Author’s response to reviews

Title: Predictive factors for response to salvage stereotactic body radiotherapy in oligorecurrent prostate cancer limited to lymph nodes: a single institution experience.

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Author’s response to reviews:

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Dr. Homayoun Zargar, MBChB FRACS (Urol)
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Dear colleague,
On behalf of my co-authors, I would like to thank you and your reviewers for the helpful suggestions, the thoughtful comments and the invitation to re-submit the manuscript.

The comments and suggestions are answered in detailed and itemized fashion as follows:

Reviewer 1

1) please explain the Contal and O'Quigley method in more detail - it will be unfamiliar to most of the readership

Cutpoints can be identified based on data oriented methods such as mean, median, quartile or certain percentiles. These are thus independent of outcome.

However, one can use outcome oriented methods which may suggest a value of a cutpoint that correspond to the most significant relation with outcome. Generally the outcome-oriented methods are expected to have better statistical indicators than data-oriented methods.

Outcome-oriented methods that can be explored in the context of time to event data are based on log rank, score, likelihood ratio and Wald statistics or can also use minimum p-value or maximum hazards ratio as a statistic of interest.

The outcome oriented method proposed by Contal and O’Quigley (1999) is based on the log rank test statistic.

We reformulated the manuscript as follows: “The optimal cut-off point for LN size was calculated using the method proposed by Contal and O’Quigley [11]; it is based on the log rank test statistic, and allows to identify a cutpoint when the outcome of interest is measured as time to event.” (Statistical analysis section, lines 199-201, page 8).

2) Can the authors describe whether the salvage RT inclusive of pelvic nodal RT?

No prophylactic whole pelvic irradiation was performed; salvage RT was limited to the prostatic bed only.

We modified the manuscript accordingly (Methods, line 119 and lines 130-131, page 5-6).

3) Discrepancy in methods - background states 1-3 nodal mets but methods state 1-5 as inclusion. There are only 1-3 nodal patients included. Please keep consistent.

It is true that no patient had 4-5 positive nodal mets in our study, it was actually an exclusion criteria. We had in 2010 a restrictive definition of oligometastatic disease before SBRT (current consensus is usually up to five lesions).
The manuscript has been amended accordingly (Methods, line 120-121 and 132, pages 5 and 6. “Five LN” have been replaced by “three LN” on lines 63, 81, 109, 120-121, 305, 315 and 346.

4) Can the authors clarify how biochemical progression was defined as PSA > 25% and > 2ug/l if PSA level > 2, but at the same time using Jereczek criteria of PSA + 10%?

Jereczek et al. used their own clinical definition of biochemical response (BR) after SBRT, which is not standard. As their series was large and with relatively similar inclusion criteria as in our study, we decided to also use their own criteria to better compare directly their BR results with ours.

I think that the manuscript is clear on this issue.

“Classical” definition of BR: lines 175-7; our corresponding results: lines 228-9 and lines 256-8 of the discussion

Jereczek own definition of BR: lines 178-9: our corresponding results: lines 230-32 and lines 261-63 of the discussion

Anyway our biochemical progression results are finally pretty similar with both BR definitions: 20% with the classical definition, 24% with the definition from Jereczek et al.

5) Why also are the criteria for time to biochemical recurrence (2nd consecutive PSA rise) different from that of the definition used to score biochemical recurrence?

Endpoints section, lines 175-7, page 7 : the definition of biochemical progression as a PSA increase ≥25% and ≥ 2ug/l if baseline PSA ≥ 2 ug/l, or a PSA increase ≥ 2ug/l if baseline PSA < 2 ug/l: these consensus criteria were published in 2016, while our patients were included between 2010 and 2015. Still now, these criteria are mainly used by our medical oncology colleagues, especially for patients enrolled in clinical studies, with often monthly PSA blood tests.

In clinical practice, radiation oncologists and urologists often rely on less sophisticated definitions for biochemical recurrence; the time interval until second consecutive PSA rise is still a popular definition of biochemical recurrence, and was common practice at the time of inclusion of our patients.

6) PTV margin of 2-4mm, is relatively tight. The authors define a method for scoring marginal or in-field or out-of-field failures, but there are no results describing patterns of failure?

Patients are usually followed up by their urologist after SBRT, and we did not have access to CT/MRI/PET-CT imaging/records performed mostly outside our center.
As stated on lines 221-224: “Three patients received a second SBRT treatment: one patient with infield relapse (obturator LN) and two cases of out-of-field relapse (obturator LN => internal iliac LN; common iliac LN => para-aortal LN; one each). Time interval between both SBRT was 8, 13 and 14 months, respectively”.

We cannot draw any conclusions on the pattern of failure based on only three documented patients referred to our center for a second SBRT, which represent most probably an underestimate of the reality considering the retrospective nature of our series (underreporting bias).

7) The authors are missing two key references of the two other prospective trials for oligorecurrent prostate cancer outside of STOMP. These are POPSTAR (Siva, S., et al. (2018). European urology, 74(4), 455-462.), which also details patterns of failure for those patients with nodal disease and ADT free survival rates, as well as ORIOLE (study protocol available Radwan et al. BMC Cancer. 2017 Jun 29;17(1):453. doi: 10.1186/s12885-017-3455-6)

We mention now both references in the background section, which has been slightly modified accordingly (lines 93-100, page 4).

Reviewer 2

1) Small patients number, heterogeneous cohort, or lack of the control group are big flaws. We acknowledge that our single institutional series has a limited number of patients. But we disagree that our cohort is heterogeneous.

Most quoted studies (even prospective ones) achieve larger patients numbers only by mixing cases with nodal, bone, or even visceral metastases. It might reflect real life and daily practice, but in our view it is in fact mixing apples with pears: the biology of LN mets is not similar to the biology of blood-borne mets.

In our series, we focused on SBRT for patients with nodal spread disease only. All patients had surgery as initial treatment modality for their prostate cancer. About half had salvage RT of the prostatic bed. No patient received at any point of time whole pelvic nodal irradiation or ADT before SBRT.

These stringent criteria contributed for a significant part to the limited number of our patients, but actually to one of the most homogeneous series published so far.

The retrospective nature of our series precluded a control group like in a prospective randomized study. Performing a case-control study would have been futile from a statistical point of view, due to the small number of our patients.

The lack of control group was already mentioned in the limitations of the paper (line 324).
2) Were there any cases who could not receive SBRT due to previous salvage radiotherapy behind the present 25 patients? This information is useful to understand the feasibility of SBRT to LNs, after salvage radiotherapy to prostate fossa.

Salvage RT after RP, when it occurred, was limited to the prostatic bed. Previous irradiation of the whole pelvic nodal basin was an exclusion criteria for SBRT (Methods, lines 130-31, page 6).

There was therefore no patient who was denied SBRT due to previous RT.

Sincerely,

Michel Zimmermann, on behalf of the co-authors