MRI-based PI-RADS score predicts ISUP upgrading and adverse pathology at radical prostatectomy in men with biopsy ISUP 1 prostate cancer

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Introduction: *Most men diagnosed with very-low and low-risk prostate cancer are candidates for active surveillance; however, there is still a misclassification risk. We examined whether PI-RADS category 4 or 5 combined with ISUP 1 on prostate biopsy predicts upgrading and/or adverse pathology at radical prostatectomy.*

Materials and methods: *A total of 127 patients had ISUP 1 cancer on biopsy after multiparametric MRI (mpMRI) and then underwent radical prostatectomy. We then evaluated them for ISUP upgrading and/or adverse pathology on radical prostatectomy.*

Results: *Eight-nine patients (70%) were diagnosed with PI-RADS 4 or 5 lesions. ISUP upgrading was significantly higher among patients with PI-RADS 4-5 lesions (84%) compared to patients with equivocal or non-suspicious mpMRI findings (26%, p < 0.001). Both PI-RADS 4-5 lesions (OR 24.3, 95% CI 7.3, 80.5, p < 0.001) and stage T2 on DRE (OR 5.9, 95% CI 1.2, 29.4, p = 0.03) were independent predictors of upgrading on multivariate logistic regression analysis. Men with PI-RADS 4-5 lesions also had significantly more extra-prostatic extension (51% vs. 3%, p < 0.001) and positive surgical margins (16% vs. 3%. p = 0.03). The only independent predictor of adverse pathology was PI-RADS 4-5 (OR 21.7, 95% CI 4.8, 99, p < 0.001) .*

Conclusion: *PI-RADS 4 or 5 lesions on mpMRI were strong independent predictors of upgrading and adverse pathology. Incorporating mpMRI findings when selecting patients for active surveillance must be further evaluated in future studies.*

Key Words: PI-RADS, magnetic resonance imaging, ISUP 1, radical prostatectomy

Introduction

The rapid adoption of PSA screening since the early 1990's increased the incidence of low-risk prostate cancer characterized by an indolent disease course with a low probability of causing symptoms or death.[1] Active surveillance (AS) is recommended for men who are diagnosed with very-low and low-risk prostate cancer with the goal of avoiding treatment-related side effects while preserving the oncologic outcomes.[2] Due to the heterogenicity of prostate cancer, the main concern in selecting patients for AS is the failure to identify men with coexistent, occult, higher-grade cancer, leading to reported reclassification rates of 20%-

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30%.[3] Moreover, roughly half of the men who embark on AS will eventually undergo definitive therapy for different reasons.[4]

Multiple studies evaluated pre-treatment predictors of adverse outcomes in an attempt to decrease misclassification rates inherent to the systematic biopsy–based diagnostic strategy.[5] Reported predictors include PSA density (PSAD), percent positive biopsy cores and biopsy-based multigene expression classifiers.[6-9] In recent years, mpMRI is becoming central to the diagnosis of prostate cancer and the management of men on AS.[10] The PI-RADS (Prostate Imaging Reporting and Data System) version 2 scoring system is associated with the likelihood of a clinically significant cancerous lesion based on the mpMRI results.[11]

The predictive value of the PI-RADS scoring system in men who were diagnosed with International Society of Urological Pathology (ISUP) 1 prostate cancer on biopsy was evaluated by three previous studies.[12-14] These studies report an association between the PIRADS score and upgrading and extracapsular extension; however, one study used 1.5T mpMRIs for evaluating prostatic lesions,[12] and the others did not include adverse pathology at radical prostatectomy as an outcome.[13,14] Moreover, two of the studies did not include patients who underwent targeted fusion biopsies, which is evolving as the standard biopsy technique for patients with mpMRI lesions.

In the current study we aimed to evaluate whether the presence of PI-RADS version 2 category 4 or 5 mpMRI findings in a contemporary cohort of patients with a biopsy ISUP 1 prostate cancer predicted ISUP upgrading and/or adverse pathology at radical prostatectomy.

Materials and methods

After obtaining Institutional Review Board approval we retrospectively reviewed the medical records of 127 consecutive patients with localized prostate cancer who had a maximal biopsy ISUP grade of 1 and underwent 3 tesla mpMRI followed by radical prostatectomy between the years 2015 to 2020.

Clinical and pathological characteristics at diagnosis were collected from the patients' electronic medical records including age, PSA, prostate volume, and clinical stage as evaluated by digital rectal examination (DRE). Patients underwent a 3-Tesla multiparametric MRI scan prior to surgery either before or after the prostate biopsy. All lesions on mpMRI scans were categorized according to the PI-RADS version 2 scoring system. Biopsy reports were reviewed and the total number of biopsy cores, number of positive cores and biopsy ISUP grade group were extracted. Data regarding the method of biopsy (systematic vs. mpMRI targeted fusion) were also collected. Patients were categorized to low- (clinical stage T1-T2a, ISUP 1, PSA < 10 ng/mL), intermediate- (clinical stage T2b-T2c, ISUP 2-3, PSA 10-20 ng/mL), and high-risk groups (clinical stage ≥ T3, ISUP 4-5, PSA > 20 ng/mL) based on the National Comprehensive Cancer Network (NCCN) guidelines.[15]

All patients underwent robotic assisted laparoscopic radical prostatectomy; pelvic lymph node dissection was performed at the discretion of the operating urologist. Surgical specimens were reviewed by a dedicated genitourinary pathologist and the ISUP grade group and presence of adverse pathology including extra-prostatic extension (EPE), seminal vesicle invasion (SVI) and positive surgical margins were reported. ISUP upgrading was defined as the presence of an ISUP ≥ 2 lesion on surgical pathology.

The study endpoints included ISUP upgrading and the presence of adverse pathology at radical prostatectomy. Continuous variables were reported as median and IQR and compared using the rank-sum test. Categorical variables were reported as number and percent and compared using the chi-squared test. The associations between ISUP upgrading and adverse pathology at radical prostatectomy and the preoperative predictors PSA, clinical stage on DRE, percent of positive biopsy cores and PI-RADS score on mpMRI were evaluated with univariable logistic regression models. Age and significant findings on univariable analyses were included in a multivariable model. Cochran-Mantel-Haenszel test was used to identify whether targeted biopsies in addition to systematic biopsies or different NCCN risk groups changed the association between the predictors and outcomes. All statistical analyses were two-sided, and significance was defined as $p < 0.05$. All analyses were conducted using SPSS version 23 (Armonk, NY, USA).

Results

The study cohort included 127 men at a median age of 65 years (IQR 61-69). Median PSA at presentation was 7 ng/mL (IQR 5.2-10). Clinical stage was T1c in 99 patients (78%) and T2 in 28 (22%). All men had a biopsy ISUP grade group of 1 and all underwent mpMRI prior to surgery. One hundred men (79%) were categorized as low risk, 21 (17%) intermediate risk and 6 (4%) high risk. In 89 patients (70%) a PI-RADS 4 or 5 lesion was recorded on mpMRI. 51 men had a fusion targeted biopsy, and 76 underwent systematic

TABLE 1. **Preoperative characteristics and pathologic findings at radical prostatectomy stratified by PI RADS 4-5 (n = 89) and PI RADS < 4 (n = 38) lesions on mpMRI; categorical variables are reported as number (%) and continuous variables as median [IQR]**

Variable	mpMRI PI RADS 4-5 (n = 89)	mpMRI PI RADS < 4 (n = 38)	p value
Age (years)	67 [61-69.5]	65 [62-68]	0.3
PSA (ng/mL)	7 [5.1-9]	7.5 [5.7-10]	0.9
Clinical stage			0.6
T1c	68 (76)	31 (81)	
T2	21 (24)	7 (19)	
Prostate volume (mL)	48 [40.5-57]	48 [39-60]	0.8
Number of positive biopsy cores	3 [2-5]	3 [1-5]	0.9
NCCN risk category			0.9
Low	70 (79)	30 (79)	
Intermediate	15 (17)	6 (16)	
High	4 (4)	2 (5)	
Radical prostatectomy ISUP grade group			< 0.001
1	14 (16)	28 (74)	
2	62 (70)	9 (24)	
3	10 (11)	1 (2)	
4	2 (2)	0 (0)	
5	1 (1)	0 (0)	
Extracapsular extension			< 0.001
No	44 (49)	37 (97)	
Yes	45 (51)	1 (3)	
Seminal vesical invasion			0.08
No	82 (92)	38 (100)	
Yes	7 (8)	0 (0)	
Soft tissue surgical margins			0.03
Negative	75 (84)	37 (97)	
Positive	14 (16)	1 (3)	

PI RADS = Prostate Imaging-Reporting and Data System; mpMRI = multiparametric MRI; PSA = prostate specific antigen; NCCN = National Comprehensive Cancer Network; ISUP = International Society of Urological Pathology

prostate biopsy. Preoperative characteristics of the study cohort categorized by PI-RADS 4-5 or less are reported in Table 1.

On final pathology the ISUP was upgraded in 85 (67%) men. Twenty patients had a PI-RADS 3 lesion on preoperative mpMRI with an upgrading rate of 35%. Due to the small size of this group and an upgrading rate similar to that of men with PI-RADS 1/2 lesions (n = 18, 17%), these groups were combined for further analyses, Table 2. Among the group of patients with PI-RADS 4-5 lesions on preoperative mpMRI 84% were upgraded to a higher than 1 ISUP score (clinically significant cancer), Figure 1. In the group without suspicious mpMRI findings only 26% were upgraded ($p < 0.01$, Table 1, Figure 1), Sankey plots depicting maximal ISUP grade group at radical prostatectomy stratified by preoperative mpMRI PIRADS score, Figure 2.

On univariable logistic regression analyses, clinical stage T2, percent of positive cores on biopsy and PI-RADS 4-5 lesions were significant predictors of upgrading, Table 3, Figure 3. On multivariable analysis both PI-RADS 4-5 (OR 24.3, 95% CI 7.3, 80.5, $p < 0.001$) and stage T2 on DRE (OR 5.9, 95% CI 1.2, 29. 4, $p = 0.03$),

TABLE 2. **Number of patients with tumor upgrading and upstaging according to the PI-RADS score on preoperative mpMRI**

PI-RADS score	Number of pts. with ISUP upgrading, all pts. (n = 127, %)	Number of pts. with ISUP upgrading, targeted Bx (n = 51, %)	Number of pts. with ISUP upgrading, systematic BX (n = 76, %)	Number of pts. with adverse pathology, all pts. (n = 127, %)
1/2	3/18 (17%)	NA	3/18 (17%)	2/18 (11%)
3	7/20 (35%)	3/11 (27%)	4/9 (44%)	0/20 (0%)
4	36/46 (78%)	18/24 (75%)	18/22 (82%)	19/46 (41%)
5	39/43 (91%)	13/16 (81%)	26/27 (96%)	28/43 (65%)

PI-RADS = Prostate Imaging-Reporting and Data System; mpMRI = multiparametric magnetic resonance imaging; ISUP = International Society for Urological Pathology; pts. = patients; Bx = biopsy

remained independent predictors of upgrading, Table 3. Among all PI-RADS groups rates of upgrading were higher in patients undergoing systematic biopsies only, Table 2. In the group of men with PI-RADS 4-5 lesions, 41 (46%) underwent fusion biopsy, 78% of them were upgraded compared to 90% of men with PI-RADS 4-5 lesions and systematic biopsy ($p < 0.01$). There were no significant differences in upgrading rates between men who underwent fusion or systematic biopsies for PI-RADS 3 lesions ($p = 0.63$). The sensitivity, specificity, positive, and negative predictive value for ISUP upgrading among men with PI-RADS 4-5 were 66%, 87%, 71%, 84%, respectively.

Forty-nine men (39%) had adverse pathology on radical prostatectomy, Table 1. EPE was found in 51% of patients with PI-RADS 4-5 lesions compared to 3% of patients without suspicious mpMRI findings ($p < 0.01$). Men with PI-RADS 4-5 lesions also had significantly higher rates of positive surgical margins (16% vs. 3%. $p = 0.03$). SVI did not differ significantly between the two groups. On univariable logistic regression analyses, only PI-RADS 4-5 lesions were significant predictors of adverse pathology, Table 4. On multivariable logistic regression analysis, when adjusting for age, PI-RADS 4-5 (OR 21.7, 95% CI 4.8, 99, $p < 0.001$) remained a significant predictor of adverse pathology. There were no significant differences between men who underwent fusion biopsy and men after systematic prostate biopsy regarding the presence of any adverse pathology. The sensitivity, specificity,

TABLE 3. **Univariable and multivariable logistic regression models for ISUP upgrading after radical prostatectomy in a cohort of patients with ISUP 1 prostate cancer on biopsy (n = 127)**

Variable	Univariable			Multivariable		
	OR	95% CI	p value	OR	95% CI	p value
Age (per 1 year)	0.8	0.4, 2.9	0.7	0.7	0.2, 3.2	0.6
PSA (per 1 ng/mL)	1.03	0.98, 1.07	0.36			
PI-RADS						
< 4	Ref			Ref		
≥ 4	37.3	5.3, 54.2	< 0.001	24.3	7.3, 80.5	< 0.001
Clinical stage						
T1c	Ref			Ref		
T2	7.6	6.3, 51	0.006	5.9	1.2, 29.3	0.03
% positive cores (per 1%)	4.6	0.8, 7.2	0.04	2.1	0.2, 3.2	0.2

OR = odds ratio; CI = confidence interval; PSA = prostate specific antigen; ISUP = International Society of Urological Pathology; Ref = reference; PI-RADS = Prostate Imaging–Reporting and Data System

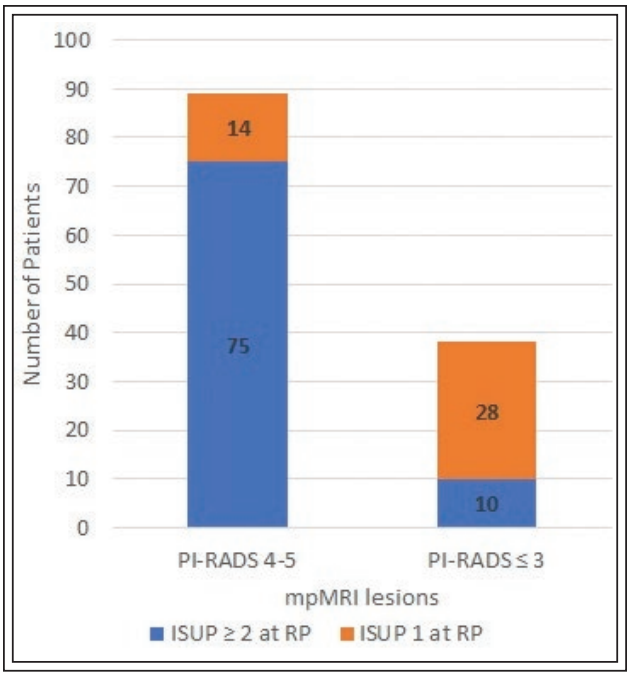

Figure 1. Bar plots depicting the number of patients with ISUP upgrading after radical prostatectomy among patients with PI-RADS 4-5 lesions (n = 89) compared to patients with PI-RADS < 4 lesions (n = 38) on preoperative mpMRI.

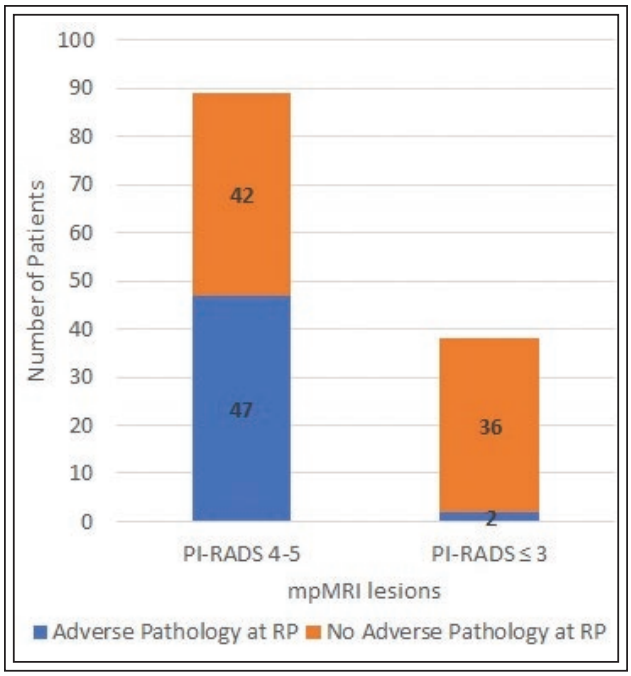

Figure 3. Bar plots of patients with adverse pathology at radical prostatectomy among patients who had PI-RADS 4-5 lesions (n = 89) compared to patients with PI-RADS < 4 lesions (n = 38) on preoperative mpMRI.

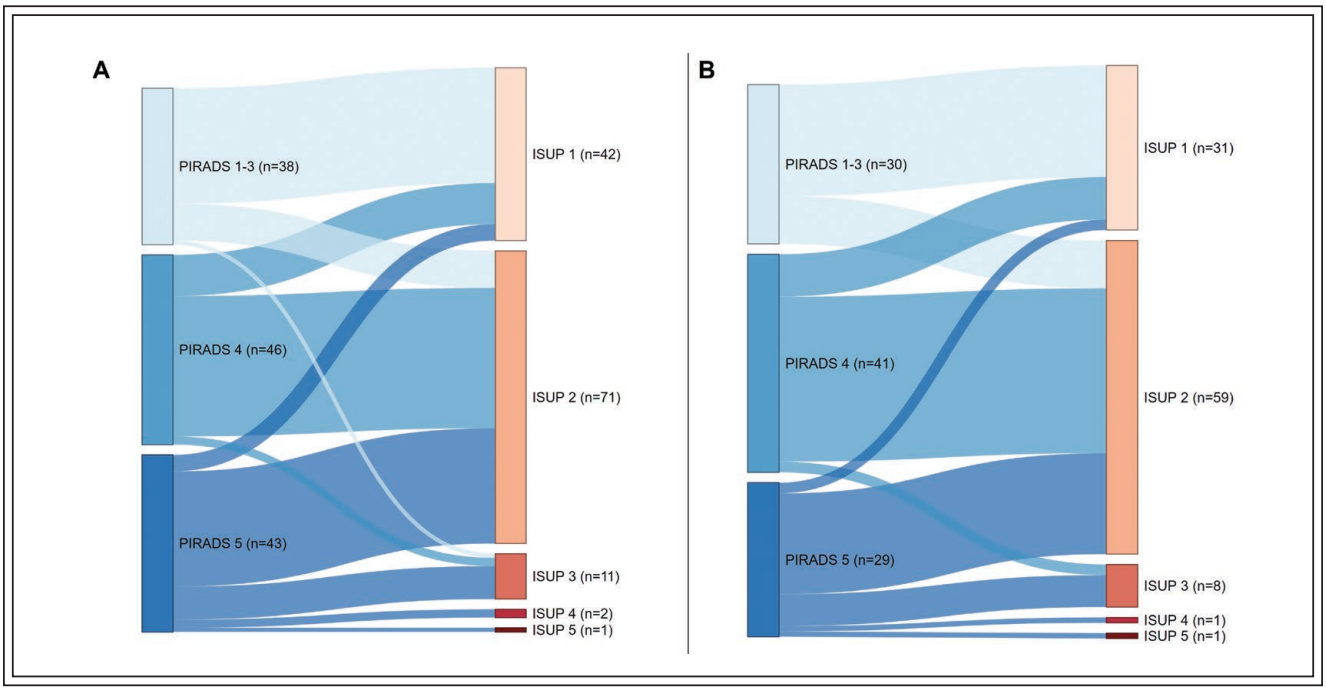

Figure 2. Sankey plots depicting maximal ISUP grade group at radical prostatectomy stratified by preoperative mpMRI PIRADS score for (A) all patients (n = 127) and (B) patients with NCCN low-risk prostate cancer (n = 100).

TABLE 4. **Univariable and multivariable logistic regression models for adverse pathology after radical prostatectomy in a cohort of patients with ISUP 1 prostate cancer on biopsy (n = 127)**

Variable	Univariable			Multivariable		
	OR	95% CI	p value	OR	95% CI	p value
Age (per 1 year)	1.3	0.3, 3.8		1.6	0.5, 5.2	0.4
PSA (per 1 ng/mL)	1.1	0.94,1.4	0.8			
PI-RADS						
< 4	Ref			Ref		
≥ 4	25.4	4.6, 78.8	< 0.001	21.7	4.8, 99	< 0.001
Clinical stage						
T1c	Ref					
T2	1.04	0.4, 2.5	0.9			
% positive cores (per 1%)	1.9	0.5, 2.9	0.5			

ISUP = International Society of Urological Pathology; OR = odds ratio; CI = confidence interval; PSA = prostate specific antigen; Ref = reference; PI-RADS = Prostate Imaging–Reporting and Data System

positive, and negative predictive value for adverse pathology among men with PI-RADS 4-5 were 46%, 96%, 95%, 53%, respectively.

We performed a sensitivity analysis to evaluate whether the association between PI-RADS scoring and outcomes differed among the different NCCN risk groups. There were no significant differences in ISUP upgrading nor adverse pathology when comparing our low-risk group and higher risk groups (p = 0.52 and p = 0.7, respectively).

Discussion

Accurate grading and staging are essential when selecting patients with prostate cancer for AS. Patients with high-risk cancers who are misclassified pose the greatest risk for metastatic progression during AS, which may result in the loss of the opportunity for cure.[16] In the current study, we evaluated a contemporary cohort of men with ISUP 1 cancer on prostate biopsy treated with radical prostatectomy, all of whom underwent mpMRI prior to surgery. PI-RADS 4 and 5 lesions on mpMRI were found to be strong, independent, predictors of adverse pathology and ISUP upgrading even among patients who would otherwise be classified as low-risk based on the NCCN guidelines criteria.

Multiple studies evaluated the associations between patient and tumor characteristics and adverse pathology at prostatectomy among patients with low-risk prostate cancer with the goal of assisting clinicians in predicting which patients are candidates for active surveillance and which are most likely to progress.[6-9,17] These studies reported that PSA density (PSAD) and percent positive biopsy cores were associated with adverse outcomes, suggesting they may assist in identifying patients who may benefit from active treatment.[18] Similarly, the Prostate Cancer Research International: Active Surveillance (PRIAS) study, which enrolled over 2000 men from 17 countries to active surveillance, reported that the number of positive biopsy cores and PSA density were significant predictors of switching from surveillance to treatment.[19] In recent years, several biopsy-based multigene expression classifiers have emerged with the aim of improving initial risk classification and identifying which patients are more likely to harbor a significant tumor.[20] While each of these tests improve the prognostic accuracy of multivariable models based on clinical characteristics in identifying men with biologically significant disease,[21,22] few have been validated in AS cohorts. Evidence suggest that specific germline mutations in DNA repair genes, mostly BRCA2, predispose men to more aggressive prostate cancers as well as a higher reclassification rate while on active surveillance.[23] The use of mpMRI for selecting patients for AS and monitoring has evolved in recent years suggesting mpMRI may be useful for selecting AS candidates.[24,25]

Data regarding the ability of mpMRI to predict upgrading, upstaging or positive surgical margins at RP in otherwise AS-eligible men are limited. De Cobelli et al reported that among a cohort of 223 patients who were eligible for AS, underwent 1.5 Tesla mpMRI, and were eventually treated with radical prostatectomy,

the PIRADS score was associated with upgrading (OR = 2.72 per 1 unit, 95% CI=1.93-3.85, p < 0.0001) and extracapsular extension (OR = 5.27 per 1 unit, 95% CI 2.94-9.44, p < 0.0001) at radical prostatectomy.[12] Similarly, Song et al evaluated a cohort of 443 patients with ISUP 1 prostate cancer who underwent mpMRI prior to radical prostatectomy and reported that PIRADS score 4-5 was associated with ISUP upgrading at radical prostatectomy (OR = 2.26, 95% CI 1.46-3.5, p < 0.001).[13] Stevens et al evaluated 33 men with biopsy ISUP 1 prostate cancer who underwent radical prostatectomy. Of these, 22 (66.6%) were upgraded to ISUP≥2, 10 (30.3%) had ISUP 1 cancer at prostatectomy, and 1 (3%) had no evidence of cancer on histopathology. Gleason score upgrading occurred in 16 out of 18 (88.9%) patients with PI-RADS 4-5 lesions, and in 6 out of 15 (40%) patients with PI-RADS scores 1-3.[14] Furthermore, PI-RADS version 2 category 5 mpMRI lesions were also significantly associated with adverse pathology in patients presenting with Gleason Score 3+4 prostate cancer.[26] Importantly, previous studies used systematic rather than targeted fusion biopsies for the diagnosis of prostate cancer. When considering the added value of combining systematic and targeted biopsies,[27] rates of upgrading and upstaging may be lower among patients who undergo combined rather than systematic biopsies. Our study demonstrates the importance of PI-RADS 4-5 as a strong predictor of adverse pathology and upgrading in a consecutive cohort of men diagnosed with ISUP 1 prostate cancer who underwent 3 Tesla mpMRI. These findings were consistent both for patient who underwent systematic biopsies and those who underwent fusion biopsies thus extending the validity of findings from previous cohorts to patients diagnosed using targeted fusion biopsies.

The main limitation of our study was selection bias, as our cohort consists mostly of men who were candidates for AS but eventually underwent radical prostatectomy, possibly explaining the high rate of upgrading and upstaging we observed. While part of our cohort underwent systematic rather than targeted biopsies, using a sensitivity analysis, we showed that performing targeted fusion biopsies did not lower the rate of adverse pathology. In addition, while performing targeted biopsies decrease the upgrading rate, the rates were still relatively high among patients with PI-RADS 4-5 and differed significantly from those with PI-RADS ≤ 3 lesions, highlighting the possible selection bias associated with the group of patients who underwent radical prostatectomy for ISUP 1 prostate cancer. Lastly, mpMRI scans did not undergo central review; however, they were all evaluated according to PI-RADS v2 classification system.

Conclusion

Our study results show that among patients diagnosed with a biopsy ISUP 1 prostate cancer who underwent preoperative mpMRI, the presence of PI-RADS v2 4 or 5 lesions was a strong independent predictor of adverse pathology and ISUP upgrading. Future prospective studies are needed to validate our results and evaluate whether incorporating mpMRI findings when selecting patients for AS can improve treatment outcome. □

References

1. Dall'Era MA, Albertsen PC, Bangma C et al. Active surveillance for prostate cancer: a systematic review of the literature. *Eur Urol* 2012;62(6):976-983.
2. Klotz L, Vesprini D, Sethukavalan P et al. Long-term follow-up of a large active surveillance cohort of patients with prostate cancer. *J Clin Oncol* 2015;33(3):272-277.
3. Bokhorst LP, Valdagni R, Rannikko A et al. PRIAS study group. A decade of active surveillance in the PRIAS study: an update and evaluation of the criteria used to recommend a switch to active treatment. *Eur Urol* 2016;70(6):954-960.
4. Simpkin AJ, Tilling K, Martin RM et al. Systematic review and meta-analysis of factors determining change to radical treatment in active surveillance for localized prostate cancer. *Eur Urol* 2015;67(6):993-1005.
5. van den Bergh RC, Ahmed HU, Bangma CH, Cooperberg MR, Villers A, Parker CC. Novel tools to improve patient selection and monitoring on active surveillance for low-risk prostate cancer: a systematic review. *Eur Urol* 2014;65(6):1023-1031.
6. Borque-Fernando Á, Rubio-Briones J, Esteban LM et al. Role of the 4Kscore test as a predictor of reclassification in prostate cancer active surveillance. *Prostate Cancer Prostatic Dis* 2019;22(1):84-90.
7. Loeb S, Folkvaljon Y, Makarov DV, Bratt O, Bill-Axelson A, Stattin P. Five-year nationwide follow-up study of active surveillance for prostate cancer. *Eur Urol* 2015;67(2):233-238.
8. Vellekoop A, Loeb S, Folkvaljon Y, Stattin P. Population based study of predictors of adverse pathology among candidates for active surveillance with Gleason 6 prostate cancer. *J Urol* 2014;191(2):350-357.
9. Lonergan PE, Washington SL 3rd, Cowan JE et al. Risk factors for biopsy reclassification over time in men on active surveillance for early stage prostate cancer. *J Urol* 2020;204(6):1216-1221.
10. Stavrinides V, Giganti F, Emberton M, Moore CM. MRI in active surveillance: a critical review. *Prostate Cancer Prostatic Dis* 2019;22(1):5-15.
11. Kasel-Seibert M, Lehmann T, Aschenbach R et al. Assessment of PI-RADS v2 for the detection of prostate cancer. *Eur J Radiol* 2016;85(4):726-731.
12. de Cobelli O, Terracciano D, Tagliabue E et al. Predicting pathological features at radical prostatectomy in patients with prostate cancer eligible for active surveillance by multiparametric magnetic resonance imaging. *PLoS One* 2015;10(10):e0139696.

13. Song W, Bang SH, Jeon HG et al. Role of PI-RADS version 2 for prediction of upgrading in biopsy-proven prostate cancer with Gleason score 6. *Clin Genitourin Cancer* 2018;16(4):281-287.
14. Stevens E, Truong M, Bullen JA, Ward RD, Purysko AS, Klein EA. Clinical utility of PSAD combined with PI-RADS category for the detection of clinically significant prostate cancer. *Urol Oncol* 2020;38(11):846.e9-846.e16.
15. Carroll PH, Mohler JL. NCCN guidelines updates: prostate cancer and prostate cancer early detection. *J Natl Compr Canc Netw* 2018;16(5S):620-623.
16. Tosoian JJ, Trock BJ, Landis P et al. Active surveillance program for prostate cancer: an update of the Johns Hopkins experience. *J Clin Oncol* 2011;29(16):2185-2190.
17. Perlis N, Klotz L. Contemporary active surveillance: candidate selection, follow-up tools, and expected outcomes. *Urol Clin North Am* 2017;44(4):565-574.
18. Olsson H, Nordström T, Clements M, Grönberg H, Lantz AW, Eklund M. Intensity of active surveillance and transition to treatment in men with low-risk prostate cancer. *Eur Urol Oncol* 2020;3(5):640-647.
19. Bul M, Zhu X, Valdagni R et al. Active surveillance for low-risk prostate cancer worldwide: the PRIAS study. *Eur Urol* 2013;63(4):597-603.
20. Eggener SE, Rumble RB, Armstrong AJ et al. Molecular biomarkers in localized prostate cancer: ASCO guideline. *J Clin Oncol* 2020;38(13):1474-1494.
21. Van Den Eeden SK, Lu R, Zhang N et al. A biopsy-based 17-gene genomic prostate score as a predictor of metastases and prostate cancer death in surgically treated men with clinically localized disease. *Eur Urol* 2018;73(1):129-138.
22. Klein EA, Cooperberg MR, Magi-Galluzzi C et al. A 17-gene assay to predict prostate cancer aggressiveness in the context of Gleason grade heterogeneity, tumor multifocality, and biopsy undersampling. *Eur Urol* 2014;66(3):550-560.
23. Carter HB, Helfand B, Mamawala M et al. Germline mutations in ATM and BRCA1/2 are associated with grade reclassification in men on active surveillance for prostate cancer. *Eur Urol* 2019; 75(5):743-749.
24. Lai WS, Gordetsky JB, Thomas JV, Nix JW, Rais-Bahrami S. Factors predicting prostate cancer upgrading on magnetic resonance imaging-targeted biopsy in an active surveillance population. *Cancer* 2017;123(11):1941-1948.
25. Alberts AR, Roobol MJ, Drost FH et al. Risk-stratification based on magnetic resonance imaging and prostate-specific antigen density may reduce unnecessary follow-up biopsy procedures in men on active surveillance for low-risk prostate cancer. *BJU Int* 2017;120(4):511-519.
26. Faiena I, Salmasi A, Mendhiratta N et al. PI-RADS version 2 category on 3 tesla multiparametric prostate magnetic resonance imaging predicts oncologic outcomes in Gleason 3 + 4 prostate cancer on biopsy. *J Urol* 2019;201(1):91-97.
27. Rouvière O, Puech P, Renard-Penna R et al. MRI-FIRST Investigators. Use of prostate systematic and targeted biopsy on the basis of multiparametric MRI in biopsy-naive patients (MRI-FIRST): a prospective, multicentre, paired diagnostic study. *Lancet Oncol* 2019;20(1):100-109.