Author’s response to reviews

Title: Three-dimensional greyscale transrectal ultrasound-guidance and biopsy core preembedding for detection of prostate cancer: Dutch clinical cohort study

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Author’s response to reviews:

Dear editor, dear reviewers,

We have received your e-mail and comments. We are thankful that you took our manuscript in consideration for publication and for the time you have invested in the reviewing process. We noted the reviewer’s comments; we found them to be thoughtful and appropriate, and we feel that attention to their concerns will substantially improve our report. Below, please find our response to the comments in italic.

Kind regards,

Anouk van der Aa
Reviewer #1:
Overall a very well-written paper, however it adds limited knowledge to current practice. While detecting more prostate cancer with 3D ultrasonography (US) using a preembedding technique, the modest increase of detected prostate cancer does not convincingly overcome the known limitations of grayscale ultrasound. At this point in time more sophisticated techniques are available to increase the detection rates of clinical significant prostate cancer, such as multiparametric MRI and consequent MR/TRUS-fusion. At the same time a pre-biopsy MR pathway limits the detection of clinically insignificant cancer, the described biopsy technique certainly does not seem to deliver on that. Whereas it is likely that the introduction of 3D US with preembedding of biopsy cores has led to significantly more overall prostate cancer detection, it remains uncertain whether it truly detects more significant prostate cancer as the two methods (2D US versus 3D US with preembedding) were used consecutively in time and not simultaneously. Detecting more significant prostate cancer could thus well be caused by Gleason score shift over time (as the authors correctly state in the discussion: the Gleason score was updated in 2014), making the conclusion of the paper that the new technique detects more significant prostate cancer at best indicative. Furthermore, it remains unclear whether the increased detection of (significant) prostate cancer is due to the use of 3D US or use of the preembedding method as both measures were introduced at the same time. The effect of preembedding might well have the most influence on prostate cancer detection, as the authors have shown in an earlier study that 2D US using a preembedding technique was not inferior to 3D US. This paper concludes that 3D US with preembedding is superior to 2D US, but this conclusion is of limited value as it is not certain which factor causes this observation, the use of 3D US or the preembedding technique. Unfortunately, it is unlikely that the authors' database will be able to answer this question. As the series represents an analysis of a large population using solid methods it is still worth publication, but the authors should formulate their conclusion less firm and give solid recommendations for future research on 3D US as well as preembedding of prostate biopsy cores. Furthermore the reported improved detection rates should be compared to those of multiparametric MRI and MR-targeted biopsies in the discussion as this should be considered the state of the art in the current era. It is at least surprising that MRI is mentioned in a paper on prostate cancer diagnosis merely once, only stating that it was not used for selecting patients for biopsy.

Author response
1. The reviewer claims that it remains unclear whether the increased detection of (significant) prostate cancer is due to the use of 3D US or use of the preembedding method as both measures were introduced at the same time. We agree with the reviewer that two diagnostic methods were introduced at the same time, but as we described in our discussion, in the results of a previous study carried out in our institution, we showed no added value of 3D TRUS guidance compared to 2D with all biopsy cores preembedded. (Discussion, line 220-222)

2. We made our conclusion less firm: “The current study suggests an added value of 3D TRUS-guidance and preembedding compared to conventional 2D GS TRUS-guidance regarding detection rate of PCa and clinically significant PCa among patients undergoing prostate biopsies”. (Conclusion, line 309-311)

3. Our discussion describes the more sophisticated techniques that are available to increase the detection rates of clinical significant prostate cancer. Multicenter studies, as the PRECISION study, 4M study and MRI FIRST, described the alternative diagnostic pathway of multiparametric Magnetic
Resonance Imaging (mpMRI) and MR-targeted biopsies.
“Multiparametric MRI (mpMRI) of the prostate is increasingly used in the diagnostic pathway of PCa and three large studies, evaluating the detection rates of an MRI-targeted biopsy approach and TRUS guided systematic biopsy approach, have recently been performed in biopsy-naïve men. 30-32 While the PRECISION trial demonstrated that an MRI targeted biopsy approach detected significantly more clinically significant PCa in comparison with a TRUS systematic biopsy approach both the MRI First and 4M Study demonstrated comparable detection rates of clinically significant PCa between the standard TRUS systematic biopsy and MRI targeted biopsy approach. Obtaining an mpMRI before biopsy improves the detection of clinically significant PCa but at present does not avoid the need for systematic biopsy as shown in the systematic review from Moldovan et. al and the MRI FIRST study where 10 to 15% of clinically significant PCa were still missed in men with a negative mpMRI.31,33 Even in the Dutch 4M study with high-quality MRI standards, 7% (21/317) of all men with a suspicious mpMRI scan had clinically significant PCa only on systematic biopsy. 32 A high-quality TRUS systematic biopsy, possibly with the use of 3D TRUS-guidance and preembedding, could therefore still be important in the current diagnostic setting where mpMRI is also included”.

At the end of the discussion we also added: “These findings highlight the need for future research regarding the complementary value of 3D TRUS guidance and preembedding in the combination with mpMRI and other new diagnostic applications”.

Reviewer #2:
Summary: This is a well-done retrospective comparison of prostate cancer detection rates using 2D (2007-2013) versus 3D (2013-2016) TRUS biopsy. The main finding is that the 3D platform (which also includes a preembedding method that the authors acknowledge may have augmented the effect of the 3D imaging) results in significantly higher detection rates of prostate cancer, both overall and "significant."

1. Abstract (line 53): Suggest revising to, "3D GS TRUS-guidance with biopsy core preembedding appears to improve PCa and clinically significant PCa detection compared to 2D TRUS-guidance."

Author response:
We have revised the conclusion also in our abstract. It now states “Our results suggest that 3D GS TRUS-guidance with biopsy core preembedding improves PCa and clinically significant PCa detection compared to 2D GS TRUS-guidance”. (Abstract, line 53-55)

2. Background (line 61): With regard to the statement that early detection reduces PC mortality, I would reference the ERSPC trial. I believe the most recent update of this trial is Schröder, et al., Lancet, 2014 Dec 6;384(2027-35).

Author response:
We agree with the reviewer referring to the most recent trial of Schröder et al. The following reference was added:
3. **Background (line 62):** I would like to suggest a primary reference (Schroder, Hugosson, Carlsson, et al. European Urology 62 (2012) 745-752) instead of the European association of urology recommendations provided in reference #2 to support the statement that early detection reduces the risk of advanced or metastatic disease.

Author response:
We agree with the reviewer referring to the study of Schröder et al. We added:
(Background, line 63, we refer to the findings from the European Randomized Study of Screening for Prostate Cancer by Schröder et al.)

4. **Results:** It would be worthwhile to repeat the fact that the 3D TRUS biopsies were performed from 2013-2016, whereas the 2D TRUS biopsies were performed from 2007-2013. (This is explicitly stated only in the Methods section.)

Author response:
We completed our sentence in results by adding the data when our biopsies were performed. “2D TRUS biopsies were performed from 2007-2013 and 3D TRUS biopsies were performed from 2013-2016”.
(Results, line 168-169)

5. **Discussion:** The authors acknowledge but downplay the possibility of residual confounding with regard to the fact that the 3D approach was undertaken by more experience operators. Please revise the statement, "...we believe that confounding by experience level in our model was accurately measured and corrected for in multivariate analysis..." All you should say about this is that you attempted to correct for this important imbalance but that there could still residual confounding.

Author response:
We have revised our statement about experience level in: “Although a correction strategy was implemented, residual confounding could still be possible”.
(Discussion, line 274-275)

6. **I** would like to know more about how 2D and 3D TRUS biopsy compare with regard to the detection of favorable and unfavorable intermediate-risk and high-risk disease. The authors chose, instead, to only look at overall PC and "significant" PC, defined as GS > 6 or > 2 cores of GS 6. Using > 2 cores of GS 6 is not an optimal way to select patients for treatment vs surveillance in the era of multi-parametric MRI. The more important question is which patients with favorable-risk intermediate prostate cancer should be offered the surveillance option.

Author response:
A valid point by the reviewer. "We decided in our study to include the Large Grade Group 1 (GS 3+3) as clinically significant PCa. Recent EAU guidelines use the definition of GG ≥ 2 (GS ≥3+4) for clinical significant PCa. This matches with the newly introduced ISUP scoring system, where no separation is made between large and small GG 1 (GS 3 + 3) prostate cancer. We decided to include large GS 3+3=6 PCa as clinically significant as this is currently still used as a criteria for active surveillance versus radical treatment in low-risk PCa patients".

(Discussion, 266-273)

7. Lines 249 to 254: I do not understand what the authors mean by "…from 42 to 64 percent for PSA levels > 10 ng/ml."

Author response:
The reviewer is right, sorry for this poorly readable sentence. The sentence was replaced by:
In line with the literature we excluded men with high PSA levels as improved detection of significant PCa is most necessary in the PSA grayzone from 4-10 ng/mL, while men with higher PSA levels tend to be diagnosed accurately with a small amount of TRUS-guided systematic biopsies.

(Discussion, line 277-280)

8. Conclusion: (Line 279) I think it would be more in keeping with the level of evidence that this study provides to say the current study "suggests" rather than "demonstrates" an added value of 3D TRUS-guidance….

Author response:
We have revised our conclusion. The conclusion is now: "The current study suggests an added value of 3D TRUS-guidance and preembedding compared to conventional 2D GS TRUS-guidance regarding detection rate of PCa and clinically significant PCa among patients undergoing prostate biopsies."

(Conclusion, line 309-311)

New references