful in confirming the diagnosis of local progression. In our experience, however, most local progression may be suggested only by careful observation of size and geometry of ablation zones. Therefore, we are of the opinion that contrast-enhanced CT is preferable but not essential to diagnose local progression. We add such suggestions. (Radiological evaluation of local efficacy, 1st paragraph, last 3 sentences)

(c) We add CT images demonstrating lung modification after RFA. (Figure 1)

(d) We are not of the opinion that RFA of lung cancer should be limited to a given center, but that this procedure should be performed only by physicians who are familiar with both CT-guided intervention and RFA. We add our opinion. (Principle and techniques of lung RFA, last paragraph, 1st sentence)

(e) We add indication and contraindication. (Principle and techniques of lung RFA, 3rd paragraph)

3 The manuscript has been improved with revision according to a lot of suggestions of the reviewer #2662478

(Suggestion 1) Abstract: A lot of statements are made without any references.

(Answer 1) We think that the abstract does not include information on references. Most statements here are made with references in the text.

(Suggestion 2) Reasons for local recurrence of tumor are not commented.

(Answer 2) Local efficacy by RFA depends on tumor size. Thus, local progression rate is high for >3 cm tumors. We add such a comment. (Abstract, lines 9-11) To make such a comment, we add data of local progression rate according to tumor size. (Review of studies on RFA of pulmonary metastases from colorectal cancer, 2nd, 5th, and 6th

paragraphs)

(Suggestion 3) I miss the average survival rates without RFA treatment in order to evaluate risk-benefit.

(Answer 3) Meta-analysis showed that the patients with untreated locally advanced or metastatic colorectal cancer have a medium survival of 8 months. We add such information not to the abstract but to the text. (Introduction, 2nd paragraph, 1st sentence)

(Suggestion 4) Surgery is still the method of choice in curative intended treatment. Although the treatment may be repeated the high risk of pneumothorax has to be taken into account.

(Answer 4) We agree that surgery is still the method of choice in curative intended treatment. We add such a comment. (Abstract, 2nd to last sentence)

(Suggestion 5) Text: Background and rationale: Page 4, second paragraph: seems irrelevant – please omit.

(Answer 5) We omit this paragraph.

(Suggestion 6) Page 4, third paragraph, line 5-6: Surgery is considered the treatment of choice in curative intended treatment. Please rephrase the sentences.

(Answer 6) We rephrase the sentences. (Introduction, 2nd paragraph, lines 7-8)

(Suggestion 7) Page 5, first paragraph: Please consider here or in the discussion, why some people are not suitable for surgery and what would be the benefit of RFA instead? Would it be feasible?

(Answer 7) The patients with pulmonary metastases who are considered nonsurgical candidates because of comorbidities and/or refusal to undergo surgery may be favorable candidates for RFA. RFA is feasible and may provide a chance of long-term survival or even cure to such patients. We add such comments. (Advantages and disadvantage of lung RFA, 1st paragraph, lines 3-5)

(Suggestion 8) Principle of lung RFA: Should be shortened.

(Answer 8) We considerably shorten this section and combine it with the next section. (Principle and techniques of lung RFA)

(Suggestion 9) Page 5, line 28: Please include references.

(Answer 9) We rephrase the sentence. (Principle and techniques of lung RFA, 2nd paragraph, 2nd sentence) It is a well-known fact that the thermal and electrical conductivity of air are low.

(Suggestion 10) Page 6, line 5-6: Please include references to this statement.

(Answer 10) We rephrase the sentence, giving references. (Principle and techniques of lung RFA, 2nd paragraph, 2nd to last sentence)

(Suggestion 11) Lung RFA techniques: Should be shortened (could be combined with the “principle of lung RFA”). Very few relevant comments are given in this section and in the section above.

(Answer 11) We shorten this section and combine it with the previous section. (Principle and techniques of lung RFA)

(Suggestion 12) Page 6, fourth paragraph: This information seems too basic.

(Answer 12) We delete this paragraph. (Principle and techniques of lung RFA)

(Suggestion 13) Page 7, line 8-10: Please include references to published papers on follow-up (for instance Fereidoun G. Abatin et al. Radiographics 2012) Radiological evaluation of local efficacy: Please include references to the statements made in this paragraph. Several (review) papers are published on this topic.

(Answer 13) We add a total of 5 references to several statements in this paragraph. Further, we modify or delete the statements that are not supported by references. (Radiological evaluation of local efficacy)

(Suggestion 14) Review of studies on RFA of pulmonary metastases from colorectal cancer: Unfortunately, I am unable to see the entire table 1. This section is difficult to get an overview from, and I miss reference to the survival rate if nothing is done to the lung metastases. Are lung metastases from colorectal cancer behaving differently than lung metastases from other cancers? And how is RFA compared with minimal resection procedures? Also I miss information on how the search for publications was performed? Which databases were searched? How were the referred papers chosen? Inclusion and exclusion criteria?

(Answer 14) We are sorry for a large table. We revise the format of the table according to the editor's suggestion.

Meta-analysis showed that the patients with untreated locally advanced or metastatic colorectal cancer have a medium survival of 8 months. We add such information.

(Introduction, 2nd paragraph, 1st sentence)

Actually, we don't know how lung metastases from colorectal cancer behave differently compared with those from other cancers.

We add our opinion on how RFA is compared with metastasectomy. (Review of studies on RFA of pulmonary metastases from colorectal cancer, last paragraph, last 2 sentences)

We add information on how to research literatures. (Review of studies on efficacy of RFA of pulmonary metastases from colorectal cancer, 1st paragraph)

We add inclusion and exclusion criteria. (Principle and techniques of lung RFA, 3rd paragraph)

(Suggestion 15) Page 8, line 21: What is meant by "actuarial"?

(Answer 15) We quoted the word "actuarial" from the text of the referred article. We delete the word because it seems confusing. (Review of studies on RFA of pulmonary metastases from colorectal cancer, 2nd paragraph)

(Suggestion 16) We also miss information on whether the patients included in the studies were candidates for surgery or not?

(Answer 16) RFA is usually performed for nonsurgical candidates. When it is clearly stated in the articles, we replace the word "patients" by "nonsurgical candidates" in the relevant sentence (Review of studies on efficacy of RFA of pulmonary metastases from colorectal cancer, 2nd-6th paragraphs)

(Suggestion 17) Advantages and disadvantages: Rather weak.

(Answer 17) In this paragraph, we add a statement that RFA is a good choice for patients who are medically inoperable or refuse to undergo surgery. (Advantages and disadvantages of lung RFA, 1st paragraph, lines 3-5) Further, we add a high risk of pneumothorax as another disadvantage, according to the suggestion 18. (Advantages and disadvantages of lung RFA, 2nd paragraph, 2nd to last sentence) Moreover, we delete the last sentence of the 2nd paragraph, because it is redundant. (Advantages and disadvantages of lung RFA, 2nd paragraph)

(Suggestion 18) Conclusion: It is debatable if a procedure is safe if 50% gets pneumothorax and half of them need thoracic drainage. Also, the local progression rate seems high.

(Answer 18) We think that grade 1 pneumothorax does not matter clinically. Chest tube placement is required after up to 25% of procedures, but the majority necessitates only a few-days placement until cure. Grade 3 or worse adverse events are quite rare. Thus, we say that the procedure is safe. However, we agree that a high risk of pneumothorax is a disadvantage of RFA. Thus, we add it to the text. (Advantages and disadvantages of lung RFA, 2nd paragraph, 2nd to last sentence)

Local efficacy depends on tumor size. We agree that local progression rate is high for tumors >3 cm. Thus, we revise the relevant sentence. (Conclusion, lines 3-5 and 11) To make such a comment, we add data of local progression rate according to tumor size to the text. (Review of studies on RFA of pulmonary metastases from colorectal cancer, 2nd, 5th, and 6th paragraphs)

(Suggestion 19) Figure: Does not add much to the manuscript.

(Answer 19) We delete this figure. We add another figure according to the suggestion by another reviewer.

4 Along with this major revision, we delete 5 references, add 9 references, and then renumber the references. Further, the English language editing company makes a lot of corrections to our manuscript.

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

Sincerely yours,

Takao Hiraki, MD
Department of Radiology
Okayama University Medical School
Phone: +81-86-235-7313,
Fax: +81-86-235-7316,
Email: takaoh@tc4.so-net.ne.jp