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Usefulness of contrast enhanced ultrasound in monitoring therapeutic response after hepatocellular carcinoma treatment

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Dear Editor,

please find attached the of the manuscript entitled: "*Usefulness of contrast enhanced ultrasound in monitoring therapeutic response after Hepatocellular Carcinoma treatment*".

We addressed all the concerns raised by the reviewers and changed accordingly in the main text. The changes, highlighted in the main text, are also described in the following paragraphs.

Reviewer-1

We thank the reviewer for raising critical points. We updated some of the references and we erased the paragraph that describes the anti-angiogenetic mechanism of Bevacizumab, highlighting the role of Sorafenib.

Reviewer-2

We thank the reviewer for the comments. We checked typos and misprints and polished English language. All abbreviations have been defined on first mention as required, both in the abstract and in the main text. Several drawbacks of CEUS are the same of conventional ultrasound and CEUS-specific drawbacks (such as differential diagnosis between inflammatory hyperemia and residual marginal tumor after ablative treatments) are described in the text. The section of CONCLUSION has been expanded.

Reviewer-3

Many thanks for the comments. We added in the main text that the usefulness of CEUS after cryoablation and irreversible electroporation was investigated only in few study which showed only preliminary and inconclusive results. Moreover we included references regarding conventional TACE by discussing a recent study on 130 HCC patients. Finally, the term "iper" was corrected with "hyper".

We hope that the manuscript in its current form could be of interest for publication in the prestigious *World Journal of Hepatology*.

Best Regards


Dr. Davide Roccarina

Dear Editor,

please, find attached the manuscript entitled: *“Usefulness of contrast enhanced ultrasound in monitoring therapeutic response after Hepatocellular Carcinoma treatment”*.

I addressed all the concerns raised by the Editor-in-Chief and changed in the main text accordingly. The changes, highlighted in the main text with different colours, are also described in the following paragraphs.

Above all, many thanks to the Editor-in-Chief for raising critical points.

I answered point-by-point the criticism and comments raised by reviewers. In particular:

- **Reviewer 1**

- the paragraph describing the anti-angiogenetic mechanism of Bevacizumab was erased and the role of Sorafenib highlighted in the first reviewing;
- references have been updated;
- After a revision of the literature I have changed the end of the paragraph “Long term follow-up” in which there were two too old references (ref. 16 and 28) and I have inserted an updated reference (World J Gastroenterol 2013 February 14; 19 (6): 797-801). In the paragraph “CEUS AND ABLATIVE TREATMENTS: RFA AND PEI” the reference 16 (Eur Radiol. 2007 Dec; 17 Suppl 6: F80-8) was used just to explain the contrastographic behavior of a HCC lesion after a complete and incomplete response to an ablative treatment. Anyway, it has been updated (Trop Gastroenterol, 2014 Jul-Sep;35(3):141-51).
- The statement, present in the “CONCLUSIONS”, that “CEUS is a promising imaging modality since provides both morphological and functional data associated with low cost and good safety profile...” is explained in different paragraphs of the main text. In particular the good safety profile and cost-effectiveness of CEUS, asserted by EFSUMB guidelines, are explained in the paragraphs “INTRODUCTION” and “HCC AND CEUS”. To clarify this point, in the statement of EFSUMB guidelines I have added “...as a cost-effective technique with a good safety profile...”. The cost-effectiveness of CEUS is an issue well demonstrated and known in the literature. Anyway, I have added at the end of the paragraph “HCC AND CEUS” the reference of a meta-analysis published in 2013 that demonstrated the cost-effectiveness of CEUS respect to CE-CT and CE-MRI.

The ability of CEUS in detecting morphological and functional data is explained in the paragraph “CEUS AND TUMOR RESPONSE”.

Moreover, I have changed, in the “CONCLUSIONS” paragraph, “CEUS is a promising imaging modality since provides both morphological and functional data associated with low cost and good safety profile...” with “Several studies demonstrated the usefulness of CEUS and D-CEUS in monitoring tumour response after HCC treatment. In fact, it is able to provide both morphological and functional data associated with low cost and good safety profile”.

- The statement, present in the “CONCLUSIONS”, that “CEUS performed within 1 hour after RFA or PEI with a correct timing scan seems to be reliable for the immediate post-treatment assessing, allowing an immediate retreatment during the same session” is explained in the paragraph “Immediate post-treatment assessment” of the main text by “In fact, when CEUS is carried out within 60 minutes after PEI or RFA...”. When we say that CEUS is performed immediately post-RFA we mean in the same RFA session. In fact, CEUS cannot be performed immediately after RFA procedure because of false-negative results due to gas production during the ablation. To avoid that at least 40 minutes should be waited. Anyway, I have modified the end of “Immediate post-treatment” paragraph changing “the role of CEUS in the immediate post-treatment assessment is to detect...” with “the role of CEUS performed within 60 minutes after treatment is to detect” and I have modified in the “CONCLUSIONS” paragraph “CEUS performed within 1 hour after...” with “CEUS performed within 60 minutes after...”.
- I corrected in the main text the reference of the statement “is characterised by only 40% of sensitivity in the detection of viable remnant tumour, due to false negative results. This high number of false negative cases could be related to the difficult interpretation of the images obtained immediately after the procedure”.
- **Reviewer 2**
 - I checked typos and misprints and polished English language.
 - All abbreviations have been defined on first mention as required, both in the abstract and in the main text.
 - Several drawbacks of CEUS are the same of conventional ultrasound and CEUS-specific drawbacks (such differential diagnosis between inflammatory hyperemia and residual marginal tumour after ablative treatments) are described in the text.
 - Clinical settings with an immediate post-treatment assessment not available may be those in which the software for CEUS is not available in the ultrasound machine used to perform the HCC ablation.
 - The useless of CEUS (and CE-CT) after one day is due to false-negatives because of the gas production into the lesion and the inflammatory hyperemia after treatment. However, both gas into the lesion and inflammatory hyperemia are reduced after one month. The useless of CEUS in long term follow-up is due to different factors as the short duration of the arterial phase that makes difficult to scan the whole liver or the intrinsic shortcomings of US technique (small lesion, unfavorable location, etc). These reasons are well explained in the main text, in the paragraphs “24-hours follow up” and “long term follow up” respectively.
 - The same reasons explain the different results of CEUS performed after TACE at different times.
 - The section of CONCLUSIONS was expanded during the first reviewing.
- **Reviewer 3:**

- I added in the main text (paragraph "CONCLUSIONS") that the usefulness of CEUS after cryoablation and irreversible electroporation was investigated only in few study which showed only preliminary and inconclusive results. Moreover, I included references regarding conventional TACE by discussing a recent study on 130 HCC patients. Finally, the term "iper" was corrected with "hyper".

Yours sincerely

Dr. Davide Roccarina