The effect of prostate-specific antigen density on positive and negative predictive values of prostate multiparametric magnetic resonance imaging to detect Gleason score 7-10 prostate cancer

Authors:
Nienke L Hansen[1,2] M.D., T Barrett[2,3] M.D., Brendan Koo[2,3] M.D., A Warren[2,4] M.D., C Kastner [2,5] M.D., and O Bratt[2,5] M.D.

Affiliations:

1) Department of Diagnostic and Interventional Radiology, University Hospital RWTH Aachen, Aachen, Germany.

2) CamPARI Clinic, Addenbrooke's Hospital and University of Cambridge, Cambridge, UK

3) Department of Radiology, Addenbrooke's Hospital and University of Cambridge, Cambridge, UK

4) Department of Pathology, Addenbrooke's Hospital, Cambridge, UK

5) Department of Urology, Addenbrooke's Hospital, Cambridge, UK

Contact information:

Nienke Lynn Hansen, M.D.

c/o Ola Bratt

Department of Urology, Addenbrooke's Hospital

Cambridge University Hospitals

Hills Road Campus

Cambridge CB2 0QQ

United Kingdom

Email: nienke.hansen@addenbrookes.nhs.uk

Phone: +44 (0)1223 216575

Abstract

Objectives: To evaluate the effect of PSA-D on positive (PPV) and negative (NPV) predictive values of mpMRI to detect GS ≥ 7 cancer in a repeat biopsy setting.

Patients and methods: Retrospective study of 514 men with previous prostate biopsy showing no or GS 6 cancer. All had mpMRI, graded 1-5 on a Likert scale for cancer suspicion, and subsequent targeted and 24-core systematic image-fusion guided transperineal biopsy in 2013-2015. NPVs and PPVs of mpMRIs for detecting GS ≥ 7 cancer were calculated ($\pm$95% confidence intervals) for PSA-D ≤ 0.1, 0.1-0.2, ≤ 0.2 and >0.2 ng/ml/cm^3, and compared by Chi-square test for linear trend.

Results: GS ≥ 7 cancer was detected in 31% of the men. NPV of Likert 1-2 mpMRI was 0.91 (± 0.04) with PSA-D ≤ 0.2 and 0.71 (± 0.16) with >0.2 (p=0.003). For Likert 3 mpMRI, PPV was 0.09 (± 0.06) with PSA-D ≤ 0.2 and 0.44 (± 0.19) with >0.2 (p=0.002). PSA-D also significantly affected the PPV of Likert 4-5 mpMRI lesions: the PPV was 0.47 (± 0.08) with PSA-D ≤ 0.2 and 0.66 (± 0.10) with >0.2 (p=0.0001).

Conclusion: In a repeat biopsy setting, PSA-D ≤ 0.2 is associated with low detection of GS ≥ 7 prostate cancer, not only in men with negative mpMRI, but also in men with equivocal imaging. Surveillance, rather than repeat biopsy, may be appropriate for these men. Conversely, biopsies are indicated in men with high PSA-D, even if an mpMRI shows no suspicious lesion, and in men with an mpMRI suspicious for cancer, even if PSA-D is low.

Keywords: image fusion; magnetic resonance imaging; prostate biopsy; prostate cancer;

prostate-specific antigen density; transperineal biopsy

Introduction

The practice of performing systematic biopsies in all men with raised PSA levels causes unacceptable rates of overdiagnosis and overtreatment of Gleason score (GS) 6 prostate cancer [1]. GS 6 cancers are currently considered indolent with a neglible capacity to metastasise [1-2]. Moreover, standard transrectal ultrasound (TRUS) guided biopsy often misses clinically significant disease, especially in the anterior and central parts of the prostate [3-**Error! Reference source not found.**]. Multiparametric magnetic resonance imaging (mpMRI) of the prostate followed by targeted biopsies is therefore increasingly used to enhance the detection of GS ≥ 7 prostate cancer and to reduce the detection of clinically insignificant GS 6 cancer. A negative mpMRI has a high negative predictive value (NPV) for the detection of GS ≥ 7 cancer on biopsy [4-9]. Guidelines currently recommend mpMRI with targeted biopsies especially for men with previous negative biopsies and for men considered for active surveillance [10-12]. Nevertheless, mpMRI may miss GS 7 cancer in up to 24% of patients, when a radical prostatectomy specimen is used as the reference method [13,14]. There is thus a need for additional predictors for men with a negative or equivocal mpMRI to select those who may not need to undergo biopsy.

One such predictor could be PSA density (PSA-D). Prostatectomy studies have shown that PSA-D is strongly associated with the presence of GS ≥ 7 cancer [15-18]. A recent study showed that PSA-D calculated by transrectal MR/US fusion software is strongly associated with the detection of GS ≥ 7 cancer in men with or without previous biopsies, but no cut-off values for PSA-D were evaluated [19]. Two other studies both reported no

GS $\geq$ 7 cancer in targeted biopsies from equivocal mpMRI lesions in men with no previous biopsies, but there were only 18 and 6 patients in this group [20,21]. We used our large database on transperineal MR-ultrasound fusion-guided prostate biopsy to define clinically useful PSA-D cut-off values, based on positive (PPV) and negative (NPV) predictive values with confidence intervals, under which men with previous biopsies may not need repeated biopsies in the absence of MRI findings suspicious for cancer.

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, and the conduct of the biopsy [22].

Study population

From January 2013 to December 2015, 712 men underwent transperineal prostate biopsies at our institution. This retrospective study was part of a service evaluation of transperineal prostate biopsies with the need for informed consent for data analysis waived by the local ethics committee. 146 patients without previous biopsies and 4 patients with previous treatment for prostate cancer were excluded from the analysis. Patients on active surveillance for GS 7 cancer (n=22) were also excluded, as their disease already met our outcome measure. Furthermore, we excluded 15 patients on active surveillance who were diagnosed with GS 6 cancer before 2010, to ensure that the diagnostic Gleason grading for all included patients was done according to the 2005 International Society of Urological Pathology (ISUP) criteria [23], and 15 patients had to be excluded due to insufficient data recording. The final study cohort thus comprised 514 men who had biopsies between January 2013 and December 2015, of whom 351 men had previous negative TRUS biopsies and 163 were on active surveillance for GS 6 cancer. The patients' clinical characteristics are shown in Table 1.

Magnetic resonance imaging

Patients underwent prostate MRI on a 1.5T MR450 or 3.0T Discovery MR750 HDx (GE Healthcare, Waukesha, USA) with an 8-16 channel surface phased array coil. Axial Fast Spin Echo T1-weighted images of the pelvis, along with T2-Weighted Fast Recovery Fast Spin Echo images of the prostate were acquired in the axial (slice thickness 3 mm; gap 0-1 mm), sagittal and coronal planes. Axial diffusion-weighted imaging (DWI) was performed using a spin-echo echo-planar imaging pulse sequence with slice thickness 3-4 mm; gap 0 mm (b-values: b-150, b-750, b-1,400 s/mm^2); apparent diffusion coefficient (ADC) maps were automatically calculated.

Image analysis

MRI images were prospectively reported by 1 of 2 subspecialised uroradiologists with more than 5 years' experience of reading prostate MRI. T2WI and DWI sequences were evaluated using a Likert scale, based on the Prostate Imaging Reporting and Data System (PI-RADS) structured scoring criteria developed by the European Society of Urogenital Radiology (ESUR) [24], together with clinical information. The final score was defined by combining all scores for T2WI and DWI sequences as is now recommended in PI-RADS version 2 [25]: 1 = cancer highly unlikely, 2 = cancer unlikely, 3 = equivocal for cancer, 4 = cancer likely, 5 = cancer highly likely. The contours of Likert 3-5 lesions were drawn on the Biopsee[TM] MRI-TRUS fusion biopsy platform (Medcom, Darmstadt, Germany). The prostate volume was measured both by MRI based prolate ellipsoid

formula (3 diameters measured directly on the MRI images, volume = length x width x height x $\pi/6$) and by MRI 3D reconstruction volumetry (automatically calculated by the MRI/US fusion software, using the manually outlined cross section areas).

Biopsy

The Biopsee[TM] MRI/TRUS fusion biopsy system version 1 or 2 (Medcom, Darmstadt, Germany) was used for all biopsies. All patients had 24 systematic biopsies taken according to the Ginsburg protocol, using a spring-loaded biopsy gun with an 18 gauge needle [9,26]. Two biopsy cores were sampled from each of 12 sectors, starting with the anterior sectors. In patients with Likert 3-5 MRI lesions, 2 biopsy cores were taken from each lesion before the systematic biopsies. All procedures were done by 1 of 3 urologists with several years' experience of transperineal biopsy using the Biopsee[TM] MRI/TRUS fusion biopsy system.

Histopathology

All biopsies were graded according to the ISUP 2005 recommendations by a specialist uropathologist and reviewed by another uropathologist before a multidisciplinary team meeting [23]. Any instances of discrepancy in grading between pathologists was resolved by discussion and with reference to a third uropathologist. The consensus agreement on the final Gleason score and presented at the meeting was used for this study.

Statistics

A multivariable model with PSA-D, MRI findings and previous biopsy results showed no difference in the effect of PSA-D on the positive (PPV) and negative (NPV) predictive values in men with GS 6 cancer on previous biopsy compared with men with previous benign biopsies (reference): odds ratio 0.92 (95% confidence interval (CI) 0.63-1.34). Moreover, the clinical characteristics of the two groups were almost identical (Table 1). We therefore merged the 2 groups and analysed them together.

The differences in the calculated prostate volumes, as measured by MRI based prolate ellipsoid formula compared with MRI 3D reconstruction volumetry, were analysed as the median difference and interquartile range (IQR). There was a neglible difference between the 2 methods and we chose to use the prolate ellipsoid formula calculated volumes for further analysis of PSA-Density, because this is available when the decision is made whether to proceed with a biopsy or not. PPVs and NPVs with 95% CI were first calculated for PSA-D of $\leq$ 0.1, 0.11-0.2, and > 0.2 ng/ml/cm^3. When we found that the results were almost identical for PSA-D $\leq$0.1 and 0.11-0.2, when applied to Likert 1-3 MRIs, we added analyses with these 2 groups merged into a single PSA-D < 0.2 group. The Chi square test with test for linear trend was used to compare differences in proportions.

Results

Overall effect of PSA-D on cancer detection

GS $\geq$ 7 cancer was detected in 31% of all men, in 16% (95% CI: 11-21%) of men with

PSA-D $\leq$ 0.1, in 30% (95% CI: 23-37%) with PSA-D 0.11-0.2, and 54% (95% CI 47-

62%) with PSA-D > 0.2 (p<0.0001 for trend). GS $\geq$ 4+3 cancer was detected in 13% of

all men, in 4 % (95% CI 1 -7%) of men with PSA-D $\leq$ 0.1, in 13% (95% CI: 8-18%) with

PSA-D 0.11-0.2, and 26% (95% CI 19-33%) with PSA-D > 0.2 (p<0.0001 for trend).

Effect of PSA-D on NPV of negative mpMRI

The NPV for GS $\geq$ 7 of negative (Likert 1-2) MRIs was 0.91 (95% CI 0.86-0.96) with

PSA-D $\leq$ 0.2 and 0.71 (95% CI 0.55-0.87) with PSA-D > 0.2 (p=0.003) (Table 2). NPVs

with PSA-D $\leq$ 0.1 and PSA-D 0.11-0.2 were both (p=0.98). Of 13 (9%) GS $\geq$ 7 cancers in

142 men with a negative mpMRI and PSA-D $\leq$ 0.2, 9 (6%) were GS 3+4, 1 (0.7%) were

GS 4+3, and 3 (1.4%) were GS 8-10 cancers.

Effect of PSA-D on PPV of equivocal mpMRI

The PPV for GS $\geq$ 7 of equivocal (Likert 3) MRIs was 0.09 (95% CI 0.03-0.15) with

PSA-D $\leq$ 0.2 and 0.44 (95% CI 0.25-0.63) with PSA-D > 0.2 (p=0.003) (Table 3). The

PPVs with PSA-D $\leq$ 0.1 and with PSA-D 0.11-0.2 were similar (0.10 versus 0.09 , p=0.

98). Of 9 (9%) GS $\geq$ 7 cancers in 96 men with an equivocal mpMRI and PSA-D $\leq$ 0.2, 6

(6%) were GS 3+4, 1 (1%) were GS 4+3, and 2 (2%) were GS 8-10 cancers.

Effect of PSA-D on PPV of mpMRIs suspicious for cancer

The PPV for GS $\geq$ 7 with suspicious (Likert 4-5) MRIs was 0.30 (95% CI: 0.18-0.42)

with PSA-D $\leq$ 0.1, 0.60 (95% CI 0.49-0.71) with PSA-D 0.11-0.2, and 0.66 (95% CI

0.56-0.76) with PSA-D > 0.2 (p<0.0001 for trend). GS $\geq$4+3 cancer was more common

among those with higher PSA-D (p<0.0001 for trend): 7% of 60 men with PSA-D $\leq$0.1,

28% of 78 men with PSA-D 0.11-0.2, and 35% of 82 men with PSA-D >0.2.

Comparison of MRI based prolate ellipsoid and 3D prostate volume measurements

Volume measurements did not significantly differ between MRI based prolate formula

calculation and 3D volume reconstruction, with median volume 59 cm^3 (IQR 38-81 cm^3)

for prolate formula calculation and 60 cm^3 (IQR 40-81 cm^3) for 3D volume

reconstruction. The 3D-volume was larger with a median of 2 cm^3 (IQR -5 to 7 cm^3)

more than the prolate ellipsoid formula. The median PSA-D was 0.13 ng/mL/cm^3 both

with prolate formula calculation and with 3D volume reconstruction.

Discussion

Our study shows that in a repeat biopsy setting, a negative mpMRI (Likert 1-2) is associated with a NPV of around 91% (95% CI 86-97%) to detect GS ≥ 7 prostate cancer in men with a PSA-D ≤0.2, with no difference between PSA-D <0.1 and PSA-D 0.11-0.2. PSA-D also strongly influenced the PPVs for equivocal and suspicious (Likert/PI-RADS 3-5) mpMRIs. The PPV of a Likert 3 mpMRI for detecting GS ≥7 cancer was as low as 9% in men with a PSA-D ≤0.2, again with no difference between PSA-D ≤0.1 and PSA-D 0.11-0.2. Conversely, the PPV was high in men with a high PSA-D and a negative mpMRI, as well as in men with suspicious cancer on mpMRI and a low PSA-D.

Our findings suggest that men with a PSA-D ≤0.2 and a negative or equivocal mpMRI (Likert/PI-RADS 3) may be spared an immediate repeat prostate biopsy. In our study population, this group of patients constituted almost half of all men and around 80% of the men with a Likert 1-2 or a Likert 3 mpMRI. Whether a 10% risk of GS ≥7 cancer is acceptable for PSA surveillance without an immediate repeat biopsy is of course debatable, and the decision should be individualised. Most urologists would, however, not recommend a prostate biopsy for men with a PSA of 2-3 ng/ml and a clinically benign prostate, despite a similar prevalence of GS ≥7 cancer*.

(Footnote: *In the placebo arm of the Prostate Cancer Prevention Trial (PCPT), 5% of men in with a PSA of 2-3 ng/ml had GS ≥7 cancer on sextant biopsy [27]. Gleason

grading in the PCPT was made before the ISUP conference revised the grading criteria in 2005 [23], so with current grading the proportion of GS 7 cancer would have been considerably higher than 5% [28]. Moreover, the transrectal sextant biopsy used in the PCPT has a low sensitivity [29], so more GS 7 cancer would have been detected with a 24-core transperineal biopsy.)

Three recent studies investigated the influence of PSA-D on GS $\geq$7 cancer detection on targeted and systematic biopsy based on mpMRI findings [19-21]. Abdi and co-workers reported that among men with no previous prostate biopsy, 34% with PSA-D >0.15 and 16% with PSA-D <0.15 had GS $\geq$7 cancer on MR/US fusion targeted plus systematic 8-12 core transrectal biopsies [20]. None of the 18 men with a PI-RADS 3 lesion and a PSA-D <0.15 had cancer on biopsy. They did not report on NPVs of PI-RADS 1-2 MRIs. Filson and co-workers studied men both with and without previous biopsies, including men on active surveillance for GS 6 cancer [19]. They found that PSA-D was significantly associated with detecting GS $\geq$7 cancer on MR/US fusion targeted plus systematic 8-12 core transrectal biopsies, but they did not report any NPVs or PPVs. Washino and co-workers reported similar findings in men with no previous biopsy, with cognitively targeted plus 14-core systematic transperineal biopsies as the reference method [21]. No GS $\geq$7 cancer was detected in the men with PSA-D <0.15 who had a PI-RADS 1-2 MRI (n=38) or a PI-RADS 3 lesion (n=6). Our study add to these 3 studies by providing NPVs and PPVs with reasonably narrow CIs for men with previous biopsies, stratified by PSA-D and MRI findings. Moreover, the extensive biopsy protocol (targeted and systematic 24-core image-fusion guided transperineal biopsy) used in our study is

less likely to miss GS ≥7 cancer [3,30].

PSA-D influenced the PPV also for positive mpMRIs (Likert/PI-RADS 4-5), but the risk of GS ≥7 PCa was high enough to warrant a biopsy also in men with a low PSA-D. An MRI reading that is incongruent with the PSA-D (positive MRI with low PSA-D or negative MRI with PSA-D >0.2) could be a trigger for a second opinion on the interpretation of the imaging by a subspecialised prostate radiologist. Our results are in agreement with those from Washino and co-workers, who reported significant cancer in 29% of 7 men with PSA-D <0.15 and in 89% of 110 men with PSA-D ≥0.15 in the presence of PI-RADS 4-5 lesions [21].

In addition to assessing the interaction between PSA-D and cancer detection, we established that using three prostate diameters for the prolate formula calculation of PSA-D is sufficient; 3D-reconstruction based prostate volume calculation, which is not always clinically available, did not meaningfully differ from the prolate formula calculated volume.

Limitations of this study include its retrospective design and that no calculation of statistical power was made in advance. We also had no information on if PSA velocity or other clinical factors were used to select patients for repeat biopsy. Large prospective multicenter studies are needed to validate our results, before guidelines can incorporate a recommendation for surveillance rather than targeted biopsies for men with a low PSA-D and an equivocal MRI. Moreover, our results were obtained at a high volume, tertiary care centre with a long experience of prostate mpMRI and image-guided targeted

biopsies, optimised MRI protocols, and subspecialist prostate radiologists. Urologists need to be aware of the experience of the reporting radiologist when making clinical decisions based on mpMRI results. Inexperienced radiologists might overcall equivocal lesions and miss suspicious lesions, whereas experienced radiologists may help limit the number of equivocal and suspicious lesions to target with biopsies and reduce the risk of missing lesions with significant cancer [30,32].

Conclusion

In a repeat biopsy setting, PSA-D ≤ 0.2 ng/ml/cm^3 is associated with a low detection of GS ≥ 7 prostate cancer, not only in men with negative multiparametric magnetic resonance imaging, but also in men with equivocal imaging. Surveillance, rather than repeat biopsy, may be appropriate for these men. Conversely, biopsies are indicated in men with a high PSA-D, even if an mpMRI shows no suspicious lesion, and in men with an MRI suspicious for cancer, even if the PSA-D is low.

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Legends to illustrations

Figure 1. Low PSA-D with an equivocal mpMRI

60-year old patient with raised PSA and a previous negative biopsy. PSA 6.8 ng/ml, gland volume 76 cm^3, PSA-D 0.09. Axial T2-weighted images show a focal area of low T2 signal in the right mid PZ (arrow in A), but with only mild/equivocal restricted diffusion on b-1400 imaging (B) and ADC maps (C); overall PIRADS-3. Targeted biopsy demonstrated focal high-grade PIN in both cores.

Figure 2: **Low PSA-D with mpMRI suspicious for cancer**.

65-year old patient on active surveillance for GS 6 disease. PSA 5.6 ng/ml, gland volume 134 cm^3, PSA-D = 0.04. T2-weighted image shows a 23 x 18 mm lesion (A) in the anterior right apex transition zone (*), with marked restricted diffusion on b-1400 imaging (B) and ADC maps (C). Targeted biopsy demonstrated Gleason 3+4=7 cancer in 80% of both cores.

Tables

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

	Total n=514	IQR	Previous benign biopsy n=351	IQR	Previous Gleason score 6 biopsy n=163	IQR
Median Age [y]	65	60-69	65	59-69	66	61-69
Median PSA [ng/mL]	7.6	5.4-11.1	7.8	5.9-11.8	6.6	4.73-10.0
Median volume [cm^3]	59	38-81	63	41-86	50	35-70
Median PSA density [ng/mL/cm^3]	0.13	0.09-0.22	0.13	0.09-0.22	0.13	0.08-0.22
Median number of targeted cores	2	2-4	2	2-4	2	2-4
Median number of systematic cores	24	24-24	24	24-24	24	24-24

Table 2: The effect of PSA density on the NPV of a negative mpMRI (Likert 1-2) for the presence of Gleason score ≥7 cancer on transperineal MRI/TRUS-fusion guided targeted and 24-core systematic prostate biopsy according to the Ginsburg protocol.

Abbreviations: PSA = prostate-specific antigen. GS = Gleason score, NPV = negative predictive value, CI = confidence interval.

PSA-Density [ng/mL/cm³]	Total [n]	GS ≥ 7 [n]	NPV	95% CI	p-value
All	173	22	0.87	0.82 - 0.92	
PSA-D≤0.1	66	6	0.91	0.84 - 0.98	
PSA-D 0.11-0.2	76	7	0.91	0.85 - 0.97	0.98
PSA-D ≤0.2	142	13	0.91	0.86 - 0.96	
PSA-D>0.2	31	9	0.71	0.55 - 0.87	0.003

Table 3: PPVs of equivocal mpMRI (Likert 3) to detect Gleason score ≥7 cancer, with transperineal MRI/TRUS-fusion guided targeted and 24-core systematic prostate biopsy according to the Ginsburg protocol as the reference test. Abbreviations: PSA = prostate-specific antigen. GS = Gleason score, PPV = positive predictive value, CI = confidence interval.

PSA-Density [ng/mL/cm³]	Total [n]	GS ≥7 [n]	PPV	95% CI	p-value
All	121	20	0.17	0.10 - 0.24	
PSA-D ≤0.1	62	6	0.10	0.03 - 0.17	0.89
PSA-D 0.11-0.2	34	3	0.09	-0.01 - 0.19	
PSA-D ≤0.2	96	9	0.09	0.03 - 0.15	0.002
PSA-D>0.2	25	11	0.44	0.25 - 0.63	

Table 4: PPVs of suspicious mpMRI (Likert 4-5) to detect Gleason score ≥7 cancer, with transperineal MRI/TRUS-fusion guided targeted and 24-core systematic prostate biopsy according to the Ginsburg protocol as the reference test. Abbreviations: PSA = prostate-specific antigen. GS = Gleason score, PPV = positive predictive value, CI = confidence interval.

PSA-Density [ng/mL/cm^3]	Total [n]	GS ≥7 [n]	PPV	95% CI	p-value
All	220	119	0.54	0.47 - 0.61	
PSA-D ≤0.1	60	18	0.30	0.18 - 0.42	0.0004
PSA-D 0.11-0.2	78	47	0.60	0.49 - 0.71	
PSA-D ≤0.2	138	65	0.47	0.39 - 0.55	0.007
PSA-D>0.2	82	54	0.66	0.56 – 0.76	