Author's response to reviews

Title: Radiofrequency Ablation of Liver Lesions: Quantitative Assessment of Treatment Completeness through CT Image Processing.

Authors:

Katia Passera (katiamarina.passera@marionegri.it)
Sabrina Selvaggi (sabrina.selvaggi@mail.polimi.it)
Davide Scaramuzza (davide.scaramuzza@istitutotumori.mi.it)
Francesco Garbagnati (francesco.garbagnati@istitutotumori.mi.it)
Daniele Vergnaghi (daniele.vergnaghi@istitutotumori.mi.it)
Luca Mainardi (luca.mainardi@biomed.polimi.it)

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Author's response to reviews: see over
Cover letter

Dear editor,

In the follow, a point-to-point response to reviewer concerns.

Reviewer: Christof M Sommer

Q1. I had the pleasure to re-review the manuscript entitled “Radiofrequency Ablation of Liver Lesions: Quantitative Assessment of Treatment Completeness through CT Imaging Processing” re-submitted to BMC Medical Imaging.

After detailed point-to-point-reply and implementations according to the reviewers, the work significantly improved. I thank the authors for their work.

Two major concerns remain from my point-of-view:

(I) tissue shrinkage occurring during thermal ablation was not adequately addressed (tissue shrinkage can be up to 30% in liver, which is relevant! (Brace CL, Diaz TA, Hinshaw JL, et al. (2010) Tissue contraction caused by radiofrequency and microwave ablation: a laboratory study in liver and lung. J VasclntervRadiol 21: 1280-1286) - the statement on P9 is not adequate, and needs revision with more detailed discussion: “coagulative local deformations were expected to be negligible”

(II) since your analysis identified incomplete tumor coverage by the RF ablation zones in almost all cases, and since (I), oncological follow-up imaging is mandatory (with potential identification of tumor growth) to confirm your results

(I) and (II) are major limitations.

A1. (I) We removed the sentence of P9 and discuss the issue in the discussion section (study limitations) adding the reference indicated by the reviewer: “In a recent study [25], it was found that RF and microwave ablation both cause significant contraction of normal bovine liver and lung tissue ex vivo. Ablation-induced contraction appears to be tissue type and ablation modality specific. This phenomenon should be studied in detail and modeled into the registration process.” 

(II) We don’t agree with the reviewer that the oncological follow-up imaging is mandatory. We explained and clearly stated in the paper that the purpose of this work was only to introduce a quantitative tool for the assessment of RFA treatment. We applied the method to only 10 lesions (5 HCC and 5 metastasis) that would be considered by clinicians very difficult cases with no other chance of alternative therapeutical approach. In this paper, we did not perform a clinical validation of the method since this type of validation would require a study designed for this aim, with a larger dataset grouped for type of lesions, in order to be statistically significant. In the article that reviewer referred to, it was reported that ablation effects appeared to be tissue type and ablation modality
specific, confirming the need to study the problem on a larger dataset grouped by lesion type.
In this paper, we performed only a validation of segmentation step, that is the main step of the image processing and we postpone to a further work the clinical validation. This is clearly stated in the discussion (Study limitations).

Q2. Title: “Treatment Completeness” might be not the perfect expression – consider “Tumor coverage”

A2. We followed the reviewer suggestion and we replaced “treatment completeness” with “tumor coverage” expression.

Q3. Abstract and Background: good

Methods: Please explain more detailed according to which criteria the RFA cases of this study were selected; please give numbers for RFA expertise (e.g. cases per year) and period for RFA cases used of this study;

A3. We add the required information into the text (selection criteria of RFA cases: 10 patients (5 men, 5 women; age range 40-86 years) treated with RFA as they were very complex cases not suitable for surgery, physician expertise: 70 RFA cases per year), RFA cases period: 2007).

Q4. P7, “The number of ...” – please give references, and comment – Do radiologists identify 7 different tissues on a liver CT image?

A4. The number of cluster is obtained after tuning of the method with different parameters setting. Since the previous sentence resulted to be not clear we removed it and leave the following sentence: “After tuning of the method, the number of cluster was set at 7.”

Q5. nomenclature: consider “tumor” and “coagulation” and “residual tumor” instead of “original lesion” and “Post-RFA lesion”, and use the identical terminology throughout the entire manuscript;

A5. Following the reviewer suggestion, we substituted throughout the entire manuscript (including title, figures and captions) “original lesion” with “tumor” and “post-RFA lesion” with “residual tumor”.

Q6. P7, “Lesions look rather compact ...” – ok for metastases, however in my clinical routine HCCs in arterial phase CT scans (at least for your size range) look either very homogeneous, or inhomogeneous not following vanishing concentric rings;

A6. The reviewer is right; metastases show a clearly concentric rings structure while HCCs result to have a different structure by a simple visual inspection. However, from a methodological point of view (considering fuzzy-C-means technique) HCCs have a similar pattern too, with a compact center and vanishing edges as shown in Figure 4.

Q7. I am not sure on the clinical importance of the O.I. – most tumors might be
classified as spherical (at least in your size range) making the orientation of the needle tract for thermal ablation procedures irrelevant (and consequently coagulation orientation which strongly correlates to the needle tract);

A7. We think that the O.I. index together with the other indexes (in particular inter-barycentric distance) gives a more comprehensive view of RFA tumor coverage. In particular, O.I. index could enhance if there are physical limitations to heat spread associated to the liver blood flow (heat loss due to convection) in a particular direction.

Q8. Results: P15 “As HCC is nourished ... reduction of thermal impedance ... heat diffusion ...” – first, please give reference for the thermal impedance point, and second comment on “portal blood flow”;

P15 “Thus, in this RFA-technique, our own hypothesis” – it is well-known that encapsulated tumors, like smaller HCCsand renal cell carcinomas (but not liver metastases), undergo the so-called “oven-effect” – this means you just need to bring enough energy (heat) into the oven, and then the tumor undergoes necrosis (irrelevant of needle configuration within the tumor (e.g. in case of multiple needle approaches)), this results in a coagulation zone almost identical with the extent of the original tumor, please delete ”our own hypothesis”, and discuss this issue (citations might be beneficial)

A8. We explained better into the text the points enhanced by the reviewer providing literature references. “It was demonstrated that a larger necrosis area can be created when RFA treatment is performed in HCC nodules after their arterial supply occlusion [22] [23] [24]. In fact, there is a different temperature distribution within and around the HCC nodule and this phenomenon seems related to the difference in vascularization between HCC and the surrounding cirrhotic hepatic tissue [23]. The latter has a dual blood supply and is nourished mainly by the portal vein, which provides about two-thirds of the blood flow. HCC, however, is nourished mainly by the hepatic artery, with the portal vein providing a minor blood supply and the main venous drainage. Therefore acute occlusion of arterial flow is soon followed by a decrease in pressure within the HCC nodule, which continues to be perfused by means of reversed portal flow and, in some cases, by small collateral arteries. Thus, although the blood flow supplying the HCC nodule is substantially impaired, changing from high to sluggish flow, the blood flow supplying the surrounding hepatic tissue is only marginally modified. This results in an almost complete lack of heat loss due to convection within the HCC nodule, whereas intact and perhaps even increased portal blood flow in the surrounding tissue acts as an efficient heat sink that prevents heat diffusion outside the HCC nodule [23]. Therefore, the resultant necrosis reproduces the shape of HCC nodules and spare surrounding non-tumor tissues, producing a really tiny T.F.M.”

Q9. Figures: Figure 2 and 3: language correction necessary

A9. We have corrected figures captions as indicated by the reviewer.
Reviewer: Gerlig Widmann

Q10. In their answer, the authors do not believe that the paper may benefit from the information of modified RECIST criteria. However, as TFM was extremely low in their series, necrosis as a lack of contrast enhancement and thus reduction of HU seems to be an essential index. Size of the necrosis may become important during follow-ups, because successful ablation necrosis will undergo continuous shrinkage. As the paper deals with a (semi-automated) quantification of treatment success, and as the above mentioned indices “could be easily computed on our images”, I am displeased that the authors did not feel that it is worth to include my comment in the discussion.

A10. We include the comment of the reviewer in the discussion section: “In this new study, we think to investigate other valuable indexes such as the largest axial diameter of tumor and necrosis and difference of the HU-units in order to provide possible surrogates for the modified RECIST criteria.”

Q11. The authors continue to focus on arterial supply occlusion plus RFA and answered that in their experience this approach gives better results than multi-electrode approaches. This is definitely wrong. The authors probably have limited experience with multi-electrode approaches. The generation of overlapping necrosis with large TFM is essential for successful RFA and the superiority of multi-electrode approaches such as SRFA is well published.

A11. The physician who performed RFA executed about 70 RFA treatments per year since 1988 and he is author of important scientific works on this argument. His opinion is that the approach used gives in his experience very good results.

Q12. The References of the manuscript are weak and the majority consists of books, theses and conference proceedings, rather than international peer-reviewed journals. A careful revision of the references including the actual literature on RFA is recommended.

A12. We reviewed the literature as suggested by the reviewer. We substituted references to books, thesis and conference proceedings with works published in international peer-reviewed journals and we added recent literature on RFA.