**Multicentre evaluation of Magnetic Resonance Imaging supported transperineal prostate biopsy in biopsy-naïve men with suspicion of prostate cancer.**

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**M****ulticentre evaluation of Magnetic Resonance Imaging supported transperineal prostate biopsy in biopsy-naïve men with suspicion of prostate cancer.**

**Abstract**

**Objectives**: To analyse the detection rates of primary MRI-fusion transperineal prostate biopsy using combined targeted and systematic core distribution in three tertiary referral centres.

**Patients and Methods**: Multicentre, prospective outcome study of 807 consecutive biopsy-naïve patients having undergone MRI-guided transperineal prostate biopsy as the first diagnostic intervention between 10/2012 and 05/2016. MRI was reported following PI-RADS criteria. 236 patients had 18-24 systematic transperineal biopsies only, and 571 patients underwent additional targeted biopsies either by MRI-fusion or cognitive targeting if PI-RADS ≥3 lesions were present. Detection rates for any and Gleason score (GS) 7-10 cancer in targeted and overall biopsy. Predictive values were calculated for different PI-RADS and PSA density (PSA-D) groups.

**Results**: Cancer was detected in 68% and GS 7-10 in 49% of patients. Negative predictive value of 236 PI-RADS 1-2 MRI in combination with PSA-D ≤0.1 ng/ml/cm3 for GS7-10 was 0.91 (±0.07, 8% of study population). In 418 patients with PI-RADS 4-5 lesions using targeted plus systematic biopsies, the cancer detection rate of GS 7-10 was significantly higher at 71% versus 59% and 61% with either approach alone (p=0.000). For 153 PI-RADS 3 lesions, the detection rate was 31% with no significant difference to systematic biopsies with 27% (p>0.05). Limitations include variability of mpMRI reading and Gleason grading.

**Conclusion**: MRI-based transperineal biopsy performed at high volume, tertiary care centres with a significant experience of prostate mpMRI and image-guided targeted biopsies yielded high detection rates of GS 7-10 cancer. Prostate biopsies may not be needed for men with low PSA-D and a non-suspicious MRI. In patients with high probability lesions, combined targeted and systematic biopsies are recommended.

**Introduction**

Prostate cancer diagnostics have recently evolved in terms of method (imaging and cognitive vs. in-bore vs. fusion-guided biopsies), route (transrectal vs. transperineal), and sampling extent (targeted only vs. systematic vs. combination of targeted and systematic). Transrectal, transperineal, and in-bore MRI-supported biopsies were found to yield prostate cancer detection rates superior to conventional transrectal ultrasound guided (TRUS) 12 core biopsies [[1](#bookmark)-[5](#bookmark1)]. Currently there is conflicting evidence in studies comparing image-fusion and cognitive targeting [[6](#bookmark2)-[10](#bookmark3)]. With regard to sampling extent of biopsies, high probability MRI lesions were found to still require a combination of targeted MRI/US image-fusion and systematic transperineal biopsies [[3](#bookmark4),[11](#bookmark5),[12](#bookmark6)]. Moreover, MRI may still miss GS 7 cancer in 8-24% of patients on a lesion-by-lesion basis when prostatectomy serves as the reference standard [[11](#bookmark7),[13](#bookmark8),[14](#bookmark9)]. The use of MRI in the setting of biopsy naïve men is thus currently not recommended in international guidelines [[15](#bookmark10)-[16](#bookmark11)]. The PROMIS study found that MRI outperforms conventional TRUS biopsy in biopsy-naïve patients and suggests that MRI, if used as a triage test, could identify one quarter of men who might safely avoid unnecessary biopsy, without impairing the detection of clinically significant cancer [[4](#bookmark12)]. The aim of this study was to analyse the outcome of MRI-guided transperineal prostate biopsy as first biopsy in patients with a suspicion of prostate cancer in three different tertiary referral centres, either by MRI/US-fusion or cognitive targeting.

**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 [[17](#bookmark13)]. The biopsy technique and data collection was standardised according to the Ginsburg consensus [[18](#bookmark14)].

*Study population*

All patients with first suspicion of prostate cancer without previous negative biopsies or previous diagnosis or treatment of prostate cancer were included in the evaluation. Patients above 79 years (n=8) and with a prostate-specific antigen (PSA) higher than 30 ng/ml (n=41) were excluded from analysis to allow interpretation of results more relevant to a screening-based population, independent of a specific health system. The final study cohort comprised 807 patients all of whom underwent multiparametric MRI and subsequent MRI supported transperineal prostate biopsies from 10/2012 to 05/2016: 163 at Centre I (Addenbrooke’s Hospital, Cambridge, United Kingdom), 402 at Centre II (University Hospital Heidelberg, Heidelberg, Germany), and 242 at Centre III (Monash University, Melbourne, Australia). Indications for MRI and biopsy were raised PSA values above age-related normal range (n=349), a suspicious digital rectal examination (n=51), both (n=350), or other, including family history (n=57). The patients’ clinical characteristics are shown in Table 1. Parts of the study populations in all centres were included in several publications addressing other aspects of transperineal prostate biopsies or prostate MRI interpretation [2,11,12,19].

*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 committees at all centres.

*Magnetic Resonance Imaging analysis*

The different MR imaging protocols are shown in Appendix A. All radiologists used team-based peer-review of images in equivocal cases and have ongoing histological feedback on more than 150 MRI per year. Feedback to radiologists was provided by quality management techniques, including complete prospective data collection, continuous data analysis and interpretation and 3-6 monthly team meetings to action results as well as weekly to monthly cancer multidisciplinary team meetings. Images were analysed according to the Prostate Imaging-Reporting and Data System (PI-RADS) version 1 [[20](#bookmark16)] and from 2015 on the subsequent PIRADS version 2 [[21](#bookmark17)]. The final overall PI-RADS score of each MRI was used for further analysis. If more than one target was present, the “index lesion” with the highest PI-RADS score was used.

*Biopsy*

The BiopseeTM MRI/TRUS fusion biopsy system (Medcom, Darmstadt, Germany) with a 5 mm spacing brachytherapy grid was used for MRI/US fusion and core placement planning in all biopsies in Centre I and II. In Centre III, all biopsies were performed cognitively using with a 5 mm spacing brachytherapy grid using a BK Medical (Peabody, Massachusetts, USA) FlexFocusTM ultrasound with 8848 transrectal probe mounted on a Civco (Kalona, Iowa, USA) MicroTouchTM stepper. All patients underwent systematic transperineal biopsies according to the Ginsburg protocol. A full description of the biopsy technique is available elsewhere [[18](#bookmark18),[19](#bookmark19)]. In brief, three to four biopsy cores were sampled from each of 6 sectors of the prostate. In patients with PI-RADS 3-5 MRI lesions, at least 2 biopsy cores were taken from each lesion before the systematic biopsies. In order to decrease the risk of sampling error caused by subsequent movement artefacts, bleeding and oedema, the lesion with the highest suspicion of cancer was targeted first. Specimen from each sector and targets were sent in separate specimen containers. 395 patients underwent fusion-targeted transperineal biopsies in Centres I and II, 176 received cognitive targeting in Centre III. All procedures were done by 1 of 3 urologists with several years’ experience of transperineal biopsy in Centre I, by supervised residents in Urology in Centre II, and 1 of 5 urologists in Centre III.

*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 [[22](#bookmark20)].

*Statistics*

All data was collected prospectively in each centre. Descriptive statistics were used and positive (PPV) and negative (NPV) predictive values were calculated for the different PI-RADS groups, using the combined systematic transperineal biopsy and targeted biopsies as reference test, which has been recently validated by correlation with prostatectomy specimens [[11](#bookmark21)]. In addition, predictive values and detection rates were calculated for benign vs. suspicious DRE, PSA levels of <4, 4-10, >10 ng/ml, as well as PSA-densities of < 0.1 ng/ml/cm3, 0.1-0.2 ng/ml/cm3 and > 0.2 ng/ml/cm3 and combined for PSA-D <0.1 and ≥0.1 ng/ml/cm3, and for PSA-D ≤0.15 and >0.15 ng/ml/cm3, using the final overall histopathology results of the biopsy as validation, similar to a previously published study in patients after previous negative biopsy [[23](#bookmark22)]. Detection rates of targeted cores and total combined biopsy were compared on a patient-per-patient basis for 507 cases with PI-RADS 3-5 lesions. Due to process errors specimen from target biopsies and systematic sector were sent to histopathological analysis in the same container in 64 cases in Centre 3 and therefore excluded from this subgroup-analysis. Exact Fisher and Mc Nemar tests were used to test for statistical significance. ROC-curves and their respective area under the curve (AUC) were calculated for PSA, PSA-density, PI-RADS, and the combination of PSA-density and PI-RADS. All statistical procedures were performed to a 5% significance level and are of explorative nature. The data were analyzed using IBM SPSS Version 23.

**Results**

The patients’ clinical characteristics and MRI findings are shown in Table 1. One or more lesion suspicious for cancer on MRI (Likert scale 3-5) was found in 71% of the patients.

*Prostate cancer detection, NPV and PPV*

In all patients, cancer was detected in 546/807 (68%) and Gleason score 7-10 cancer in 392/807 (49%) (Figure 1, Appendix B). The respective predictive values for the different PI-RADS groups are shown in table 2 and Appendix C. In the 236 patients without suspicious lesions, systematic biopsies detected cancer in 94 patients (40%), of whom 46 had GS 3+3, 37 GS 3+4, and 11 GS ≥4+3. The resulting NPV of PI-RADS 1-2 was 0.80±0.05 for excluding Gleason score 7-10.

PI-RADS 3-5 lesions were reported on MRI in 571 men. For 153 PI-RADS 3 lesions, the targeted and systematic biopsies detected any cancer in 87 (57%) of whom 40 had GS 3+3, 37 GS 3+4, and 10 GS ≥4+3. For 418 PI-RADS 4-5 lesions, any cancer was detected in 365 (87%) of whom 68 had GS 3+3, 158 GS 3+4, and 139 GS ≥4+3. The PPV increased with increasing PI-RADS score: the PPV for detecting 7-10 cancer was 0.31±0.07 for PI-RADS 3 and 0.71±0.04 for PI-RADS 4-5.

*Demographic factors, PI-RADS scores and detection rate*

NPV for any cancer for benign DRE was 0.37 (217/587) overall with GS 7-10 detection rates of 42% (245/587) for a negative DRE compared to 72% (135/187) with suspicious DRE and missing DRE information in 33 patients. A combination of benign DRE with a PI-RADS 1-2 MRI lead to a NPV for any cancer of 0.63 (126/200) with 17% (33/200) missed GS 7-10. For the combination of suspicious DRE with a positive MRI finding, PPV for GS 7-10 was 0.48 (13/27) for PI-RADS 3 and 0.82 (109/133) for PI-RADS 4-5 (all p<0.05, Figure 2a).

PPV for GS 7-10 cancer significantly increased with rising PSA levels for PI-RADS 4-5: from 0.55 (30/55) with PSA <4 ng/ml to 0.69 (194/280) with 4-10 ng/ml to 0.87 (73/83) with >10 ng/ml (p=0.0006-0.0415, Figure 2b). There was no significant difference for PI-RADS 1-3.

PSA-D strongly influenced the detection rate of cancer and GS 7-10 cancer (Table 3, Figure 2c): NPV for GS 7-10 of PI-RADS 1-2 MRI was 0.91 (59/65) with PSA-D <0.1, 0.79 (98/124) with ≥0.1-0.2, and 0.66 (31/47) with >0.2 ng/ml/ml (p=0.0105 for cut-off of 0.1). For PI-RADS 3, PPV for GS 7-10 was 0.18 (7/39) with PSA-D <0.1, 0.31 (28/89) with ≥0.1-0.2, and 0.48 (12/25) with >0.2 (p=0.0473 for cut-off of 0.1). For PI-RADS 4-5, PPV was 0.48 (35/73) with PSA-D <0.1, 0.66 (114/174) with ≥0.1-0.2, and 0.87 (148/171) with >0.2 (p=0.0001 for cut-off of 0.1). The respective areas under the curve (AUC) are shown in Figure 3. Using a PSA-D cutoff of 0.15 ng/ml/cm3, NPV for GS 7-10 of PI-RADS 1-2 MRI was 0.84 (121/144) with PSA-D ≤0.15 and 0.73 (67/92) with >0.15 ng/ml/ml (p=0.0465). For PI-RADS 3, PPV for GS 7-10 was 0.26 (26/100) with PSA-D ≤0.15 and 0.40 (21/53) with >0.15 ng/ml/ml (p=0.0984). For PI-RADS 4-5, PPV was 0.52 (85/162) with PSA-D ≤0.15 and 0.83 (212/256) with >0.15 ng/ml/ml (p=0.0001).

*Comparison of targeted cores, systematic cores and total biopsy*

The combination of targeted and systematic biopsies was significantly better than either method alone for the detection of GS 7-10 cancer in patients with suspicious lesions (PIRADS 4-5) (Table 4). Systematic biopsies would not have detected 13 GS 3+4 and 24 GS ≥4+3 cancer (p=0.000) while performing only targeted biopsies of suspicious lesions would have failed to diagnose 15 GS 3+4 and 29 GS ≥4+3 cancer (p=0.000).

In equivocal lesions (PIRADS 3), targeted biopsy alone would not have diagnosed 6 GS 3+4 and 6 GS ≥4+3 cancer, whereas performing only systematic biopsies would have only missed 4 GS 3+4 and no GS ≥4+3 cancer, with no significant difference in detection rate between either method alone and the combined biopsy (p>0.05).

Centres II and III, which took 4 target cores per target, had significantly higher detection rates of GS 7-10 cancer in their target cores than Centre I, which took only 2 target cores (p=0.0001-0.0074), but did not show a corresponding increase in systematic pick-up rate. There was no significant difference in detection of any cancer between Centre 1 and 2 (p>0.05).

**Discussion**  
Our study shows that in a first biopsy setting, a negative MRI (PI-RADS 1-2) is associated with a NPV of around 80% to detect GS ≥ 7 prostate cancer as compared to a stringent reference test. In combination with a PSA-D ≤0.15 ng/ml/ml, the NPV increased to 0.84 and with a PSA-D ≤0.1 to 0.91. PSA-D also strongly influenced the PPVs for equivocal and suspicious MRI (PI-RADS 3-5), with PPVs of up to 96% for any cancer and 87% for GS 7-10 cancer with a PI-RADS 4-5 MRI and a PSA-D>0.2. In patients with high probability MRI lesions, the significantly higher 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 with no significant difference to the combined approach.

Although our data cannot provide a direct comparison of the transperineal Ginsburg scheme and 12-core TRUS biopsy, the detection rates with the Ginsburg scheme used in our multicentre analysis are similar to the results published for the extensive template mapping biopsy with biopsy cores taken every 5 mm in the PROMIS trial and the PROMIS trial did find a clear advantage over 12-core TRUS biopsy [4]. This suggests that the MRI-guided Ginsburg biopsy scheme can provide similar histopathological validation yet using fewer cores than template biopsy and likely better diagnostic security than conventional 12-core TRUS biopsy. Regarding the sampling extent, the question remains whether systematic transperineal biopsy alone instead of a combined targeted and systematic approach could be sufficient enough for diagnostic work-up of biopsy-naive patients with suspicious MRI. The combined approach in our study led to significantly higher detection rates of 71% GS 7-10 cancer for PI-RADS 4-5 lesions compared to 59% in the targeted and 61% in the systematic biopsy alone (p<0.001). This corresponds to 71% significant cancer identified by template prostate mapping biopsy in patients with suspicious MRI findings in the recent PROMIS trial [4]. For equivocal MRI, we found 30% GS 7-10 by the combined approach (21% with targeted, p= p<0.001, and 27% by systematic only biopsies, p>0.05) compared to 21% by template mapping in the PROMIS study. In our study, we found significantly higher detection rates of any cancer by the combined biopsy of both PI-RADS 3 and 4-5 lesions compared to the targeted only biopsies.

Of note, we found lower GS 7-10 targeted biopsy detection rates in Centre I, which took only two fusion target cores, than Centre II with a median of four fusion target cores, and highest in Centre III with four cognitive target cores. This could indicate an advantage of higher target core numbers, with a denser sampling of target tissue, minimising any targeting error. On the basis of this data we advise to increase the number of cores taken in the target, aiming for saturation biopsy of the target region. MRI has been shown to significantly underestimate the final histopathological tumour volume at prostatectomy [24-27], providing a further rationale for this approach. More studies are needed to confirm which biopsy approach is better with regard to increased detection of significant cancer and reduced detection of insignificant cancer.

Our study shows that in a first biopsy setting, a negative MRI (PI-RADS 1-2) is associated with a NPV of around 80% to detect GS ≥ 7 prostate cancer as compared to a stringent reference test. In combination with a PSA-D ≤0.15 ng/ml/ml (18% of the study population), the NPV increased to 0.84 and with a PSA-D ≤0.1 (8% of the study population), the NPV increased to 0.91. PSA-D also strongly influenced the PPVs for equivocal and suspicious MRI (PI-RADS 3-5), with PPVs of up to 96% for any cancer and 87% for GS 7-10 cancer with a PI-RADS 4-5 MRI and a PSA-D>0.2. Improved risk stratification with PSA density is consistent with the results of previous studies [23,28]. Our findings suggest that men with a PSA-D <0.1 and a negative mpMRI may be spared a prostate biopsy (at least 8% of our population). Whether a 9 % risk of missing GS ≥7 cancer (4% risk of Gleason ≥4+3) is acceptable is debatable, and the decision should be individualised. For equivocal MRI lesions, even in the group with low PSA-D of < 0.1, 18% GS 7-10 cancers would have been missed if these patients had not undergone biopsy. This is in contrast to the findings of Venderink et al. who found only 6% significant cancer in patients with a PSA-D of 0.15 and a PI-RADS 3 MRI by targeted in-bore-biopsy [5], we therefore continue to advise our patients to undergo biopsy in case of an equivocal MRI. Demographical factors such as DRE, PSA or PSA-D alone without the addition of MRI, were insufficient for predicting clinically significant cancer.

An NPV of 80% for GS 7-10 in men with a negative MRI is lower than previous cohorts incorporating smaller patient numbers, with NPV >90% [29-30], however these used only 12-core transrectal systematic biopsies as validation, which is known to be an unreliable reference test [[4](#bookmark25)]. Patients with previous TRUS biopsy are less likely to harbour significant disease [31] and biopsy-naïve men therefore may need to be more closely followed if biopsy is omitted on the basis of a negative MRI. Additionally the background prevalence of cancer in our cohort (overall 68%) was relatively high which will impact on NPV rate, independent of the MRI as the reference test; a recently published meta-analysis reports an expected NPV of 47-79% with an overall cancer prevalence of 60-70% [32]. Likewise, our 80% NPV with 49% GS 7-10 prevalence is comparable to the PROMIS study, where NPV for a negative MRI ranged from 76-89% for significant cancer, with a GS 7-10 cancer prevalence of 38% [[4](#bookmark28)], using a template mapping biopsy as gold standard in biopsy-naïve patients..

Our study has the advantage of being prospective, with multicentre data collection according to an agreed template. The cohort is the largest reported involving purely biopsy-naive patients and is the only one offering information on combined NPV for negative MRI and PSA-D in this common clinical scenario, providing evidence for the use of MRI-based biopsies. As not all patients underwent prostatectomy, we cannot provide the final gold standard pathology for all cases in the study population. Nevertheless, our biopsy approach has recently been validated by correlation with prostatectomy specimens [11]. Limitations of this study include the lack of data on comparability of individual radiological performance, urological operator experience and histopathological Gleason grading among the different centres. The demographics of each centre as well as the natural prevalence of prostate cancer in the different health communities varied significantly: in centre III, prostate volume (mean) was smaller and detection rates in the target cores, the systematic cores and the total biopsy were higher than in the other centres. With a consequently increased PSA density, radiologists are more likely to see lesions with a higher grade, therefore they could perform better in MRI outcomes and, in the biopsy, more dense sampling in a smaller volume of prostate would make targeting per proportion of tissue more likely to be successful. Although data from each centre is available we decided not to present centre comparative data or comparative data of fusion and cognitive targeting as it would not be statistically sound to draw conclusions on the basis of the above. Instead, we decided to focus on the mixed multicentre population data as this gives readers a broad overview of what biopsy results to expect in established practice. A definite link of detection rate and cognitive vs. fusion targeting would require a prospective blinded multicentre trial.

Lastly, it has to be pointed out that our results were obtained at high volume, tertiary care centres with a significant experience of prostate mpMRI and image-guided targeted biopsies. Translation of these results should therefore be made with caution [33]. The practice of using MRI for prostate biopsies truly requires a learning curve of the whole team in collaboration using quality management based on outcome data [34].

Conclusions

MRI-supported transperineal prostate biopsy yielded high detection rates of Gleason score 7-10 cancer. Prostate biopsies may not be needed for men with low PSA-D and a non-suspicious MRI. In patients with high probability lesions, denser sampling of target tissue may lead to increased detection rates in patients with suspicious MRI and combined targeted and systematic MRI/TRUS image-fusion biopsies is recommended.

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**Legends to illustrations**

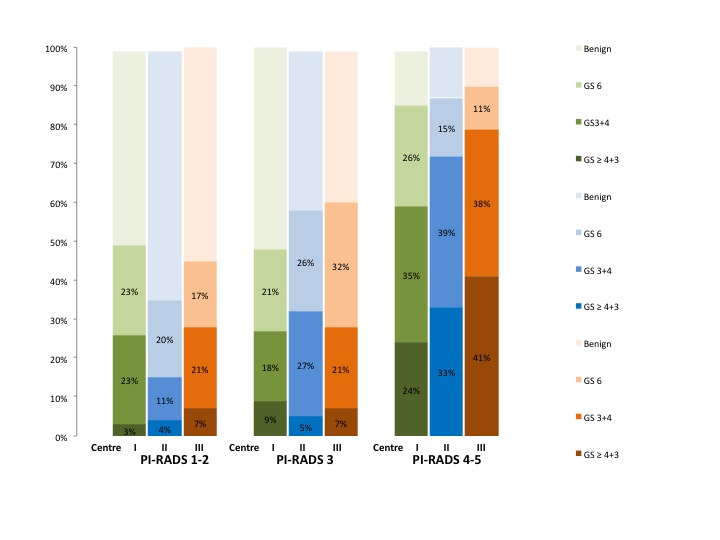
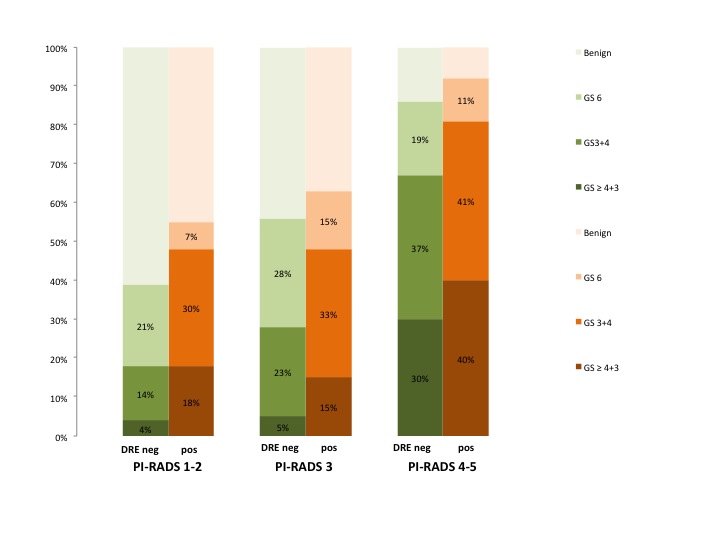
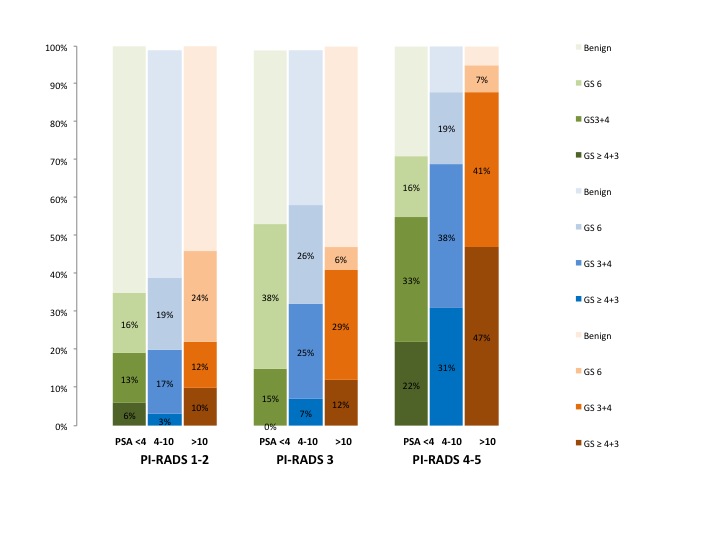


Figure 1: Detection rates among the different centres depending on PI-RADS category.





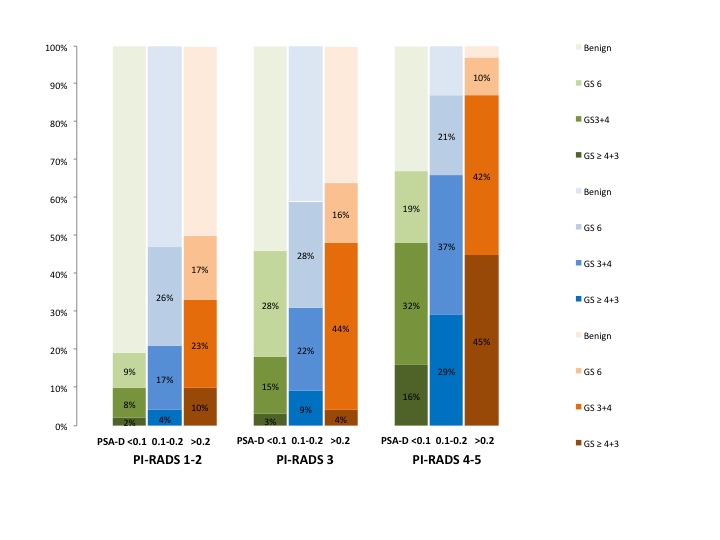


Figure 2: Detection rates depending on PI-RADS category and a) DRE findings b) PSA levels for <4, 4-10, and >10 ng/ml/, and c).PSA-density for <0.1, 0.1-0.2, and >0.2 ng/ml/cm3.

Figure 3.tif

Figure 3: ROC-curves for PSA = light grey line (AUC 0.612), PSA-Density = mid grey line (AUC 0.712), PI-RADS = dark grey line (AUC 0.772) and the combination of PSA-Density and PIRADS = black line (AUC 0.809).

**Tables**

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

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Overall  n= 807 | Centre I  n= 163 | Centre II  n= 402 | Centre III  n= 242 |
| Age (years): median / IQR | 65 / 59-70 | 64 / 57-69 | 65 / 60-70 | 65 / 60-70 |
|  |  |  |  |  |
| PSA (ng/ml): median / IQR | 6.5 / 4.9-8.8 | 6.6 / 4.6-9.0 | 6.9 / 5.2-9.1 | 5.9 / 4.6-8.0 |
| PSA < 4 ng/ml: n / % | 113 / 14% | 32 / 20% | 38 / 9% | 43 / 18% |
| PSA 4-10 ng/ml: n / % | 552 / 68% | 102 / 63% | 284 / 70% | 166 / 69% |
| PSA >10 ng/ml: n / % | 142/ 18% | 29 / 18% | 80 / 20% | 33 / 14% |
|  |  |  |  |  |
| DRE negative | 587 / 73% | 102 / 63% | 308 / 77% | 177 / 73% |
| DRE positive | 187 / 23% | 39 / 24% | 94 / 23% | 54 / 22% |
| DRE not known | 33 / 4% | 22 /13% | 0 / 0% | 11 / 5% |
|  |  |  |  |  |
| Prostate volume(ml):  median / IQR | 42 / 30-58 | 44 / 33-55 | 47 / 32-62 | 25 / 25-47 |
| PSA-Density median / IQR | 0.15 / 0.10-0.22 | 0.14 / 0.09-0.22 | 0.15 / 0.10-0.21 | 0.17 / 0.12-0.24 |
|  |  |  |  |  |
| PI-RADS 1-2 | 236 / 29% | 30 / 18% | 140 / 35% | 66 / 27% |
| PI-RADS 3 | 153 / 19% | 34 / 21% | 91 / 23% | 28 / 12% |
| PI-RADS 4-5 | 418 / 52% | 99 / 61% | 171 / 42% | 148 / 61% |
|  |  |  |  |  |
| target cores (n): median /IQR | 4 / 2-5 | 2 / 2-2 | 3 / 2-4 | 4 / 4-5 |
| total cores (n): median /IQR | 26 / 24-28 | 26 / 24-28 | 26 / 24-29 | 24 / 24-26 |

**Table 2.** The negative (NPV) and positive (PPV) predictive values of multiparametric MRI using a transperineal MRI guided targeted and 24-core systematic prostate biopsy as the reference test. The suspicion of cancer on MRI was reported according to PI-RADS. Abbreviation: GS = Gleason score.

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Overall**  **n=807** | | | **Centre I**  **n=163** | | | **Centre II**  **n=402** | | | **Centre III**  **n=242** | | |
|  | **n** |  | **95% CI** | **n** |  | **95% CI** | **n** |  | **95% CI** | **n** |  | **95% CI** |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
| **PI-RADS 1-2:**  **total** | 236 | 29% |  | 30 | 18% |  | 140 | 35% |  | 66 | 27% |  |
| **NPV any cancer** | 94 | 0.60 | 0.54-0.66 | 15 | 0.50 | 0.32-0.68 | 50 | 0.64 | 0.56-0.72 | 29 | 0.56 | 0.44-0.68 |
| **NPV GS 7-10** | 48 | 0.80 | 0.75-0.85 | 8 | 0.73 | 0.57-0.89 | 22 | 0.84 | 0.78-0.90 | 18 | 0.73 | 0.62-0.84 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
| **PI-RADS 3:**  **total** | 153 | 19% |  | 34 | 21% |  | 91 | 23% |  | 28 | 12% |  |
| **PPV any cancer** | 87 | 0.57 | 0.49-0.65 | 16 | 0.47 | 0.30-0.64 | 54 | 0.59 | 0.49-0.69 | 17 | 0.61 | 0.43-0.79 |
| **PPV GS 7-10** | 47 | 0.31 | 0.24-0.38 | 9 | 0.26 | 0.11-0.41 | 30 | 0.33 | 0.23-0.43 | 8 | 0.29 | 0.12-0.46 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
| **PI-RADS 4-5:**  **total** | 418 | 52% |  | 99 | 61% |  | 171 | 42% |  | 148 | 61% |  |
| **PPV any cancer** | 365 | 0.87 | 0.84-0.90 | 85 | 0.86 | 0.79-0.93 | 147 | 0.86 | 0.81-0.91 | 133 | 0.90 | 0.85-0.95 |
| **PPV GS 7-10** | 297 | 0.71 | 0.67-0.75 | 59 | 0.60 | 0.50-0.70 | 122 | 0.71 | 0.64-0.78 | 116 | 0.78 | 0.71-0.85 |

**Table 3.** The negative (NPV) and positive (PPV) predictive values of multiparametric MRI for different PSA-Density groups using a transperineal MRI guided targeted and 24-core systematic prostate biopsy as the reference test. The suspicion of cancer on MRI was reported according to PI-RADS. Abbreviation: GS = Gleason score. PSA-D = Prostate specific antigen density.

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **PSA-D <0.1 ng/ml/cm3**  **n=177** | | | **<0.1 vs. 0.1-0.2** | **PSA-D 0.1-0.2 ng/ml/cm3**  **n=385** | | | **0.1-0.2 vs. >0.2** | **PSA-D >0.2 ng/ml/cm3**  **n=245** | | | **<0.1 vs. >0.1** |
|  | **n** |  | **95% CI** | **p** | **n** |  | **95% CI** | **p** | **n** |  | **95% CI** | **p** |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Overall:**  **PPV any cancer** | 79 | 0.45 | 0.38-0.52 | 0.0001 | 262 | 0.68 | 0.63-0.73 | 0.0001 | 205 | 0.84 | 0.79-0.89 | 0.0001 |
| **PPV GS 7-10** | 48 | 0.27 | 0.20-0.34 | 0.0003 | 168 | 0.43 | 0.38-0.48 | 0.0001 | 176 | 0.72 | 0.66-0.78 | 0.0001 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
| **PI-RADS 1-2:(n=236)**  **NPV any cancer** | 12 | 0.82 | 0.73-0.91 | 0.0001 | 58 | 0.53 | 0.44-0.62 | 0.7319 | 24 | 0.49 | 0.35-0.63 | 0.0001 |
| **NPV GS 7-10** | 6 | 0.91 | 0.84-0.98 | 0.0433 | 26 | 0.79 | 0.72-0.86 | 0.1102 | 16 | 0.66 | 0.52-0.80 | 0.0105 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
| **PI-RADS 3: (n=153)**  **PPV any cancer** | 18 | 0.46 | 0.30-0.62 | 0.1800 | 53 | 0.60 | 0.50-0.70 | 0.8179 | 16 | 0.64 | 0.45-0.83 | 0.1362 |
| **PPV GS 7-10** | 7 | 0.18 | 0.06-0.30 | 0.1351 | 28 | 0.31 | 0.21-0.41 | 0.1563 | 12 | 0.48 | 0.28-0.68 | 0.0473 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
| **PI-RADS 4-5:(n=418)**  **PPV any cancer** | 49 | 0.67 | 0.56-0.78 | 0.0007 | 151 | 0.87 | 0.82-0.92 | 0.0015 | 165 | 0.96 | 0.93-0.99 | 0.0001 |
| **PPV GS 7-10** | 35 | 0.48 | 0.37-0.59 | 0.0105 | 114 | 0.66 | 0.59-0.73 | 0.0001 | 148 | 0.87 | 0.82-0.92 | 0.0001 |

**Table 4.** The detection rate of targeted MRI guided transperineal and 24-core systematic prostate biopsy of the total study population. Abbreviation: SB = systematic biopsies, TB = targeted biopsies, GS = Gleason score. \*Specimen from target cores were not analysed in separate pots as systematic cores in 64 cases in Centre 3 and therefore excluded from this analysis.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **n=507\*** | **n any cancer** | **Detection rates %** | **p** | **n GS 7-10** | **Detection rates %** | **p** |
| **PI-RADS3 (n=137):** |  |  |  |  |  |  |
| **SB vs. TB** | 72 vs 52 | 53% vs 38% | 0.000 | 37 vs 29 | 27% vs 21% | 0.007 |
| **Combination vs. TB** | 77 vs 52 | 56% vs 38% | 0.000 | 41 vs 29 | 30% vs 21% | 0.000 |
| **Combination vs. SB** | 77 vs 72 | 56% vs 53% | 0.063 | 41 vs 37 | 30% vs 27% | 0.125 |
|  |  |  |  |  |  |  |
| **PI-RADS 4-5 (n=370):** |  |  |  |  |  |  |
| **SB vs. TB** | 295 vs 270 | 80% vs 73% | 0.007 | 227 vs 220 | 61% vs 59% | 0.464 |
| **Combination vs. TB** | 327 vs 270 | 88% vs 73% | 0.000 | 264 vs 220 | 71% vs 59% | 0.000 |
| **Combination vs. SB** | 327 vs 295 | 88% vs 80% | 0.000 | 264 vs 227 | 71% vs 61% | 0.000 |

**Appendix A.**  3.0 Tesla MRI protocols of the three different centres. Abbreviations: TR = Repetition Time, TE = Echo Time, FOV = Field of View, DWI = Diffusion Weighted Imaging, DCE = Dynamic contrast enhancement.

|  |  |  |  |
| --- | --- | --- | --- |
| Parameter | I | II | III |
| Magnet | 1.5 T MR450 or 3.0 T Discovery MR750 HDx (GE Healthcare, Milwaukee, Wisconsin, USA) | 3.0 T Magnetom Trio, Magnetom Prisma or Biograph mMR (Siemens Healthcare, Erlangen, Germany) | 3.0 T Magnetom (Siemens, Erlangen, Germany) |
| T1 TR ms/ TE ms | 561/11 | 792/11 | 510/11 |
| T1 section thickness (mm) | 3 | 5 | 1.5 |
| T1 FOV (mm) | 240 | 320 | 350 |
| T2 TR ms/ TE ms | 4273/102 | 5120/143 | 4000-6000/101 |
| T2 section thickness (mm) | 3 | 3 | 3 |
| T2 FOV (mm) | 220 | 300 | 150 |
| DWI TR ms/ TE ms | 3775/70 | 3100/52 | 3800/71 |
| DWI b-values | 150, 750, 1400 | 0, 50, 100, 150, 200, 250, 800, 1000 | 50,400,800,  Calculated 1400 |
| DWI Section thickness (mm) | 3 | 3 | 4 |
| DWI FOV (mm) | 280 | 280 | 170 (Sag + Ax) |
| DCE TR ms/ TE ms | 4.1/1.8 | 4.42/2.2 | 4.83/1.87 |
| DCE section thickness (mm) | 3 | 1.5 | 3.5 |
| DCE FOV (mm) | 240 | 400 | 260 |

**Appendix B.** Biopsy results after a transperineal MRI guided targeted and 24-core systematic prostate biopsy according to the Ginsburg protocol. Abbreviation: GS = Gleason score.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Overall** | | **Centre I** | | **Centre II** | | **Centre III** | |
|  | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** |
| Any cancer | 546 | 100% | 116 | 100% | 251 | 100% | 179 | 100% |
| GS 7-10 | 392 | 72% | 76 | 65% | 174 | 70% | 142 | 79% |
| GS 3+3=6 | 154 | 28% | 40 | 35% | 77 | 31% | 37 | 21% |
| GS 3+4=7 | 232 | 42% | 48 | 41% | 108 | 44% | 76 | 42% |
| GS 4+3=7 | 86 | 16% | 14 | 12% | 32 | 13% | 40 | 22% |
| GS 8-10 | 74 | 14% | 14 | 12% | 34 | 14% | 26 | 14% |

**Appendix C.** Biopsy results after a transperineal MRI guided targeted and 24-core systematic prostate biopsy according to the Ginsburg protocol. The suspicion of cancer on magnetic resonance imaging was reported according to PI-RADS. Abbreviation: GS = Gleason score.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Overall** | | **Centre I** | | **Centre II** | | **Centre III** | |
|  | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** |
| All patients | 807 | 100% | 163 | 100% | 402 | 100% | 242 | 100% |
|  |  |  |  |  |  |  |  |  |
| PI-RADS 1-2: All | 236 | 100% | 30 | 100% | 140 | 100% | 66 | 100% |
| PI-RADS 1-2: Any cancer | 94 | 40% | 15 | 50% | 50 | 35% | 29 | 44% |
| PI-RADS 1-2: GS 3+4=7 | 37 | 16% | 7 | 23% | 16 | 11% | 14 | 21% |
| PI-RADS 1-2: GS 4+3=7 | 8 | 3% | 1 | 3% | 4 | 3% | 3 | 5% |
| PI-RADS 1-2: GS 8-10 | 3 | 1% | 0 | 0% | 2 | 1% | 1 | 2% |
|  |  |  |  |  |  |  |  |  |
| PI-RADS 3: All | 153 | 100% | 34 | 100% | 91 | 100% | 28 | 100% |
| PI-RADS 3: Any cancer | 87 | 57% | 16 | 47% | 54 | 59% | 17 | 61% |
| PI-RADS 3: GS 3+4=7 | 37 | 24% | 6 | 18% | 24 | 26% | 6 | 21% |
| PI-RADS 3: GS 4+3=7 | 7 | 5% | 2 | 6% | 3 | 3% | 2 | 7% |
| PI-RADS 3: GS 8-10 | 3 | 2% | 1 | 3% | 2 | 2% | 0 | 0% |
|  |  |  |  |  |  |  |  |  |
| PI-RADS 4-5: All | 418 | 100% | 99 | 100% | 171 | 100% | 148 | 100% |
| PI-RADS 4-5: Any cancer | 365 | 87% | 85 | 86% | 147 | 86% | 133 | 90% |
| PI-RADS 4-5: GS 3+4=7 | 158 | 38% | 35 | 35% | 67 | 39% | 56 | 38% |
| PI-RADS 4-5: GS 4+3=7 | 71 | 17% | 11 | 11% | 25 | 15% | 35 | 24% |
| PI-RADS 4-5: GS 8-10 | 68 | 16% | 13 | 13% | 30 | 18% | 25 | 17% |