A combined MRI-PSAD risk stratification system for prioritizing prostate biopsies

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Introduction: *Prostate cancer screening with PSA is associated with low specificity; furthermore, little is known about the optimal timing of biopsy. We aimed to evaluate whether a risk classification system combining PSA density (PSAD) and mpMRI can predict clinically significant cancer and determine biopsy timing.*

Materials and methods: *We reviewed the medical records of 256 men with a PI-RADS ≥ 3 lesion on mpMRI who underwent transperineal targeted and systematic biopsies of the prostate between 2017-2019. Patients were stratified into three risk groups based on PSAD and mpMRI findings.*

The study endpoint was clinically significant prostate cancer (CSPC). The association between the risk groups and CSPC was evaluated.

Results: *Based on the proposed risk stratification system 42/256 men (16%) were high-risk (mpMRI finding of extra-prostatic extension and/or seminal vesicle invasion and/or a PI-RADS 5 lesion with a PSAD > 0.15 ng/mL^2), 164/256 (64%) intermediate-risk (PI-RADS 4-5 lesions and/or PSAD > 0.15ng/mL^2 with no high-risk features) and 50/256 (20%) low-risk (PI-RADS 3 lesions and PSAD ≤ 0.15 ng/mL^2). High-risk patients had significantly higher rates of CSPC (76%) when compared to intermediate-risk (26%) and low-risk (4%). On multivariable logistic regression analysis adjusted for age, previous biopsy, and clinical T-stage we found an association between intermediate-risk (OR = 4.84, p = 0.038) and high-risk (OR = 40.13, p < 0.001) features and CSPC. High-risk patients had a shorter median biopsy delay time (110 days) compared to intermediate- and low-risk patients (141 and 147 days, respectively). We did not find an association between biopsy delay and CSPC.*

Conclusions: *Our findings suggest that a three-tier risk classification system based on mpMRI and PSAD can identify patients at high-risk for CSPC who may benefit from earlier biopsy.*

Key Words: prostate biopsy, magnetic resonance imaging, prostate cancer, prostate-specific antigen, risk stratification

Introduction

Prostate-specific antigen (PSA) screening has led to an increase in the diagnosis of early stage clinically significant prostate cancer (CSPC); however, this was associated with an increase in the detection and treatment of clinically insignificant cancer.[1-3] PSA derivates including free/total PSA, PSA density (PSAD), PHI and the 4K score, among others, have been evaluated with the aim of identifying clinically significant cancer while reducing the detection and treatment of clinically insignificant cancer.[4-9]

Level 1 evidence from the MRI-FIRST, PRECISION and other trials support the use of targeted biopsies for diagnosing patients with visible lesions on multiparametric magnetic resonance imaging (mpMRI) of the prostate.[10-12] mpMRI findings are categorized according to the *Prostate Imaging–Reporting and*

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Data System (PI-RADS) score: PI-RADS 3 lesions are considered equivocal and an increase in the score was associated with an increase in the rate of clinically significant cancer.[13,14] Combining targeted and systematic biopsies leads to an increase in the detection of CSPC. Combined biopsies are also associated with an increased detection of clinically insignificant cancer which may not require treatment.[11]

Several studies have shown a benefit in combining mpMRI findings and PSAD for predicting the presence of CSPC in biopsy naïve patient. PSAD > 0.15 and PI-RADS > 3 were associated with an increased risk of clinically significant cancer (57%-75%), while PSAD < 0.1 and PI-RADS < 4 were associated with a very low risk of clinically significant cancer (2%-6%).[15-17] Furthermore, patients with insignificant cancer on biopsy who underwent radical prostatectomy with PI-RADS > 3 or PSAD > 0.15 had pathological upgrading in 88.9% and 81.3%, respectively, highlighting the importance of these parameters.[16] When evaluating the role of extra-prostatic extension (EPE) and seminal vesicle invasion (SVI) on mpMRI in predicting adverse pathology at radical prostatectomy, a significant association was found between imaging and pathologic findings.[18,19] Despite these previous publications, few studies have validated the association between a standardized risk classification system based on PSAD and mpMRI findings, including the presence of EPE and SVI, and findings at prostate biopsy.

We previously reported that under current practice delaying prostate biopsy for up to 8 months was not associated with adverse pathologic outcomes.[20] However, little is known regarding the optimal timing of prostate biopsy. In the current study, we explore whether a three-tier risk classification system incorporating both mpMRI findings and PSAD is associated with biopsy outcome and timing and thus may be used for risk stratifying and prioritizing future biopsies.

Materials and methods

After obtaining Institutional Review Board approval we reviewed the medical records of 297 patients who had a PI-RADS ≥ 3 lesion on mpMRI performed due to an elevated PSA or suspicious digital rectal examination and underwent transperineal targeted fusion and systematic biopsies of the prostate between the years 2017-2019. We excluded 41 patients: 20 patients who underwent 1.5 Tesla mpMRI, 16 patients without prostate volume measurements, and five patients without data on biopsy delay time, leaving a total of 256 patients for further analyses.

Baseline clinical characteristics of the study cohort were collected. All patients underwent mpMRI prior to biopsy and prostate lesions were categorized using the Prostate Imaging Reporting and Data System (PI-RADS) v2 score. PSAD was calculated by dividing the pre-biopsy PSA and prostate volume as measured on mpMRI. Patients were stratified into three risk groups based on the following criteria: (1) High risk - suspected extra-prostatic extension and/or seminal vesicle invasion on mpMRI and/or a PI-RADS 5 lesion with a PSAD > 0.15 ng/mL^2, (2) Intermediate risk – does not fulfil the high-risk criteria and has a PI-RADS 4-5 lesions and/or PSAD > 0.15 ng/mL^2, (3) Low risk - PI-RADS 3 lesions and PSAD ≤ 0.15 ng/mL^2 Table 1.

TABLE 1. **Pre-biopsy risk classification system**

High risk	Extraprostatic extension on mpMRI and/or Seminal vesicle invasion on mpMRI and/or PI-RADS 5 lesion with a PSAD > 0.15 ng/mL^2
Intermediate risk	Does not fulfill the high-risk criteria and PI-RADS 4 - 5 lesion and/or PSAD > 0.15 ng/mL^2
Low risk	PI-RADS 3 lesion and PSAD ≤ 0.15 ng/mL^2

PI-RADS = prostate imaging-reporting and data system; mpMRI = multiparametric magnetic resonance imaging; PSAD = prostate-specific antigen density

Patients underwent an mpMRI-transrectal ultrasound (TRUS) fusion guided transperineal prostate biopsy under general anesthesia using the BioJet system (D&K Technologies GmbH, Barum, Germany) as previously reported. Biopsy delay time was evaluated from the time of mpMRI to the time the biopsy was performed. Biopsy samples were evaluated for the presence of cancer and graded using the International Society of Urological Pathology (ISUP) system by a dedicated genitourinary pathologist.

Descriptive statistics were used to report the baseline clinical characteristics, biopsy delay time, and biopsy findings categorized by the different risk groups. Continues variable were reported as median and interquartile range and compared using the rank sum test. Categorical variables were reported as number and percent and compared using the Chi squared and Fisher exact tests. The primary study outcome was the finding of clinically significant cancer on prostate biopsy defined as Gleason Grade Group ≥ 2. The secondary outcome was the finding of any cancer on prostate biopsy. We created cross-tabulations of the highest grade group detected (categorized as no cancer, grade group 1 and ≥ grade group 2) by biopsy method used (targeted vs. systematic) for patients in the low-, intermediate- and high-risk groups. Receiver operating characteristic curves were plotted to evaluate the diagnostic ability of the maximal PI-RADS score, PSAD and a combination of the two in identifying CSPC. The DeLong test was used to compare the area under the curve between the different curves. Multivariable logistic regression analyses adjusted for patient age, previous biopsy and clinical stage were used to evaluate the association between PI-RADS score, PSAD and the proposed risk system and the finding of CSPC. After excluding patients with a biopsy delay time of over 1 year and patients on active surveillance, we created a similar multivariable model including time to biopsy to evaluate the association of the various outcomes with a finding of CSPC on biopsy when accounting for biopsy delay time. All statistical analyses were two-sided, and significance was defined as $p < 0.05$. All analyses were conducted using R Statistical Software (version 3.5.1; R Foundation for Statistical Computing, Vienna, Austria).

Results

The study cohort included a total of 256 men at a median age of 68 years (IQR 63, 72). The baseline characteristics of the study cohort are reported in Table 2.

TABLE 2. **Baseline characteristics of the study cohort (n = 256)**

Variable	Value*
Age (years)	68 [63, 72]
Family history of prostate cancer	
No	219 (85.5)
Yes	37 (14.5)
Previous biopsy	
No	111 (43)
Yes	145 (57)
Active surveillance	
No	208 (81)
Yes	48 (19)
PSA (ng/mL)	6.86 [5.25, 9.93]
Clinical stage	
< T2b	236 (92)
> T2a	20 (8)
Maximal PI-RADS score on mpMRI	
3	62 (24)
4	144 (56)
5	50 (20)
Prostate volume (mL)	56.5 [37, 82]
PSAD (ng/mL^2)	0.13 [0.08, 0.2]
PSAD category	
0.1 and lower	98 (38)
> 0.1	55 (22)
> 0.15	103 (40)
Extraprostatic extension on imaging (n = 255)	
No	232 (91)
Yes	23 (9)
Seminal vesicle invasion on imaging (n = 255)	
No	249 (98)
Yes	6 (2)
Combined risk category†	
Low	50 (20)
Intermediate	164 (64)
High	42 (16)

PSA = prostate specific antigen; PI-RADS = prostate imaging-reporting and data system; mpMRI = multiparametric magnetic resonance imaging; PSAD = prostate-specific antigen density.
*continuous variables are reported as median [interquartile range] and categorical variables as number (percent).
†combined risk category defined as - (1) High risk - suspected extraprostatic extension and/or seminal vesicle invasion on mpMRI and/or a PI-RADS 5 lesion with a PSAD > 0.15 ng/mL^2, (2) Intermediate risk – does not fulfill the high-risk criteria and has a PI-RADS 4-5 lesions and/or PSAD > 0.15 ng/mL^2, (3) Low risk - PI-RADS 3 lesions and PSAD ≤ 0.15 ng/mL^2.

Median PSA value was 6.86 ng/mL (IQR 5.25, 9.93) and clinical stage based on digital rectal examination was < T2b in most patients (236/256, 92%). Median prostate volume was 56.5 mL (IQR, 37, 82) and median PSAD was 0.13 ng/mL^2 (IQR, 0.08, 0.2); 103 men (40%) had a PSAD > 0.15. Most patients had a PI-RADS 4 lesion on mpMRI (144/256, 56%) and based on the mpMRI images 23/256 men (9%) were suspected to have extra-prostatic extension while 6/256 men (2%) had a radiological finding of seminal vesical invasion. When utilizing the combined risk classification system 42/256 men (16%) were considered high risk, 164/256 (64%) intermediate risk and 50/256 (20%) low risk.

Table 3 summarized the pathologic findings of prostate biopsies stratified by the combined risk groups. Overall, CSPC was diagnosed in 76/256 men (30%) and any cancer was diagnosed in 162/256 men (63%). Men who were high-risk had significantly higher rates of CSPC (76%) and any prostate cancer (98%) when compared to men in the intermediate-risk group (26% CSPC and 64% any cancer) and low-risk group (4% CSPC and 32% any cancer). Figure 1 depicts biopsy results for the different PSAD levels, PI-RADS scores and the combined risk-group.

Among the low-risk patients with insignificant cancer, 7/14 were diagnosed by systematic biopsies alone and 3/14 were diagnosed by targeted biopsies alone. The rate of patients diagnosed with insignificant cancer solely by systematic or targeted biopsies did not differ substantially among intermediate- and high-risk patients. CSPC was diagnosed in 8/42 intermediate-risk patients by systematic biopsies alone and in 16/42 patients by targeted biopsies alone. Similarly, among high-risk patients, CSPC was diagnosed in 4/32 patients by systematic biopsies alone and in 8/32 patients by targeted biopsies alone, Table 4.

ROC curves were plotted to evaluate the diagnostic ability of the maximal PI-RADS score, PSAD and the combination of the two in identifying CSPC, Figure 2. The area under the curve (AUC) was significantly larger when combining both PI-RADS and PSAD (AUC = 0.8) when compared to PI-RADS score alone (AUC = 0.723, $p < 0.001$), but not when compared to PSAD alone (AUC = 0.772, $p = 0.255$). On multivariable logistic regression analysis adjusted for age, previous biopsy, and clinical T-stage we found an association between intermediate-risk (OR = 4.84, 95% CI 1.34, 31.02, $p = 0.038$) and high-risk (OR = 40.13, 95% CI 9.56,

TABLE 3. **Prostate biopsy findings stratified by risk groups**

Variable*	**Risk category**			**p value**
	Low (n = 50)	**Intermediate (n = 164)**	**High (n = 42)**	
Number of cores obtained from ROI	7 [5, 10]	9 [6, 11]	10 [7, 12]	0.011
Number of cores positive from ROI	0 [0, 0]	1 [0, 3]	5 [3, 7]	< 0.001
Number of random cores obtained	20 [19, 23]	20 [19, 23]	19 [17, 21]	0.059
Number of positive random cores	0 [0, 1]	1 [0, 2]	3 [1, 5]	< 0.001
Maximal ISUP grade group on biopsy (%)				< 0.001
No cancer	34 (68)	59 (36)	1 (2)	
1	14 (28)	63 (38)	9 (21)	
2	2 (4)	29 (18)	18 (43)	
3	0 (0)	6 (4)	5 (12)	
4	0 (0)	7 (4)	6 (14)	
5	0 (0)	0 (0)	3 (7)	
Clinically significant prostate cancer on biopsy (%)				< 0.001
No	48 (96)	122 (74)	10 (24)	
Yes	2 (4)	42 (26)	32 (76)	
Any prostate cancer on biopsy (%)				< 0.001
No	34 (68)	59 (36)	1 (2)	
Yes	16 (32)	105 (64)	41 (98)	

PSAD = prostate-specific antigen density; PI-RADS = prostate imaging-reporting and data system; ROI = region of interest; ISUP = International Society of Urological Pathology

*continuous variables are reported as median [interquartile range] and categorical variables as number (percent)

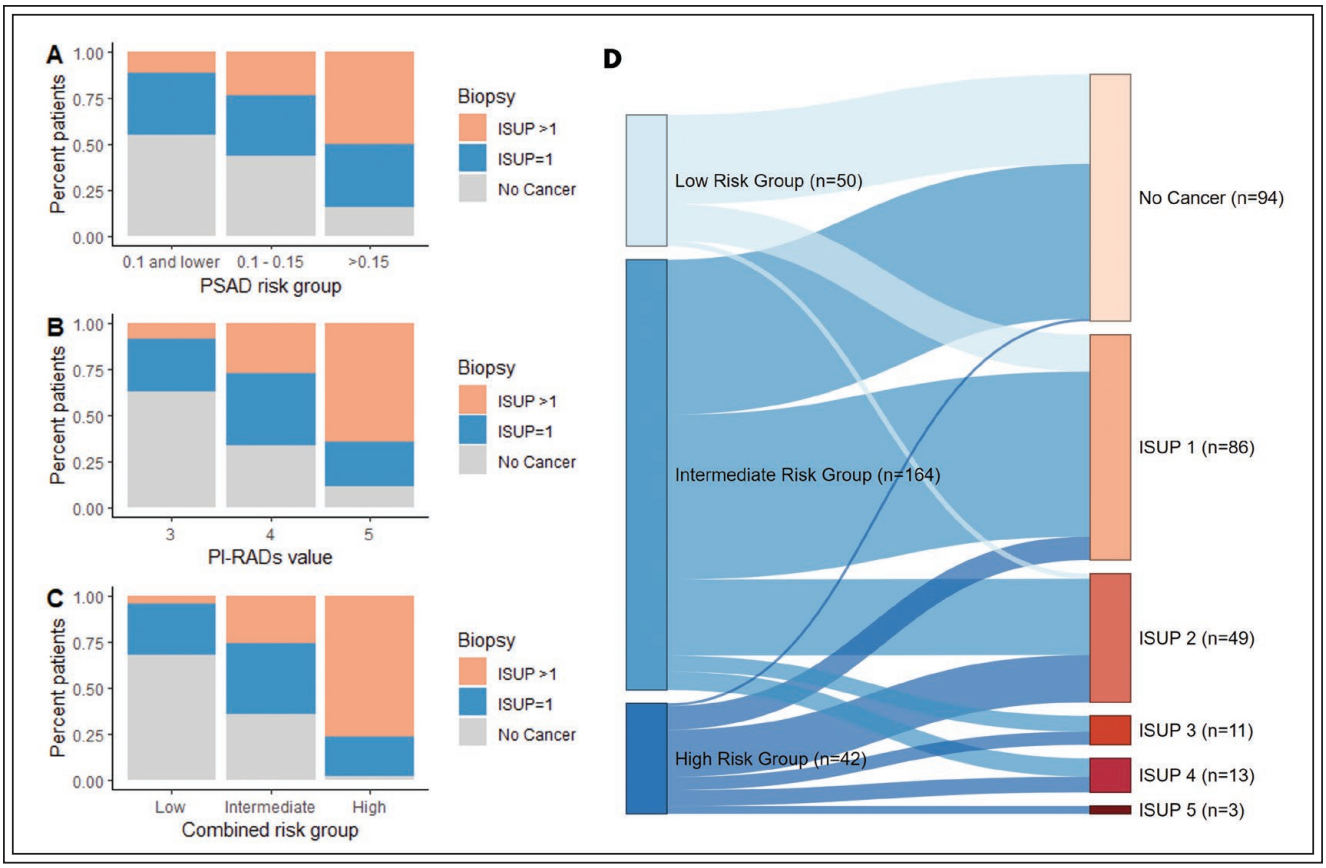

Figure 1. Bar-plots and a Sankey plot depicting prostate biopsy findings when stratified according to **(A)** PSAD risk groups, **(B)** maximal mpMRI PI-RADS score and **(C, D)** a risk stratification system combining PI-RADS score and PSAD.

281.73, $p < 0.001$) patients and a finding of CSPC on biopsy when compared to low-risk patients. Similar associations were found between maximal PI-RADs score and PSAD category and CSPC; however, the odds ratios of these associations were lower, Table 5.

For analyses associated with biopsy delay time we excluded 58 patients with a delay time of ≥ 1 year between mpMRI and prostate biopsy or patients treated as part of an active surveillance protocol, leaving a total of 198 patients. The median delay time for biopsy was 136 days (IQR 84, 188). Patients who were in the high-risk combined group (n = 34) had a shorter median delay of 110 days (IQR 40, 156) when compared to patients in the intermediate risk group (n = 125, 141 days, IQR 93, 196) and low risk group (n = 39, 147 days, IQR 89, 215, Figure 3). On multivariable logistic regression analysis adjusted for age, previous biopsy, clinical T-stage, and combined risk group we did not find a significant association between biopsy delay time and CSPC (OR = 1.13 per 1 months, 95% CI 0.97, 1.31, $p = 0.118$). On post-hoc subgroup univariable logistic regression analyses, we did not find a significant association between biopsy delay time and a finding of CSPC in either of the combined risk groups.

Discussion

In the current study we found that the suggested three-tier classification system based on mpMRI findings and PSAD was associated with different CSPC detection rates in each group. In the high-risk group 76% had CSPC compared with 26% in the intermediate-risk group and 4% in the low-risk group. The median time from mpMRI to biopsy was 110 days in the high-risk group, 141 in the intermediate group and 147 in the low-risk group, and biopsy delay time was not associated with the finding of CSPC.

MRI guided prostate biopsy has gained popularity and is becoming a leading method for prostate cancer detection. Data from the PRECISION trial showed that MRI guided biopsy outperformed standard 12

TABLE 4. **Shown are the number of patients with no prostate cancer, clinically insignificant prostate cancer (GG 1) and clinically significant prostate cancer (≥ GG 2) diagnosed on systematic or MRI-targeted biopsies. Separate tables were created for the low, intermediate, and high risk patients.**

		Low risk patients Systematic biopsies		
Targeted biopsies	**No PCa**	**GG 1 PCa**	**≥ GG 2 PCa**	**Total**
No PCa	34	7	0	41
GG 1 PCa	3	4	1	8
≥ GG 2 PCa	0	1	0	1
Total	37	12	1	50
		Intermediate risk patients Systematic biopsies		
Targeted biopsies	**No PCa**	**GG 1 PCa**	**≥ GG 2 PCa**	**Total**
No PCa	59	15	2	76
GG 1 PCa	13	35	6	54
≥ GG 2 PCa	3	13	18	34
Total	75	63	26	164
		High risk patients Systematic biopsies		
Targeted biopsies	**No PCa**	**GG 1 PCa**	**≥ GG 2 PCa**	**Total**
No PCa	1	0	2	3
GG 1 PCa	1	8	2	11
≥ GG 2 PCa	3	5	20	28
Total	5	13	24	42

PCa = prostate cancer; GG = grade group

TABLE 5. **Multivariable logistic regression analyses for CSPC**

Variable*	**OR**	**95% CI**	**p value**
Maximal PI-RADS score			
3	Ref		
4	2.99	1.13, 9.48	0.04
5	12.1	4.1, 42.14	< 0.001
PSAD			
≤ 0.1	Ref		
> 0.1 and ≤ 0.15	5.31	1.93, 15.39	0.002
> 0.15	11.11	4.87, 27.76	< 0.001
Combined risk category			
Low	Ref		
Intermediate	4.84	1.34, 31.02	0.038
High	40.13	9.56, 281.73	< 0.001

CSPC = clinically significant prostate cancer; PI-RADS = prostate imaging-reporting and data system; PSAD = prostate-specific antigen density; OR = odds ratio; CI = confidence interval; Ref = reference
*each row represents a separate model evaluating the association between maximal PI-RADS score, PSAD and the combined risk classification system and findings of clinically significant prostate cancer adjusted for age, previous biopsy and clinical T-stage as evaluated by digital rectal examination.

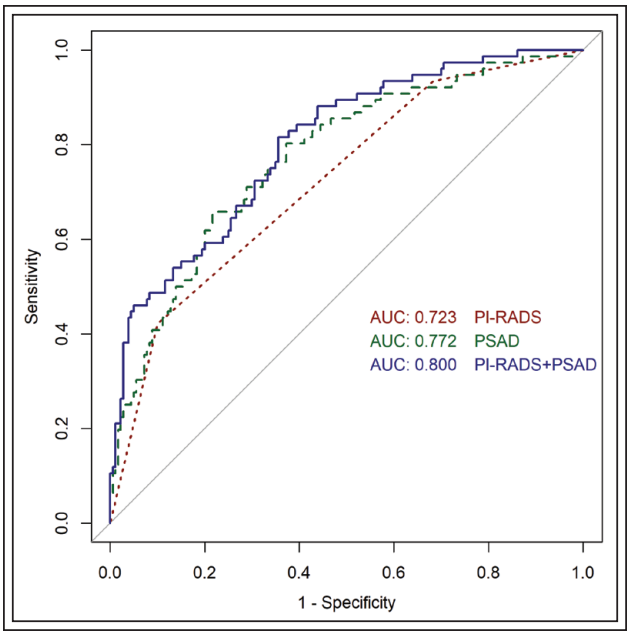

Figure 2. Receiver operator characteristic (ROC) curves evaluating the diagnostic ability of the maximal PI-RADS score, PSAD and the combination of the two in identifying clinically significant prostate cancer.

cores biopsy with a 38% detection rate for patients with a positive mpMRI findings (PI-RADS ≥ 3) and 13% less insignificant cancer detection.[10] The 4M trial reported a detection rate of 25% for CSPC and 14% for insignificant PC in the mpMRI guided biopsy group compared to detection rates of 23% for CSPC and 25% for insignificant PC in the standard biopsy group.[21] The MRI FIRST trial compared MRI guided biopsy and standard core biopsy in the same session, in this trial the overall CSPC detection rate was 37% (MRI-guided 32.3% vs. 29.9% systematic) favoring a combination of targeted and systematic biopsies at the cost of over detection of insignificant cancer (5.8% MRI-guided vs. 20% systematic).[11] Those result are in line with our study with 30% CSPC and 33% insignificant cancer detection. The use of systematic biopsy in all patient groups regardless of MRI finding might account for the relatively high rate of insignificant cancer detected in our intermediate and high-risk groups.

To further decrease insignificant cancer detection while maintaining low false negative rates, several studies incorporated the use of PSAD in combination with MRI fusion biopsy. Falagario et al used the international multicenter prostate outcome database (PROMOD) to evaluate the association between PSAD and PI-RADS score and prostate biopsy result. Men who had PI-RADS 3 lesions and a PSAD of < 0.1 or 0.1-0.15 had a 7.6% and 17.6% CSPC detection rate, respectively. Men with PI-RADS 5 lesions and a PSAD of 0.15-0.19 or > 0.2 had a 78% and 75.5% CSPC detection rate if they underwent a previous biopsy and a 85.2% and 89.1% CSPC detection rate if they were biopsy naïve, respectively.[16] Schoots et al conducted a meta-analysis of studies of men undergoing prostate MRI-guided biopsy with PSAD risk categories (including the above trial); men who had a PSAD < 0.1 and PI-RADS 3 lesions had only a 4% CSPC detection rate, while men with PI-RADS 4-5 lesions and PSAD 0.15-0.2 or PSAD > 0.2 had 69% and 77% CSPC detection rates, respectively.[15] Consistent with previous studies, in our cohort the low-risk group had a 4% CSPC detection rate while the high-risk group had a 76% CSPC detection rate; thus, we may consider omitting prostate biopsies within the low-risk group of patients. We also found a 21% insignificant cancer detection rate in our high-risk group compared to only a 12% detection rate in the Falgario study. Among

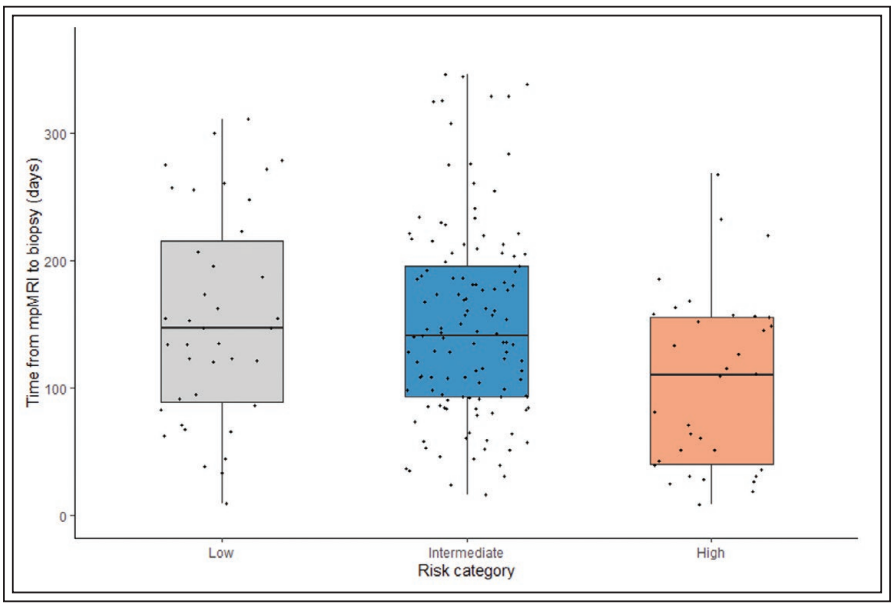

Figure 3. Boxplots of the time from mpMRI to biopsy stratified by the combined risk classification system (n = 198).

the low-risk patients in our cohort the high rate of insignificant cancer detected is attributed mostly to the addition of systematic biopsies. However, among intermediate-risk and high-risk patients there was no substantial difference in the rate of insignificant cancers detected solely by the targeted or systematic biopsies. Furthermore, among the intermediate-risk and high-risk patients the rate of significant cancers detected by the systematic biopsies alone was not negligible (8/42 for intermediate risk patients and 4/32 for high-risk patients), supporting the use of combined targeted and systematic biopsies.

In a previous study conducted by our group, we reported that a delay of up to 8 months between mpMRI and targeted prostate biopsy was not associated with adverse pathology on biopsy.[20] In a systematic review, Van den Bergh et al found that delaying time from diagnosis to radical treatment in low-risk patients did not affect long term oncological outcomes. Limited data from their work suggest that in high-risk patients treatment delay of a few months may have a deleterious effect.[22] In the current study, among patients who were not on active surveillance and did not have a biopsy delay of over 1 year, the median time to biopsy in the low- and intermediate-risk groups were 147 and 141 days respectively and, as expected, were not significantly associated with a finding of CSPC on biopsy. In the high-risk group median time to biopsy was 110 days, reflecting the tendency of the referring physician to prioritize this group of patients. Within these time frames for biopsy, we did not find a significant association between biopsy delay time and a finding of CSPC on biopsy. Given the high rate of CSPC in the combined high-risk group, and the possible association between treatment delay and adverse outcomes reported in previous publications, we believe performing an early biopsy in this group is warranted and aim to biopsy this group within 1 month. Furthermore, our study suggests delaying biopsy for patients in lower risk groups, as required due to biopsy prioritizing, will not lead to a higher rate of CSPC on subsequent biopsy. Thus, we suggest the three-tier system as an objective approach to prioritizing patient with mpMRI lesions for prostate biopsy.

The limitations of our study include its retrospective, single center nature. The timing of biopsy reflects the referring physician's clinical judgment and therefore the delay time is biased; however, the high-risk group delay time was significantly shorter and correlated well with the three-tier system. Finally, since not all patients biopsied were subsequently treated within our center, we did not have information regarding pathology findings of patients who underwent radical prostatectomy precluding us from evaluating the effect of delay time on final pathology and surgical outcome.

Conclusions

Our findings suggest that a three-tier risk classification system based on mpMRI PI-RADS score and PSAD can help define patients at high-risk for CSPC who may benefit from earlier biopsy due to a substantially high rate of ISUP ≥ 2 disease at biopsy. Furthermore, we identified a low-risk group with a CSPC rate of 4% in whom we may consider delaying or omitting the biopsy. Future studies should evaluate whether timing biopsy according to the proposed risk classification system may influence prostate pathology for patients eventually treated with radical prostatectomy.

Disclosure

Dr. Roy Mano is a paid consultant for NIXIO LTD. □

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