**Reviewer’s report**

**Title:** Have we achieved adequate recommendations for target volume definitions in anal cancer? A PET-imaging based patterns of failure analysis in the context of established contouring guidelines

**Version:** 0  **Date:** 18 May 2019

**Reviewer:** Julian Rogasch

**Reviewer's report:**

The authors present interesting and clinically relevant data on the appropriateness or failure of guidelines on CTV definition for RCT in AC. The methodological description, presentation of results and the extent of discussion is generally appropriate. Especially the visual depiction of LNs in Figures 1 and 2 is appreciated.

My concerns and remarks:

**General:**

I recommend a thorough review of the manuscript regarding specifics of the English grammar (e.g. the correct use of hyphens in words such as "PET-imaging").

In the discussion, I would prefer a less colloquial and/or imprecise language (e.g. page 16, line 44: "In our study we had quite a high number of superomedial [...]"").

**Background:**

Page 6, line 54: Please specify what is meant by "patterns of spread". Is it the spread to LN?

Page 6, line 54: "(CT or MRI)": Please use PET-CT or PET-MRI instead to prevent confusion with the stand-alone imaging modalities CT and MRI.

**Methods:**

Page 8, line 5: Please use the term PET-CT and PET-MRI instead of "CT or MRI based" throughout the manuscript.
Although I understand that the PET imaging protocol is not a central part of the manuscript, a minimal description should be added (injected FDG activity in MBq [with median and range or IQR], interval between injection and start of PET acquisition ["uptake time"], and the examined field [e.g. base of skull to proximal femora, …]).

22 patients were included into final analysis, but $18 + 5 = 23$ examinations were performed with PET-CT or PET-MRI. Please check or briefly explain the discrepancy in examination/patient counts.

Please correct the typo in "AGIGT"

I recommend rewriting this paragraph to make it readily understandable. More specifically, the reader should be able to answer the following questions:

a) Was each patient and each CTV in all patients delineated by each radiation oncologist? Or were different patients/CTV delineated by different readers? Were all three CTV in a specific patient delineated by the same reader?

b) What was the purpose of the template patient? Was it to ensure "training" of the radiation oncologists to ensure uniform understanding of the anatomical regions?

Please consider using table 1 instead of 2 as the reference for the 154 LNs.

Results:

Please explain that "(14/7/5)" refers to the three different guidelines, e.g. "(RTOG: 14; AGITG: 7; BNG: 5)".

In the context of logistic regression (or other methods that are not "true" correlation methods), I recommend avoiding the term "correlation" not to confuse two different statistical methods. Please consider terms like "association" or "relationship". Generally, I recommend reconsidering the choice of statistical method. As I understand, the authors aim at evaluating merely the association between a single clinical variable (e.g. T stage) and the LNs being inside or outside of the CTV. The combination of several factors in one model (e.g. T stage and grading) appears dispensable. For this purpose, a chi square test applied to each clinical variable separately should be the appropriate (and simpler) test. A logistic regression would only be necessary if the aim was to test and model the predictive significance of several variables (T stage, grading, ...) in a combined model. However, this would imply a more differentiated description of the model (choice of independent variables) in the methods section, a more complex description of the results (overall accuracy of the model, details on the regression coefficients of the variables) and a different terminology in the results description ("prediction" instead of "association"/"relationship"). Furthermore, considering the limited sample size and
limited selection of independent variables (only T stage and grading!?, the reliability and power of a method such as a binary logistic regression seems generally questionable.

Discussion:

Page 17, line 1: Please correct the typo in "leed"

Page 18, line 26: For a reader who is not experienced in radiation oncology, it may be difficult to understand the concept of transferring the "positive LNs of 22 patients on one patients' planning CT scan", especially if this appears to result in distortion of anatomical marks. In analogy to my initial remark, I recommend describing the benefit or aim of the one patient's planning CT in the framework of the current study (especially considering that some readers may be inexperienced in radiation oncology).

"Limitations" paragraph: I agree with the authors that the detected LNs and the misses have to be interpreted considering the overall tumor spread (and thus M0 / M1 situation and risk for further LN metastases). However, I recommend specifying or clarifying the discussion on two issues:

a) What is the guidelines' general application of "elective" CTV? What is the clinical framework (e.g. cT and cN stage) that implies the appropriateness of an elective CTV instead of an individually confined / extended CTV?

b) To which degree do all 22 patients in the current study and, more importantly, the patients with LN misses, comply with the guidelines' framework of an "elective" CTV use? This could include a brief statement on the in-/exclusion criteria (patients with common iliac or para-aortic LN were not excluded).

Page 18, line 28: Please correct the typo in "seize"

Are the methods appropriate and well described?  
If not, please specify what is required in your comments to the authors.

Yes

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?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

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Please indicate the quality of language in the manuscript:

Needs some language corrections before being published

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