Peer Review File

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Reviewer A

45-46: Mention % + number of patients in a consistent way

A: Thank you for the comment. We have updated the text to reflect consistency (page 2, line 42).

> ***Only ten patients were diagnosed with csPCa by SBx alone, all of whom had GG2 disease; of these, six were managed with active surveillance, while the remaining four with surgery or radiation.***

59: Until now SBx + TBx is still necessary for PIRADS 3 and 4 lesions and this is the majority of cases where prostate biopsies are necessary. This you may mention because we are not ready yet to omit SBx in these cases.

A: Thank you for the comment. We have kept this datapoint within the manuscript text (page 3, line 51).

> ***Taken together, the authors note the benefits of combination SBx+TBx appear to be concentrated in men with PI-RADS 3 and 4 lesions and the decision to forgo SBx in PI-RADS 5 and TBx in PI-RADS 2 cohorts will spare 40.1% of men from undergoing a combined biopsy, with only a 1% risk of misdiagnosis among the entire cohort with an abnormal MRI.***

91: For the surgeons it is also important to now if there is low grade prostate cancer in the other parts of the prostate (what you can not see on a mpMRI prostate). This is important when they want to do nerve sparing surgery of the prostate.

A: Thank you for the comment. We have included this discussion point within the manuscript (page 5, line 94).

> ***In cases with limited MRI sensitivity, the performance of SBx and detection of low grade PCa in non-regions of interest may be beneficial in informing surgeons who intend to perform nerve-sparing surgery while decreasing rates of adverse pathologic features.***

Reviewer B

Compliments to the authors for writing on this important topic. The diagnostic value of systematic prostate biopsies (SBx) has already been questioned since the introduction of mpMRI, and more and more literature is becoming available advocating the omission of systematic biopsies. However, I have some comments on its content.

A: Thank you.

First of all, even though the diagnostic value of SBx is heavily debated, ommission of

all SBx in the is currently not recommendable. The diagnostic accuracy of a TBx-only approach has shown to miss clinically significant PCa (defined as ISUP GG2-5) in approximately 1 in 5 men. This is most likely due to imprecise lesion registration (underestimation of tumor volume) and targeting errors due to (cognitive) fusion inaccuracies. To correct for these SBx should not be ommitted, but limited to the vicinity of MRI-positive lesions. I'd recommend you to incorporate the papers by Hagens et al. (PMID: 35540708, 34556389, 36353069) on perilesional SBx approaches.

A: Thank you for the constructive feedback. We have incorporated the references as suggested above and additional discussion to support these references (page 3, line 66).

> ***While the diagnostic value of SBx have been heavily debated, complete omission of all SBx is still not currently recommended. The diagnostic accuracy of TBx alone has been shown to miss csPCa, which may be secondary to underestimation of tumor volume, suboptimal image fusion, or targeting errors during cognitive inaccuracies. Rather, Hagens et al. previously described the performance of MRI-directed TBx plus perilesional/regional biopsies to minimize targeting errors, biopsy cores, and grade migration. A single institutional analysis of 235 men found that this sampling technique would have detected 92/95 (96.8%; 95% CI 91.0-99.3%) csPCa while reducing diagnosis of insignificant cases by 11/86 (12.8%; 95% CI 6.6-21.7%) and also reducing the number of biopsy cores (mean difference -5.2; 95% CI 4.9-5.6, p<0.001). A subsequent meta-analysis of this technique demonstrated that csPCa detection rates were not significantly different when compared to SBx+TBx approaches (risk ratio 0.95, 95% CI 0.90-1.01, p=0.09) but significantly better when compared to TBx alone (risk ratio 1.18, 95% CI 1.10-1.25, p<0.001). This technique also used significantly fewer biopsy cores compared to SBx+TBx approach and avoided contralateral SBx altogether.***

Pointing out the clinical implications of a TBx-only approach should be complimented. Within our own institution we have observed an increase in downgrading rates after radical prostatectomy since the introduction of mpMRI-directed TBx. Though authors should also address the implications of a TBx-only approach on surgical planning, nerve sparing surgery, positive surgical margins, etc..

A: Thank you for the comment. We have including this discussion point within the manuscript, which is similar to the comment as recommended by reviewer A (page 5, line 94).

> ***In cases with limited MRI sensitivity, the performance of SBx and detection of low grade PCa in non-regions of interest may be beneficial in informing surgeons who intend to perform nerve-sparing surgery while decreasing rates of adverse pathologic features.***

All in all, I do think the authors have done a fine job in writing this letter. I do believe it could be improved as full ommision of SBx is not recommended by current literature. SBx should be limited to perilesional areas.

A: Thank you again for the feedback. We have included literature and references by Hagens et al. to discuss the utility of perilesional biopsies (page 3, line 66).

> ***While the diagnostic value of SBx have been heavily debated, complete omission of all SBx is still not currently recommended. The diagnostic accuracy of TBx alone has been shown to miss csPCa, which may be secondary to underestimation of tumor volume, suboptimal image fusion, or targeting errors during cognitive inaccuracies. Rather, Hagens et al. previously described the performance of MRI-directed TBx plus perilesional/regional biopsies to minimize targeting errors, biopsy cores, and grade migration. A single institutional analysis of 235 men found that this sampling technique would have detected 92/95 (96.8%; 95% CI 91.0-99.3%) csPCa while reducing diagnosis of insignificant cases by 11/86 (12.8%; 95% CI 6.6-21.7%) and also reducing the number of biopsy cores (mean difference -5.2; 95% CI 4.9-5.6, p<0.001). A subsequent meta-analysis of this technique demonstrated that csPCa detection rates were not significantly different when compared to SBx+TBx approaches (risk ratio 0.95, 95% CI 0.90-1.01, p=0.09) but significantly better when compared to TBx alone (risk ratio 1.18, 95% CI 1.10-1.25, p<0.001). This technique also used significantly fewer biopsy cores compared to SBx+TBx approach and avoided contralateral SBx altogether.***

<u>Reviewer C</u>

A limited, subjective opinion piece. Regrettably, there are no new insights.
No data was given to support grade or volume migration for PLND; just concerns about artificially elevated predicted outcomes. They extend their concerns to focal therapy considerations and for AS.

A: We thank the reviewer for this comment. Based on collective comments from other reviewers as well, we have included much more extensive literature and studies regarding systematic and targeted biopsies, and significantly reduced the discussion focusing on PLND, focal therapy and AS (page 4, line 88).

> ***The omission of SBx has several clinical implications. Patients presenting solely with TBx data may result in discordant and artificially elevated predicted nomogram outcomes, resulting in potentially unnecessary lymph node dissection, which itself is associated with inherent risks. Recent analyses have also demonstrated the impact of regional tumor involvement among serial biopsies performed for active surveillance (AS) over time. Higher regional cancer involvement is associated with higher rates of progression to treatment and omitting SBx may alter the ability to interpret longitudinal biopsy results. In cases with limited MRI sensitivity, the performance of SBx and detection of low grade PCa in non-regions of interest may be beneficial in informing surgeons who intend to perform nerve-sparing surgery while decreasing rates of adverse pathologic features. While not currently recommended yet, the basis of focal therapy relies on the destruction of localized prostatic lesions reproducibly visualized on imaging. PCa can be multifocal and limitations on mpMRI may result in missed lesions or incomplete ablation of identified tumor. In these cases, SBx may play an important***

role in patient selection and post-treatment surveillance, especially for men with PCa recurrence after radiation therapy in the absence of metastatic disease.

There is not a comprehensive literature evaluation of the relative value of SB to TB and TB to SB. This was reviewed in the Cochrane analysis and there have been other meta-analyses. The reference to population screening is probably inappropriate given differences in prevalences.

A: Thank you for the comment. We have included more comprehensive literature which includes recent published meta-analyses into our manuscript (page 3, line 56).

According to a meta-analysis by Drost et al., pooled data from 25 studies on agreement analyses found a detection ratio of 1.12 (95% CI 1.02-1.23) for ≥GG2 disease and 1.20 (95% CI 1.06-1.36) for ≥GG3 disease among patients undergoing the MRI pathway (MRI +/- TBx) vs SBx pathway, thus favoring TBx. Yet another meta-analysis among biopsy-naïve men by Goldberg et al., similarly demonstrated that TBx results in a significantly higher diagnosis rate of any, high grade and csPCa, while excluding SBx was associated with lower rates of clinically insignificant PCa. This seems true even when SBx are indicated after risk stratification with an ultrasound-based risk calculator. Among patients with previously negative SBx, TBx also detected more csPCa than SBx, with only 1.3% of csPCa being missed when SBx are omitted altogether.

No discussion on alternate methods of improving risk stratification (region-directed biopsies or adopting the ISUP guidelines for targeted biopsies). viz:
Hagens MJ, et al. Diagnostic performance of MRI-directed targeted-plus-regional biopsy approach in prostate cancer diagnosis – a systematic review and meta-analysis. Euro Urol Open Science Eur Urol Open Sci. 2022 May 2;40:95-103.
van Leenders GJLH, et al. The 2019 ISUP Consensus Conference on Grading of Prostatic Carcinoma. Am J Surg Pathol. 2020 Aug;44(8):e87-e99.

A: Thank you for providing the relevant references. We have incorporated both these references and its associated discussion points within the manuscript to strengthen the overall letter (page 3, line 66).

While the diagnostic value of SBx have been heavily debated, complete omission of all SBx is still not currently recommended. The diagnostic accuracy of TBx alone has been shown to miss csPCa, which may be secondary to underestimation of tumor volume, suboptimal image fusion, or targeting errors during cognitive inaccuracies. Rather, Hagens et al. previously described the performance of MRI-directed TBx plus perilesional/regional biopsies to minimize targeting errors, biopsy cores, and grade migration. A single institutional analysis of 235 men found that this sampling technique would have detected 92/95 (96.8%; 95% CI 91.0-99.3%) csPCa while reducing diagnosis of insignificant cases by 11/86 (12.8%; 95% CI 6.6-21.7%) and also reducing the number of biopsy cores (mean difference -5.2; 95% CI 4.9-5.6, p<0.001). A subsequent meta-analysis of this technique demonstrated that csPCa detection rates were not significantly different when compared to SBx+TBx

approaches (risk ratio 0.95, 95% CI 0.90-1.01, p=0.09) but significantly better when compared to TBx alone (risk ratio 1.18, 95% CI 1.10-1.25, p<0.001). This technique also used significantly fewer biopsy cores compared to SBx+TBx approach and avoided contralateral SBx altogether.

Further methods for improving risk stratification include the adoption of the 2019 International Society of Urological Pathology (ISUP) guidelines for reporting TBx results. They proposed the recommendation of providing an aggregate Gleason score for each suspicious MRI lesion rather than individual TBx core separately, while SBx cores should continue to be reported separately for each location. Benign histologic findings should also be intentionally reported for TBx of suspicious MRI lesions (PIRADS 4-5).

Reviewer D

The title of the submitted letter to the Editor is informative of the subject matter and correct.
A: Thank you.

You present original data essentially from two studies, the GÖTEBORG-2 trial and the TRIO study. In my opinion, these trials do not provide the best evidence to decide about omitting systematic prostate biopsy or not. Methodologically, the results could be presented in a more orderly fashion, indicating at the outset the number of patients under study, as well as the inclusion and exclusion criteria used to assess the possible representativeness with respect to the reference population. Articles should be referenced.
A: We thank the reviewer for this comment and the references relevant to the topic at hand. We have included them and the associated discussion points within the manuscript.

There is better evidence in the literature. According to the systematic review and metanalysis of Drost et al (Drost et al., 2019), in pooled data of 25 reports on agreement analysis (head-to-head comparisons) between systematic biopsy (median number of cores: 8–15) and MRI-targeted biopsies (median number of cores: 2–7), the detection ratio (i.e. the ratio of the detection rates obtained by MRI-targeted biopsy alone and by systematic biopsy alone) was 1.12 (95% CI: 1.02–1.23) for ISUP grade > 2 cancers and 1.20 (95% CI: 1.06–1.36) for ISUP grade > 3cancers, and therefore in favor of MRI-targeted biopsy.
A: This meta-analysis is now included in page 3, line 56.

According to a meta-analysis by Drost et al., pooled data from 25 studies on agreement analyses found a detection ratio of 1.12 (95% CI 1.02-1.23) for ≥GG2 disease and 1.20 (95% CI 1.06-1.36) for ≥GG3 disease among patients undergoing the MRI pathway (MRI +/- TBx) vs SBx pathway, thus favoring TBx.

Another meta-analysis of studies limited to biopsy-naive patients with a positive MRI found that MRI-targeted biopsy detected significantly more ISUP grade > 2 cancers than systematic biopsy (risk difference, -0.11 [95% CI: -0.2 to 0.0]; p = 0.05), in prospective cohort studies (risk difference, -0.18 [95%CI: -0.24 to -0.11] [235]; p 2cancers than systematic biopsy (34% vs. 16%; p < 0.001, detection ratio of 2.1), which is a finding consistent with the Cochrane agreement analysis (detection ratio: 1.44). An ISUP grade > 2 cancer would have been missed in only 1.3% (2/152) of patients, had systematic biopsy been omitted. These findings support that MRI-targeted biopsy significantly out-performs systematic biopsy for the detection of ISUP grade > 2 in the repeat-biopsy setting. In biopsy-naive patients, the difference appears to be less marked but remains in favor of MRI-targeted biopsy. [237]

A: Both these studies are included in page 3, line 59 and line 63.

> ***Yet another meta-analysis among biopsy-naïve men by Goldberg et al., similarly demonstrated that TBx results in a significantly higher diagnosis rate of any, high grade and csPCa, while excluding SBx was associated with lower rates of clinically insignificant PCa.***
>
> ***Among patients with previously negative SBx, TBx also detected more csPCa than SBx, with only 1.3% of csPCa being missed when SBx are omitted altogether.***

MRI-targeted biopsy without systematic biopsy significantly reduces over-diagnosis of low-risk disease, as compared to systematic biopsy. This seems true even when systematic biopsies are indicated after risk stratification with a US-based risk calculator (i.e. Rotterdam Prostate Cancer Risk Calculator) (Wagensveld et al., 2022).

A: We have included this reference in page 3, line 62.

> ***This seems true even when SBx are indicated after risk stratification with an ultrasound-based risk calculator.***

The role of pelvic lymph node dissection has no interest in this paper, as the focus is on whether systematic biopsies are of interest.

A: We thank the reviewer for this comment and have reduced this discussion on pelvic lymph node dissection to only one sentence (page 4, line 88).

> ***Patients presenting solely with TBx data may result in discordant and artificially elevated predicted nomogram outcomes, resulting in potentially unnecessary lymph node dissection, which itself is associated with inherent risks.***

The conclusion is ok, but the structure of the letter can be improved. Include the references indicated and improve the structure about it.

A: Thank you for the feedback. References have been updated accordingly and we have re-arranged the structure of the manuscript to as recommended.