Author’s response to reviews

Title: Heterogeneity in high-risk prostate cancer treated with high-dose radiation therapy and androgen deprivation therapy

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Version: 1 Date: 07 Apr 2017

Author’s response to reviews:

Dr Hayley Henderson
Editor
BMC Urology
April 7, 2017

Dear Dr Henderson & Members of the Editorial Board,

We would like to thank you for taking the time to review our manuscript titled “Heterogeneity in high-risk prostate cancer treated with high-dose radiation therapy and androgen deprivation..."
therapy” submitted for consideration of publication in BMC Urology as an original paper. We feel that your journal’s review has significantly improved the quality of our work and we are now pleased to submit a revised manuscript that addresses the Editors’ and Reviewers’ comments and suggestions.

We have pasted the Reviewers’ comments into this letter (in italics) and responded to each comment (in bold). In addition, any changes that were made to the manuscript are depicted in this response letter as well as in the revised version of the manuscript (where they are tracked). All page numbers refer to the tracked version of the manuscript. We also enclosed a cleaned version of the manuscript. Thank you very much for considering our study.

Sincerely,

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Reviewer reports:

Young Kwok (Reviewer 1):

The major finding of this manuscript is not earth-shattering but is quite important nonetheless. It continues to add to the literature that prostate is a very heterogeneous even within one risk group. The data are solid. The major strength of this report is that the large cohort was treated on successive, prospective trials. The stats and conclusions were appropriate and solid. There are some minor issues:

1. Methods (page 6): The 2 stats references should be numbered like the rest of the references.
We thank the reviewer for pointing out this to us and we have made the requisite changes on Page 6 Line 11. It has been incorporated into references

2. Conclusions (page 10): Line 33 ("We sought to incorporate…") is repeated in line 53.

We thank the reviewer for highlighting this to us. We have removed the repetitive line on page 10 Line 19 of the conclusions

Mack Roach (Reviewer 2):

There is nothing "new" here. All been published many times by many different people

We thank the reviewer for taking the time to review our paper. We agree this is not a new finding. However the strength of our study is that all data is utilizing clinical trial data which have been prospective gathered. We feel that our study is important as it utilizes trial data. However as highlighted in our discussion this is purely hypothesis generating. We have edited the discussion on page 12 Line 16 to highlight this point

David Pryor (Reviewer 3):

The authors conducted a retrospective study of prostate cancer patients treated in their health service to evaluate whether the NCCN "High Risk" group could be further sub-stratified into relevant prognostic subgroups in the context of modern dose-escalated radiotherapy combined with androgen deprivation therapy.

They conclude that a grouped cohort with multiple high risk factors had worse outcomes (PSA failure, distant metastases) than a grouped cohort with multiple intermediate risk or just one high risk factor. Looking at Figure 1 this appears to be largely driven by the intermediate risk group. The "unfavourable" high-risk group had outcomes more in line with the NCCN very high-risk disease group.

As the authors' note, there have been many publications on this topic both in the surgical and radiation literature. The findings of this study are not novel but do confirm heterogeneity amongst the high-risk group found with previous studies.

I think it is worth highlighting that the sub-stratification of NCCN high risk group into "high" versus "very high" was largely based on the large radical prostatectomy series from the Johns Hopkins group, not referenced in this paper (Sundi et al Very-High-Risk Localized Prostate Cancer: Definition and Outcomes Prostate Cancer Prostatic Dis. 2014;17(1):57-63.). They were
able to categorise a "very high-risk" group based on primary Gleason pattern 5, or $\geq 5$ cores with Gleason sum 8-10 but also included multiple NCCN high-risk features (as used in this current paper). Furthermore the Johns Hopkins group subsequently validated this risk stratification in patients receiving definitive radiation (Narang et al. Int J Radiat Oncol Biol Phys. 2016 Feb 1;94(2):254-62.)

The authors should discuss how their current paper adds to the above.

We appreciate the reviewer for highlighting this to us and have incorporated these papers into our discussion. We highlighted the fact that our paper emphasizes that DMFS is worse in the UHR cohort. See discussion Page 11 Line 19

Statistically, all comparisons should have accompanying p-values, including the K-M curves in Figure 1.

We thank the reviewer for this comment and have adjusted Figure 1 & Figure 2 to include p-values.

The authors note in the discussion that "Our findings might help to direct future clinical trial design and may help personalize care for individual patients." It would be worth highlighting whether any current trials are looking at these high / very-high risk groups.

We again have adjusted our discussion to highlight current clinical trials which are looking at these high / very-high risk groups. (Page 13 Line 9)

Seungtaek L Choi (Reviewer 4):

This paper looks at a very relevant issue in the treatment of prostate cancer by trying to improve risk classification of patients to better personalize treatment.

However, I had several questions/issues:

1) I would not recommend adding patients with 2-3 intermediate risk features in the "favorable" high risk group. They should be either excluded from this analysis, or be used as a comparison for the patients with 1 high risk feature to see they have similar outcomes.

We appreciate the reviewer for highlighting this. We have edited our results in the abstract (Page 2 Line 21). We have edited both the Methods section (Page 7 Line 2,3) and the results section (Page 8 Line 11) to clarify this issue. We have adjusted our analysis to not incorporate intermediate risk factors into the analysis but we purely used them as a comparative arm.
2) Also, as the patients with very unfavorable high risk patients received a lower dose of radiation (median dose of 70 Gy) and shorter duration of hormone ablation therapy, it's difficult to know if the reason for their worse outcome is the disease or the treatment given.

We agree with the author regarding this observation. The very high risk category did indeed receive a lower median radiation dose and a shorter duration of ADT. The purpose of including this cohort was merely to act as a comparison for the unfavorable high risk category (2-3 high risk factors). Inspite of the UHR cohort receiving higher radiation doses and a longer duration of ADT their outcomes were comparable to the very high risk group (who received suboptimal RT/ADT). We have edited the discussion to clarify our rationale for including this cohort. (Page 12 Line 15)

3) Gleason score of 7 is used as the cutoff point for the analysis. Was Gleason 8 or 9 looked as well?

We apologize for not being clearer. We did not find a difference between Gleason 8 to 10 in terms of outcomes. As NCCN suggest high risk disease is Gleason 8-10 we looked at this group all together. We have edited the results section to clarify. (Page 7 Line 20 and Page 7 Line 22)

4) The current standard of care for high-risk prostate cancer is to give long-term hormone ablation therapy (defined as greater than 28 months). Looking at Table 3, less than 30% of patients received that duration (or longer).

Yes this is reflective of real world experiences of tolerance to ADT. A significant proportion of our patients, despite of being enrolled on trials, were unable to tolerate longer duration of ADT.

5) Was image guidance used for the 3D CRT or IMRT treatment?

We thank the reviewer for highlighting this weakness in our discussion. All 3D CRT/IMRT treatment was image guided. We have amended our methods section to include this. (see page 5, Line 16)

I therefore recommend analysing only patients with high-risk prostate cancer who received modern radiation therapy (74 Gy or higher, ideally with image guidance) of radiation therapy.

See comment above. All were treated with image guidance and the FHR cohort and UHR cohort received a median of 74Gy. The very high risk group acts as a comparative arm.