Reviewer’s report

Title: Development and validation of a novel MR imaging predictor of response to induction chemotherapy in locoregionally advanced nasopharyngeal cancer: a randomized controlled trial substudy (NCT01245959)

Version: 0 Date: 16 Apr 2019

Reviewer: Charlotte Robert

Reviewer's report:

This paper proposes a radiomics score deduced from pre-treatment MR images to predict treatment outcome to additional induction of chemotherapy in loco-regionally advanced nasopharyngeal carcinoma. The study is based on two large cohorts. The first one is retrospective and includes 254 patients and the second is prospective and part of a randomized clinical trial. The radiomics score, named ICTOS for Induction Chemotherapy Outcome Score, is composed of three histogram-based and textural features extracted from enhanced-T1 MRI. Results are promising in both cohorts. In the validation cohort, high ICTOS score patients have a 5-year failure-free survival of 89.7% for ICT + CCRT compared to 50.3% for CCRT alone. My main concerns are about MR images pre-treatment and radiomics features extraction.

- MR images were acquired using 8 different devices and 3 magnetic fields. Some details are given in Supplemental data 3 about MR images normalization. Why was this simple method used instead of more popular ones (zero mean-unit variance, histogram matching…)? How did the authors check the validity of the used normalization method?
- A home-made software has been used for feature extraction. Public software should be preferred in radiomics studies for reproduction by external teams. Have the authors compared the validity of their feature formulas with the IBSI reference formula (https://arxiv.org/abs/1612.07003)?
- Authors should add references in Appendix 3 as different definitions can exist for a same feature name.
- In the feature description, it is not clear if 2D or 3D textural features were extracted. Can the authors give more precision on the feature extraction methodology? If I am not wrong, 2D shape and texture features only have been extracted. Why this choice? Can the authors comment on that?
- Which discretization method was used for feature extraction? Can the authors precise the bin size that was selected and its impact on the radiomics feature value and on the clinical results?
- Figure 1 should be improved and include details regarding image pre-processing, feature selection and model construction

Formal statistical review would be beneficial to evaluate the statistical methodology

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.
No

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Yes

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

Yes

**Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?**
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