

ANSWERING REVIEWERS



Feb 22, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 8615-review.HIFU.WJG.Format for Answering Reviewers.doc).

Title: Safety trial of High-Intensity Focused Ultrasound (HIFU) therapy for pancreatic cancer

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

REVIEWER 1

The authors designed a case series of patients with unresectable pancreatic cancer treated by HIFU therapy to evaluate its safety and clinical output. They found no severe adverse events occurred and concluded that HIFU therapy is safe and has the potential to be a new method of combination therapy for PC. The study design is good and the manuscript is written in clear style. It still has some limitations:

1. Figure 3-5 cannot appear in the word file for unknown reason, so I can not see them.

A; I apologize you could not open the file. Please check the revise file again.

2. Some articles about the safety of unresectable pancreatic cancer treated by HIFU therapy has been published. Please discuss what is the new information from your study and compare your results with others' study results. If there are different, please analyze the reason.

A; This study was designed as the safety trial, and the sample size was calculated by a two-tailed test. Thirty patents were required for statistical evaluation of an adverse event. Therefore, this study was confirmed as the rigid statistical judging for safety of HIFU therapy for unresectable pancreatic cancer. This type paper is never seen before.

3. The adverse events were pseudocyst formation in 2 patients and development of mild pancreatitis in 1 patient. Please supply the treatment for the pseudocyst and pancreatitis and how patients recover. Did they have sytmptons and need interventions for the pseudocyst?

A; Answers are added in Results (Adverse events) section.

REVIEWER 2;

The manuscript describes clinical trials results from a pancreatic cancer treatment with high-intensity focused ultrasound (HIFU) trial. This is a timely and important topic, as HIFU applications continue to emerge, and their safety, efficacy, and applicability are being evaluated in a clinical setting. The manuscript is well written and should be published. To strengthen the manuscript, please address some remaining points, as described below:

p. 7: for the sake of completeness, also define WBC and PLT in the abbreviations section.

A; It was added in Abbreviations section.

p. 8: rephrase 'The focal path of ultrasonic waves can be secured' with: 'An adequate acoustic window for treatment is available'

A; 'The focal path of ultrasonic waves can be secured' was rephrased to 'An adequate acoustic window for treatment is available'.

p. 9: aperture and diameter are synonyms for a spherical array. Rephrase to: 'The aperture of the ultrasound array is 37 cm...'

A; 'aperture and diameter are synonyms for a spherical array' was rephrase to 'The aperture of the ultrasound array is 37 cm...'

p. 9: the input electric power is a useless parameter. For appeal to a larger reader audience, I suggest to also include a HIFU treatment clinically relevant treatment parameter, such as either the in-situ total acoustic power, the in-situ intensity (maximum, average, etc.), or the in- situ pressure. Please add this value.

A; Treatment dose was affected by the attenuation by the organization. An attenuation (α) was calculated with the thickness of the abdominal wall (t) and the distance with skin and target focus (DSF). The energy of the focus was calculated with an attenuation (α), electric power (W), pulse (P), transmit time (t1), intermission time (t2), and the distance of the treatment focus, and set it up in dose of 1000J. They were added in Methods section.

p. 10: please provide additional information on the treatment plan/execution. In particular, what pattern was the focal zone scanned over in order to treat/target the tumor (back-and-forth, inside-out, raster-scan, etc.). Also, please describe the tumor margin (if any) that was used during the treatment plan.

A; The treatment was planed and performed using a dot accumulation type, i.e. the line is formed by dots, the plane is formed by lines, the space is formed by planes. After a treatment area focused, an echo probe was scanned in accordance with the size of the tumor in front and back, in the right and left, and top and bottom, and the focal zone was set up in advance. The detailed parameters as followed: 1) the distance between dots was 0.2-0.3 cm; 2) the focal area was extended 1 cm out of the tumor boarder; 3) the distance between planes was 0.5-1.0 cm. The number of treatments per individual patient was dependent upon the size of tumor.

They were added in Methods section.

p. 11: Why were the patients not anesthetized? This is mentioned at several places in the manuscript, and should only be mentioned once. On p. 11, for example, this is (again) mentioned 2 times, in one sentence following the other, and is not needed. Are there literature references that the authors can point to that anesthesia is not needed for HIFU PC treatments? Patients undergoing other HIFU treatments (i.e. such as those for prostate cancer and uterine fibroids) are under anesthesia (partial or full) during the procedure. Please provide justification.

A; It is important that anesthesia is not needed for HIFU therapy. But it is not needed to repeat the same phrase. 'No patient received anesthesia or sedation' and 'and no anesthesia was given' in Results section were removed.

p. 12: As the authors mention, HIFU is distinctly different to hyperthermia. Thus, I suggest to remove the sentence: 'HIFU may be regarded...', as it is distracting and does not help with the clarity of the manuscript. Furthermore, change a follow up sentence to: 'HIFU can reach temperatures...'

A; I removed this sentence ('HIFU may be regarded...' and 'HIFU can reach temperatures...').

General comment to discussion section: this section focuses too much on describing HIFU, animal results, and the China study. It only in passing discusses and summarizes the results of the current

study, significantly weakening this manuscript. The authors need to strengthen this section, focusing the discussion on the results of the currently completed study, and demonstrating how it either strengthens or weakens the case for PC HIFU. I suggest to add statements similar to: 'The current study shows that ...'; 'The adverse events during this study are similar to...'; 'Treatment efficacy for the current study is comparable to/better than/etc. previous studies...'; 'Treatment parameters chosen for this study yielded adequate tumor recession without increased risk for detrimental bioeffects...', etc. for this purpose.

A; I rewrite the discussion section.

Figure 2 caption: '...energy at 150,000 times that of normal...' This statement is not helpful, as both imaging ultrasound intensities, as well as HIFU intensities can vary greatly. Remove.

A; 'The HIFU therapy system provides energy at 150,000 times that of normal US.' was removed from Figure 2 and Figure legend.

Figure 3 caption: 'Patented multi-element array technology ensures an even acoustic field.' This is a marketing/promotional statement, and should be removed from this scientific manuscript. Furthermore, there is no such thing as an 'even acoustic field.'

A; 'Patented multi-element array technology ensures an even acoustic field.' was removed from Figure 3 caption.

Figure 4 caption: replace 'echo jelly' with 'ultrasound gel'. Replace 'bombardment range' with 'target region'.

A; 'echo jelly' was replaced to 'ultrasound gel'. 'bombardment range' was replaced to 'target region'.

Figure 6 caption: replace 'shift of focus' with 'focus steering'. Replace '... focal point.' With '... is the target location of the focal point.' Replace: 'The echogenic region below the yellow mark is indicative of cavitation bubbles generated by the application of HIFU.'

A; 'shift of focus' was replaced to 'focus steering'. '... focal point.' was replaced to '... is the target location of the focal point.' 'The echogenic area below the yellow mark reflects the imaging of cavitation after HIFU.' was replaced to 'The echogenic region below the yellow mark is indicative of cavitation bubbles generated by the application of HIFU.'

REVIEWER 3;

This study evaluated the feasibility of High-Intensity Focused Ultrasound (HIFU) therapy for pancreatic cancer. The authors concluded that HIFU therapy was safe and had the potential to alternative therapy for pancreatic cancer. This was well written, but there were several points to be clarified.

Major comments

Abstract 1, "Background" is necessary. Please provide it.

A; "Background" was added in Abstract.

2, Continuous variable should be described as 'mean and standard deviation' or 'median and range'.

A; 'Mean and standard deviation' or 'median and range' was described in Abstract and results.

3, The primary end points of this study is not clear. Please provide it in the Abstract.

A; The primary end points were to evaluate the safety of HIFU therapy for pancreatic cancer and to establish HIFU therapeutic method for pancreatic cancer. They were described in Abstract.

4, What does 'complete tumor ablation' mean?

A; It means that tumor is ablated completely.

Patients and Methods 1, 'Aim' should be described in Introduction.

A; 'AIM' was moved from 'Patients and Methods' section.

2, Please provide the date of the end of this study.

A; It was added in Patients section.

3, In Patients section, what is other location? Does this mean other than pancreas? If it means the tumor other than pancreas, inclusion criteria is incorrect. Please provide it.

A; Other location means that residual pancreas after surgery. I changed 'Other location' to 'residual pancreas after surgery'.

4, In three patients who underwent operation as pre-HIFU-therapy, what is the target? Is it the local recurrence? Please provide it.

A; Yes, it is the local recurrence.

5, Please provide the definition of defective pain control.

A; It was added in 'Diffinition' section.

6, Please provide the baseline NRS pain score and CA19-9 value.

A; It was added in 'Diffinition' and 'Outcome' section.

7, In Inclusion criteria, what is radiological therapy?

A; It was modified as 'radiation therapy'.

8, In Inclusion criteria 4), please provide the period of waiting.

A; The period (4 weeks) was added in 'Inclusion Criteria' section.

9, How about the pancreatic cancer with liver metastasis? If excluded, please provide it.

A; Pancreatic cancer with liver metastasis is included. It was described in 'Patients' section, but it was added again in 'Inclusion criteria' section.

10, The primary outcome of this study was safety, so please describe the definition of adverse event more precisely.

A; The definition of adverse event was added in 'Definition' section.

Results 1, Continuous variable should be described as 'mean and standard deviation' or 'median and range'.

A; 'Mean and standard deviation' or 'median and range' was described in Abstract and results.

2, In Table 2, please provide the definition of complete tumor ablation.

A; It was added in 'Definition' section.

3, Please provide how to decide the number of procedure.

A; It was decided under the evaluation of the degree of tumor ablation every session.

4, Two patients underwent operation after HIFU therapy. Those were very interesting cases because the efficacy of HIFU therapy could be evaluated by surgical specimens, Please provide the pathological evaluation of them.

A; The aim of study is the safety of HIFU therapy and to establish of HIFU therapeutic method, so the result of operated specimen don't describe in this manuscript. But the specimen was fibrotic change and R0 resection was performed.

5, In therapeutic effects, what is primary lesion?

A; Primary lesion is not distance metastatic lesion but pancreatic mass lesion.

6, In clinical benefit rate, please provide the baseline pain, appetite, fatigue, sleep and weight. Also please provide those data after HIFU therapy.

A; Pain relief was based on NRS pain score. The baseline score of pain was 7~9 on the average before HIFU therapy. If there is more than a 30% improvement in pain relief it is considered effective. Moreover, other symptoms effect was based on the patient's declaration ('up' or 'down'). They was added in 'Outcome' and Table 3.

7. Please provide the tumor size after HIFU therapy. Also provide when the efficacy of HIFH was evaluated?

A; The tumor size before HIFU therapy is 31.7(\pm 1.7SD) mm. The tumor size after HIFU therapy is 30.9(\pm 1.7SD)mm. The efficacy of HIFU therapy was evaluated at once and every 3 months after HIFU therapy. It was added in Abstract, Outcomes, and Results section.

8, In Adverse events, please provide how to define severe adverse events.

A; Severe adverse event is which threatens life like death, urgent open surgery, and the hospitalization of one month and more. I added this phrase in 'Adverse events' section.

9, In Adverse events, please provide more precisely about 2 pseudocyst. When did it occur? How long? How about the management?

A; One case of pseudocyst was treated by medication conservatively to disappear. Another case of pseudocyst was 20 mm size and first observed for a while. But the pseudocyst was growing up and the patient complained the symptom of pressure after 3 months. Therefore, endoscopic drainage and stenting was performed. Mild pancreatitis case was treated by medication and recovered after about 2 weeks. The details were added in 'Adverse events' section.

10, In table 3, what is rate of usefulness of evaluation after HIFU using CE-US and/or CE/PET? Please provide it precisely.

A; It means that if which examination was useful in evaluating therapeutic effect by WHO criteria (CR,PR, SD, PD).

11, Is there any efficacy differences in accordance with body weight of patients? Obesity might affect the HIFU therapy.

A; Obesity influences the visualization of tumor, and when fat is thicker, the depth of the tumor from the surface becomes deep, and it is hard to focus. Therefore obesity influences HIFU therapy.

12, Please provide the CT image of the patients who get PR after HIFU therapy. Pre-HIFU and post-HIFU. It would be helpful for readers.

A; This paper is for the evaluation of safety of HIFU therapy. Therefore their imagings will be used for the next evaluation of therapeutic effect of HIFU therapy.

Minor comments

Abstract 1, The first sentence of 'RESULT' should be in the METHODS section.

A;The first sentence of 'Result' was cut and was arranged in 'Methods' section.

Patients and Methods 1, Please provide the number of the institutional IRB approval.

A; IRB number is 890. It was added in 'Patients and Methods' section.

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

Sincerely yours,



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