Reviewer's report

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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Reviewer: Giuseppe Sanguineti

Reviewer's report:

Jungu et al report on a dosimetric study comparing 3DCRT to PET/CT guided IMRT for treating locoregional recurrences of rectal cancer. While the Authors claim that in Japan patients with rectal cancer are treated with surgery alone and about 10% would end up failing locoregionally, the topic is of limited interest in the western countries since most of the patients would receive upfront radiotherapy (preop or postop) as part of their initial treatment. In the Introduction, the Authors would need to try to estimate how many patients worldwide skip initial RT.

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? 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?

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. 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.

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....);

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;

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

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; 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...

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;

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.

**Level of interest:** An article of limited interest

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests