Author's response to reviews

Title: Assessment of lower urinary symptom flare with overactive bladder symptom score and International Prostate Symptom Score in patients treated with iodine-125 implant brachytherapy: Long-term follow-up experience at a single institute

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Author’s response to reviews:

We appreciate your considerable editorial work. We have decided to submit the revised manuscript to BMC Urology. Here is response to the reviewers’ comments.
Figure 3 was replaced with colored one, which must be leaders-friendly. We appreciate the editor's understanding.

Reviewer #1: Nice study using OAB SS and IPSS to investigate the symptom flare associated with brachytherapy.

➤ We appreciate your review work.

Reviewer 2:

1) The author's indicate they performed a "threshhold sensitivity analysis" to choose their cutpoints for symptom flare. They do not provide enough detail about the statistical methods to allow a review to criticize if these methods were valid. As the author's indicate, they chose different threshold values of clinical significance then others (Cesaretti et al and Keyes et al.) I believe the authors need to add more detail, and the journal should have a statistician review the methodology in the revised manuscript.

> We understand the reviewer's point. As the reviewer pointed out, a "threshhold sensitivity analysis" is not a defined technical terminology. We deleted the word, "threshhold sensitivity analysis" from the manuscript and added more detailed explanation of this analysis (mainly, Methods section, 2nd paragraph). Along with this issue, the abstract and figure legends were also changed.

2) In the results section, the author's state

"To evaluate the correlation between IPSS flare and OABSS flare, the number of additional points (peak subtracted by nadir) in total IPSS and total OABSS were plotted and examined using Spearman's correlation (Figure 3A). There was a STRONG correlation between the increased points of total IPSS and total OABSS ( \( \rho = 0.49, P < 0.0001 \))."

However, a correlation coefficient of 0.49 is a MODERATE correlation at best. in fact, many would read this as somewhat discordant between IPSS and OABSS scoring. Since my interpretation of the main conclusion of the author's is that 11% of additional people may be identified as at flare risk on OABSS, this lack of excellent correlation may better support their argument, and they should revise the wording. If the OABSS and IPSS were truly concordant (which they are not) there would be no clinical utility of also getting OABSS in addition to IPSS.

> We totally agree with the reviewer. We replaced “a strong correlation” with “a moderate correlation”. (Results section, 4th paragraph). We appreciate this reviewer’s comments.
3) the author's emphasize that 11% of people with flare were identified by OABSS but not IPSS. Figure 3 reveals highly implies that a similar number of people were identified with flare on IPSS but not OABSS. The authors should report this finding as well.

That’s a critical point of this study. We reported “In contrast, we found that assessment solely with the OABSS questionnaire failed to detect 45 patients (13%) with urinary symptom flare.” in Results section, 4th paragraph

4) The fact that a certain percentage of people will be independently discovered as flare on OABSS and IPSS, without overlap, is the major finding to support addition of OABSS to either clinical use or as a PRO measure on clinical trials. This should be made a little more clear.

We appreciate this reviewer’s comments. To get more understanding of the leads, we added “Our findings revealed that a certain percentage of people will be independently discovered as flare on OABSS and IPSS, without overlap. The OABSS can be used as a validated patient reported outcome to assess LUTS after brachytherapy in addition to the IPSS.” in the last of Results section, 4th paragraph.

5) Gleason score was found to be significant for predicting flare, as was biologically equivalent dose (BED). However, Gleason 9 and 10 patients were almost certainly likely to receive EBRT + Brachy instead of brachy alone, which means that Gleason 9 and 10 could merely be a surrogate for high BED. The author's do state that they tried to do analyses to exclude the effect of EBRT, but it was not clear to this reviewer if their analyses addressed this potential interaction. I recommend a statistician address the issue of whether or not BED and High Gleason score (or high D'amico risk group) had a statistical interaction confounding the significance testing.

We agree with the reviewer. We noticed that high Gleason patients received high BED, because all of them received EBRT. Still, the authors would like to know which parameters mostly affected the urinary flare. The multivariate analysis revealed that high Gleason itself was not independent predictive factor of the flare. It means that other factors including BED might be associated with the flare in high Gleason patients, for example, the high Gleason tumors may be easy to get late inflammation.

We really appreciate the reviewer’s understanding.