Author’s response to reviews

Title: Quantitative margin assessment of radiofrequency ablation of a solitary colorectal hepatic metastasis using MIRADA RTx on CT scans: a feasibility study

Authors:

Babs Sibinga Mulder (b.g.sibinga_mulder@lumc.nl)
Pim Hendriks (p.hendriks@lumc.nl)
Tarik Baetens (t.r.baetens@lumc.nl)
Arjen van Erkel (a.r.van_erkel@lumc.nl)
Carla van Rijswijk (c.s.p.van_rijswijk@lumc.nl)
R van der Meer (r.van_der_meer@lumc.nl)
Cornelis van de Velde (c.j.h.van_de_velde@lumc.nl)
Alexander Vahrmeijer (a.l.vahrmeijer@lumc.nl)
Sven Mieog (j.s.d.mieog@lumc.nl)
Mark Burgmans (m.c.burgmans@lumc.nl)

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Author’s response to reviews:

Dear Dr. Krüger,

Thank you for your careful and thoughtful review of our manuscript entitled “Quantitative margin assessment of radiofrequency ablation of a solitary colorectal hepatic metastasis using MIRADA RTx: a feasibility study” by Sibinga Mulder et al. We are pleased to provide the following point-by-point revision in response to the reviewer comments. Changes to the manuscript are marked using Track Changes.

Editor Comments:

Special attention is required for more detailed description of the Mirada RTX.

We added in the method section an additional paragraph explaining the Mirada RTX software. Line 145-162.
Reviewer reports:

Reviewer #1

Overall

- Important topic of which accurate knowledge is lacking
- Generally well written
- Should the word "CT" be mentioned in the title?

We added ‘on CT scans’ in the title.

Abstract

- Good description of background and aims
- Clear presentation of methods and results
- Conclusion can be formulated a bit more to the point

We changed the conclusion to: ‘Co-registration using MIRADA is reproducible and potentially a valuable tool in defining technical success. Feasibility of co-registration of pre- and post-ablation CT scans is suboptimal if scans are not acquired concordantly. Co-registration may potentially aid in the prediction of LR after percutaneous ablation.’ Line: 44-49.

Background

- Nice overview of the existing literature
- The importance of the need of accurate margin evaluation is highlighted
- A possible solution to the currently challenging co-registrations was explored

Thanks for the compliments.

Methods

- Patient selection is not completely clear. Of the 313 patients 284 were excluded (p6, line 40 50). However, the summation of 112 + 25 + 8 + 19 + 13 + 3 + 4 = 184 instead of 284. What happened to the other 100 patients?
We thank the reviewer for noticing this miscalculation, 100 patients had a pre-ablation MRI scan. We included: ‘a pre-ablation MRI scan (n=100)’ line 99-100.

- P6, line 49-60 can be deleted, multifocality was already mentioned as an exclusion criterion.

We deleted the sentence.

- P7, line 18: were there also ultrasound guided procedures (this is in contrast to the paragraph title)? If yes, how many?

We changed the title and added: ‘Percutaneous RFA was performed under general anesthesia under ultrasound guidance and in case of suboptimal ultrasonic guidance the procedure was performed with and/or CT guidance.’ Line 115-117

Furthermore, we added in the results: ‘Twenty tumors were ablated ultrasound guided, in nine patients the tumors could not be visualized with ultrasound, their ablation was performed CT guided.’ Line 220-221

- Full description of the CT parameters should be provided (p7, line 36-45), also from the pre RFA scan

We have added a supplementary table with the scanning protocol.

- Location of the metastases should be mentioned as it might be of influence on the success of co-registration

We thank the reviewer for the suggestion and added the segments in which the lesions were located in Table 1. Patient characteristics.

- P8, line 10: more info about the radiologists: years of experience, subspecialization etc

We added the requested information: ‘Three interventional radiologists specialized in RFA of the liver performed the RFA procedures and had at start of the inclusion period an experience of at least two years.’ Line 113-114. And ‘Two interventional radiologists of the LUMC staff, experienced in RFA of liver lesions,’ line 165.

- P8, line 16: more detailed description of the Mirada RTX should be given. This is very important as this is the system on which the whole article is based.

We agree, therefore, added in the method section an additional paragraph explaining the Mirada RTX software. Line 145-162.

- P8, line 16: "manual co-registration"; is this part of the semi-automatic system or is it not semi-automatic? Who performed this? Please explain.
Co-registration of the scans are manually performed by the interventional radiologists. Selecting and demarcating of the lesions is performed automatically. We have clarified this by mentioning the two steps: First (manual co-registration) and Secondly (automatic contour detection)

- P8, line 23-39: Grading system: did the score of both radiologist have to be 4 or 5 or was there a consensus reading? Please provide extra information.

We added: ‘by both radiologists’ line 179.

And: ‘In case the observers measured different margins for the same patient, resulting in a difference in category grouping, a consensus reading was applied.’ Line 193-195.

Furthermore we added: The average of the minimal obtained margin determined by both observers was compared to development of LR.’ Line 205-207.

In the results section we added the number of consensus and number in the final categories.

- P8, line 39: "manually altered if necessary"; how many times was this necessary and who did the alteration?

After automatic contour detection the radiologists checked whether the lesions were completely demarcated, otherwise they could change this. Therefore we added for clarification: ‘Secondly, the automatic contour detection was evaluated by the radiologist and manually altered in case contour detection was not considered to be inaccurate. Both delineations (tumor and ablation zone) were projected in one scan, resulting in an overlay of pre- and post-ablation CT scans.’ Line 182-185.

- P8, line 50: define complete margin

We added for clarification: ‘total encompassment of the tumor by the ablation zone; meaning that the tumor was inside the ablation zone, or without total encompassment of the tumor; meaning that the ablation zone did not cover the tumor completely,’ line 189-192.

- P8, line 52-55: please provide the number of patients for each category

We will provide the numbers of the patients in the results. We added: ‘In case the observers measured different margins for the same patient, a consensus reading was applied.’ Line 193-195.

Results

- P9, line 13: the numbers of co-registration grade 1-3 should be mentioned with explanations of the reasons for the low score as this is a main part of the conclusions of the article.
We agree with the reviewer that we should mention the explanation of suboptimal co-registration, therefore we added: ‘The cause for suboptimal co-registration (grade 1, 2 or 3) was the difference in liver position during the pre- and post-ablation scan. This could be due to a difference in position of the patient (diagnostics scans were acquired with the patient in a supine position, whereas some RFA procedures were performed with the patient in a left lateral position to allow a lateral intercostal approach) or because the scans were obtained during a different breathing phase (in- or expiration). In two of the excluded patients there were artefacts in the post-ablation scans, therefore co-registration was not possible (grade 1).’ Line 229-237.

- P9, line 13: grade 4 or 5; evaluated by which radiologist? Both or consensus or one of them?

We added: ‘Eventually, 10 patients were graded 4 and 8 patients were graded 5. In 8 patients consensus reading was performed.’ Line 236-237.

- P9, line 26-32: evaluated by which radiologist? Both or consensus or one of them?

We have added: ‘Eventually, 13 patients were in the ≤ 0mm group, six in the 1-5mm group, and two in the ≥ 5 mm group. In three a consensus reading was performed.’ Line 244-245.

- P10, line 26-32: provide the number of patients per category of ablation margin

As mentioned above we have added the number of patients per category.

Discussion

- Good overview of the current literature in relation to this study.

Thank you.

- More discussion is needed concerning the 11 patients who had an insufficient quality of co-registration.

We agree, therefore we have mentioned the reason for these suboptimal co-registrations in the results section as mentioned above. We added the following sentence to the discussion: ‘The reason for suboptimal co-registration in the remaining 11 patients is due to difference in liver position and/or shape.’ Line 266-267.

- P13, line 26-29: the mentioned number (mean 1 mm, range 0-6 mm) does not correlate with the number mentioned in the results section on p10: mean 2.2 ±1.9 mm; please explain.

In the discussion we mentioned the median with range. We thank the reviewer for highlighting that this may cause confusion. For consistency we replaced it with mean and SD (just like in the result section).
References

- Ok

Tables

- Additional mentioning of the lesion location is appreciated

We agree, therefore we have added the segments.

Figures

- Is it possible to provide us with a Figure of a real case?

The lower part of figure 1 gives an overview of a real case: the delineation of the tumors and ablation zones were demonstrated in transverse, sagittal and coronal slides.

We added an additional case: figure 2.

Reviewer #2

In this manuscript the authors evaluate the feasibility and reproducibility of CT-CT co-registration using the commercially available MIRADA RTx software to assess the minimal thickness of the ablative margins after RFA for colorectal metastases.

29 patients with a solitary metastasis measuring an average of 2.1 cm were included. Co-registration was considered good enough for analysis in 18 cases (61%).

Strength of the manuscript: important subject and potential simple method to assess ablative margin in clinical practice. The need for an adjunct to visual methods is evident and a simple approach ideal. The authors show that this may be possible with Mirada RTx.

Weakness: Insufficient information on the use of the software, how co-registration was performed and reason for failure, the relative value of visual versus quantitative assessment is not presented objectively, discrepancy between visual and co registration in this series needs to be reevaluated, superior accuracy of 3D images only without the co-registration could be explored.

Background:

- Line 21 : The need for 3-5 mm margin is supported by the literature.

We have added the suggested reference.

- Line 36: Assessment with co-registration is superior to qualitative visual assessment. It all depends on what type of visual assessment one is talking about as shown in Ref 5 and in 7. In ref 7 co-registration was not superior for experienced reader.

We thank the reviewer for the attention and added the following sentences: ‘Although, different results are obtained between experienced readers and less experienced readers. Quantitative assessment offers a more objective and reproducible method to evaluate technical success of ablation.[8]’ line 68-70.

Material and Methods:

- A description of the process of co-registration beyond saying Mirada was used, would be good. Was co-registration only manually done, was there any automatic phase? What are the evidence of the performance of the software in the liver? Describe what you did so that anyone with access to Mirada can do the same.

We have added an additional section in the methods describing the Mirada RTx Software.

For clarification: co-registration of the scans was manually performed by the interventional radiologists. Selecting and demarcating of the lesions is performed automatically. We have clarified this by mentioning the two steps: First (manual co-registration) and Secondly (automatic contour detection)

Furthermore, in the method section we describe that the co-registration of the pre- and post-ablation scans was performed manually based on venous structures and liver landmarks, which we supplemented with: ‘Landmarks were placed on bi- or trifurcation of the portal vein to co-register the pre- and post-ablation CT. At the start of the co-registration process landmarks were placed centrally. Then, peripheral landmarks were chosen that were located closer to the tumor.’. line 170-174.

- Completeness of ablation was judged on eyeballing? Doing what? Judging the centering of the defect in relation to the tumor? Looking only for enhancing or non-enhancing residual tumor at margins? What was the definition of completeness? No visible tumor at margin regardless of the centering of the defect?

We changed the visual assessment part to: ‘Visual assessment was performed by eye-ballling and two-dimensional measurements. Pre- and post-ablation CT scans were projected side-by-side on the computer screen. By scrolling up and down both scans the interventional radiologist assessed whether the ablation area was correctly located and was thought to fully encompass the tumor
with a margin of at least 5mm. Also, the post-ablation scan was assessed to rule out residual tumor enhancement. In addition to this, the distance was measured of the tumor and ablation zone to anatomical landmarks such as the liver edges and veins in order to confirm that the ablation zone was in a correct position and ablation margins were considered to be sufficient.’ Line 135-143.

We changed the definition of completeness for clarification:

After delineating both the tumor and the ablation zone these were projected in one slide. We added for clarification: ‘1) total encompassment of the tumor by the ablation zone; meaning that the tumor was inside the ablation zone, or without total encompassment of the tumor; meaning that the ablation zone did not cover the tumor completely,’ line 189-192.

The lower part of figure 1 gives a demonstration of how the projection looks in all (transverse, sagittal, coronal) slices.

Results:

- Would put the tumor size here not just in the S1.

We agree and have added this suggestion.

- Would also be interesting to impact of long delay between diagnostic scan and RFA, especially for those with a month delay.

We agree, this is mentioned in table 1 (patient characteristics). There was no significant difference between both groups.

Scoring:

- Need for more details on the reasons why co-registration was insufficient in 48 % of cases. You mentioned patient positioning in the discussion, was it the only reason? Bolus quality? Artifacts? Etc..

We agree with the reviewer that we should mention the explanation of suboptimal co-registration, therefore we added: ‘The cause for suboptimal co-registration (grade 1, 2 or 3) was the difference in liver position during the pre- and post-ablation scan. This could be due to a difference in position of the patient (diagnostics scans were acquired with the patient in a supine position, whereas some RFA procedures were performed with the patient in a left lateral position to allow a lateral intercostal approach) or because the scans were obtained during a different breathing phase (in- or expiration). In two of the excluded patients there were artefacts in the post-ablation scans, therefore co-registration was not possible (grade 1).’ Line 229-235.
- Need to define complete incomplete ablation. You say the extension of the tumor beyond the ablation zone was measured so it was visually accessible?

As mentioned above in the methods part, we have clarified this with: ‘1) total encompassment of the tumor by the ablation zone; meaning that the tumor was inside the ablation zone, or without total encompassment of the tumor; meaning that the ablation zone did not cover the tumor completely,’ line 189-192.

Local recurrence rate:

- Incomplete ablation could not be diagnosed visually in this series however you measured the tumor extension beyond the ablation zone that is a visual observation. I am also puzzled by the assumption that all RFA were complete and suspect that a more accurate way of visually judging quality of RFA would be to assess how well the defect was centered over the target. My inclination is to believe that co-registration helps but not that visual assessment is that unreliable that co-registration is needed to diagnose incomplete ablation. RFA defect could be classified as optimal (visually large margin) versus suboptimal (insufficient margin) rather than complete versus incomplete.

We agree with the reviewer that our definition of complete and incomplete ablation was too suggestive for a successful or unsuccessful procedure. Therefore we changed the nomenclature: ‘1) total encompassment of the tumor by the ablation zone; meaning that the tumor was inside the ablation zone, or without total encompassment of the tumor; meaning that the ablation zone did not cover the tumor completely,’ line 189-192.

Discussion

- The distinction between low risk and high risk of recurrence can be done visually at restaging as reported in the literature. In this series the immediate post procedure scan is used and the conclusion that co-registration is the only way to recognized incomplete ablation is not convincing for the following reasons:
  
  o the apparent weakness of the post procedure "eye balling". Residual tumour may not be visualized but centring of the defect is possible on immediate post RFA scan.

Indeed, we have projected the tumor in the post RFA scan with co-registration to optimize evaluation of ablation and correlate this to possible recurrence. According to the suggestion of the reviewer we changed the definition of complete and incomplete ablation (as mentioned above multiple times). And in the discussion we address this matter as follows: ‘Another explanation might be that we did not take possible tumor shrinkage into account during measurements of the ablation and tumor borders. Therefore, obtained margins may have been wider in reality than how they were assessed in this study on the direct post-procedural CE-CT.’ line 302-305.
Kim et al The difference in accuracy to measure ablation margin has nothing to do with fusion but with the 3D data, there are more data points than with 2D images and consequently the accuracy is increased. I would suggest to review the 3D images to assess the ablation margin visually and see when the fusion is the key to accuracy or if the 3D is, fusion makes it easier but is probably not the key.

We are of the opinion that 3D reconstruction without previous co-registration of the scans has no additional value because this makes it impossible to project the tumor and the ablation zone sufficiently in one scan. But, we are of the opinion that automatic evaluation of the co-registration and the ablation zones could improve the evaluation, therefore we added to the discussion: ‘Another feature that might increase the reliability of the Mirada RTx could be automatic evaluation of the delineated tumor and ablation zone. Since complete tumor ablation was in this study assessed by checking the projection of both borders in all scans visually.’ Line 312-315.

Park et al do not conclude inaccuracy of visual assessment but that the visual accuracy is related to experience. Fusion being better for inexperienced readers.

Indeed, we have mentioned this also in the background section.

- The gain of fusion compared to visual evaluation is probably in the simplification of the process, faster evaluation and adjunct for inexperience readers. The major gain in term of accuracy, I suspect, is the availability of 3D analysis of the ablative margin.

Indeed, and therefore in our discussion we clarify that this study was a feasibility study and has the potential to reduce local recurrence in future studies by immediate quantification of the ablation margins. Which is mentioned in our conclusion.

Conclusion: ok

Illustration:

- Would like to see an illustration of measurement.

We added an additional case: Figure 2.

We thank the reviewers for the suggestions, which have strengthened the manuscript considerably. We thank you again for the possibility to submit a revised manuscript. Please do not hesitate to contact me if you have any further questions or comments.

Sincerely,