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315-321 Lockhart Road, Wan Chai, Hong Kong, China

ESPS Peer-review Report
Name of Journal: World Journal of Gastroenterology
ESPS Manuscript NO: 8615
Title: Safety trial of High-Intensity Focused Ultrasound (HIFU) therapy for pancreatic cancer
Reviewer code: 02462687
Science editor: Qi, Yuan
Date sent for review: 2013-12-31 19:34
Date reviewed: 2014-01-10 17:01

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[ ] Grade A: Priority Publishing	Google Search:	[ ] Accept
[ ] Grade B (Very good)	[ ] Grade B: minor language polishing	[ ] Existed	[ ] High priority for publication
[ ] Grade C (Good)	[Y] Grade C: a great deal of language polishing	[ ] No records	[ ]Rejection
[ ] Grade D (Fair)	[ ] Grade D: rejected	BPG Search:	[ ] Minor revision
[Y] Grade E (Poor)		[ ] Existed	[Y] Major revision
		[ ] No records	

COMMENTS TO AUTHORS

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. 2, Continuous variable should be described as 'mean and standard deviation' or 'median and range'. 3, The primary end points of this study is not clear. Please provide it in the Abstract. 4, What does 'complete tumor ablation' mean? Patients and Methods 1, 'Aim' should be described in Introduction. 2, Please provide the date of the end of this study. 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. 4, In three patients who underwent operation as pre-HIFU-therapy, what is the target? Is it the local recurrence? Please provide it. 5, Please provide the definition of defective pain control. 6, Please provide the baseline NRS pain score and CA19-9 value. 7, In Inclusion criteria, what is radiological therapy? 8, In Inclusion criteria 4), please provide the period of waiting. 9, How about the pancreatic cancer with liver metastasis? If excluded, please provide it. 10, The primary outcome of this study was safety, so please describe the definition of adverse event more precisely. Results 1, Continuous variable should be described as 'mean and standard deviation' or 'median and range'. 2, In Table 2, please provide the definition of complete tumor ablation. 3, Please provide how to decide the number of procedure. 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. 5, In therapeutic effects, what is primary lesion? 6,

In clinical benefit rate, please provide the baseline pain, appetite, fatigue, sleep and weight. Also please provide those data after HIFU therapy. 7. Please provide the tumor size after HIFU therapy. Also provide when the efficacy of HIFH was evaluated? 8, In Adverse events, please provide how to define severe adverse events. 9, In Adverse events, please provide more precisely about 2 pseudocyst. When did it occur? How long? How about the management? 10, In table 3, what is rate of usefulness of evaluation after HIFU using CE-US and/or CE/PET? Please provide it precisely. 11, Is there any efficacy differences in accordance with body weight of patients? Obesity might affect the 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. Minor comments Abstract 1, The first sentence of 'RESULT' should be in the METHODS section. Patients and Methods 1, Please provide the number of the institutional IRB approval.

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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[ ] Grade A: Priority Publishing	Google Search:	[ ] Accept
[ ] Grade B (Very good)	[Y] Grade B: minor language polishing	[ ] Existed	[ ] High priority for publication
[Y] Grade C (Good)	[ ] Grade C: a great deal of language polishing	[ ] No records	
[ ] Grade D (Fair)		BPG Search:	[ ]Rejection
[ ] Grade E (Poor)	[ ] Grade D: rejected	[ ] Existed	[Y] Minor revision
		[ ] No records	[ ] Major revision

COMMENTS TO AUTHORS

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. p. 8: rephrase 'The focal path of ultrasonic waves can be secured' with: '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…' 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. 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. 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. 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…' 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. 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. 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.' Figure 4 caption: replace 'echo jelly' with 'ultrasound gel'. Replace 'bombardment range' with '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.'

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COMMENTS TO AUTHORS

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 can not appear in the word file for unknown reason, so I can not see them. 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. 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?