Reviewer’s report

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

Version: 0 Date: 10 Mar 2017

Reviewer: David Pryor

Reviewer's report:

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 ≥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.

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

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.
Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I recommend additional statistical review

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Nil

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