Author’s response to reviews

Title: Focal dose escalation using FDG-PET-guided intensity-modulated radiation therapy boost for postoperative local recurrent rectal cancer: a planning study with comparison of DVH and NTCP

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Author's response to reviews: see over
Dear professor Melissa Norton

Thank you for an opportunity to revise our manuscript. We answer for reviewers' comments as follows point by point. The revised manuscript was reviewed and approved by all authors. I would like to ask you to consider again our manuscript for publication in BMC Cancer as an original research article.

Sincerely,


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To Professor Giuseppe Sanguineti

Major Compulsory Revisions

Other points I have major concerns on are represented by the overall strategy. I do not understand why boosting after 40 Gy. Is 40 Gy considered sufficient on a recurrent (*and therefore) aggressive disease even if microscopic? Traditionally 45-50 Gy are considered the `dose` needed to sterilize microscopic-previously untreated disease (adenocarcinoma: breast, prostate, rectum…); here we are in the setting of recurrent disease, with a higher locoregional aggressiveness…. Do the Authors have data to support it? What is the reason to underdose a RT-naïve field?

We did not think that only 40 Gy could suppress even microscopic lesion;
however, we also consider that 60 Gy or less is not sufficient for macroscopic lesion. Therefore, we usually irradiate 60 Gy (or more) for only significant lesions without a prevention irradiation for regional lymph nodes in patients with local recurrent rectal cancer. Also in this study, we decided to perform irradiation for only macroscopic lesions in order to prevent intestinal complications.

At some point (page 14) the Authors state that `there was a significant difference between GTV2 and BTV` or between the residual GTV as identified on the CT and the one uptaking FDG (SUV>2). Which is the difference between these volume and their respective ones before treatment? In other words, how much 40 Gy helped to shrink or `inactivate` the original failure?

Thank you for your important comment. I agree your opinion, thus, I added the sentences about the difference between GTV and GTV2, and I wrote GTV (ml) of each patient in Table 1. There is no significant difference between GTV and GTV2. This means that gross tumor in CT could not be reduced by 40 Gy.

Moreover, why using a sophisticated approach (IMRT) for only a portion of treatment and after the tolerance of some structures may have been `drastically` reduced with upfront 3DCRT? (the use of the term dose painting is misleading since IMRT, de facto, is always used in the present paper as a sequential plan after initial 3DCRT….). It would be interesting to have a plan that explores the use of IMRT from the beginning. There is no doubt that the success of organ sparing in this setting is dictated mostly by the location of the failure (as the Authors discuss). However, there is very limited information on this. Surely, IMRT from the beginning of radiotherapy might be able to improve the dose-distribution. However, because we did not know before this study even how much GTV and BTV of recurrent rectal cancer shrink with 40 Gy and because we hoped to make the dose-escalation to only the region with radio-resistance, we used IMRT with dose-painting after conventional therapy.

I would suggest that they breakdown their results by tumor location (local, regional, presacral….). Please note that also the clinical (tumor volume definition) and physical (tumor movement) are likely to be influenced by tumor location and
thus a `general` definition of GTV/CTV may not apply and should be discussed as well: for example, I would expect a presacral failure to be at higher risk of subclinical spread (along the nerves) and thus require a larger margin around and at the same time `stuck` to the sacrum compared to an anastomotic failure that may be less prone to local spread but at the same time more mobile. This is a very heterogeneous clinical setting where also the timing of detection of the failure would have implications and strict standard rules may not always apply. You are right, I think. We hope the dose-distributions of each recurrent location in more detail, not only dividing lateral pelvic lymph node metastasis or perineum recurrence and presacral or anastomostic recurrence. But, there were small number of patients enrolled into this study, therefore I could not show in more detail. The least we can do is showing in Table1 the recurrent location of each patient. We will analyze the failure pattern after radiotherapy in each location to show appropriate margin.

Minor Essential Revisions
Other points:
1. It look like the initial 40 Gy were delivered throughout a `common` 3DCRT approach. More details are needed on this (field arrangement, energy….); Thank you for your comment. I added sentences about the energy and the number of ports in Materials and Methods.

2. How much is equivalent the dose of 26 Gy delivered at 2.6 Gy per fraction supposed to equivalent to when delivered at 2 Gy per fraction on the tumor? In other words, the Authors need to provide the reader an idea on how much they are pushing the dose the tumor. Once this estimate is done, they should also hypothesize and discuss what to expect in terms of locoregional tumor control based on the available literature; Thank you for your comment. I added the sentences as follow in Materials and Methods. “(total D95 of PTV-PET >66 Gy, which means normalized 2-Gy-equivalent biologically effective dose, 67.3 Gy, calculated using an alpha/beta value of 10)”.

3. When they define a Dmax they should also specify how many cc of the structure are considered; 

**They meant really Dmax. If D1cc, there might be no significant differences among summed plans.**

4. As metric for toxicity they select the small bowel and V50. Other organs can be at risk of tox, depending on the location of the failure. The bladder, the rest of the rectum.... A more comprehensive evaluation of toxicity is desirable; I agree with your comments. However, in this study, we investigated the dose-distribution of only small bowel, because small bowel is the weakest organ for radiation.

Moreover, I am not sure that small bowel tox can be expressed only by V50. There are also reports on a lower dose level to be potentially important as well. I would suggest looking at a series of dose points, V50, V40 and V30...

**I see. I showed V30 and V40 in Table 1 and Results.**

5. They should provide data to support the idea that locoregional failures (as opposed to primary tumors) are less prone to `large inter and intra-fraction motions because of adhesions due to the operation` as stated at page 16; **Unfortunately, we have no data to show appropriate margin in local recurrent, and we could not find out reports about such data.** As I had already written in Discussion, it is necessary to investigate such misalignment using on-line imaging (e.g., cone-beam CT) before clinical application.

6. The limitations of PET/CT during RT are discussed extensively and satisfactorily. I am still not fully convinced on the opportunity/appropriateness to scan patients during treatment. More data are needed to support this strategy. **You are right. We also do not understand clearly whether it is appropriate to perform FDG-PET during or soon after radiotherapy.** However, recently, review of FDG-PET for rectal cancer was published, in which described the timing of FDG-PET after radiotherapy. Thus, I added the review as a reference.

31) de Geus-Oei LF, Vriens D, van Laarhoven HW, et al. Monitoring and predicting response to therapy with 18F-FDG PET in colorectal cancer: a

Thank you for your reviewing of our manuscript.
Major Compulsory Revisions

- Page 10: You summed two dose distributions based on different CT data sets. Consequently, I expect to be your soft-tissue organs-at-risk at different positions, especially the small bowel. Consequently, a summation of the dose distributions without deformable image registrations is NOT possible. You either use deformable image registration for summation of treatment plans or report dose distributions of the boost plans, only.

Yes, that’s true. We made irradiation fields on boost RTP-CT (/PET) using DRR, which were same size, same shape of MLC and same MU as initial irradiation fields. Therefore, the NTCP of small bowel may be lower than those results due to peristalsis. However, because this study is absolutely a planning study, those results were considered to be helpful for readers to show that focal-dose escalation did not increase the probability of complication.

- Page 15: you report a smaller NTCP for small bowel toxicity by the use of dose painting compared to IMRT, only. This is very hard to understand In summed plans 2 and 3, you used IMRT planning, the difference is an integrated boost in summed plan 3 with a dose escalation of 30% -> I do not understand how an ADDITIONAL integrated boost could DECREASE the NTCP (all dose parameters in table 2 show higher doses for summed plan 2 compared to summed plan 3).

I am extremely sorry about that. We made an important mistake. We miswrote the NTCP of summed plan with dose-painting and that of without dose-painting. We replaced each other and revised the results and discussions a little. But the conclusions were not changed. Thank you again for your point-out.

- Neoadjuvant radiochemotherapy is the standard for rectal cancer UICC stage > I. This has been shown be a significant number of randomized trials. It should be made more clearly that most of the patients with rectal cancer in current days have been treated with radiotherapy at primary treatment, which would not allow a treatment as described in this article.

Surely, we know it. But, in Japan and Asia, the extended surgery alone is a
gold-standard method. And, based on SEER, over 30% of patients with advanced-stage rectal cancer in the United States also did not undergo radiation therapy. We showed such information in Introduction.


Minor Essential Revisions

• Page 8: “Residual abnormal shadows in CT images after 40 Gy were defined as GTV2” please explain more in detail.

We re-wrote there. “Residual gross extent of the tumor shown in CT images at 40 Gy was defined as GTV2”.

• Page 9: you used an IMRT objective of “maximum dose to small bowel <20Gy. This sounds strange considering that the prescribed dose is 20Gy and you treated patients with 40Gy before the boost. That could end up with a maximum dose of 60Gy – the total dose!

I see. We added the information of total irradiation dose as inverse planning objectives in Materials and Methods.

• Page 9: you did not use any ring shaped help volumes for inverse planning or any objectives for the small bowel?

No, we did not use such methods in any IMRT plan. And I had already written in Discussion about it. When PTV-PET overlaps PRV, we may have to further modify the irradiation dose setting of the overlapping part.

• Page 14: was morphological tumor regression in the CT images prior to treatment and after 40Gy correlated with decrease of the SUV?

No. there was no significant correlation with the change of GTV and the change of FDG accumulation. I showed the volumes of GTV before radiation therapy in Table 1.
• The documentation of acute effects of 3D-CRT hardly fits to the general topic of the article, a retrospective planning study.

We agree with your opinion. We deleted the sentences about actual adverse effect of 3D-CRT from the Result.

Thank you for your reviewing of our manuscript.