# Multicentre evaluation of target and systematic biopsies using Magnetic Resonance and Ultrasound Image-Fusion guided Transperineal Prostate Biopsy in patients with a previous negative biopsy.

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**Abstract**

**Objectives:** To evaluate the detection rates of targeted and systematic biopsies in magnetic resonance (MRI) and transrectal ultrasound (US) image-fusion transperineal prostate biopsy for patients with previous benign transrectal US guided biopsies in two high-volume centres.

**Patients and methods:** Two centre, prospective outcome study of 487 patients with previous benign biopsies that underwent transperineal MRI/US fusion-guided target and systematic saturation biopsy from 2012 to 2015. MRI was reported according to PIRADS Version 1. Detection of Gleason score (GS) 7-10 cancer (PCa) on biopsy was the primary outcome. Positive (PPV) and negative (NPV) predictive values including 95% confidence intervals were calculated. Detection rates of targeted and systematic biopsies were compared using McNemar's test.

**Results:** Median PSA was 9.0 (IQR 6.7-13.4) ng/ml. PIRADS 3-5 MRI lesions were reported in 343 (70%) patients. GS 7-10 PCa was detected in 149 (31%). PPV for detecting GS 7-10 PCa was 0.20 (±0.07) for PIRADS 3, 0.32 (±0.09) for PIRADS 4, and 0.70 (±0.08) for PIRADS 5. NPV of PIRADS 1-2 was 0.92 (±0.04) for GS 7-10 and 0.99 (±0.02) for GS ≥ 4+3 cancer. Systematic biopsies alone found 125/138 (91%) GS 7-10 cancers. In patients with suspicious lesions (PIRADS 4-5) on MRI, systematic biopsies would not have detected 12/113 significant PCa (11%), while targeted biopsies alone would have failed to diagnose 10/113 (9%). In equivocal lesions (PIRADS 3), targeted biopsy alone would not have diagnosed 14/25 (56%) of GS 7-10, whereas systematic biopsies alone would have missed 1/25 (4%). Combination with PSA-density improved the AUC of PIRADS from 0.822 to 0.846.

**Conclusion:**

In patients with high probability MRI lesions, the highest detection rates of GS 7-10 cancer still required combined targeted and systematic MRI/TRUS image-fusion, however, systematic biopsy alone may be sufficient in patients with equivocal lesions. Repeated prostate biopsies may not be needed at all for patients with a low PSA-density and a negative MRI read by experienced radiologists.

**Introduction**

Multiparametric magnetic resonance imaging (MRI) of the prostate plays an increasingly important role in prostate cancer (PCa) diagnostics. A non-suspicious MRI has a high negative predictive value (NPV) for the detection of Gleason score (GS) ≥7 cancer on biopsy [1-4] International guidelines therefore currently recommend MRI of the prostate for men with previous negative biopsies and for staging purposes in patients with biopsy proven cancer [5-7]. The use of MRI/TRUS image-fusion promises to be useful in primary biopsy. Most importantly, the technique may provide more accurate primary risk stratification [8-10]: Localisation, extent and GS of cancer found in fusion biopsies correlate with the final result of prostatectomy specimens [11,12]. Yet, MRI may miss GS ≥7 cancer in 8-24% of patients, when a radical prostatectomy specimen is used as the reference method [13-15]. There is conflicting evidence whether targeted biopsies alone or a combination of targeted and systematic biopsies are the best approach as well as controversy to the number of cores taken and the route [16] [10,15,17-20]. Given the conflicting evidence to date, the aim of our study was therefore to prospectively clarify the detection rates of targeted and systematic transperineal MR/US image-fusion prostate biopsies in patients with previous negative transrectal US guided biopsies using the data from two different tertiary referral centres.

## Patients and Methods

### Standards of reporting

The Standards of Reporting for MRI-targeted Biopsy Studies (START) were used to describe the study population, the conduct and reporting of the MRI, the conduct of the biopsy, and the results [21]. The biopsy technique and data collection was prospectively standardised according to the Ginsburg consensus [22].

### Study population

Patients with previous negative TRUS biopsies according to local standard without the diagnosis or treatment of prostate cancer were included in the evaluation. From 10/2012 to 11/2015, 287 patients underwent multiparametric MRI and subsequent transperineal prostate biopsies in centre 1, and 200 patients in centre 2. None of the patients had previously undergone transperineal biopsy. The objective was to identify clinically significant cancer, defined as Gleason score 7-10. The final study cohort comprised 487 patients. The indication for repeat biopsy in the patients were either rising PSA values (n=404) or a previous biopsy specimen showing suspicion of cancer (atypical small acinar proliferation) or multifocal high-grade prostatic intraepithelial neoplasia (n=83). The patients' clinical characteristics are shown in Table 1.

### Ethical approval

All patients were counselled about the risks of the procedure and thereafter signed a consent form that included a permission to use their clinical data for research. The study was approved as a service evaluation by local ethics and audit committees in both centres.

### Magnetic resonance imaging

In centre 1, all patients underwent prostate MRI on a 3.0 T Magnetom (Siemens, Erlangen, Germany) with the use of the manufacturer´s standard multi-channel body coil and integrated spin phased-array coil as previously described [15]. Patients in centre 2 underwent prostate MRI on a 1.5 T MR450 (n=20) or 3.0 T Discovery MR750 HDx (n=180) (GE Healthcare, Waukesha, USA) with an 8-16 channel surface phased array coil as previously described [4] The MR imaging protocols are shown in Supplementary Table 1.

### Image analysis

The MRIs were read by at least one uro-radiologists with more than 3 years' experience of prostate MRI at a high-volume prostate cancer centre. All radiologists have ongoing histological feedback on more than 150 MRI per year. Images were analysed according to the Prostate Imaging-Reporting and Data System (PIRADS) version 1 [23] and a final score was defined by combining all three scores for T2w, DWI and DCE, respectively according to criteria as described in PIRADS version 2 [24].

### Biopsy

The Biopsee[TM] MRI/TRUS fusion biopsy system (Medcom, Darmstadt, Germany) was used for all biopsies. All men underwent systematic transperineal biopsies volume-

based with a median of 24 cores according to the Ginsburg protocol [4,22]. In patients with PIRADS 3-5 MRI lesions, at least 2 biopsy cores were taken from each lesion before the systematic biopsies. All procedures were done by residents in Urology in centre 1 and by 1 of 3 urologists with several years' experience of transperineal biopsy in centre 2.

**Histopathology**

For the time period of this study, all biopsies were graded with a Gleason score according to the ISUP 2005 recommendations by at least one specialist uropathologist [25]. The final histology result following this specialist assessment was used as data for this study. According to the recently internationally accepted new prostate cancer grading system, adopted by the WHO in 2016, the clinically significant cancers as defined in this study as Gleason Score 7-10 would be equivalent to combined Grade Groups 2-5, with Gleason score 4+3=7 alone being Grade Group 3, and those Gleason Score 6 cancers regarded as clinically insignificant are equivalent to Grade Group 1 [26].

**Statistics**

All data was collected prospectively in each centre. Descriptive statistics were used and positive (PPV) and negative (NPV) predictive values including 95% confidence intervals were calculated, using the combined systematic transperineal biopsy +/- targeted biopsies as reference test, which has been recently validated [15]. In addition, predictive values and detection rates were calculated for PSA-densities of ≤ 0.15 ng/ml/cm$^3$ and > 0.15 ng/ml/cm$^3$. Detection rates of targeted and systematic cores were compared for each centre and combined. McNemar test was used to test for statistical significance. Statistics was done using IBM SPSS Statistics 22 (IBM, Armonk, USA).

**Results**

The distribution of MRI findings is shown is Table 2. One or more lesion suspicious for cancer on MRI (PIRADS 3-5) was found in 70% of the patients. The median number of target lesions was 1 (IQR: 1-3). The median number of targeted biopsy cores per patient was 3 (IQR: 2-4) and the median number of systematic cores was 24 (IQR 24-26).

**Prostate cancer detection, NPV and PPV of MRI**

The biopsy results are shown in Table 3. Gleason score 7-10 cancer was detected in 31% (149/487) of the patients. In our study, 13/87 GS 7-10 cancers in centre 1 and 27/62 in centre 2 were found exclusively in the anterior zone of the prostate, resulting in 27% of clinically significant tumours. Nevertheless, the other 73% were found in areas supposedly representatively sampled previously by TRUS biopsies. The systematic biopsies in the 144 patients with PIRADS 1-2 MRI findings (i.e. with no suspicious lesion) detected cancer in 40 patients (28%), the majority of whom had Gleason score 6 cancer (29 patients). The NPV of PIRADS 1-2 findings was 0.72 for excluding any cancer, 0.92 for excluding Gleason score 7-10 and 0.99 for excluding Gleason score ≥ 4+3=7 cancer (Table 4), with no significant differences between the centres. Of 11 (8%) GS 7-10 cancers in 144 patients with PIRADS 1-2 lesions were 10 (7%) GS 3+4 and 1 (1%) GS 8.

PIRADS 3-5 lesions were found on MRI in 343 men. The targeted and systematic biopsies detected cancer in 209 (61%) and GS 7-10 cancer in 138 (40%) of these patients. The PPV of MRI PIRADS 3-5 was 0.61 for detecting any cancer, 0.40 for detecting GS 7-10 cancer, and 0.20 for detecting GS ≥ 4+3=7 cancer. The PPV increased with increasing PIRADS score: the PPV for detecting 7-10 cancer was 0.20 for PIRADS 3, 0.32 for PIRADS 4, and 0.70 for PIRADS 5, with no significant difference between both centres. The PPVs for any and for GS ≥ 3+4=7 cancer, stratified for the 3 different patient groups, are shown in Table 4. Of 25 (20%) GS 7-10 cancers in 128 patients with an equivocal PIRADS 3 lesion on MRI, 13 (10%) were GS 3+4, 9 (7%) GS 4+3, and 3 (2%) GS 8-10.

**Combination of PIRADS and PSA-density**

Taking PSA-density into account improved the predictive values of PIRADS 3-5. The NPV of PIRADS 1-2 findings for excluding GS 7-10 cancer was 0.93 (79/85) for men with a PSA-density ≤ 0.15 ng/ml/cm$^3$ and 0.92 (54/59) for men with a PSA-density > 0.15 ng/ml/cm$^3$. Positive predictive values were higher with rising PSA-density, from 0.11 with a PSA-Density ≤ 0.15 ng/ml/cm$^3$ to 0.33 with a PSA-Density > 0.15 ng/ml/cm$^3$ for PIRADS 3 lesions and from 0.33 with ≤ 0.15 ng/ml/cm$^3$ to 0.65 with > 0.15 ng/ml/cm$^3$ for PIRADS 4-5 lesions (Table 5). The area under the curve (AUC) for the two density-groups alone was 0.674 and for PIRADS alone 0.822. The combination of both improved the AUC to 0.846, which is significant compared to PIRADS alone (p=0.046) (Figure 2).

**Comparison of detection rates in targeted and systematic cores**

Systematic biopsies in patients with PIRADS 3-5 lesions on MRI did not detect 13/138 significant PCa with 2 GS 3+4, 11 GS 4+3. Targeted biopsies of PIRADS 3-5 lesions

alone failed to diagnose 24/138 significant PCa with 8 GS 3+4, 12 GS 4+3 and 4 GS 8-10. A combination of targeted and systematic biopsies was significantly better than either method alone for the detection of significant GS 7-10 cancer (p=0.0001-0.0009) (Table 6). Systematic biopsies alone in patients with suspicious lesions (PIRADS 4-5) on MRI would not have detected 12/113 significant PCa (p=0.0015) while performing only targeted biopsies of suspicious lesions would have failed to diagnose 10/113 significant PCa (p=0.0044). In equivocal lesions (PIRADS 3), targeted biopsy alone would not have diagnosed 14/25 of GS 7-10, whereas performing only systematic biopsies would have only missed 1/25 GS 4+3 cancer, with no significant difference in detection rate between systematic and combined biopsy (p=1.0).

**Discussion**

Our report presents the largest series of MRI/TRUS image-fusion guided transperineal prostate biopsies in patients with previous negative TRUS biopsies, with the advantage of a multicentre comparison based on a prospectively standardised technique and data collection to evaluate the introduction of the use of MRI-based diagnostics in our centres.

Despite previous negative conventional transrectal biopsies, 51% of patients had cancer in the transperineal MR/US fusion biopsy and 31% had clinically significant disease. 73% GS 7-10 cancers were found in the previously sampled mid to posterior zone of the prostate. With a suspicious MRI (PIRADS 4-5), detection rates rose to 71% for any cancer and 53% with GS 7-10. With a non-suspicious MRI (PIRADS 1-2), the negative predictive value for excluding Gleason score 7-10 cancer was 92%, using systematic transperineal saturation biopsy as reference test. Our results suggest that in men without suspicious lesions on high quality MR imaging, biopsy might be omitted altogether, and replicate the high negative predictive values that have been repeatedly published previously [4,17,19,27,28]. In our study, 11 (8%) GS 7-10 cancers in 144 patients with PIRADS 1-2 MRI would have remained undiagnosed, only 1/11 being a GS ≥ 4+3, whilst sparing 144 men (30%) a repeat biopsy. By adding a PSA density cutoff, it may be possible to further increase the negative predictive value of mpMRI [29]. In our study, the NPV of MRI for men with PSA-density <0.15 was 0.93, with 5 GS 3+4 and 1 GS 8.

The combination of targeted and systematic biopsies was significantly superior to either method alone for the detection of significant GS 7-10 cancer (p=0.0001-0.0009). This multicentre result complements previous results from Radtke et al. in prostatectomy patients [15]. Several other studies have compared MR/US targeted biopsy to systematic ultrasound-guided (TRUS) biopsy with diverging results depending on type of systematic biopsy employed or number of cores taken: Some found that MR/US fusion targeted transrectal biopsy leads to increased detection of high-risk cancer and decreased detection of low-risk cancer but missed up to 6% higher risk tumors [10,17,30,31], others found similar detection rates in systematic and targeted transrectal biopsies [18,32].

In patients with equivocal lesions (PIRADS 3), there was no significant difference between systematic biopsies alone and the combination of both targeted and systematic biopsy methods (p=1.000). Systematic biopsies alone would have missed only 1/25 (4%) GS 7-10 cancer, whereas targeted biopsy alone would not have diagnosed 14/25 (56%) of GS 7-10. These results suggest that the confidence of our radiologist to call the visible lesion significant (PIRADS 4 instead of 3) was clearly and rightly low which is proven by the fact that the addition of targeted biopsy does not add value to systematic biopsies in this group. Work is needed to distinguish these equivocal lesions further into insignificant and significant. When counselling such patients whether or not and how to undergo repeat biopsy, urologists should include clinical risk factors like PSA, and PSA density. In our study, equivocal (PIRADS 3) lesions on MRI in patients with a low PSA density had a NPV of 0.89. Proceeding without biopsy can be considered for such patients with follow-up in place.

For suspicious lesions (PIRADS 4-5), both biopsy methods alone were inferior to the combination of both (p =0.0001 and p=0.0009) but systematic biopsies missed more significant PCA (12/113) than targeted biopsy (10/113). These results stress the need to improve the technique of targeted biopsies before an omission of systematic biopsies in patients with suspicious MRI can be taken into further consideration. Failure to detect significant cancer in targeted biopsies can have several explanations: communication of reports between radiology and urology, patient factors, fusion-technique, and biopsy core number can affect the accuracy of cancer detection. Additionally, patient positioning, breathing movements, and deformation of the prostate gland during the biopsy procedure can lead to incorrect fusion of previously acquired MR images and real-time ultrasound despite using software registration, general anaesthesia and experienced operators. A way to overcome these limitations, would be the use of "saturation" target cores, with more cores per lesion to improve detection rates. For this reason, centre 1 had started to take a minimum of 4 targeted biopsies per lesion or more (Figure 1) towards the end of the study period and centre 2 since analysis of joint data was available.

A strength of our study is that we prospectively collected data on a repeat biopsy population in a multicentre setting using a combination of targeted and systematic transperineal saturation biopsy as the reference. Next to radical prostatectomy specimens and transperineal mapping, this is the most valid means of assessing for clinically significant PCa, especially in a patient population in which not all patients need to undergo prostatectomy.

Our study has several limitations. Despite prospective collection of data, the analysis performed was retrospectively. Our results cannot necessarily be applied to patients without previous biopsies. As Radtke et al. and Hansen et al demonstrated, first biopsy patients are more likely to have higher predictive values in transperineal MR/US fusion biopsy than patients with previous negative TRUS biopsies [4,19]. Also, the high cancer detection rate in systematic cores could be influenced by the fact that these also included the cores from the sector where a target was found, resulting in a possible bias to resampling the targets as urologists were not blinded to them. We also acknowledge that the parameter of GS 7-10 cancer as the definition of clinically significant cancer is debatable. Our analysis has not taken into account the amount of large volume GS 6 or small volume GS 3+4. The incorporation of cancer volume via the number of infiltrated cores and the maximum cancer core length is currently being incorporated into clinical practice.

**Conclusion**
In patients with high probability MRI lesions, the highest detection rates of GS 7-10 cancer still required combined targeted and systematic MRI/TRUS image-fusion, however, systematic biopsy alone may be sufficient in patients with equivocal lesions. Repeated prostate biopsies may not be needed at all for patients with a low PSA-density and a negative MRI read by experienced radiologists.

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**Figures**

**Figure 1.** Patient with two suspicious MRI lesions with four targeted cores in each lesion (L26-L29 in lesion 1; L30-L33 in lesion 2). **A** Contoured and fused transversal MRI slice on the level of lesion 2. **B** Systematic, transversal projection of the whole prostate.

**Figure 2.** ROC-curves for the two density-groups ($\leq 0.15$ ng/ml/cm$^3$/>0.15 ng/ml/cm$^3$) = line 1(AUC 0.674), PIRADS = line 2 (AUC 0.822) and the combination of density-groups and PIRADS = line 3 (AUC 0.846)

**Tables**

**Table 1.** Clinical characteristics of the patients included in the study. Abbreviation: PSA = prostate-specific antigen. IQR = interquartile range.

|  | Overall n=487 | Centre 1 n=287 | Centre 2 n=200 |
|---|---|---|---|
| Age (years): median / IQR | 66 / 60-71 | 66 / 61-72 | 65 / 60-69 |
| PSA (ng/ml): median / IQR | 9.0 / 6.7-13.4 | 9.7 / 7.1-13.9 | 7.9 / 6.0-11.8 |
| Prostate volume(ml): median / IQR | 56 / 40-80 | 52 / 36-75 | 66 / 44-84 |
| PSA- Density (ng/ml/ml): median / IQR | 0.15 / 0.10-0.24 | 0.17 / 0.12-0.31 | 0.13 / 0.09-0.19 |
| Number of targeted cores Median / IQR | 3 / 2-4 | 2 / 2-4 | 4 / 2-5 |
| Number of systematic cores median / IQR | 24 / 24-26 | 24 / 24-25 | 24/ 23-26 |

**Table 2.** Findings on multiparametric magnetic resonance imaging (MRI) in 487 men with suspicion of prostate cancer after previous negative biopsies.

| MRI findings | All patients | | Centre 1 | | Centre 2 | |
|---|---|---|---|---|---|---|
|  | N | % | n | % | n | % |
| PIRADS 1-2 | 144 | 30% | 91 | 32% | 53 | 27% |
| PIRADS 3-5 | 343 | 70% | 196 | 68% | 147 | 74% |
| PIRADS 3 | 128 | 26% | 76 | 26% | 52 | 26% |
| PIRADS 4 | 100 | 21% | 58 | 20% | 42 | 21% |
| PIRADS 5 | 115 | 24% | 62 | 22% | 53 | 27% |
| Total | **487** | **100%** | **287** | **100%** | **200** | **100%** |

**Table 3.** Biopsy results after a transperineal MRI/TRUS-fusion guided targeted and 24-core systematic prostate biopsy. Abbreviation: GS = Gleason score.

| | Overall | | Centre 1 | | Centre 2 | |
|---|---|---|---|---|---|---|
| | n | % | n | % | n | % |
| All patients | 487 | 100% | 287 | 100% | 200 | 100% |
| Any cancer | 249 | 51% | 148 | 52% | 101 | 51% |
| GS 3+4=7 | 77 | 16% | 44 | 15% | 33 | 17% |
| GS 4+3=7 | 44 | 9% | 30 | 10% | 14 | 7% |
| GS 8-10 | 28 | 6% | 13 | 5% | 15 | 8% |
| | | | | | | |
| PIRADS 1-2: | 144 | 100% | 91 | 100% | 53 | 100% |
| Any cancer | 40 | 28% | 24 | 26% | 16 | 30% |
| GS 3+4=7 | 10 | 7% | 5 | 5% | 5 | 9% |
| GS 4+3=7 | 0 | 0% | 0 | 0% | 0 | 0% |
| GS 8-10 | 1 | 1% | 0 | 0% | 1 | 2% |
| | | | | | | |
| PIRADS 3-5: | 343 | 100% | 196 | 100% | 147 | 100% |
| Any cancer | 209 | 61% | 124 | 63% | 85 | 58% |
| GS 3+4=7 | 67 | 20% | 39 | 20% | 28 | 19% |
| GS 4+3=7 | 44 | 13% | 30 | 15% | 14 | 10% |
| GS 8-10 | 27 | 8% | 13 | 7% | 14 | 10% |
| | | | | | | |
| PIRADS 3: | 128 | 100% | 76 | 100% | 52 | 100% |
| Any cancer | 56 | 44% | 37 | 49% | 19 | 37% |
| GS 3+4=7 | 13 | 10% | 8 | 11% | 5 | 10% |
| GS 4+3=7 | 9 | 7% | 8 | 11% | 1 | 2% |
| GS 8-10 | 3 | 2% | 1 | 1% | 2 | 4% |
| | | | | | | |
| PIRADS 4: | 100 | 100% | 58 | 100% | 42 | 100% |
| Any cancer | 58 | 58% | 35 | 60% | 23 | 55% |
| GS 3+4=7 | 20 | 20% | 10 | 17% | 10 | 24% |
| GS 4+3=7 | 6 | 6% | 4 | 7% | 2 | 5% |
| GS 8-10 | 6 | 6% | 4 | 7% | 2 | 5% |
| | | | | | | |
| PIRADS 5: | 115 | 100% | 62 | 100% | 53 | 100% |
| Any cancer | 95 | 83% | 52 | 84% | 43 | 81% |
| GS 3+4=7 | 34 | 30% | 21 | 34% | 13 | 25% |
| GS 4+3=7 | 29 | 25% | 18 | 29% | 11 | 21% |
| GS 8-10 | 18 | 16% | 8 | 13% | 10 | 19% |

**Table 4.** The negative (NPV) and positive (PPV) predictive values of multiparametric MRI using a transperineal MRI/TRUS-fusion guided targeted and 24-core systematic prostate biopsy as the reference test. Abbreviation: GS = Gleason score.

| | Overall n=487 | | | Centre 1 n=287 | | | Centre 2 n=200 | | |
|---|---|---|---|---|---|---|---|---|---|
| | n | | 95% CI | n | | 95% CI | n | | 95% CI |
| **PIRADS 1-2:** | | | | | | | | | |
| NPV any cancer | 104 | 0.72 | ±0.07 | 67 | 0.74 | ±0.09 | 37 | 0.70 | ±0.12 |
| NPV GS 7-10 | 133 | 0.92 | ±0.04 | 86 | 0.95 | ±0.04 | 47 | 0.89 | ±0.08 |
| NPV GS ≥ 4+3 | 143 | 0.99 | ±0.02 | 91 | 1.00 | ±0.00 | 52 | 0.98 | ±0.04 |
| **PIRADS 3-5:** | | | | | | | | | |
| PPV any cancer | 209 | 0.61 | ±0.05 | 124 | 0.63 | ±0.07 | 85 | 0.58 | ±0.08 |
| PPV GS 7-10 | 138 | 0.40 | ±0.05 | 82 | 0.42 | ±0.07 | 56 | 0.38 | ±0.08 |
| PPV GS ≥ 4+3 | 71 | 0.20 | ±0.04 | 43 | 0.22 | ±0.06 | 28 | 0.19 | ±0.06 |
| **PIRADS 3:** | | | | | | | | | |
| PPV any cancer | 56 | 0.44 | ±0.09 | 37 | 0.49 | ±0.11 | 19 | 0.37 | ±0.13 |
| PPV GS 7-10 | 25 | 0.20 | ±0.07 | 17 | 0.22 | ±0.09 | 8 | 0.15 | ±0.10 |
| PPV GS ≥ 4+3 | 12 | 0.09 | ±0.05 | 9 | 0.12 | ±0.07 | 3 | 0.06 | ±0.06 |
| **PIRADS 4:** | | | | | | | | | |
| PPV any cancer | 58 | 0.58 | ±0.10 | 35 | 0.60 | ±0.13 | 23 | 0.55 | ±0.15 |
| PPV GS 7-10 | 32 | 0.32 | ±0.09 | 18 | 0.31 | ±0.12 | 14 | 0.33 | ±0.14 |
| PPV GS ≥ 4+3 | 12 | 0.12 | ±0.06 | 8 | 0.14 | ±0.09 | 4 | 0.10 | ±0.09 |

PIRADS 5:

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| PPV any cancer | 95 | 0.83 | ±0.07 | 52 | 0.84 | ±0.09 | 43 | 0.81 | ±0.11 |
| PPV GS 7-10 | 81 | 0.70 | ±0.08 | 47 | 0.76 | ±0.11 | 34 | 0.64 | ±0.13 |
| PPV GS ≥ 4+3 | 47 | 0.41 | ±0.09 | 26 | 0.42 | ±0.12 | 21 | 0.40 | ±0.13 |

**Table 5.** The detection rates of transperineal MRI/TRUS-fusion guided targeted and 24-core systematic prostate biopsy depending on PSA density. Abbreviation: SB = systematic biopsy, TB = targeted biopsy.

| | Overall n=487 | | Centre 1 n=287 | | Centre 2 n=200 | |
|---|---|---|---|---|---|---|
| | n | Detection rates % | n | Detection rates % | n | Detection rates % |
| PIRADS 3-5 | | | | | | |
| PSA Density ≤ 0.15 | 164 | | 76 | | 88 | |
| Overall GS7-10 | 37 | PPV 0.22 ± 0.06 | 14 | PPV 0.18 ± 0.09 | 23 | PPV 0.26 ± 0.09 |
| TB GS7-10 | 24 | 65% | 12 | 86% | 12 | 52% |
| SB GS7-10 | 32 | 87% | 14 | 100% | 18 | 78% |
| | | | | | | |
| PSA Density > 0.15 | 179 | | 120 | | 59 | |
| Overall GS7-10 | 101 | PPV 0.56 ± 0.07 | 68 | PPV 0.57 ± 0.09 | 33 | PPV 0.56 ± 0.13 |
| TB GS7-10 | 90 | 89% | 62 | 92% | 28 | 85% |
| SB GS7-10 | 92 | 91% | 64 | 94% | 29 | 88% |
| | | | | | | |
| PIRADS 3 | | | | | | |
| PSA Density ≤ 0.15 | 80 | | 38 | | 42 | |
| Overall GS7-10 | 9 | PPV 0.11 ± 0.07 | 3 | PPV 0.08 ± 0.09 | 6 | PPV 0.14 ± 0.10 |
| TB GS7-10 | 2 | 22% | 1 | 33% | 1 | 17% |
| SB GS7-10 | 9 | 100% | 3 | 100% | 6 | 100% |

| | | | | | | |
|---|---|---|---|---|---|---|
| PSA Density > 0.15 | 48 | | 38 | | 10 | |
| | | PPV 0.33 ± 0.13 | | PPV 0.37 ± 0.15 | | PPV 0.20 ± 0.25 |
| Overall GS7-10 | 16 | | 14 | | 2 | |
| TB GS7-10 | 9 | 56% | 9 | 64% | 0 | 0% |
| SB GS7-10 | 14 | 88% | 13 | 93% | 2 | 100% |
| | | | | | | |
| PIRADS 4-5 | | | | | | |
| PSA Density ≤ 0.15 | 84 | | 38 | | 46 | |
| | | PPV 0.33 ± 0.10 | | PPV 0.29 ± 0.14 | | PPV 0.37 ± 0.14 |
| Overall GS7-10 | 28 | | 11 | | 17 | |
| TB GS7-10 | 22 | 79% | 11 | 100% | 11 | 65% |
| SB GS7-10 | 23 | 82% | 11 | 100% | 12 | 71% |
| | | | | | | |
| PSA Density > 0.15 | 131 | | 82 | | 49 | |
| | | PPV 0.65 ± 0.08 | | PPV 0.66 ± 0.10 | | PPV 0.63 ± 0.14 |
| Overall GS7-10 | 85 | | 54 | | 31 | |
| TB GS7-10 | 81 | 95% | 53 | 98% | 28 | 90% |
| SB GS7-10 | 78 | 92% | 51 | 94% | 27 | 87% |

**Table 6. The detection rates of transperineal MRI/TRUS-fusion guided targeted and 24-core systematic prostate biopsy for significant prostate cancer GS7-10. Abbreviation: SB = systematic biopsy, TB = targeted biopsy, n.c. = not calculated.**

| | Overall | n=487 | | Centre 1 | n=287 | | Centre 2 | n=200 | |
|---|---|---|---|---|---|---|---|---|---|
| | n | Detection rates % | p | n | Detection rates % | p | N | Detection rates % | p |
| **PIRADS 3:** | | | 0.001 | | | 0.077 | | 100.0 vs 12.5 | 0.0233 |
| SB vs. TB | 24 vs 11 | 96.0 vs 44.0 | 9 | 16 vs 10 | 94.1 vs 58.8 | 1 | 8 vs 1 | | |
| Combination vs. TB | 25 vs 11 | 100.0 vs 44.0 | 0.000 5 | 17 vs 10 | 100.0 vs 58.8 | 0.023 3 | 8 vs 1 | 100.0 vs 12.5 | 0.0233 |
| Combination vs. SB | 25 vs 24 | 100.0 vs 96.0 | 1.000 0 | 17 vs 16 | 100.0 vs 94.1 | 1.000 0 | 8 vs 8 | 100.0vs 100.0 | n.c. |
| | | | | | | | | | |
| **PIRADS 4:** | | | 1.000 | | 100.0vs 100.0 | n.c. | | | 1.0000 |
| SB vs. TB | 28 vs 29 | 87.5 vs 90.6 | 0 | 18 vs 18 | | | 10 vs 11 | 71.4 vs 78.6 | |
| Combination vs. TB | 32 vs 29 | 100.0 vs 90.6 | 0.248 2 | 18 vs 18 | 100.0vs 100.0 | n.c. | 14 vs 11 | 100.0 vs 78.6 | 0.2482 |
| Combination vs. SB | 32 vs 28 | 100.0 vs 87.5 | 0.133 6 | 18 vs 18 | 100.0vs 100.0 | n.c. | 14 vs 10 | 100.0 vs 71.4 | 0.1336 |
| | | | | | | | | | |
| **PIRADS 5:** | | | 1.000 | | | 0.617 | | | 1.0000 |
| SB vs. TB | 73 vs 74 | 90.1 vs 91.4 | 0 | 44 vs 46 | 93.6 vs 97.9 | 1 | 29 vs 28 | 85.3 vs 82.4 | |
| Combination vs. TB | 81 vs 74 | 100.0 vs 91.4 | 0.023 3 | 47 vs 46 | 100.0 vs 97.9 | 1.000 0 | 34 vs 28 | 100.0 vs 82.4 | 0.0412 |
| Combination vs. SB | 81 vs 73 | 100.0 vs 90.1 | 0.013 3 | 47 vs 44 | 100.0 vs 93.6 | 0.248 2 | 34 vs 29 | 100.0 vs 85.3 | 0.0736 |

**Supplementary Table 1.** 3.0 Tesla MRI protocols of the two different centers. Abbreviations: TR = Repetition Time, TE = Echo Time, ETL = Echo Train Length, FOV = Field of View, epi = Echo Planar Imaging, TSE = Turbo Spin Echo, SE = Spin Echo, DCE = Dynamic contrast enhancement.

| Parameter | T1 TSE | | T2 TSE | | epi-2d | | DCE | |
|---|---|---|---|---|---|---|---|---|
| TR ms / TE ms | 792/11 | 561/11 | 5120/142 | 4273/102 | 3100/52 | 3775/70 | 4.42/2.2 | 4.1/1.8 |
| Flip angle (*) | 90 | 70 | 90 | 111 | 90 | 90 | 15 | 13 |
| ETL length / Epi-factor | 72 | 4 | 12 | 16 | 96 | 1 | x | X |
| Averages | 2 | 2 | 4 | 1.5 | 5 | 6 | x | X |
| b-value | x | x | x | x | 0, 50, 100, 150, 200, 250, 800, 1000 | 150, 750, 1400 | x | X |
| Section thickness (mm) | 5 | 8 | 3 | 3 | 3 | 3 | 1.5 | 3 |
| FOV (mm) | 320 | 240 | 300 | 220 | 280 | 280 | 400 | 240 |
| Aquisation time (min) | 03:51 | 03:43 | 04:14 | 06:59 | 05:04 | 02:58 | 05:18 | 05:57 |