

ESPS Peer-review Report

Name of Journal: World Journal of Gastroenterology

ESPS Manuscript NO: 9664

Title: Contrast-enhanced ultrasound (CEUS) combined with contrast-enhanced computed tomography (CE-CT) or magnetic resonance imaging (CE-MRI): improving accuracy of the diagnosis of hepatocellular carcinoma and guiding individual treatment

Reviewer code: 00503536

Science editor: Yuan Qi

Date sent for review: 2014-02-23 18:29

Date reviewed: 2014-03-03 20:40

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B (Very good)	<input checked="" type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input checked="" type="checkbox"/> Grade C (Good)	<input type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D (Fair)		BPG Search:	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)	<input type="checkbox"/> Grade D: rejected	<input type="checkbox"/> Existed	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

COMMENTS TO AUTHORS

The manuscript written by Zhang et al. analyzed the sensitivity, specificity, accuracy positive predictive value and negative predictive value of contrast-enhanced ultrasound (CEUS) combined with contrast-enhanced computed tomography (CE-CT) or magnetic resonance imaging (CE-MRI), and compared with those of other modalities. They found that CEUS combined with CE-CT/MRI improves accuracy of the diagnosis of hepatocellular carcinoma (HCC). The data are practically important and interesting, but there are some serious concerns that need to be addressed. Major points; 1.It is surprising that sensitivity of CE-CT/MRI for the diagnosis of both small and large HCC is too low (72-84%). According to our experience and other reports, HCC over 2cm in diameter is easy to be diagnosed by either CE-CT or CE-MRI, and sensitivity should be >95%. The authors should discuss or explain on that point. 2.It is quite reasonable that combination of the modalities shows higher sensitivity and accuracy than single modality as shown in this study. The authors should discuss why addition of CEUS to CE-CT/MRI improves the accuracy of HCC diagnosis in this study. 3.The authors should discuss on the cost-effectiveness of the examination (single or in combination). Do the author recommend the combination of CEUS with CE-CT/MRI as a routine surveillance in high risk patients? Minor points 1.Tables 4 and 5 are not organized ones and need to be revised. 2.There are some spelling mistakes.

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Title: Contrast-enhanced ultrasound (CEUS) combined with contrast-enhanced computed tomography (CE-CT) or magnetic resonance imaging (CE-MRI): improving accuracy of the diagnosis of hepatocellular carcinoma and guiding individual treatment

Reviewer code: 00183029

Science editor: Yuan Qi

Date sent for review: 2014-02-23 18:29

Date reviewed: 2014-03-10 07:43

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B (Very good)	<input type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C (Good)	<input checked="" type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input checked="" type="checkbox"/> Grade D (Fair)		BPG Search:	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)	<input type="checkbox"/> Grade D: rejected	<input type="checkbox"/> Existed	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

COMMENTS TO AUTHORS

In this prospective study, authors assessed the diagnostic efficacy and change in the therapeutic decision after adding contrast enhanced ultrasound (CEUS) to contrast enhanced CT or MRI for patients with hepatocellular carcinoma (HCC) undergoing hepatic resection. They concluded that CEUS combined with CT or MRI improves accuracy of the diagnosis of HCC and could be helpful to guide individual treatment for patients with HCC. However, the information presented is incomplete and expressed loosely. The study design does not appear adequate to prove the role of CEUS in HCC patients undergoing hepatic resection, which has been studied previously in several reports. To improve the reliability of this study, it is necessary to describe the methodology in detail, including the technical aspects. Comments: 1) In their study, CEUS was performed in 69 patients after CT or MRI evidence of focal liver lesions and under the diagnosis of HCC. To differentiate between malignant and benign liver lesions, their CEUS diagnostic efficacy was excellent, with 89.4% sensitivity, 97.0% specificity, 98.8% positive predictive value, 76.2% negative predictive value and 91.3% accuracy. The CEUS + CE-CT/MRI imaging modality had 100% positive predictive value in both tumor size < 5 cm and in tumor size > 5 cm, the diagnostic performance appeared much better than might be expected in clinical practice. Given the fact that the diagnostic accuracy of CEUS for HCC may be compromised by a high rate of operator- and machine-dependent variability, which calls for authors to explain how they standardized the procedures to achieve good results. There is no clear description on the techniques and the procedures how to obtain such a good diagnostic efficacy.

In addition, authors should explain why their CEUS accuracy, specificity, positive predictive value and negative predictive value for differentiation between malignant and benign liver lesions were better in tumors with diameter ≤ 5 cm than those with diameter > 5 cm. 2) This is a prospective study. Please describe methods of patient selection. Was a consecutive or random sample of patients enrolled? Is there inclusion or exclusion criteria? Were all patients included in the final analysis? 3) Authors should comment whether the conduct or interpretation of the CEUS findings have introduced bias? Were the CEUS and CE-CT/MRI imaging results interpreted and documented by experts before operation, most importantly, without knowledge of the results of the operative findings? 4) It is helpful if authors could present the clinicopathological features and preoperative liver function status of patients, including sex, age, interval between two images, liver function, Child-Pugh score, MELD score, tumor characteristics, alpha fetoprotein level, tumor size, tumor number, frequency of vascular invasion, and liver cirrhosis. 5) Intrahepatic peripheral cholangiocarcinoma (ICC) in cirrhosis patients may display a vascular pattern similar to HCC on CEUS, it has been reported that CEUS misdiagnosed ICC as HCC in 52% of cases, compared to 4.2 and 9.1% of CT and MRI respectively. Had any patients with ICC misdiagnosed as HCC preoperatively in the series? 6) Please illustrate the change of therapeutic decision in the decision-making process before and after adding CEUS in the imaging modalities for the patients. 7) There are many typographic and grammar errors in the manuscript.

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Title: Contrast-enhanced ultrasound (CEUS) combined with contrast-enhanced computed tomography (CE-CT) or magnetic resonance imaging (CE-MRI): improving accuracy of the diagnosis of hepatocellular carcinoma and guiding individual treatment

Reviewer code: 02753135

Science editor: Yuan Qi

Date sent for review: 2014-02-23 18:29

Date reviewed: 2014-04-23 20:51

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B (Very good)	<input checked="" type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input checked="" type="checkbox"/> Grade C (Good)	<input type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D (Fair)		BPG Search:	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)	<input type="checkbox"/> Grade D: rejected	<input type="checkbox"/> Existed	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

COMMENTS TO AUTHORS

Manuscript ; ESPS 9664:

Contrast-enhanced ultrasound combined with

CE-CT or CE-MRI: improving the accuracy of the diagnosis of hepatocellular ca. General comments:

- the work presented in this manuscript has clinical significance and benefit to the patients and the medical community at large. - The basic research approach is solid - The readability is unfortunately hampered by fairly poor English, and the word choice, grammar, and spelling are in need of improvement. Specific comments: Title: - seeing that all patients had a pre-op histological diagnosis, a more accurate reflection of the work presented in the paper would be to refer to staging, i.e. :improving staging of HCC..... Abstract: - again review the use of the word "diagnosis" - the paper basically deals with the value of CEUS prior to surgery. IOUS is done during all operations, so the surgical strategy changes due to IOUS are not really new. The basic question is; what is the potential for CEUS to change surgical strategies pre-op. - Follow-up should read Follow-up - Either the P value is stated as being < 0.05 or the exact value is given, no need for both General: - It would be considered standard to do both CT and MRI prior to surgery. In this study only 2 patients had both which is a bit surprising. Can the authors comment on this. - It would enhance the value of the paper if the authors can say which of the tests (CT or MRI independently) correlates best with the CEUS, and if a conclusion can be drawn for when both are not feasible. - Although all patients had surgery, how many would have had their management changed based on CEUS findings? - The study ended in October 2013, so only a very short follow up period is available. Are there any



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findings during the follow up period that confirm the benign nature of some of the lesions? - 4 patients had their surgical strategy changed; can the authors perhaps clarify in what way this was? Please refer also to the manuscript in which poor grammar is highlighted in green and paper content comments in yellow. Classification of the manuscript: I would classify this manuscript as a C
Language evaluation: B

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ESPS Manuscript NO: 9664

Title: Contrast-enhanced ultrasound (CEUS) combined with contrast-enhanced computed tomography (CE-CT) or magnetic resonance imaging (CE-MRI): improving accuracy of the diagnosis of hepatocellular carcinoma and guiding individual treatment

Reviewer code: 00070915

Science editor: Yuan Qi

Date sent for review: 2014-02-23 18:29

Date reviewed: 2014-05-05 01:54

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B (Very good)	<input type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C (Good)	<input type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D (Fair)	<input type="checkbox"/> Grade D: rejected	<input type="checkbox"/> Existed	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)		<input type="checkbox"/> No records	<input type="checkbox"/> Major revision

COMMENTS TO AUTHORS

This manuscript tests the accuracy of the combination of CEUS + CE CT/MRI for the preoperative diagnosis of HCC. I have the following comments: ? Title: the word “preoperative” should be added to the title before diagnosis of hepatocellular carcinoma... in order to differentiate from the intraoperative diagnosis provided by the IOUS which is analyzed in the paper. ? The results section of the abstract is too long. There is no need to present so many numbers in that section, just the main result points. In the same section the phrase: “To investigate the impact of tumor size... in diameter.” Should be in the methods section and not in the results. ? Several grammatical and spelling errors are found within the manuscript; the quality of English is marginally acceptable so the text requires further language editing. ? Table 5 presents nodules in L-group while in the text it is used to link to a table from the S-group paragraph. ? Tables 4 and 5 are unnecessary; they do not help in presenting the results clearly and descriptively. ? The way results are presented is confusing and requires extra effort from the reader to comprehend them. Tables (especially 4 & 5) do not contribute to that cause. ? Specific results numbers should not be repeated in Discussion section. Results needed to support key points in Discussion should be presented in a descriptive and concise way. ? The major advantage of the combination of CEUS+CE CT/MRI that is to improve the accuracy of diagnosis preoperatively was not thoroughly investigated. Instead of detecting the patients in whom treatment strategy was altered because of the use of the CEUS+CE CT/MRI, just the surgical strategy change because of the use of IOUS was investigated. The point stated by the authors that in only 5.7%



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surgical strategy was changed is just an indirect finding.