Detection of significant prostate cancer using target saturation in transperineal MRI/TRUS-fusion biopsy

Running Title: Target saturation biopsy for significant prostate cancer detection

Stephan Tschirdewahn, MD[1]; Manuel Wiesenfarth, PhD[2]; David Bonekamp, MD[3]; Lukas Püllen, MD[1]; Henning Reis, MD[4]; Andrej Panic, MD[1]; Claudia Kesch, MD[1]; Christopher Darr, MD[1]; Jochen Heß, MD[1]; Francesco Giganti, MD[5,6]; Caroline M Moore MD[6,7] ; Nika Guberina, MD[8]; Michael Forsting, MD[8]; Axel Wetter, MD[8]; Boris Hadaschik MD[1]; Jan Philipp Radtke, MD[1,3]

[1]Department of Urology, University Hospital Essen, Essen, Germany

[2] Division of Biostatistics, German Cancer Research Center (DKFZ), Heidelberg, Germany

[3] Department of Radiology, German Cancer Research Center (DKFZ), Heidelberg, Germany

[4] Institute of Pathology, University Duisburg-Essen, Essen, Germany

[5] Department of Radiology, University College London Hospitals NHS Foundation Trust, London, UK

[6] Division of Surgery and Interventional Science, University College London, London, UK

[7] Department of Urology, University College London Hospitals NHS Foundation Trust, London, UK

[8] Institute of Diagnostic and Interventional Radiology, University Hospital Essen, Essen, Germany

Corresponding author:

PD Dr. med. Jan Philipp Radtke

Department of Urology, University Hospital Essen

Hufelandstrasse 55, 45147 Essen

Tel.: +49 20172383069; Fax: +49 201723

Word count abstract: 300, Word count manuscript: 2699

MeSH Key words: Prostate cancer, MRI, targeted biopsy, target saturation, MRI/TRUS-fusion, detection accuracy of target saturation biopsy

Abbreviations:

DCE: Dynamic contrast-enhanced Imaging

DRE: Digital-rectal examination

ESUR: European Society of Urogenital Radiology

GGG: Gleason Grade group

mpMRI: multiparametric Magnetic Resonance Imaging

MRI: Magnetic Resonance Imaging

NPV: Negative predictive value

PC: Prostate cancer

PI-RADS: Prostate Imaging - Reporting and Data System

PSA: Prostate specific antigen

PV: Prostate volume

RP: Radical prostatectomy

SB: Systematic biopsy

sPC: Significant prostate cancer

STARD: Standards of Reporting of Diagnostic Accuracy

TB: Targeted biopsy

TRUS: transrectal ultrasound

TS: Target saturation biopsy

Abstract:

Background:

Multiparametric magnetic resonance imaging (mpMRI) and targeted biopsies (TB) facilitate accurate detection of significant prostate cancer (sPC). However, it remains unclear how many cores should be applied per target.

Objective:

To assess sPC detection rates of two different target-dependent MRI/transrectal ultrasonography **(TRUS)-fusion** biopsy approaches (TB and target saturation (TS)) **compared** to extended systematic biopsies (SB).

Design, setting and participants:

Retrospective single-centre outcome of transperineal MRI/TRUS-fusion biopsies of 213 men. All men underwent TB with 2-4 cores per MRI lesion, followed by a median of 24 SB, **performed by experienced urologists**. Cancer and sPC (ISUP grade group ≥ 2) detection rates were analyzed. TB was compared to SB and to TS with 9 cores per target, calculated by the Ginsburg scheme and using individual cores of the lesion and its “penumbra”.

Outcome measurements and statistical analysis:

Cancer detection rates were calculated for TS, TB and SB at both lesion and patient level. Combination of SB+TB served as reference. **Statistical differences in PC detection between groups were calculated using McNemar`s tests with Confidence intervals.**

Results and limitations:

TS detected 99% of 134 sPC lesions, which was significantly higher compared to TB (87%, p=0.001) and SB (82%, p<0.001). SB detected significantly more of the **72** low-risk PC lesions than TB (99 vs. 68%, p=0.01) and **10% (p=0.04)** more than TS. At a per-patient level, 99% of men harbouring sPC were detected by TS. This was significantly higher compared to TB and SB (89%, p=0.03 and 81%, p=0.001). Limitations include limited generalisability, as a transperineal biopsy route was used.

Conclusions:

TS detected significantly more sPC compared to TB and extended SB. Given that each 99% of sPC lesions and men harboring sPC were identified by TS, **the results suggest that** this approach allows to omit SB cores without compromising sPC detection.

Patient summary (40 words):

Target saturation of MRI-suspicious prostate lesions provides excellent cancer detection and finds less low-risk tumors than the current gold standard combination of targeted and systematic biopsies.

1. Introduction

Multiparametric MRI (mpMRI) of the prostate is increasingly used to accurately diagnose significant prostate cancer (sPC) [1–4]. **Recently evidence suggests that upfront MRI and targeted biopsy (TB) detect more sPC, while decreasing detection of low-risk PC [2–5]**. Subsequently, mpMRI **is recommended** prior to prostate biopsy [6,7]. This has led to debate whether TB alone is sufficient to accurately diagnose sPC, or if additional systematic biopsies (SB) are still necessary [2–6,8].

One issue in this context is the high negative predictive value (NPV) of mpMRI, which allows appropriate exclusion of sPC in over 90% of cases, indicating that patients with suspicious MRI lesions do not always require extensive SB in addition to the TB [9]. Bryk reported that the addition of six ipsilateral SB to TB significantly increased sPC detection, while contralateral SB detected mainly insignificant disease [10]. This elucidates the problem of potentially missing the most representative area within the target and the so called “penumbra” [7]. Transrectal (TRUS) MRI/ultrasonography (US) image fusion with 2–6 TB cores has been shown to detect up to 90% of sPC found at radical prostatectomy (RP) specimen [11,12]. Within the PRECISION trial, four TB cores outperformed a standard 10–12-core TRUS SB and comparable results have been recently demonstrated for two TB [2,8]. Although TB alone has advantages, especially for reducing the detection of Gleason grade group (GGG) 1 PC, this approach may lead to an unacceptable proportion of missed sPC [3,13]. Calio et al. reported that four TB cores predicted Gleason score at RP better than a single TB core [14]. The transperineal Ginsburg MRI/TRUS-fusion biopsy protocol includes two TB and an extended number of 18-24 SB cores [15]. Compared to this extended SB, two

TB cores alone detected 80% of sPC, suggesting that only two TB cores alone are insufficient [12]. The addition of four perilesional cores (“focal saturation”) improved the detection of sPC has been recently shown [4]. These results suggest that SB may be reduced if the lesion and adjacent tissue are adequately sampled.

The aim of this study is to analyse the sPC detection rate of a target saturation (TS) biopsy approach with 9-10 cores compared to TB and SB.

2. Patients and methods

2.1 Patient cohort

Consecutive patients were prospectively enrolled at University Hospital Essen between 2016-2018. Institutional review board approval was obtained (19-TEMP579281-BO) and all subjects provided written informed consent. **213** men without previous treatment or diagnosis of PC underwent 3T mpMRI and transperineal saturation biopsy with additional MRI-targeted cores in case of MRI-suspicious lesions, including **132** biopsy-naive patients with elevated prostate specific antigen (PSA)-levels and/or suspicious digital rectal examination (DRE) and **82** with previously negative TRUS-biopsy. Subgroups of this cohort were reported previously [16].

Inclusion criterion was a PI-RADS Version v2.0 guidelines-conform mpMRI prior to MRI/TRUS-fusion biopsy [17].

2.2 Imaging

Two 3T MR scanners (Magnetom Prisma and Biograph mMR, Siemens Healthcare, Erlangen, Germany) with a body coil (Supplementary Material 1) [17]. **The protocol was concordant with Prostate Imaging Reporting and Data System (PI-RADS) v2 guidelines [17].**

Image reporting was performed by an expert uroradiologist (AW, 10 years of experience in prostate MRI) unblinded to clinical data [17].

Lesions were reported using a 27-regions form-sheet [17]. The contours of PI-RADS 2–5 lesions were drawn on the MIM platform (MIM Symphony Inc., Cleveland, Ohio, USA).

2.3 MRI/TRUS-fusion biopsy:

The MIM MRI/TRUS-fusion biopsy system was used for all biopsies. All men had in median 24 SB cores according to the Ginsburg protocol [15]. Depending on the prostate volume, additional basal cores for larger prostates were taken using a customized software that calculates spatial organ coverage by biopsy-cores [18]. Grid-directed transperineal sector-biopsy under general anesthesia is the standard technique at our centre**.** Two to four TB cores were taken from each lesion prior to SB cores. All procedures were done by one of two urologists with 1-4 years of experience of transperineal fusion biopsy. The operator had access to all mpMRI data with radiologist-marked lesions of interest. All targets were sampled under live TRUS-visualisation. TB and SB cores were potted and reported separately.

2.4 Pathological work-up:

A dedicated uropathologist (HR, 12-year of experience) performed the histopathological assessment [19]. sPC was defined as Gleason Score ≥ 3+4, equivalent to GGG 2–5 [19]. (Supplementary Material 2).

2.5 Data analysis, definition and calculation of Target Saturation

Data were collected as per START guidelines [20]. Different biopsy templates were defined as follows:

i) SB: 24 systematic cores

ii) TB: 2-4 targeted cores

iii) TS was calculated from the four targeted cores from the target lesion plus cores from the adjacent SB sectors (Ginsburg protocol) resulting in 9-10 TS cores (Figure 1).

This scheme is slightly different from Hansen et al., where transperineal biopsies based on the Ginsburg scheme were also used, but 10-16 cores were applied to the target [13,15].

2.6 Statistical analysis:

Patient, MRI and biopsy data were analysed descriptively (Table 1).

To evaluate the magnitude of differences in detection rates among the different biopsy approaches for low-risk PC and sPC, we calculated rate differences along with 95% confidence intervals, according to Tango and performed McNemar`s-tests [21].

Potential predictors for favourable performance of TS over TB were calculated by logistic regression analysis. All tests were two-sided with a significance level of 5%. Bonferroni-Holm correction was used for multiple testing.

Statistical analyses were performed using R version 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria), SPSS version 22 (IBM, Armonk, NY, USA) and MedCalc version 14 (MedCalc Software, Ostend, Belgium). Reporting followed Standards of Reporting of Diagnostic Accuracy [22].

3. Results:

Demographics, baseline statistics, MRI and biopsy data of the **all** patients are listed in Table 1. In summary, 432 lesions occurred on mpMRI. 210 lesions (47%) were PI-RADS 3, 37% PI-RADS 4 and 12% PI-RADS 5. 131 (59%) of men harboured PC, 88 (40%) of which had sPC.

The results of the different PI-RADS lesions **on lesion- and patient-basis** according to non-PC, PC and sPC are in Table 2. Results of SB, TB and TS to detect low-risk PC and sPC are stratified to different PI-RADS lesions. Importantly, the sPC detection rate of TS was superior to TB for PI-RADS 4 lesions (100% vs. 85%, **p=0.007**), whereas the detection rate was comparable for bigger PI-RADS 5 lesions (100% vs. 92%, **p=0.13**). As compared to SB, the detection rate of TS was higher for PI-RADS 4 (81%, **p<0.001**) and PI-RADS 5 lesions (82%,**p=0.008**). **For PI-RADS 3 lesions, the detection rates were comparable between the biopsy approaches: 93% for TS and SB (p=1) versus 86% for TB (p=1).**

On a per-lesion level, TS detected 99% of the 134 sPC, which was significantly more than TB (87%, p=0.001) and SB (82%, p<0.001) (Table 3). Detection rates of SB and TB were comparable (p=1). SB detected significantly more low-risk cancers than TS (99% vs. 84%, p=0.02) and TB (99% vs. 65%, p<0.001).

On a per-patient level, TS detected 99% men with sPC and was significantly in favour compared to both SB (81%, p=0.001) and TB (89%, p=0.03). Low-risk cancer detection was lower for TB than SB (p=0.01) (Table 3). TS detected more GGG 1 PC than TB (p=0.06). **Substratifications for different PI-RADS scores on patient-level are in Table 2B.**

Subgroup analyses of detection rates for biopsy-naïve men and those after previous negative biopsy are presented in Table 3.

We also analyzed potential clinical and radiological predictors for **beneficial applying TS compared to TB for** detection of GGG ≥ 2 PC **(Table 4)**. **Only PSA was a significant predictor. Besides this, we give information on the detection rate of the different biopsy approaches for men with only one PI-RADS lesion and a flow-chart with a potential clinical decision pathway based on clinical and radiological findings (Supplementary Material 3 and 4).** Clinical parameters of missed lesions by each biopsy approach are in Table 5.

4. Discussion:

We demonstrate that a TS approach detected significantly more sPC compared to an extended SB and a TB approach on a per-lesion- and per-patient analysis, as proposed in the PI-RADSv2.1 guidelines, [7].

TB detected 87% sPC, as compared to the gold-standard of combined SB and TB.

Of note, the detection rate using a four-core TB with a rigid fusion-biopsy was higher than previously reported [10,23,24]. Using prostatectomy specimen as reference standard, the detection rate was comparable with a rate of 80% by our group and 82% by Ahdoot et al. [8,12]. However, the detection rate (87%) was lower than that reported by Calio et al. (94%) using a four-core TB approach [14]. One reason for our detection rate might be that only highly-experienced surgeons participated in our study, whereas less-experienced surgeons performed biopsy in other reports [12,23]. **When more experienced surgeons perform biopsies the detection rate improves** [25]**.** Importantly, missing the lesion on TB let to misclassification of sPC in 10% of men on a patient-level.

Despite the good results of TB only, targeting errors exist as demonstrated by the significant superiority of TS to detect sPC. On a per-lesion basis, the calculated TS approach detected 99% of sPC, compared to SB+TB. Our TS biopsy approach was similar to the one reported by Hansen et al., as shown by comparable detection rates [23]. Thus, one might conclude that in order to achieve an optimal detection rate for sPC, target saturation is needed.

Our TS approach, whichh includes four targeted cores plus 5-6 biopsies from the adjacent prostate, detects nearly all sPC and reduces total biopsy core numbers from a median of 33 to 9-10, depending on the number of suspicious lesions.

When the detection rates are analysed in detail (Tables 2, 3, 5 and Supplementary Material 3, 4), the PI-RADS score is important, as big lesions (i.e. PI-RADS 5) might need fewer cores because they are easier to target, whereas smaller lesions (i.e. PI-RADS 3 and 4) might suffer more from fusion errors and require a more extensive saturation of the target. However, on regression analysis, only the PSA-level was a significant predictor and neither PI-RADS score, nor DRE. Nevertheless, from a clinical point of view, in case of positive DRE and a PI-RADS 5 lesion, TB alone is sufficient (Supplementary Material 4). Beside this, TS is the favourable approach in PI-RADS 3 and 4 lesions (Table 2). TS (97%) was also in favour as compared to TB (84%) and SB (78%) for men with a solitary PI-RADS lesion. This was significant as compared to SB (p=0.04), but not to TB (p=0.13). Lastly, the proposed TS method is also in favour for anterior and smaller lesions. This is proven by the fact that missed lesions on TB are small (median 0.5 ml) and anteriorly located in 47% (Table 5). As only one lesion is missed by TS, the detection rates of >90% for the TS approach for those anterior, small or PI-RADS 3 and 4 lesions are comparable with previous literature [23].

This is in line with the PI-RADSv2.1 guidelines , recommending to target both the lesion and the perilesional ‘penumbra’. The concept that lesion size on MRI is underestimated compared to prostatectomy is also supported by other studies [12,26,27]. In

conclusion, all ‘target saturation biopsy methods’ are effective in overcoming potential targeting errors by surgeons or fusion-software and lesion size underestimation on MRI [23].

While the present study supports a TS biopsy approach for accurate detection of sPC, the role of the different approaches to detect low-risk PC should be also discussed. Applying TS would reduce the diagnosis of low-risk PC. As compared to SB, **10%** of low-risk PC lesions would not have been detected by TS. **This rate is comparable to the PRECISION trial (9% reduction) [2].**

A reduction to a TS template could safely replace the standard 20–26-core Ginsburg template [15]. As transperineal saturation biopsies are usually performed under general anaesthesia, a reduction to TS could also facilitate the biopsy procedure under local anaesthesia.

Regarding overall quality of MRI, detection rate of sPC in PI-RADS 3 lesions has become a surrogate parameter for experienced reading. In our cohort, the sPC detection rate in PI-RADS 3 was 7%, and therefore comparable to Ullrich et al., (6%) and the PRECISION trial (12%), with comparable population characteristics [2,28]. However, we certainly acknowledge the high number of PI-RADS 3 lesions, which are currently being addressed in order to be able to spare more men biopsy at all.

Our study has some limitations. **First, this is a retrospective single-centre analysis and the results need further confirmation in a prospectivemulticenter study, to investigate the detection rate of the TS approach in a head-to-head comparison. Another limitation is that TS biopsies have been calculated from TB and SB. The results should be confirmed by analysing TS versus TB and SB prospectively.**

Third, the applicability to other cohorts using a transrectal route may be limited by the administered transperineal biopsy route. **Extrapolating TS results to compare combined TB and 12-core TRUS SB cohorts is hypothetical because of the lack of direct comparison.** Most recently, Ahdoot et al. **found a 90% detection rate of such an approach as compared to RP specimen** [8]. **As TS detected 99% of sPC as compared to combined TB and extended SB, that in turn was comparable to RP pathology, one might suggest a detection rate increase in 5-10% compared to TB and conventional TRUS-biopsy [12].**

We did not assess the interobserver-variability for PI-RADS as previously reported [29].

Cost-effectiveness **is another limitation**. For this study, all MRIs had been performed for the MRI/TRUS-fusion biopsy, and cost-effectiveness of diagnostic MRI has been recently suggested [30].

We analysed only men with PI-RADS≥3 lesions. While this is necessary for an intra-lesion analysis of different biopsy-approaches, this may limit generalizability for men without PI-RADS lesions.

We also emphasize that the results of our study might not be generalizable to cohorts and centres without experienced radiologists and surgeons.

Lastly, a limitation of this study is the lack of RP specimens as reference standard. However, this design allowed us to include all men in the analysis and not only those who had PC. In addition, our group has recently demonstrated that TB combined with SB according to the Ginsburg protocol detected sufficiently sPC in 97% of cases, as compared to RP specimen [12].

312

5. Conclusion

The TS approach detected significantly more sPC compared to TB and extended SB. Given that each 99% of sPC lesions and men harboring sPC were identified by TS alone, **our findings suggest** omitting SB cores without compromising sPC detection, particularly in PI-RADS 4 lesions.

Conflict of interest:

All authors of this manuscript indicate no conflicts of interest for the present work.

Francesco Giganti is funded by the UCL Graduate Research Scholarship and the Brahm PhD scholarship in memory of Chris Adams.

References:

[1] Ahmed HU, El-Shater Bosaily A, Brown LC, Gabe R, Kaplan R, Parmar MK, et al. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. Lancet 2017;389:815–22. doi:10.1016/S0140-6736(16)32401-1.

[2] Kasivisvanathan V, Rannikko AS, Borghi M, Panebianco V, Mynderse LA, Vaarala MH, et al. MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis. N Engl J Med 2018;318:1767–77. doi:10.1056/NEJMoa1801993.

[3] Rouvière O, Puech P, Renard-Penna R, Claudon M, Roy C, Mège-Lechevallier F, et al. Use of prostate systematic and targeted biopsy on the basis of multiparametric MRI in biopsy-naive patients (MRI-FIRST): a prospective, multicentre, paired diagnostic study. Lancet Oncol 2019;20:100–9. doi:10.1016/S1470-2045(18)30569-2.

[4] van der Leest M, Cornel E, Israël B, Hendriks R, Padhani AR, Hoogenboom M, et al. Head-to-head Comparison of Transrectal Ultrasound-guided Prostate Biopsy Versus Multiparametric Prostate Resonance Imaging with Subsequent Magnetic Resonance-guided Biopsy in Biopsy-naïve Men with Elevated Prostate-specific Antigen: A Large Prospective Mu. Eur Urol 2019;75:570–8. doi:10.1016/j.eururo.2018.11.023.

[5] Drost FJ, Osses DF, Nieboer D, Bangma CH, Steyerberg EW, Roobol MJ, et al. Prostate MRI, with or without targeted biopsy and standard biopsy for detecting prostate cancer: A Cochrane systematic review and meta-analysis. Cochrane Database Syst Rev 2019;4:CD012663. doi:10.1016/s1569-9056(19)30534-2.

[6] Mottet N, van den Bergh RCN, Briers E, Cornford P, De Santis M, Fanti S, et al. EAU - EANM - ESTRO - ESUR - SIOG Guidelines on Prostate Cancer 2019 2019;978-94–926.

[7] Padhani AR, Weinreb J, Rosenkrantz AB, Villeirs G, Turkbey B, Barentsz J. Prostate Imaging-Reporting and Data System Steering Committee: PI-RADS v2 Status Update and Future Directions. Eur Urol 2019;75:385–96. doi:10.1016/j.eururo.2018.05.035.

[8] Ahdoot M, Wilbur AR, Reese SE, Lebastchi AH, Mehralivand S, Gomella PT, et al. MRI-Targeted, Systematic, and Combined Biopsy for Prostate Cancer Diagnosis. N Engl J Med 2020;382:917–28. doi:10.1056/NEJMoa1910038.

[9] Panebianco V, Barchetti G, Simone G, Del Monte M, Ciardi A, Grompone MD, et al. Negative Multiparametric Magnetic Resonance Imaging for Prostate Cancer: What's Next? Eur Urol 2018;74:48–54. doi:10.1016/j.eururo.2018.03.007.

[10] Bryk DJ, Llukani E, Taneja SS, Rosenkrantz AB, Huang WC, Lepor H. The Role of Ipsilateral and Contralateral Transrectal Ultrasound-guided Systematic Prostate Biopsy in Men With Unilateral Magnetic Resonance Imaging Lesion Undergoing Magnetic Resonance Imaging-ultrasound Fusion-targeted Prostate Biopsy. Urology 2017;102:178–82. doi:10.1016/j.urology.2016.11.017.

[11] Baco E, Ukimura O, Rud E, Vlatkovic L, Svindland A, Aron M, et al. Magnetic Resonance Imaging-Transectal Ultrasound Image-fusion Biopsies Accurately Characterize the Index Tumor: Correlation with Step-sectioned Radical Prostatectomy Specimens in 135 Patients. Eur Urol 2015;67:787–94. doi:10.1016/j.eururo.2014.08.077.

[12] Radtke JP, Schwab C, Wolf MB, Freitag MT, Alt CD, Kesch C, et al. Multiparametric Magnetic Resonance Imaging (MRI) and MRI – Transrectal Ultrasound Fusion Biopsy for Index Tumor Detection: Correlation with Radical Prostatectomy Specimen. Eur Urol 2016;70:846–53. doi:10.1016/j.eururo.2015.12.052.

[13] Hansen NL, Kesch C, Barrett T, Koo B, Radtke JP, Bonekamp D, et al. Multicentre evaluation of targeted and systematic biopsies using magnetic resonance and ultrasound image-fusion guided transperineal prostate biopsy in patients with a

previous negative biopsy. BJU Int 2017;120:631–8. doi:10.1111/bju.13711.

[14] Calio BP, Sidana A, Sugano D, Gaur S, Maruf M, Jain AL, et al. Risk of Upgrading from Prostate Biopsy to Radical Prostatectomy Pathology—Does Saturation Biopsy of Index Lesion during Multiparametric Magnetic Resonance Imaging-Transrectal Ultrasound Fusion Biopsy Help? J Urol 2018;199:976–82. doi:10.1016/j.juro.2017.10.048.

[15] Kuru TH, Wadhwa K, Chang RT, Echeverria LM, Roethke M, Polson A, et al. Definitions of terms, processes and a minimum dataset for transperineal prostate biopsies: a standardization approach of the Ginsburg Study Group for Enhanced Prostate Diagnostics. BJU Int 2013;112:568–77. doi:10.1111/bju.12132.

[16] Püllen L, Radtke JP, Wiesenfarth M, Roobol MJ, Verbeek JFM, Wetter A, et al. External validation of novel magnetic resonance imaging-based models for prostate cancer prediction. BJU Int 2020;125:407–16. doi:10.1111/bju.14958.

[17] Weinreb JC, Barentsz JO, Choyke PL, Cornud F, Haider M, Macura KJ, et al. PI-RADS Prostate Imaging and Reporting and Data System: 2015, Version 2. Eur Urol 2016;69:16–40. doi:10.1016/j.eururo.2015.08.052.

[18] Kesch C, Radtke JP, Popeneciu IV, Gasch C, Dieffenbacher SC, Klein T, et al. TOP: Prospective evaluation of a volume based, computer assisted method for transperineal optimized prostate biopsy. Urol Int 2017;99:149–55. doi:10.1159/000458764.

[19] Epstein JI, Egevad L, Amin MB, Delahunt B, Srigley JR, Humphrey PA. The 2014 international society of urological pathology (ISUP) consensus conference on gleason grading of prostatic carcinoma definition of grading patterns and proposal for a new grading system. Am J Surg Pathol 2016;40:244–52. doi:10.1097/PAS.0000000000000530.

[20] Moore CM, Kasivisvanathan V, Eggener S, Emberton M, Futterer JJ, Gill IS, et al.

Standards of reporting for MRI-targeted biopsy studies (START) of the prostate: recommendations from an International Working Group. Eur Urol 2013;64:544–52. doi:10.1016/j.eururo.2013.03.030.

[21] Tango T. Equivalence test and confidence interval for the difference in proportions for the paired-sample design. Stat Med 1998;17:891–908. doi:10.1002/(SICI)1097-0258(19980430)17:8<891::AID-SIM780>3.0.CO;2-B.

[22] Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis C a, Glasziou PP, Irwig LM, et al. Towards complete and,accurate reporting of studies of diagnostic accuracy: the STARD initiative. Radiology 2003;226:24–8. doi:10.1136/bmj.326.7379.41.

[23] Hansen NL, Barrett T, Lloyd T, Warren A, Samel C, Bratt O, et al. Optimising the number of cores for magnetic resonance imaging-guided targeted and systematic transperineal prostate biopsy. BJU Int 2020;125:260–9. doi:10.1111/bju.14865.

[24] Mischinger J, Kaufmann S, Russo GI, Harland N, Rausch S, Amend B, et al. Targeted vs systematic robot-assisted transperineal magnetic resonance imaging-transrectal ultrasonography fusion prostate biopsy. BJU Int 2018;121:791–8. doi:10.1111/bju.14089.

[25] Calio B, Sidana A, Sugano D, Gaur S, Jain A, Maruf M, et al. Changes in prostate cancer detection rate of MRI-TRUS fusion vs systematic biopsy over time: Evidence of a learning curve. Prostate Cancer Prostatic Dis 2017;20:436–41. doi:10.1038/pcan.2017.34.

[26] Le Nobin J, Rosenkrantz AB, Villers A, Orczyk C, Deng F-M, Melamed J, et al. Image Guided Focal Therapy Of MRI-Visible Prostate Cancer: Defining a 3D Treatment Margin based on MRI-Histology Co-registration Analysis. J Urol 2015;194:364–70. doi:10.1016/j.juro.2015.02.080.

[27] Bonekamp D, Schelb P, Wiesenfarth M, Kuder TA, Deister F, Stenzinger A, et al. Histopathological to multiparametric MRI spatial mapping of extended systematic

sextant and MR / TRUS-fusion-targeted biopsy of the prostate Standards of Reporting of Diagnostic Accuracy. Eur Radiol 2018;29:1820–30.

[28] Ullrich T, Quentin M, Arsov C, Schmaltz AK, Tschischka A, Laqua N, et al. Risk stratification of 'equivocal' PI-RADS lesions in mp-MRI of the prostate. J Urol 2018;199:691–8. doi:10.1016/j.juro.2017.09.074.

[29] Rosenkrantz AB, Ginocchio LA, Cornfeld D, Froemming AT, Gupta RT, Turkbey B, et al. Interobserver Reproducibility of the PI-RADS Version 2 Lexicon: A Multicenter Study of Six Experienced Prostate Radiologists. Radiology 2016;280:793–804.

[30] Faria R, Soares MO, Spackman E, Ahmed HU, Brown LC, Kaplan R, et al. Optimising the Diagnosis of Prostate Cancer in the Era of Multiparametric Magnetic Resonance Imaging: A Cost-effectiveness Analysis Based on the Prostate MR Imaging Study (PROMIS). Eur Urol 2018;73:23–30. doi:10.1016/j.eururo.2017.08.018.

Table legends:

Table 1:

Demographic, MRI and histopathologic results of the study population according to START criteria

Table 2:

Histological biopsy outcomes of different PI-RADSv2 Likert scores on a A) per-lesion level and B) on per-patient level

Table 3:

Results of McNemar`s tests for the comparison of detection rates for different biopsy approaches for a) lesion-based analysis and b) patient-based analysis including Confidence intervals according to Tango [21]

Table 4:

Clinical parameters of missed significant PC lesions by each biopsy approach

Table 5:

Clinical parameters of missed lesions by each biopsy approach

Supplementary Material 1:

Exemplary protocol of prostate mpMRI performed at Siemens Biography mMR

Supplementary Material 2:

Histopathologic details on fixation and reported parameters per lesion

Supplementary Material 3:

Supplementary Material 4:

Figure legends:

Figure 1:

Ginsburg scheme for prostate biopsy including 24 systematic cores and four targeted cores (blue)[15]. Template for Target saturation is given in red, including the combination of four targeted cores and 5 cores from the Ginsburg template.