Author's response to reviews

Title: Radiation therapy of anal canal cancer: from conformal therapy to volumetric modulated arc therapy.

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Author's response to reviews: see over
1st Reviewer’s report
1) In the section “Method” (pag. 4) erroneously you have reported reference number 13, while this was omitted in the section “Reference”, please correct.

We thank the referee for the suggestion. We fixed it.

2nd Reviewer’s report
1. The authors need to give precise definitions for the terms used for radiotherapy techniques, and be consistent in the use. Definitions are needed for the terms such as volumetric modulated arc therapy (VMAT), and Rapid Arc (RA), conformal radiotherapy (CRT), simultaneous integrated boost (SIB), IMRT. The characteristics of these techniques, or how they differ, should be briefly explained. Furthermore, later in the manuscript, a new abbreviation occurs, concurrent CT-RT, which is an unusual abbreviation and should be defined. An abbreviation CT is probably meant to be chemotherapy, but is not defined. We tried to consolidate the list of definitions and added some short clarification in the background about the differences between CRT and VMAT. CT stands for computed tomography and we tried to separate the symbol from chemotherapy (CH). We nevertheless believe that within the frame of a scientific article it is impossible to provide all the conceptual background for all elements, in this case for all the radiotherapy elements. For this reason we tried to comply with the request but also to limit as much as possible the details in order to keep the focus on the study.

2. Abstract: It is stated that RA treatments lead to lower incidence of higher grade events. I presume this refers to toxicity, but it should be stated clearly. The toxicity reporting must be rewritten. Since these are two patient series, one can not state that toxicity was "reduced of 20\% for GI" etc, one must report the differences in toxicity occurring between the two series. Furthermore, the authors should report how toxicity was graded, whether it was recorded prospectively or retrieved from medical charts, the time-frame, etc. We tried to modify the abstract section as requested. Acute toxicity data are now provided for the two cohorts without mentioning the differences that can be derived automatically by the readers.

3. In general: The manuscript should be edited by an author fluent in English, to reduce the number of grammatical errors in the present manuscript. The first sentence on page 3 "Patients in the CRT cohort, ..." is an example of poor grammar, and difficult to understand. We tried to review and improve the English at our best.

4. Methods: The delineation of the GTV, the two CTVs, and the PTV, could be explained more clearly. Also, how were positive lymph nodes handled, and which doses were prescribed to the different volumes.
The definition of GTV, CTV and PTV have been revised and improved in the new version of the manuscript. An isotropic CTV-PTV margin of 10mm was applied to expand the CTVs. The GTV was as identified in the staging images and the CTV (the boost one for the primary tumor and the pelvic CTV for the nodal region) were defined as described.

The positive nodes, if any, were included in the CTV_boost

The dose prescriptions, depending upon the technique, have been defined in the CRT and VMAT sections.

5. The chemotherapy regimens used must be described and discussed, in the methods or results section, since this may have impact on the treatment results and the toxicity. Please also define the chemotherapy abbreviations later used (such as MMC, CDDP).
We better described the chemotherapy regimens and abbreviations used.

6. Further details of the scoring of acute and late toxicities should be provided. Was the scoring systematic and prospective, weekly, or retrieved retrospectively as "worst toxicity reported". Was toxicity scored at all follow-up visits?
We clarified this aspect in the revised manuscript.

7. In Table 1, there is a large difference in the chemotherapy regimens used. 57% of patients in the CRT group had FU/CDDP, compared to 5.5% of patients in the RA group (where 80.5% had FU/MMC. This must be discussed, since CDDP has been shown in randomised trials to produce more toxicity than MMC.
Both the Long-Term Update of RTOG 98-11 Phase III (2012) and the ACT II trial (2013) showed that toxic effects during chemo-radiation were much the same in the mitomycin and cisplatin treatment groups. Grade 3-4 hematologic toxicity was more common in the mitomycin group. The rate of acute non-hematologic grade 3 or 4 toxicity was 74% in both groups according to the RTOG trial. We discussed this in the revised text.
In our work we only report gastrointestinal, genitourinary and dermatological toxicity, for this reason in the text we didn’t quote toxicity according to chemotherapy regimen.

8. Please comment the finding of Table 2 in the text. It seems to be favourable for bladder, bowel, femoral heads in the RA group. The same applies to figure 1.
We tried to improve and expand the comments on the findings of table 2 and figure 1.

9. Please also provide the statistical significance test and value.
In table 2, the values found to be significant with a \( p<0.05 \) have originally marked with a *. We have now reported the \( p \) values from the independent samples non-parametric tests.

10. Please provide the number who obtained complete response after chemoradiotherapy, and the number who needed surgery such as APR. These are significant outcomes and should be reported.
We added more information about the pathological response in the Results paragraph.
11. Figure 2 can be omitted, as it does not provide necessary information. If this type of figure should be included it should show the different dose distributions obtained by CRT and RA techniques. 
Removed as requested

12. The paragraph on survival and local control should be structured better, to improve readability. Details of individual patients should be omitted. 
We tried to improve the paragraph as required
We have decided to keep the details on the individual failures but in a reduced form.

13. Table 3 should include p-values. 
We have now added the independent samples mann-whitney U test results showing that the various toxicity profiles are the same between the two categories

14. Discussion: It is stated that the treatment is based on four RCTs; why these four, whereof only 1 (Ajani) is recent, and why is not ACT II referred to (James RD, 2013). 
We better introduced the Discussion and added the ACT II trial to the references.

15. What is Al-Sarraf chemotherapy? And what is Nigro regimen? 
We better clarified in the revised text