Author's response to reviews

Title: Minimal percentage of the dose received by 90% of the urethra (%UD90) is the most significant predictor of PSA bounce in patients who underwent low-dose-rate brachytherapy for prostate cancer

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Author's response to reviews: see over
Dear Dr Jigisha Patel, MRCP, PhD:

Enclosed please find our revised manuscript entitled “Minimal percentage of the dose received by 90% of the urethra (%UD90) is the most significant predictor of PSA bounce in patients who underwent seed implantation” by N. Tanaka et al., which we would like to submit for consideration for publication in “BMC Urology”.

We revised the original manuscript according to the reviewers’ comment as below.

Reviewer's report
Reviewer: Jonathan Izawa
Reviewer's report:
Comments to Authors:
Major Revisions:
1. The authors should clearly state that the retrospective nature of this study leads to significant selection bias that can affect their results and lead to data that is different from other studies.

This study was conducted as a prospective study fashion.

Review comments:
The issue of distinguishing PSA bounce from PSA failure is an important distinction following radiation treatment for prostate cancer. This study aims to find factors that may contribute to the benign condition of PSA bounce. The following changes are suggested:

Title
Should include the words “brachytherapy” and “prostate cancer”. The disease prostate cancer is not even mentioned until the Methods section!
We have changed the title including brachytherapy and prostate cancer.

Methods/Design
Was the data collected prospectively (implied with statement of patient consent)?

Yes, we have described the sentence of prospective study in revised version.

This needs to be stated explicitly in the methods.
The treatment is so heterogenous, that it is hard to make sense of the data.
Really the authors should limit themselves to the summary in Table 4 (brachy, no ADT) for assessing risk factors.
• While a bounce may be seen with and with ADT and with either form of radiation, it doesn’t make intuitive sense to lump all together and look at bounce.
• 54 months of neoadjuvant ADT, for example, would likely have an effect on bounce! How many patients had more than 12 months of ADT?

The number of patients who received neoadjuvant ADT more than 12 months was 7 patients.

• The fact that no patients with adjuvant ADT had bounce implies that this may interfere with a bounce (when given over 2 years). Did the authors measure testosterone recovery?

We measured the testosterone level but not all patients. So we had not mentioned this issue in the manuscript.

• It also stands to reason, as shown in the data, that combined brachy and external beam radiation lessen the risk of bounce – so these patients cannot be included in an assessment of risk factors. Higher risk disease was presumably treated with combined therapy, so it would stand to reason that the higher PSA seen in the non-bounce group was a reflection that these patients received combined therapy for their higher risk disease. These associations need to be addressed. The only fair way to look at the long list of potentially confounding factors is with a multivariable analysis.
The longer follow up and more frequent PSA checks are a significant confounder in the PSA bounce group. The lack of follow-up to observe 32 PSA rises come back down to nadir is also a significant limitation.
Did the change from one planning system to another in 2008 have an impact on the results? Dosimetry is measured in part as % of prescribed doses – yet the prescribed dose changed in 2007 – how does this affect the results? Dose is thought to be a predictor of bounce (Stock 2003). The authors would need to include year of treatment in a multivariable analysis. How was dose calculated in patients who received EBRT boost?
The definition of PSA Bounce is controversial. The authors have taken the lowest conceivable threshold (0.1), which may explain why the median height of bounce is so low – presumably in many other series these would never have become bounces. Are the results still significant if rise of >0.4ng/ml is used, or >35% of previous value? The median bounce in this series is less than a 0.4 cut-off.

We discussed several issues as above in discussion.

Discussion
The introduction states that the importance of PSA bounce lies in its confusion
with, or delayed diagnosis, of PSA failure. However, the discussion does not attempt to address this issue with the study data or how the data might be useful. SA bounce is not clinically relevant. Therefore, some attempt should be made to put the usefulness of the data in a clinical context. Furthermore, no pathobiological explanation of the novel finding is given. Why might an increased dose to the urethra cause a bounce - or is it statistical chance given the multiple comparisons?

**We added some comments in discussion.**

Minor points
Table 1 uses mean PSA for non-parametric data; text uses median.

**We have changed Table.1**

Table 5 uses “confidential interval” instead of confidence.

**We have changed the description from confidential to confidence.**

We all have consented to publication and the manuscript has not been nor will be published elsewhere. None of the authors have any conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subjective matter or materials discussed in the manuscripts. No funding or financial support was received.

Thank you very much in advance for your kind consideration.

*Sincerely yours,*

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