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Research article

Which clinical and radiological characteristics can predict clinically significant prostate cancer in PI-RADS 3 lesions? A retrospective study in a high-volume academic center

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ABSTRACT

Objective: To investigate which clinical and radiological characteristics can predict clinically significant prostate cancer (csPCa) in PI-RADS 3 lesions. To investigate which clinical and radiological characteristics influence the clinician to biopsy a PI-RADS 3 lesion.

Materials and methods: mpMRI PI-RADS 3 lesions scored by 1 out of 3 highly specialized radiologists in a single high-volume center during the period March 2015 to August 2017 were investigated. This score was based on T2 weighted and diffusion weighted imaging (DWI) sequences. Clinical characteristics of all patients with PI-RADS 3 lesions were collected from medical records. Radiological characteristics were collected from radiology reports. Some radiological characteristics such as apparent diffusion coefficient (ADC) in a region of interest at the tumor site and ADC at a site contralateral to the tumor site were calculated on DWI sequences. Cox regression analysis was performed to identify which characteristics could predict csPCa in PI-RADS 3 lesions and which characteristics could influence the behavior of a clinician whether or not to biopsy a PI-RADS 3 lesion.

Results: csPCa could be detected in 31 out of 131 patients with PI-RADS 3 lesions (22.9%). A lower median prostate volume ($p = 0.015$) and a lower ratio of ADC of the tumor on ADC of the contralateral prostate (ADCT/ADCCLP) ($p < 0.001$) significantly predisposed for csPCa in multivariate logistic regression. For peripheral zone lesions, a diagnostic model with biopsy of only those PI-RADS 3 lesions with a prostate volume < 44 cc and a ratio of ADCT/ADCCLP < 70% showed a sensitivity for detection of csPCa of 59% with a specificity of 88%. (area under the curve 0.780) A suspicious rectal examination ($p = 0.011$) and the mentioning of prostatitis on the MRI report ($p = 0.020$) influenced clinicians to biopsy a PI-RADS 3 lesion positively and negatively respectively. For transition zone lesions, previous negative biopsies ($p = 0.044$) predisposed for csPCa.

Conclusion: Prostate volume and the ratio of ADC tumor on ADC of the contralateral prostate have the potential to predict csPCa in PI-RADS 3 lesions with a sensitivity of 59% and specificity of 88%. A suspicious rectal examination and the mentioning of prostatitis on the MRI report influenced the decision of clinicians to biopsy a PI-RADS 3 lesion.

1. Introduction

Prostate cancer (PCa) is the second most commonly occurring cancer in men worldwide. It is also the fifth leading cause of cancer mortality in men and it represents a global public health burden [1]. An abnormal digital rectal examination or elevated prostate specific antigen (PSA) in the blood can raise suspicion for prostate cancer. Pathological confirmation of the disease is obtained by prostate biopsies. In addition, multiparametric magnetic resonance imaging (mpMRI) is gaining acceptance in the diagnosis of PCa [2].

PI-RADS (Prostate Imaging Reporting and Data System) has been introduced by the European Society of Urogenital Radiology (ESUR) in 2012 to improve the diagnostic quality of prostate mpMRI and to simplify and standardize radiology reporting [3]. In 2015 a second version of this system has been introduced (PI-RADS v2) [4]. The PI-RADS score assesses the likelihood of a clinically significant prostate

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Table 1
mpMRI acquisition parameters.

	3.0 Tesla Magnetom Trio, Siemens, Erlangen, Germany
T2-weighted imaging	Coronal, transverse, sagittal T2 TSE, 3 mm slice thickness, no interslice gap TR 8000 ms, TE 96 ms, FA 120°, FOV 300 x 300 mm, matrix size 410 × 512, BW 305 Hz, acquisition time 6-8min
Diffusion weighted imaging	Transverse REVEAL, 5 mm slice thickness b-values 50, 250, 500, 750 and 1000 TR 2500 ms, TE 77 ms, FA 90°, number of averages: 4

TSE = turbo spin echo, TR = repetition time, TE = echo time, FA = flip angle, FOV = field-of-view, BW = bandwidth.

cancer (csPCa) on the basis of various MRI characteristics. Assessment categories 1 or 2 indicate (very) low likelihood of csPCa, whereas categories 4 or 5 indicate a (very) high likelihood of csPCa. PI-RADS 3 lesions, however, are equivocal. MRI fusion biopsy studies have confirmed PCa in 35% of PI-RADS 3 lesions and csPCa (defined as a Gleason Score of > = 3 + 4) in only 17% of PI-RADS 3 lesions [5]. Despite this evidence, there are no clear recommendations whether or not to biopsy PI-RADS 3 lesions.

The primary aim of this study was to investigate which clinical and radiological characteristics can predict csPCa in PI-RADS 3 lesions. The secondary aim of this study was to investigate which clinical or radiological characteristics potentially influence the clinician to biopsy a PI-RADS 3 lesion in our study center.

2. Materials and methods

2.1. Study population

A retrospective analysis of all mpMRI data from a single high-volume center was performed from March 2015 to August 2017. PI-RADS 1,2,4 and 5 lesions were excluded. Examinations where a PI-RADS 3 lesion was present alongside a PI-RADS 4 or 5 lesion were excluded as well. MRI examinations that were conducted in an active surveillance protocol were also excluded as we believe that these indications for prostate MRI represent another clinical problem beyond the scope of this article. Only mpMRI examinations that were performed to detect prostate cancer and that were rated as a single new PI-RADS 3 lesion were included. This study was approved by the local ethics committee (Belgian registration number B670201524204).

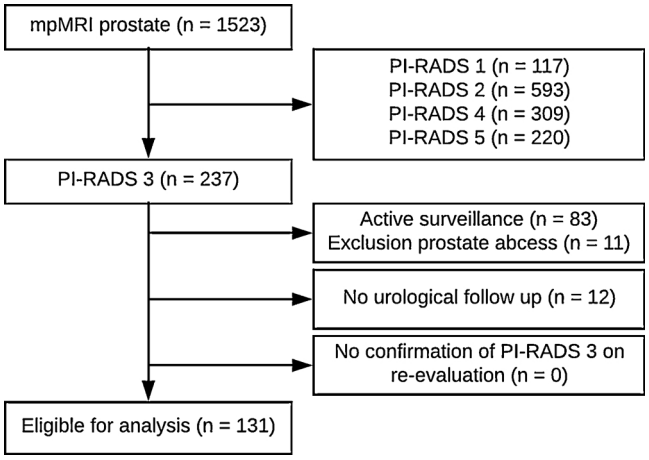

Fig. 2. Outline of enrollment.
mpMRI = multiparametric MRI during period March 2015 to August 2017

Table 2
Characteristics of the study cohort.

PI-RADS 3 lesions (n = 131)	
median age (years)	64.00 (SD 7.02)
previous negative biopsy	n = 32 (24.4%)
previous negative MRI (PI-RADS 1 or 2)	n = 24 (18.3%)
previous acute prostatitis	n = 19 (14.5%)
first degree relative with prostate cancer	n = 22 (16.7%)
previous TURP/Adenomectomy	n = 4 (3.0%)
median PSA value (ng/dl)	7.20 (SD 6.07)
suspicious rectal examination	n = 25 (19.0%)
suspicious TRUS	n = 17 (12.9%)

SD = standard deviation, TURP = transurethral resection of the prostate, TRUS = transrectal ultrasound.

2.2. Magnetic resonance imaging

The MRI consisted of T2-weighted (T2w) images and diffusion-weighted images (DWI) performed on a 3 T system (Magnetom Trio, Siemens Medical Systems, Erlangen, Germany) without use of an endorectal coil. Dynamic contrast enhancement was not performed. The acquisition parameters used for the study are presented in Table 1.

All mpMRI images were interpreted by one of three highly experienced radiologists with a subspecialty in urological radiology. One last

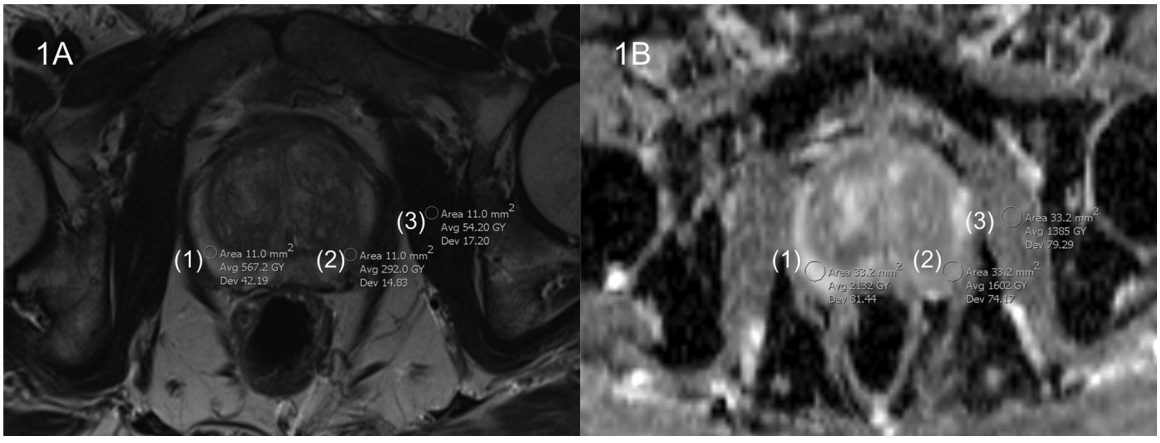

Fig. 1. Example of image analysis.
Fig. 1A: Signal intensity on T2 weighted images was calculated in a region of interest (5 × 5 mm, 19.6 mm^2) (1) at the tumor site, (2) at a site contralaterally from the tumor site and (3) at the internal obturator muscle. Fig. 1B: Apparent diffusion coefficient was calculated on diffusion weighted imaging sequences in a region of interest (5 × 5 mm, 19.6 mm^2) (1) at the tumor site, (2) at a site contralaterally from the tumor site and (3) at the internal obturator muscle.

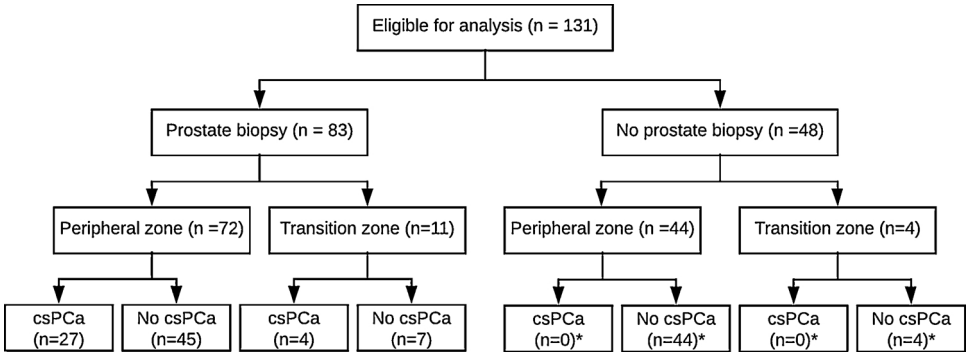

Fig. 3. Schematic description of study results.
csPCa = clinically significant prostate cancer, * = if we consider the unbiopsied lesions to be negative for csPCa

year radiologist in training (with experience in > 400 mpMRI cases) re-evaluated the lesions to confirm the PI-RADS 3 score. The imaging sequences were interpreted according to the Prostate Imaging Reporting and Data System (PI-RADS v2). PI-RADS 3 was defined as a focal abnormality that is mildly to moderately hypointense on ADC-maps and isointense to mildly hyperintense on high-b value DWI in the peripheral zone or a heterogeneous signal intensity with obscured margins on T2w images in the transition zone.

2.3. Urological and histopathological practice

All patients were treated according to common urological practice. The decision whether to perform a prostate biopsy was not influenced by a study protocol. Prostate biopsies were performed transrectally with cognitive fusion or transperineally with MRI-Ultrasound (MRI-US) fusion biopsy. Histopathology of prostate biopsies was reported by specialized pathologists. Clinically significant prostate cancer was defined as a Gleason Score 3 + 4 or higher or International Society of Urological Pathology (ISUP) score 2 or higher [6]. The unbiopsied lesions were considered to be negative for csPCa.

2.4. Collection of clinical and radiological characteristics

Retrospective review of urology and histopathology reports of all patients was conducted by one urologist in training to collect the following clinical characteristics: age, previous negative biopsy, previous negative mpMRI, previous acute prostatitis, first degree relative with prostate cancer, previous transurethral resection or adenomectomy of the prostate, absolute PSA value (ng/ml), suspicious rectal examination, suspicious transrectal ultrasound examination.

One last year radiologist in training retrospectively read each MRI protocol to collect the following radiological characteristics: prostate volume, PSA density, the mentioning of prostatitis, the presence of an apical/midprostate/base or diffuse prostate lesion and the presence of only 1 well demarcated lesion (index lesion). All MRI images were subsequently reviewed by the same radiologist in training. Signal intensity was calculated on T2w sequences in a region of interest (ROI) (5 × 5 mm) at the tumor site, at a site in the same prostate contralaterally from the tumor site and in the internal obturator muscle. Apparent diffusion coefficient (ADC) was calculated on DWI sequences in a ROI (5 × 5 mm) at the tumor site, at a site in the same prostate contralaterally from the tumor site and in the internal obturator muscle. (Fig. 1)

2.5. Statistics

For the biopsied PI-RADS 3 lesions, univariate and multivariate cox regression analysis was performed to identify clinical or radiological characteristics that were risk factors for csPCa. Statistical interpretation for peripheral zone lesions and transition zone lesions was performed separately since interpretation of a PI-RADS 3 lesion on mpMRI imaging is also different in peripheral zone and transition zone lesions. Only those parameters with $p < 0.05$ in univariate cox regression analysis were retained in the multivariate analysis. For each parameter p-value, odds ratio and confidence interval was calculated.

For the unbiopsied PI-RADS 3 lesions, it was assumed that csPCa was not present. Since there was no pathological proof, these patients were not included in the statistical analysis that calculated risk factors for csPCa.

For the total group of biopsied and unbiopsied lesions, univariate and multivariate cox regression analysis was performed to identify clinical or radiological characteristics that were risk factors to perform a prostate biopsy in case of PI-RADS 3 lesions. Only those parameters with $p < 0.05$ in univariate cox regression analysis were retained in the multivariate analysis. For each parameter p-value, odds ratio and confidence interval was calculated.

Statistical analysis was performed using SPSS 25.0 with a 2-sided p-value of < 0.05 indicating statistical significance. For those parameters that were significant predictors of csPCa, receiver operating characteristics (ROC) curve analysis was performed to calculate Youden's index of each individual predictor. Based on area under the curve (AUC) of ROC curves, specificity and sensitivity of univariate and multivariate models was tested.

3. Results

3.1. Study cohort

Outline of enrollment is depicted in Fig. 2. mpMRI of the prostate was performed in 1523 consecutive patients. PI-RADS 1,2,4 and 5 lesions were reported in 117 (7.7%), 593 (38.9%), 309 (20.3%) and 220 (14.4%) patients respectively. Two hundred and thirty-seven patients (15.6%) had a lesion considered to be equivocal (PI-RADS 3). Eighty-three mpMRI's were excluded because they were conducted in an active surveillance protocol. From the remaining 154 mpMRI's, 11 mpMRI's were conducted to exclude prostate abscess in case of chronic prostatitis and in 12 mpMRI's there was no urological follow up data available. Re-evaluation of the lesions by an experienced radiologist in training confirmed a PI-RADS 3 score in the remaining 131 patients. The analysis of our study results was based on 131 mpMRI's with a new diagnosis of a PI-RADS 3 lesion.

Characteristics of the study cohort are displayed in Table 2 and schematic description of study results are depicted in Fig. 3. One hundred and sixteen lesions (88%) were situated in the peripheral zone, 15 lesions (12%) were situated in the transition zone. Clinically significant prostate cancer was detected in 22.9% (31/131) of all PI-RADS 3 lesions included in the study. Only in 83 patients (63%) biopsies were performed. (Seventy-six biopsies (91.5%) were performed transrectally

Table 3
Significant versus insignificant or no prostate cancer in biopsied peripheral zone lesions.

Biopsied peripheral zone lesions (n = 72)	negative for PCa or gleason 3 + 3 (n = 45)	> = Gleason 3 + 4 (n = 27)	p - value univariate logistic regression	odds ratio	confidence interval	p-value multivariate logistic regression	odds ratio	confidence interval
Clinical characteristics								
median age (years)	65.00 (SD 7.10)	65.00 (SD 7.17)	0.717	1.012	0.949-1.079			
previous negative biopsy	14 (31.1%)	3 (11.1%)	0.405	0.633	0.216-1.857			
previous negative MRI (PI-RADS 1 - 2)	8 (17.8%)	2 (7.4%)	0.218	0.424	0.108-1.661			
previous acute prostatitis	6 (13.3%)	3 (11.1%)	0.853	0.870	0.201-3.765			
first degree relative with prostate cancer	8 (17.8%)	6 (22.2%)	0.567	1.406	0.437-4.525			
previous TURP/adenomectomy	2 (4.4%)	1 (3.7%)	0.918	0.879	0.076-10.122			
median PSA value (ng/ml)	7.28 (SD 7.38)	6.45 (SD 3.77)	0.421	1.028	0.961-1.101			
suspicious rectal examination	12 (26.7%)	9 (33.3%)	0.588	1.319	0.485-3.587			
suspicious TRUS	7 (15.6%)	4 (14.8%)	0.987	1.011	0.270-3.782			
Radiological characteristics								
median prostate volume (ml)	57.00 (SD 34.22)	40.90 (SD 15.17)	0.008*	0.963	0.936-0.990	0.015*	0.970	0.947-0.994
median PSA density (ng/ml^2)	0.12 (SD 0.08)	0.17 (SD 0.12)	0.009*	1.089	1.022-1.161			
mentioning of prostatitis on MRI	27 (60.0%)	16 (59.3%)	0.996	1.003	0.406-2.475			
apical peripheral	13 (28.9%)	10 (37.0%)	0.767	1.156	0.443-3.017			
midprostate peripheral	35 (77.8%)	18 (66.7%)	0.632	0.789	0.300-2.075			
base peripheral	12 (26.7%)	6 (22.2%)	0.779	0.854	0.284-2.571			
diffuse peripheral	14 (31.1%)	5 (18.5%)	0.315	0.578	0.198-1.685			
one well demarcated lesion	20 (44.4%)	11 (40.7%)	0.763	0.870	0.350-2.161			
median Si tumor T2	276.00 (SD 89.88)	300.00 (SD 94.65)	0.635	1.001	0.996-1.006			
ratio median Si tumor T2w/median SI prostate CL	0.61 (SD 0.15)	0.59 (SD 0.76)	0.329	1.957	0.509-7.524			
ratio median Si tumor T2w/median SI Muscle CL	4.26 (SD 1.44)	3.99 (SD 1.24)	0.270	0.829	0.594-1.157			
median ADC tumor (mm^2/s)	1.16×10^{-3} (SD 0.28)	1.07×10^{-3} (SD 0.23)	0.112	0.999	0.997-1.000			
ratio median ADC tumor/median ADC prostate CL	0.72 (SD 0.12)	0.60 (SD 0.14)	0.031*	0.961	0.927-0.996	< 0.001*	0.939	0.909-0.971
ratio median ADC tumor/median ADC muscle CL	1.16 (SD 0.38)	0.98 (SD 0.50)	0.507	0.723	0.278-1.882			

PCa = prostate cancer, SD = Standard deviation, * = significantly different, FA = family anamnesis, TURP = transurethral resection of the prostate, TRUS = transrectal ultrasound, Si = signal intensity, T2w = T2 weighted MRI image, CL = contralateral, ADC = Apparent diffusion coefficient.

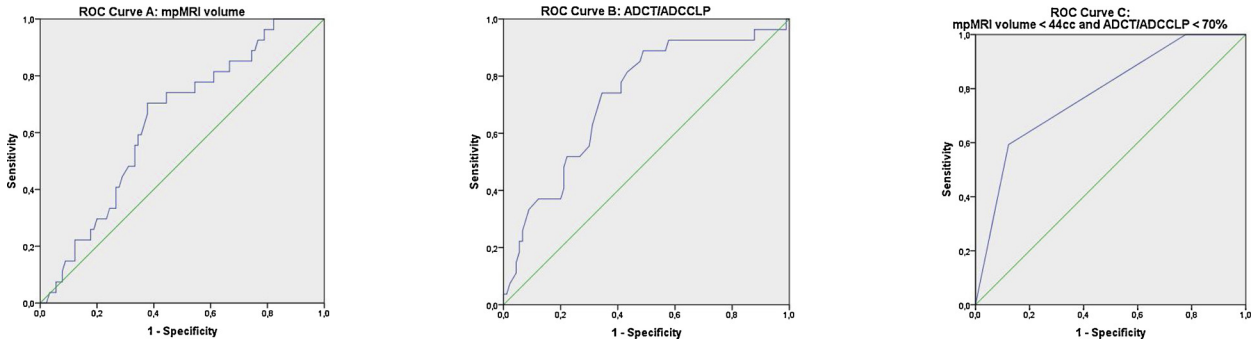

Fig. 4. ROC curve analysis.
receiver operating characteristics (ROC) curves for clinically significant prostate cancer (csPCa) versus insignificant PCa or no PCa in biopsied peripheral zone PI-RADS 3 lesions (n = 72). (A) ROC curve for mpMRI volume. Youden's index 44cc. Area under the curve 0.640 with a sensitivity of 70% and specificity of 60% to detect csPCa in PI-RADS 3 lesions in case of prostate biopsy only when prostate volume < 44cc. (B) ROC curve for the ratio apparent diffusion coefficient of the tumor (ADCT) on apparent diffusion coefficient of the contralateral prostate (ADCCLP). Youden's index 70%. Area under the curve 0.724 with a sensitivity of 78% and specificity of 59% to detect csPCa in PI-RADS 3 lesions in case of prostate biopsy only when ADCT/ADCCLP < 70%. (C) ROC curve for the combination of a prostate volume < 44cc and ADCT/ADCCLP < 70%. Area under the curve 0.780 with a sensitivity of 59% and a specificity of 88% to detect csPCa in PI-RADS 3 lesions in case of prostate biopsy only when prostate volume < 44cc and ADCT/ADCCLP < 70%.

and 7 (8.5%) biopsies transperineally)

3.2. Risk factors for csPCa in biopsied peripheral zone lesions (n = 72)

Seventy-two out of 83 biopsied lesions (87%) were situated in the peripheral zone. Clinical and radiological characteristics of csPCa versus insignificant or no PCa in biopsied peripheral zone lesions are shown in Table 3. In 37.5% (27/72) of biopsied lesions csPCa was detected.

In univariate cox regression analysis, the presence of a lower median prostate volume (p = 0.008, OR 0.963), a higher median PSA density (p = 0.009, OR 1.089) and a lower ratio of ADC tumor (ADCT) on ADC of the contralateral prostate (ADCCLP) (p = 0.031, OR 0.961) seemed to predispose for csPCa in biopsied peripheral PIRADS 3 lesions. For the multivariate logistic regression PSA density was not **used** since this parameter is a combination of prostate volume and PSA value. In multivariate logistic regression a lower median prostate volume (p = 0.015, OR 0.970) and a lower ratio of ADCT/ADCCLP (p < 0.001, OR 0.939) remained independent prognostic variables for csPCa.

ROC curve analysis was performed to calculate Youden's index of a lower median prostate volume and a lower ratio of ADCT/ADCCLP. Univariate ROC curve analysis of MRI volume as a continuous variable showed a sensitivity of 70% and a specificity of 60% for detection of csPCA in case of a prostate volume < 44cc with AUC 0.640. (Fig. 4a) Univariate ROC curve analysis of ratio of ADCT/ADCCLP as a continuous variable showed a sensitivity of 78% with a specificity of 59% for detection of csPCA in case of a ratio ADCT/ADCCLP < 70% with AUC of 0.724. (Fig. 4b)

Multivariate ROC curve analysis with prostate volume and the ratio ADCT/ADCCLP as multivariate statistically significant parameters showed in case of a prostate volume < 44cc, and a ratio of ADCT/ADCCLP < 70% a sensitivity for detection of prostate cancer of 59% with a specificity of 88% and AUC 0.780. (Fig. 4c)

3.3. Risk factors for csPCa in biopsied transition zone lesions (n = 11)

Only 11 out of 83 biopsied lesions (13%) were situated in the transition zone. In 36% (4/11) of the biopsied lesions significant prostate cancer was detected. In univariate cox regression analysis previous negative biopsies (p = 0.044, OR 0.971) seemed to predispose for significant prostate cancer in biopsied transition zone PI-RADS 3 lesions.

3.4. Risk factors to perform prostate biopsies in all PI-RADS 3 lesions (n = 131)

The mean follow-up of the unbiopsied lesions was 2.3 years and during this period no csPCa was found. Characteristics of biopsied versus unbiopsied PI-RADS 3 lesions are shown in Table 4. In univariate cox regression analysis, a lower mean age (p = 0.017, OR 1.059), the mentioning of prostatitis in the MRI report (p = 0.001, OR 0.187), a lesion in the base of the prostate (p = 0.030, OR 0.423) and description of a diffuse lesion (p = 0.001, OR 0.281) seemed to negatively influence the decision to biopsy. The presence of a suspicious rectal examination (p = 0.009, OR 5.410) and the presence of only 1 well demarcated lesion (p = 0.008, OR 3.160) seemed to stimulate biopsy. In multivariate logistic regression a suspicious rectal examination (p = 0.011, OR 5.653) did affect the decision to perform biopsy positively and the mentioning of prostatitis on the MRI report (p = 0.020, OR 0.272) did affect the decision to perform biopsy negatively.

4. Discussion

The diagnosis of a PI-RADS 3 is an acknowledgement of uncertainty. It means that the presence or absence of csPCa is equivocal. Some urology departments have agreed always to perform targeted biopsies of these lesions in order not to miss csPCa. Retrospective MRI fusion biopsy studies indeed have shown csPCa (defined as Gleason Score > = 3 + 4) in 15–21% of PI-RADS 3 lesions [7,8] This approximately corresponds to the 22.9% csPCa that was found in our study group if we consider the unbiopsied lesions to be negative for csPCa.

Recently a few studies have tried to investigate the possibility to subdivide the group of PI-RADS 3 lesions. Hansen et al. examined objective imaging criteria to differentiate clinically significant from insignificant lesions. In a group of 143 MRI-US fusion biopsy patients they found 21% csPCa. For peripheral zone lesions, low ADC values significantly predisposed for csPCa on multivariate analysis (p < 0.001) [8]. In our study, we found that median ADC values were not significantly different on univariate analysis (p = 0.112). However, we created a surrogate radiological characteristic, the ratio ADCT/ADCLP, that was significantly different in multivariate analysis (p < 0.001, OR 0.939). Felker et al. examined both clinical and MRI characteristics of 90 men with PI-RADS 3 lesions. They found csPCa in 15% of their biopsies. Comparable to our results, prostate volume (p = 0.047) and PSA density (p = 0.002) were significantly different in univariate analysis. ADC values (p = 0.076) showed a trend towards significance, a finding comparable with the results in our study (p = 0.112). They

Table 4
Biopsied versus unbiopsied peripheral and transition zone lesions.

PI-RADS 3 lesions (n = 131)	biopsy (n = 83)	no biopsy (n = 48)	p-value univariate logistic regression	odds ratio	confidence interval	p-value multivariate logistic regression	odds Ratio	confidence interval
Clinical characteristics								
median age (years)	65.00 (SD 7.02)	60.00 (SD 9.27)	0.017*	1.059	1.010 - 1.110	0.128	1.040	0.989-1.094
previous negative biopsy	21 (25.3%)	11 (22.9%)	0.760	1.139	0.494-2.627			
previous negative MRI (PI-RADS 1 - 2)	14 (16.9%)	10 (20.8%)	0.572	0.771	0.313-1.902			
previous acute prostatitis	9 (10.8%)	10 (20.8%)	0.123	0.462	0.173-1.234			
first degree relative with prostate cancer	14 (16.9%)	8 (16.7%)	0.976	1.014	0.392-2,628			
previous TURP/Adenomectomy	3 (3.6%)	1 (2.1%)	0.628	1.763	0.178-17.433			
median PSA value (ng/ml)	7.20 (SD 6.07)	7.10 (SD 6.63)	0.184	1.056	0.975-1.144			
suspicious rectal examination	22 (26.5%)	3 (6.3%)	0.009*	5.410	1.525-19.192	0.011*	5.653	1.489-21.455
suspicious TRUS	11 (13.3%)	6 (12.5%)	0.902	1.069	0.369-3.102			
Radiological characteristics								
median prostate volume	46.50 (SD 29.26)	44.60 (SD 42.98)	0.696	1.002	0.991-1.013			
median PSA density (ng/ml^2)	0.14 (SD 0.17)	0.14 (SD 0.42)	0.554	1.009	0.978-1.042			
mentioning of prostatitis on MRI	47 (56.6%)	42 (87.5%)	0.001*	0.187	0.071-0.487	0.020*	0.272	0.091-0.811
lesion peripheral zone	72 (86.7%)	44 (91.7%)	0.309	0.498	0.130-1.907			
apical peripheral	26 (31.3%)	19 (39.6%)	0.338	0.696	0.332 - 1.461			
midprostate peripheral	58 (69.9%)	33 (68.8%)	0.892	1.055	0.488-2.277			
base peripheral	18 (21.7%)	19 (39.6%)	0.030*	0.423	0.194-0.921	0.975	1.016	0.387-2.667
diffuse peripheral	22 (26.5%)	27 (56.3%)	0.001*	0.281	0.132-0.594	0.121	0.446	0.160-1.238
one well demarcated lesion	35 (42.2%)	9 (18.8%)	0.008*	3.160	1.356-7.361	0.784	1.171	0.379-3.618

SD = Standard deviation, * = significantly different, TURP = Transurethral resection of the prostate, TRUS = transrectal ultrasound.

concluded that a combination of PSA density > 0.15 ng/mL^2 and ADC values of < 1000 mm^2/s yielded an AUC of 0.91 for csPCa [7].

Our study was unable to find *clinical* characteristics that could predict csPCa. As in the previously described studies we were able to find *radiological* characteristics that could predict csPCa. In the peripheral zone, a lower median prostate volume and a lower ratio ADCT/ADCCLP were independent prognostic variables for csPCa on multivariate analysis of a PI-RADS 3 lesion. A higher median PSA density significantly predisposed for csPCa on univariate analysis but was excluded from the multivariate analysis since it is obviously dependent on prostate volume.

For the peripheral zone lesions, we searched for a predictive model with multivariate ROC curve analysis. The combination of median prostate volume < 44cc and a ratio of ADCT/ADCCLP < 70% showed a sensitivity of 59% and specificity of 88% for detection of csPCA with AUC 0.780. Although these results seem promising, the use of this model in clinical practice remains limited because no combination of these 2 parameters was found that had both a very high sensitivity and specificity for detection of csPCa. Considering a pretest probability of 37.5% (27/72) for csPCa in biopsied peripheral zone lesions, our model showed a positive predictive value of 74% and a negative predictive value of 78%. This relatively high negative predictive value could be used in frail or co-morbid patients with a PI-RADS 3 lesion where "do not harm" prevails.

Only 11 lesions were situated in the transition zone. Despite this small sample size, we found that previous negative biopsies predisposed for csPCa in transition zone tumors. However, 3 out of 4 lesions that showed csPCa had not had a prostate MRI before and csPCa easily could have been missed on a first biopsy. These results need to be interpreted cautiously.

The secondary goal of our study was to investigate which clinical or radiological characteristics potentially influence the clinician to biopsy a PI-RADS 3 lesion. In multivariate analysis suspicious rectal examination independently seemed to stimulate biopsy. This corresponds to the guidelines of the European Association of Urology which considers a suspicious rectal examination as a clear indication for prostate biopsy [9]. The mentioning of prostatitis on an MRI report independently caused fewer prostate biopsies. It might be that clinicians attributed a PSA rise to (chronic) prostatitis rather than csPCa and avoided biopsies for this reason. On univariate analysis the presence of only 1 well demarcated lesion caused more prostate biopsies and the mentioning of diffuse lesions on MRI seemed to cause fewer prostate biopsies. Possibly, clinicians are more eager to biopsy a well-defined zone where they can target their biopsies. This remains a hypothesis since this review was retrospective and we could not question the clinicians for their reasons for biopsy on a patient to patient basis.

Our study has limitations. The study design is retrospective, single center and comprises a relatively small group of patients. Also, unlike other studies that have investigated this topic, only 8.5% of our biopsied lesions were performed transperineal with MRI-US fusion and the rest was performed with cognitive fusion. One would expect lower detection ratios of csPCa but our study showed 30 csPCa patients in 83 biopsied patients (36%) and 30 csPCa patients in 131 patients with PI-RADS 3 lesions (22.9%). These percentages are comparable or higher than other studies that did use MRI-US fusion biopsy.[758] Also, 48 PI-RADS 3 lesions were unbiopsied. The mean follow-up of these unbiopsied lesions was 2.3 years and during this period no csPCa was found. Although we assume that csPCa was not present in this group, it was not proven by pathology and these 48 patients were not used to calculate risk factors for csPCa. The fact that dynamic contrast enhancement was not used can be counted as a limitation although the usefulness of this technique is debated [10].

In conclusion this study has shown that csPCa could be detected in 36% of biopsied PI-RADS 3 lesions and 22.9% of all PI-RADS 3 lesions in our study center. A lower prostate volume, a lower ratio of ADC values of the tumor on ADC values of the contralateral prostate

potentially predict the presence of csPCa in biopsied PI-RADS 3 lesions. Combination of these 2 parameters could not show both a high specificity and high sensitivity. A suspicious rectal examination and the mentioning of prostatitis on the MRI report independently influenced the decision to perform a prostate biopsy. Larger trials will have to check reproducibility of our results in order to refine the latest PI-RADS score and potentially increase both the negative and the positive predictive value of a PI-RADS 3 lesion.

Conflict of interest

None.

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