Author’s response to reviews

Title: A prospective study of magnetic resonance imaging and ultrasonography (MRI/US)-fusion targeted biopsy and concurrent systematic transperineal biopsy with the average of 18-cores to detect clinically significant prostate cancer

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Author’s response to reviews:

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Dear Prof. Hayley Henderson,

We greatly appreciate your review of our manuscript. We performed the editorial revisions. In addition, this manuscript received English check. Some expressions are changed to the common expressions. We are sorry that there were unclear expressions in our manuscript. We revised our manuscript according to the reviewer reports and used text highlights to the changed part. Red text indicates revised part according to the comments of Reviewer 1 and green text indicates revised part according to the comments of Reviewer 2. A point-by-point response is shown below.

Response to Reviewer 1
We greatly appreciate your helpful comments.

Changes parts according to your comments are shown in red text in the revised manuscript.

Comment 1: One of the main aspects that sets this investigation apart from prior MRI-ultrasound fusion biopsy papers is the transperineal, rather than transrectal, approach. This should be stressed in the abstract and, I would suggest, the title. It should also be addressed in the Introduction, and again in the first paragraph of the Discussion.

Based on the reviewer’s suggestion, we indicated this study was performed by transperineal biopsy in the title, abstract, background and the first paragraph of the Discussion.

Comment 2: Some aspects of language render the meaning unclear. E.g., the last paragraph in the introduction, “Image guided biopsy methods were classified as cognitive targeting without any technological guidance, targeting in the MRI gantry and real-time MRI/US fusion guided biopsies.” Does this mean that the investigators considered these, or are they being listed as potential methods of image fusion targeted biopsy? Also, in the Discussion, the 3rd sentence states, "Regrettably, such trend resulted in a substantial number of indolent PC." I think the authors mean it resulted in the detection of indolent cancers.

We corrected the unclear expression. In the last paragraph in the background, we listed image guided biopsy methods as potential methods of image fusion targeted biopsy, so we corrected the manuscript: “Imaging-guided biopsy can be classified into three categories such as cognitive targeting without any technological guidance, targeting in the MRI gantry and real-time MRI/US fusion guided biopsies. However, there is no visual feedback in the absence of technological guidance, and TB in the MRI gantry is time-consuming, so we adopted MRI/US fusion guided biopsies using the transperineal technique in our hospital.” (p. 3, lines 74-79) In the discussion, we corrected the 3rd sentence: “However, this approach can also detect indolent cancers.” (p. 6, lines 150)

Comment 3: The first paragraph in the Methods states this was prospective. How does this differ from clinical practice at this hospital?

We applied the 10-core biopsy in usual and we performed the extended biopsy to specify the benefits of targeted biopsy as a prospective study.

Comment 4: It is unclear from table 1 what the temporal resolution of dynamic contrast-enhanced (DCE) imaging was. Although DCE does not add much to suspicion assessment, it may add to detection.

We added the time resolution of dynamic contrast-enhanced imaging in the paragraph of multiparametric MRI and biopsy methods as follows, “The time resolution of the DCE images was 27.1 s.” (p. 4, lines 95) Other parameters were modified as well.
Comment 5: Please define explicitly the CSPC criteria used; the "insignificant" criteria are unclear. Must all of these be true for the cancer to be considered insignificant? Since the number of cores is a "per-subject" rather than a "per-core" parameter, how did this relate to targeted vs. systematic biopsies? When the authors mention "Gleason score was under 3+3," does this mean that any GS 3+3 was significant? Did PSA density overrule GS?

We revised CSPC definition as follows in the manuscript. “We defined CSPC as cancers that did not fulfill any of the Epstein criteria for clinically insignificant cancer [5]: (i) prostate-specific antigen (PSA) density of <0.15, (ii) ≤50% involvement of any 1 core, (iii) a Gleason score of ≤ 3 + 3, and (iv) <3 positive biopsy cores.” (p. 5, lines 106-109)

Comment 6: In the results, a further description of demographics is needed to define the population. How many patients had never had a prior biopsy? How many had a prior negative biopsy? How many were on active surveillance (prior positive biopsy for clinically insignificant disease)? Please consider using the START criteria (Moore et al, Eur Urol 2013; 64(4):544-552) to define the biopsy cores.

We modified the table 2 according to the START criteria. 145 patients had no prior biopsy. In the patients with prior biopsy, one patient was under the active surveillance and other patients had no history of prostate cancer. We added “One patient was under active surveillance and had a Gleason score of 3 + 3.” (p. 6, lines 130) in the first paragraph of the results.

Comment 7 and 8: How many subjects did, and how many did not, have targets on MRI? Were only subjects with targets included? In other words, we do not know how many subjects without targets would have been found to have any or significant cancer by 18-core transperineal systematic biopsy, correct? Can we determine the performance of a "negative" MRI with no targets to exclude significant cancer?

Assuming all subjects had targets by MRI, is there any means to determine whether positive systematic biopsies occurred in the region of MRI-based targets? In other words, is it possible to infer whether the insensitivity of TB is based on MRI not finding targets, or the image-fusion targeted biopsy system missing them?

15.3% (27/177) of patients are diagnosed as significant cancers for only systematic biopsy. These cancers are detected from negative MRI lesions or surroundings of the targeted lesion. It is difficult to distinguish precisely because the latter depends on the interpretation of the imaging and target biopsy technique. This rate suggests the sensitivity of MRI per patients. We added in the fourth paragraph of the discussion; “SB may detect PC when the MRI findings are negative or when TB does not effectively target the PC, which could be caused by inaccurate interpretation of imaging results. Cash et al. reported that TB failure is the main cause of negative TB findings [9], and histopathological results from radical prostatectomy and needed to address this issue, although only a few patients in the present study underwent radical prostatectomy.” (p. 8, lines 182-188) This part is also revised according to the reviewer 2 comments.
Comment 9: In the 3rd paragraph of the Discussion, the authors state "The upgraded rates by TB over SB were reported as 22%(43/198) (3). We performed extended systematic biopsies and the rate of upgrading by TB was lower (9.0%, 16/177)" but I cannot determine in which case there was upgrading by TB over SB, and which was upgrading by SB over TB.

We revised to clarify the definition of the upgrade. We added a definition of upgrade in method as follows: “The highest Gleason score from the SB and TB specimens was considered the patient’s score. Pathology results were obtained for MRI/US-fusion TB and SB specimens, and cases were considered upgraded if one method provided a higher Gleason score, or if one method detected prostate cancer (PC) when the other did not detect PC.” (p. 5, lines 121-125)

Comment 10: Do the authors have any explanation why so few subjects had insignificant cancer? Could it be due to the definition? Many subjects had 3+3 cancer, so significance must have included size or number of positive biopsies. It may be that the definition of <3 positive cores does not apply to 18 vs. 12 or fewer cores.

We applied to Epstein criteria, so there are few insignificant prostate cancers. We mentioned it in the new third paragraph of the discussion: “the Epstein criteria, which only consider insignificant cancer to be present in cases with a Gleason score of 3 + 3, and only a few patients in the present study had insignificant cancers.” (p. 7, lines 173-176)

Response to Reviewer 2

We greatly appreciate your helpful comments and suggestions.

Changes parts according to your comments are shown in green text in the revised manuscript.

Based on the reviewer’s comment, we added three paragraphs in the discussion as follows; “The results indicate that SB provided a higher detection rate of CSPC, compared to TB (57.1% vs 48.0%), and that only SB was able to diagnose 25 patients with CSPC. In contrast, some previous studies have indicated that TB provides high rates of PC detection [6,7]. There are two reasons why SB provided higher rates of PC and CSPC detection in the present study. The first reason is that we performed biopsy along the parasagittal and far lateral lines with an interval of 5mm and a prostate volume- dependent number of biopsy cores. This technique is similar to the template biopsy technique, and the PROMIS study revealed that the template biopsy technique was able to detected PC (119/452, 26.3%) in some cases that were missed by standard TRUS [8]. Although we did not perform template biopsy, our SB technique may have provided better PC detection, compared to standard 10-12-core random biopsy. The second reason is that we used the Epstein criteria, which only consider insignificant cancer to be present in cases with a Gleason score of 3 + 3, and only a few patients in the present study had insignificant cancers. Baco et al. used the same definition for significant/insignificant PC, and reported that 12-core random biopsy provides a higher detection rate, compared to MRI/TRUS-guided TB (49% vs 38%) [2]. It is possible that TB can fail to detect PC, as Ahmed et al. reported that CSPC was detected using template biopsy in 10.8% of patients (17/158) who had
negative MRI findings [8]. We also detected CSPC using SB when TB provided negative results in 15.3% of the patients (27/177). In this context, SB may detect PC when the MRI findings are negative or when TB does not effectively target the PC, which could be caused by inaccurate interpretation of imaging results. Cash et al. reported that TB failure is the main cause of negative TB findings [9], and histopathological results from radical prostatectomy and needed to address this issue, although only a few patients in the present study underwent radical prostatectomy.” (p. 7-8, lines 161-188)

The reference was out of date, so we included PROMIS study and other randomized control studies. We appreciate helpful proposal.

We look forward to hearing from you regarding our submission. We would be glad to respond to any further comments that you may have.

Thank you in advance for considering the paper for publication in the BMC urology.

Respectfully yours,

Yuji Hakozaki, MD