

Manuscript ID: 21175

We would like to thank the editor and the reviewers for their compliments and for pointing out that the paper is interesting. Their insightful and very useful comments helped us to create an improved manuscript. For clarity, we have adopted the following annotations: e.g., R1-1 indicates the response to comment #1 of reviewer 1. Page numbers refer to the pages of the annotated manuscript.

Reviewer 1 (03364027)

This paper describes a study to assess the treatment response in patients with head and neck squamous cell carcinoma (HNSCC) using quantitative texture metrics of energy (E) and homogeneity (H). The authors observed that the heterogeneity of the tumors has been reduced after the treatment and the texture biomarkers can be used to evaluate the treatment response. Overall, the paper is well written and relative easy to follow.

R1-1: However, there are several issues that need to be addressed. Firstly and probably the most importantly, as the authors mention in the paper, the study had a really small cohort of patients. This makes the conclusion of the statistical analysis rather weak. This is most problematic for the locoregional failure (LF) group with only 2 patients. In this case, the statistical analysis for LF patients is not really valuable. I recommend the author to either recruit more LF patients or remove the statistical analysis that involves LF patients.

Answer: We agree with the reviewer that the statistical power of the analysis incorporating the 2 LF patients is less ideal, and we have therefore removed it from the focus of the manuscript by deleting all referrals to the analysis regarding the comparison LC versus LF from the abstract, the summarizing statement in the discussion and the conclusion. As we do think the comparison is still of relevance for this pilot study (as it illustrates the potential of the texture method), we decided to leave the sections in the main text describing this comparison intact.

R1-2: Secondly, please provide more details of the DCE-MRI acquisition. Specify the acquisition parameters, such as, field of view, image size, bandwidth, number of slices, slice thickness, etc, so that the readers can replicate the acquisition.

Answer: We have now added the requested details to the materials and methods section.

R1-3: Thirdly, similar to Figure 1, it will be helpful to show another example with locoregional control before and after the treatment. It will also be very helpful to indicate the energy and homogeneity values of the ktrans and ve map for both figures. That will give the readers a better understanding of the proposed texture metrics.

Answer: As per reviewer's request for R1-1, we do not want to focus on the difference between LC and LF anymore. Therefore, adding a figure of a patient with LC would only confuse the

reader, in our humble opinion. The purpose of Figure 1 is to provide an example of the acquired images, the quality and the calculated metrics, for which 1 patient is sufficient. However, we do like the idea to provide the numeric texture values of the images, which we have now added to the figure legend.

Reviewer 2 (02667199)

This manuscript evaluated the merits of parameters, energy (E) of v_e and H, on parametric maps derived from pharmacokinetic modeling with DCE-MRI as imaging biomarkers for the prediction of treatment response in patients with head and neck squamous cell carcinoma. The results revealed that the imaging biomarker energy (E) of v_e was significantly higher in intra-treatment scans, relative to pretreatment scans, while no significant changes were found for the mean and standard deviation for K_{trans} and v_e . These results were very exciting and might be helpful in evaluation of early treatment response to chemo-radiation therapy.

R2-1: General questions “All patients had chemo-radiation treatment” in methods was not accurate, since methods in the section of materials and methods described “All patients were treated with intensity-modulated radiation therapy with dose prescriptions of 70 Gy for gross disease, 59.4 Gy for high-risk regions, and 50 to 54 Gy for low-risk regions”. Chemotherapy was not administered for all patients according to . Therefore, chemo-radiation treatment should be replaced with radiation therapy in the sections of abstract, materials, results, and conclusion.

Answer: *Radiation therapy is always given in combination with chemotherapy (bevacizumab, cetuximab, and cisplatin). This has been added to the manuscript.*

R2-2: Abstract Results were too simple. Results There was no unit for K_{trans} and v_e , E, and H value.

Answer: *We have updated the abstract and the results section of the manuscript. It is important to note that parameters E and H do not have a unit.*

Comments for the editor:

We have updated the manuscript, and applied all changes as requested in the editorial comments. All changes are marked in yellow, and deleted sentences are marked with ~~strikeout~~.