

Association of one single visible mpMRI PI-RADS index lesion with prostate cancer adverse pathology at robot-assisted radical prostatectomy: a 505-patient study

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PORCARO AB, CERRUTO MA, BERTOLO R, BOLDINI M, VECCIA A, RIZZETTO R, ARTONI F, FRANCESCHINI A, BAIELLI A, MONTANARO F, COSTANTINO S, BRUNELLI M, SIRACUSANO S, ANTONELLI A. Association of one single visible mpMRI PI-RADS index lesion with prostate cancer adverse pathology at robot-assisted radical prostatectomy: a 505-patient study. *Can J Urol* 2026;33(5):1187–1196.

Backgrounds: Multiparametric MRI (mpMRI) and the PI-RADS scoring system play a central role in the detection and risk stratification of prostate cancer; however, the prognostic significance of a single visible index lesion remains incompletely defined. The aim of the study was to evaluate associations of one single visible PI-RADS (Prostate Imaging–Reporting and Data System) index lesion varying from 3 to 5 with adverse pathology after robotic surgery and with clinical prostate cancer (PCa) including EAU (European Association of Urology) prognostic risk classes.

Materials and methods: The study included only cases with one single visible PI-RADS index lesion which varied from 3 to 5 with MRI procedures performed by dedicated radiologists. EAU prognostic risk classes were classified according to standard clinical parameter including PSA (Prostate-Specific Antigen), ISUP (International Society of Urological Pathology), percentage of biopsy positive cores, cTNM system. Adverse pathology was defined as any of the following at final specimen: ISUP

grade group 4–5, extracapsular extension, seminal vesicle invasion, positive surgical margins, pelvic lymph node invasion. Analysis was carried out by the multinomial logistic regression model including PI-RADS lesions 3, 4, 5 as outcomes predicted by adverse pathology and EAU prognostic risk classes.

Results: From January 2014 to December 2021, the study selected 505 patients who presented with one single visible PI-RADS index lesion varying from 3 (11.5%) to 4 (54.9%) up to 5 (33.7%); accordingly, adverse pathology, which was detected in 46.5% of specimens, was less likely to occur for index scores 3 vs. 5 (OR (Odds Ratio) = 0.272, 95% CI (Confidence Interval): 0.144–0.514; $p < 0.001$) as those for 4 vs. 5 (OR = 0.404; 95% CI: 0.273–0.598; $p < 0.001$); likewise, after adjusting for EAU risk classes, PI-RADS scores 3 vs. 5 were less likely to belong to the high risk class when compared with both the EAU low (OR = 0.092; 95% CI: 0.032–0.268; $p < 0.001$) and the EAU intermediate one (OR = 0.171; 95% CI: 0.063–0.464; $p < 0.001$).

Conclusions: Single visible PI-RADS index lesions varying from 3 to 5 associated with both adverse pathology and unfavorable EAU prognostic risk classes; accordingly, they may allow stratification of patients while associating with adverse cancer biology.

Key Words: prostate cancer, multiparametric magnetic resonance imaging, prostate imaging-reporting and data system, prostate biopsy, radical prostatectomy, prognostic risk groups

Received date 24 November 2025

Accepted for publication 13 April 2026

Published online 30 October 2026

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Introduction

Clinically significant prostate cancer (PCa) is an epidemic issue for the aging male population, gaining more and more life expectancy.^{1,2} Accordingly, unrecognized cancer may become a life-threatening disease that is worsened by age which is an adverse prognostic factor; nevertheless, cancer specific mortality may be decreased by prostate specific antigen (PSA) screening which has recently shown to be protective; likewise, screened as well as diagnosed PCa patients need appropriate prognostic stratification in order to avoid both over and undertreatments, which may impair quality of life, as well.³⁻⁷ As recommended by the European Association of Urology (EAU) and National Comprehensive Cancer Network (NCCN), patients diagnosed with clinical PCa may be stratified through prognostic risk classes according to clinical parameters including PSA, biopsy tumor grade according to the International Society of Urologic Pathology (ISUP) system, percentage of biopsy positive cores (BPC) and tumor stage according to the TNM (Tumor, Node, Metastasis) system.^{1,2} Likewise, as recommended by both EAU and NCCN, patients diagnosed with PCa have already undergone pre-biopsy multiparametric magnetic resonance imaging (mpMRI) evaluation in order to plan appropriate biopsy strategy which is firstly systemic and eventually targeted when the Prostate Imaging-Reporting and Data System (PI-RADS) describe lesions which are scored from one to five by mpMRI parameters; accordingly, discovered significant lesions ranging from 3 to 5 need to be biopsied for the high probability of associating with significant PCa; moreover, standard parameters for describing PI-RADS lesions have evolved from version 1 through 2 up to 2.1 with the latter describing lesions localized at the transitional zone of the prostate better than the formers, as well.^{1,2,8-10} So far, prognostic factors are required to further stratify patients diagnosed with clinical PCa who have been staged into risk groups in order to plan appropriate management that aims to avoid both overtreatment and undertreatment, which may have drawbacks on disease-specific mortality and quality of life.^{1,2,8-10}

Accordingly, in patients with clinical PCa treated with robot-assisted radical prostatectomy (RARP), eventually associated with extended pelvic lymph node dissection (ePLND), we wanted to test the hypothesis that one significant PI-PIRADS lesion (*index lesion*) could be associated with both adverse pathology in the surgical specimen and unfavorable clinical parameters defining prognostic risk groups.

Materials and methods

Selection of the study population

An observational retrospective study on natural history of PCa after robotic surgery was planned by Azienda Ospedaliera Universitaria Integrata di Verona and University of Verona before 25 September 2024; accordingly, our Internal Review Board (IRB) granted an exemption status from formal approval. The study was conducted in accordance with ethical standards and the principles of the Declaration of Helsinki. The local ethics committee (Comitato Etico Territoriale Area Sud-Ovest Veneto–CET-ASOV) did not require a formal application for the present data evaluation, as all data were routinely collected and recorded by the institution in the context of close follow-up for this specific clinical condition. Written informed consent was obtained from each of the patients. From January 2014 to December 2021, 664 patients provided informed consent and underwent mpMRI evaluation before surgery. Among them, 505 patients (76.1%) presented with only one visible PI-RADS index lesion and were included in the study cohort. Conversely, 159 patients (23.9%) presented with more than one visible lesion and were excluded to avoid potential staging ambiguity related to multifocal disease. Specifically, 129 patients (19.4%) had two lesions, 24 (3.6%) had three lesions, 5 (0.7%) had four lesions, and 1 (0.1%) had five lesions. In addition, 94 out of 758 evaluated cases (12.4%) showed no visible PI-RADS lesion on mpMRI. Therefore, the present analysis focused on 505 operated patients presenting with a single visible PI-RADS index lesion ranging from 3 to 5. Accordingly, subjects presenting at our institution with clinical PCa were treated with RARP, eventually associated with ePLND, according to guidelines.^{1,2} Patients were classified according to the EAU prognostic system which was defined by standard clinical variables including biopsy ISUP tumor grade system, percentage of biopsy positive core (BPC), PSA, cTNM system, but excluding PSA density. PI-RADS lesions were classified according to version 1 for those detected up to 2016, to version 2 from 2016 to 2019 and version 2.1 since 2020 with magnet strength of 3-T without endorectal coil; MRI readings were performed by dedicated radiologists; accordingly, the study included only one visible lesion including PI-RADS scores 3, 4 and 5. Further investigated factors included age (years), body mass index (BMI; kilograms/square meters), PSA (ng/mL), prostate volume (mL), percentage of biopsy positive cores (BPC; %), tumor grade and stage according to the TNM and ISUP system; moreover, patients were staged and classified by EAU

prognostic risk categories as well as by the single visible PI-RADS index score lesions ranging from 3 to 5, as recommended.^{1,2} According to pathology findings in the surgical specimen, patients were further stratified into the favorable and adverse pathology risk groups with the latter including subjects having ISUP 4/5 and/or extracapsular extension (ECE) and/or seminal vesical invasion (SVI) and/or positive surgical margins (R1) and/or pelvic lymph node invasion (PLNI), as well. Biological adverse pathology was defined as the composite event of ISUP 4/5 and/or ECE and/or SVI and/or PLNI; likewise positive surgical margins which depends on both cancer biology and surgical technique was considered secondary; nevertheless, it did not impact on results for being closely related to aggressive cancer biology (ISUP 4/5, ECE, SVI, PLNI) and also because procedures were performed by high-volume surgeons who limited potential biases related to surgical technique.

Statistical methods

Continuous variables were reported as medians (interquartile range; IQR), while categorical variables were expressed as frequencies (percentages; %). The hypothesis of an association between the PI-RADS system and adverse pathology was tested using appropriate statistical methods. Continuous variables were compared using the Kruskal–Wallis test or the Mann–Whitney U test, as appropriate, while categorical variables were evaluated using the Pearson chi-square test.

The analysis of the risk of adverse cancer parameters across PI-RADS groups was performed by comparing PI-RADS 3 vs. 5, PI-RADS 4 vs. 5, and PI-RADS 3 vs. 4. This analysis was conducted using a multinomial logistic regression model, in which PI-RADS categories were treated as the multinomial outcome and predicted by a binary composite pathological endpoint (adverse vs. non-adverse pathology). Results from regression analyses are reported as odds ratios (ORs) with corresponding 95% confidence intervals (95% CIs) and *p*-values.

In a multivariate framework, outcomes were also modelled according to EAU prognostic risk groups (intermediate vs. low, high vs. low, and intermediate vs. high). All analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 26 (IBM Corp., Armonk, NY, USA), and all tests were two-sided with *p* < 0.05 considered statistically significant.

Results

PI-RADS index lesions 4 were the most frequently detected (54.9%) followed by lesions 5 (33.7%) and 3 (11.5%); likewise, adverse pathology was detected in 46.5% of specimens; furthermore, the most frequently EAU category was the intermediate one (56.0%) followed by high-risk (22.6%) and low risk (21.4%) groups, as well. An extended PLND was performed in 375 cases, with PLNI being detected in 36 (9.6%). Supplementary Table S1 shows cross classification of one single visible PI-RADS lesion of patients diagnosed with PCa with adverse pathology features in the surgical specimen; accordingly, as PI-RADS increased from 3 to 5, so patients were more likely to have adverse pathology features including lethal tumor grades (ISUP 4-5), extra-prostatic extension (ECE, SVI), positive surgical specimens (R1) and PLNI as detailed in the Table, as well. Demography of the patient population stratified by both single PI-RADS index lesions and adverse pathology is reported in Table 1, showing positive association of PI-RADS lesions with unfavorable clinical and pathological parameters involving PSA, tumor grade and BPC for the former as well as tumor grade, extension and PLNI for the latter; conversely, decreasing PI-RADS lesions associated with more favorable parameters, as well. Similarly, adverse pathology while associating with adverse clinical parameters also showed positive association with pathology features, including ISUP 1 to 3, pT2, and pN0 stage, as well.

So far, increasing PI-RADS lesions have been associated with features of aggressive cancer biology; conversely, decreasing PI-RADS lesions have been associated with factors indicating less aggressive disease as well. These findings were confirmed by a risk analysis using the multinomial logistic regression model, as reported in Table 2. Accordingly, patients presenting with a single PI-RADS index lesion 3 compared with grade 5 were less likely to have unfavorable clinical parameters such as increased PSA levels, percentages of BPC and high tumor grades as well as adverse pathology features such as ISUP grade 4/5, ECE; moreover, they were also less likely to present with high-grade cancers when compared with subjects presenting with single PI-RADS index 4 lesions, as well; likewise, single PI-RADS index 4 compared with grade 5, were not only less likely associate with unfavorable clinical parameters including cN1 stage, but also with all adverse pathology features including high-grade cancers, ECE, SVI, R1 and PLNI, as well.

TABLE 1. Demographics and adverse pathology of 505 operated patients with clinical prostate cancer presenting with one visible PI-RADS index lesion

Statistics (*)	Population n = 505	PI-RADS 3 n = 58 (11.4%)	PI-RADS 4 n = 277 (54.9%)	PI-RADS 5 n = 170 (33.7%)	p-value	Adverse pathology (°) n = 235 (46.5)	p-value
Clinical factors							
Age (years)	65 (60–70)	64 (56.7–68.2)	65 (60–70)	66 (60–71)	0.109	66 (60–70)	0.115
BMI (kg/m ²)	25.9 (24.1–27.9)	25.3 (23.9–27.1)	26 (24.3–27.8)	25.5 (23.8–28.4)		25.9 (24.2–27.8)	0.964
PSA <10 (ng/mL)	395 (78.2)	47 (81)	230 (83)	118 (69.4)	<0.001	159 (40.3)	<0.001
PSA 10–20 (ng/mL)	90 (17.8)	11 (19)	42 (15.2)	37 (21.8)		59 (65.6)	
PSA >20 (ng/mL)	20 (4.0)	0 (0.0)	5 (1.8)	15 (8.8)		17 (85)	
PV (mL)	38 (30–50)	39 (30–49)	38 (30–50)	38.5 (28.8–53.2)	0.799	37 (29–50)	0.231
BPC <50 (%)	386 (76.4)	47 (81)	223 (80.5)	116 (68.2)	0.008	165 (42.7)	0.002
BPC ≥ 50 (%)	119 (23.6)	11 (19.1)	54 (19.5)	54 (31.8)		70 (58.8)	
ISUP 1	149 (29.5)	28 (48.3)	76 (27.4)	45 (26.5)	<0.001	43 (28.9)	<0.001
ISUP 2/3	290 (57.4)	27 (46.6)	181 (65.3)	82 (48.2)		132 (45.5)	
ISUP 4/5	66 (13.1)	3 (5.2)	20 (7.2)	43 (25.3)		60 (90.9)	
cT1	254 (50.3)	24 (41.4)	136 (49.1)	91 (53.5)	0.267	109 (42.9)	0.101
cT >1	251 (49.7)	34 (58.6)	141 (50.9)	79 (46.5)		126 (50.2)	
cN0	472 (93.5)	56 (96.6)	266 (96.0)	150 (88.2)	0.003	215 (45.6)	0.094
cN1	20 (4.8)	2 (3.4)	11 (4.0)	20 (11.8)		20 (60.6)	
EAU low-risk	108 (21.4)	22 (37.9)	58 (20.9)	28 (16.5)	<0.001	26 (24.1)	<0.001
EAU intermediate-risk	283 (56.0)	31 (53.5)	179 (64.5)	73 (42.9)		125 (44.2)	
EAU high-risk	114 (22.6)	5 (8.6)	40 (14.4)	69 (40.6)		84 (73.7)	
Pathology factors							
Weight (gr)	51.2 (42–65)	48.5 (40–60)	51 (42–64)	52 (43–65)	0.251	51 (42–63)	0.724
ISUP 1	48 (9.5)	10 (17.2)	26 (9.4)	12 (7.1)	<0.001	6 (12.5)	<0.001
ISUP 2/3	336 (66.5)	41 (70.3)	198 (71.5)	97 (57.1)		108 (32.1)	
ISUP 4/5	121 (24.0)	7 (12.1)	53 (19.1)	61 (35.9)		121 (100)	
pT2	395 (78.2)	50 (86.2)	231 (83.4)	114 (67.1)	<0.001	125 (31.6)	<0.001
pT3a	44 (8.7)	1 (1.7)	19 (6.9)	24 (14.1)		44 (100)	
pT3b	66 (13.1)	7 (12.1)	27 (9.7)	32 (18.8)		66 (100)	
R0	372 (73.7)	44 (75.9)	216 (78)	112 (65.9)	0.017	102 (27.4)	<0.001
R1	133 (26.3)	14 (24.1)	61 (22)	58 (34.1)		133 (100)	
pN0 (**)	330 (90.4)	33 (94.3)	185 (94.4)	121 (84.0)	0.004	160 (47.2)	<0.001
pN1	36 (9.6)	2 (5.7)	11 (5.6)	23 (16.0)		36 (100)	

Note. Legend: (*) continuous variables are reported as medians (interquartile ranges) while categorical parameters as frequency (percentage); PI-RADS: Prostate Imaging–Reporting and Data System; BMI: Body Mass Index; PSA: Prostate-Specific Antigen; PV: Prostate Volume; BPC: biopsy positive core; EAU: European Association of Urology; ISUP, tumor grade system of International Society of Urologic Pathology; pT, TNM pathological tumor extension; R, surgical margin status; pN, TNM pathological staging of pelvic lymph nodes; (**) extended pelvic lymph node dissection was performed in 375 cases; (°), defined as ISUP 4/5 and or pT3a/3b and/or R1 and/or pN1.

So far, there was a strong association between one visible PI-RADS index lesion and the risk with adverse surgical pathology as well as with unfavorable clinical parameters involving EAU prognostic risk classes. Accordingly, as PI-RADS scores increased from 3 to 5, so the rates of adverse pathology increased from 31% (PI-RADS 3) through 40.1% (PI-RADS 4) up to 62.4% (PI-RADS 5) with differences being significant ($p < 0.001$), as depicted in Figure 1 showing increasing adverse pathology rates related to increasing PI-RADS index lesions; conversely, decreasing PI-RADS scores associated with decreasing adverse pathology rates, as well.

Likewise, these findings showed clinical impact for managing clinical PCa, as reported in Table 3; accordingly, adverse pathology was less likely to occur for patients presenting with PI-RADS score 3 vs. 5 (OR = 0.272, 95% CI: 0.144–0.514; $p < 0.001$) as those for PI-RADS 4 vs. 5 (OR = 0.404; 95% CI: 0.273–0.598; $p < 0.001$); moreover, the former group was less likely to belong to the EAU high risk class when compared with both the low (OR = 0.092; 95% CI: 0.032–0.268; $p < 0.001$) as well as with the intermediate one (OR = 0.171; 95% CI: 0.063–0.464; $p < 0.001$); likewise, patients belonging to the latter group were less likely to belong to the EAU unfavorable prognostic risk category when compared with both the low

TABLE 2. Associations of prostate cancer factors among groups presenting with visible single PI-RADS index lesions

Statistics (*)	PI-RADS 3 vs. PI-RADS 5		PI-RADS 4 vs. PI-RADS 5		PI-RADS 3 vs. PI-RADS 4	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Age	0.948 (0.909–0.989)	0.014	0.993 (0.965–1.027)	0.608	0.955 (0.918–0.994)	0.024
BMI	0.947 (0.856–1.046)	0.284	1.001 (0.940–1.066)	0.974	0.945 (0.860–1.040)	0.251
PSA	0.97 (0.868–0.989)	0.022	0.934 (0.901–0.968)	<0.001	0.993 (0.930–1.060)	0.825
PV	0.988 (0.972–1.005)	0.174	0.997 (0.998–1.007)	0.540	0.991 (0.975–1.008)	0.293
BPC	0.984 (0.969–0.999)	0.034	0.985 (0.976–0.995)	0.002	0.998 (0.984–1.013)	0.823
bISUP 1	1.0		1.0		1.0	
bISUP 2/3	0.529 (0.279–1.05)	0.052	1.307 (0.832–2.053)	0.247	0.405 (0.224–0.732)	0.003
bISUP 4/5	0.112 (0.032–0.390)	<0.001	0.275 (0.144–0.525)	<0.001	0.407 (0.112–1.477)	0.172
cT1	1.0		1.0		1.0	
cT >1	0.613 (0.335–1.120)	0.112	0.837 (0.577–1.128)	0.363	0.732 (0.413–1.298)	0.286
cN0	1.0		1.0		1.0	
cN1	0.268 (0.061–1.183)	0.082	0.310 (0.145–0.665)	0.003	0.854 (0.186–4.004)	0.851
PW	0.987 (0.970–1.004)	0.102	0.999 (0.989–1.008)	0.760	0.988 (0.972–1.004)	0.154
pISUP 1	1.0		1.0		1.0	
pISUP 2/3	0.507 (0.203–1.267)	0.146	0.942 (0.456–1.947)	0.872	0.538 (0.241–1.202)	0.131
pISUP 4/5	0.138 (0.044–0.434)	<0.001	0.401 (0.184–0.872)	0.021	0.343 (0.117–1.005)	0.051
pT2	1.0		1.0		1.0	
pT3a	0.095 (0.013–0.722)	0.023	0.391 (0.206–0.743)	0.004	0.243 (0.032–1.859)	0.173
pT3b	0.499 (0.206–1.206)	0.122	0.416 (0.238–0.728)	0.002	1.198 (0.494–2.904)	0.690
R0	1.0		1.0		1.0	
R1	0.614 (0.311–1.213)	0.160	0.545 (0.356–0.825)	0.005	1.127 (0.579–2.191)	0.725
pN0	1.0		1.0		1.0	
pN1	0.319 (0.071–1.122)	0.134	0.313 (0.147–0.665)	0.003	1.019 (0.216–4.809)	0.981

Note. Legend: (*), univariate analysis; bISUP, biopsy ISUP grade group; pISUP, pathology ISUP grade group; OR, odds ratio; CI, confidence interval; BMI: Body Mass Index; PSA: Prostate-Specific Antigen; PI-RADS: Prostate Imaging–Reporting and Data System; PV: Prostate Volume; BPC: biopsy positive cores; PW: prostate weight; ISUP: International Society of Urological Pathology; pT, TNM pathological tumor extension; R, surgical margin status; pN, TNM pathological staging of pelvic lymph nodes.

risk (OR = 0.280; 95% CI: 0.154–0.508; $p < 0.001$) as with the intermediate (OR = 0.236; 95% CI: 0.147–0.380; $p < 0.001$) risk categories; furthermore, subjects presenting with PI-RADS score 3 compared with those having score 4 were less likely to belong to the EAU intermediate (OR = 0.457; 95% CI: 0.245–0.850; $p = 0.013$) and high risk group (OR = 0.330; 95% CI: 0.115–0.943; $p = 0.038$) when both compared to low risk subjects. Accordingly, patients could be stratified by both EAU prognostic risk categories and single PI-RADS index score lesions as shown in Figure 2.

Discussion

Patients presenting with suspect PCa and mpMRI showing a visible index lesion may be stratified in risk groups with scores varying from 3 to 5; accordingly, the risk of detecting significant cancer is low for

lesions categorized as 3 (16%) and intermediate-high for those classified as 4/5 (62%), as well.^{1,2,8–10} Likewise, when subjects are diagnosed with PCa with a single index lesion, it may be associated with unfavorable cancer features; our study tested this hypothesis in surgical specimens and clinical parameters defining PCa prognostic risk categories. Accordingly, it demonstrated that increasing index lesions associated with the risk of adverse pathology which involved a large set of combined unfavorable events occurring in the surgical specimen varying from high grade cancers through extra-prostatic invasion with positive surgical margins up to PLNI; conversely, subjects presenting with a single index lesion score 3 as those with score 4 were less likely to associate with adverse pathology features when compared index lesion score 5. Notably, among patients presenting with a single MRI-visible PI-RADS 3 lesion, adverse pathology was observed in 31% of cases; within this

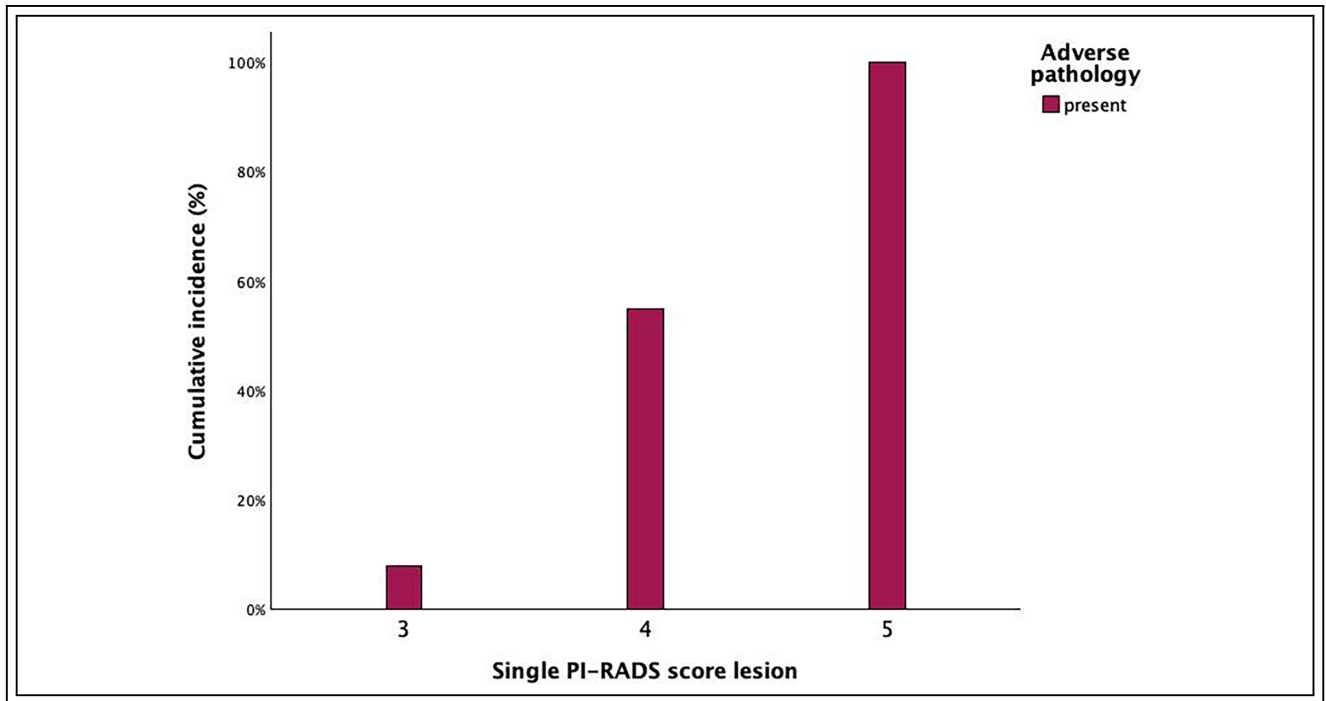


FIGURE 1. Cumulative incidence of one visible single PI-RADS lesion with surgical adverse pathology. As PI-RADS scores increased from 3 to 5, so the rates of adverse pathology increased from 31% (PI-RADS 3) through 40.1% (PI-RADS 4) up to 62.4% (PI-RADS 5) with differences being significant ($p < 0.001$). See text for details

subgroup, 22.2% were classified as EAU low risk, 55.6% as intermediate risk and 22.2% as high risk. These findings underscore that even equivocal MRI lesions may conceal aggressive disease and have relevant implications for the management of patients considered for active surveillance, particularly within the EAU low- and intermediate-risk categories. These findings highlight the clinical importance of carefully evaluating patients presenting with a single PI-RADS 3 lesion. As shown in Supplementary Table S1, such lesions were associated with adverse pathological features including ISUP 4–5, ECE, SVI, positive surgical margins, and pelvic lymph node invasion, with an overall adverse pathology rate of 31%. This observation indicates that PI-RADS 3 lesions, although often considered equivocal, may harbor aggressive disease in a substantial proportion of patients. Therefore, in patients who may otherwise be considered candidates for active surveillance, confirmatory biopsy and/or closer clinical monitoring should be considered to reduce the risk of underestimating clinically significant prostate cancer. Moreover, single index lesions were positively associated with unfavorable clinical parameters including high PSA levels, high-grade cancers and higher percentages of BPC; conversely, cases having lesion 3 and 4 compared

with those having score 5 were less likely to present with adverse clinical parameters, as well; interestingly, patients presenting with index lesion 3 vs. 5 were less likely to fall into the high-risk group when compared with both the low and the intermediate ones as well as those classified as 4 vs. 5; likewise, patients having lesions 3 vs. 4 were still less likely to belong to the unfavorable prognostic risk group when compared to low risk one. Accordingly, these findings represent a novel contribution with meaningful clinical implications, as well.

Clinical factors predicting adverse PCa pathology enter into validated nomograms which also consider mpMRI parameters, as well.^{4,2} Accordingly, a study aiming at computing a novel nomogram has considered to associate PLNI with specific mpMRI findings, including PI-RADS score lesions, number of lesions, diameter of the index lesion and clinical tumor stage; however, both diameter and score of index lesion did not sustain multivariate models when associated with mpMRI tumor staging which however did not enter into the novel nomogram, but only maximum diameter of the index lesion, as well; moreover, the study showed several limitations including the retrospective nature, the small sample, the multi-institutional nature of the study referring to several

TABLE 3. Clinical prostate cancer through single PI-RADS index lesions by adverse pathology and EAU prognostic risk groups

Statistics	PI-RADS 3 vs. 5 OR (95% CI)	p-value	PI-RADS 4 vs. 5 OR (95% CI)	p-value	PI-RADS 3 vs. 4 OR (95% CI)	p-value
Adverse pathology						
present vs. absent	0.272 (0.144–0.514)	<0.001	0.404 (0.273–0.598)	<0.001	0.673 (0.367–1.234)	0.200
EAU risk group						
intermediate vs. low	0.540 (0.269–1.087)	0.084	1.184 (0.699–2.005)	0.530	0.457 (0.245–0.850)	0.013
high vs. low	0.092 (0.032–0.268)	<0.001	0.280 (0.154–0.508)	<0.001	0.330 (0.115–0.943)	0.038
high vs. intermediate	0.171 (0.063–0.464)	<0.001	0.236 (0.147–0.380)	<0.001	0.722 (0.264–1.972)	0.525

Note. CI, confidence interval; EAU, European Association of Urology; PI-RADS, Prostate Imaging Reporting and Data System; OR: Odds Ratio; CI: Confidence Interval; ISUP: International Society of Uro pathology; Adverse pathology includes ISUP grade group 4/5 and/or extracapsular extension (ECE) and/or seminal vesicle invasion (SVI) and/or positive surgical margins and/or pelvic lymph node invasion (PLNI).

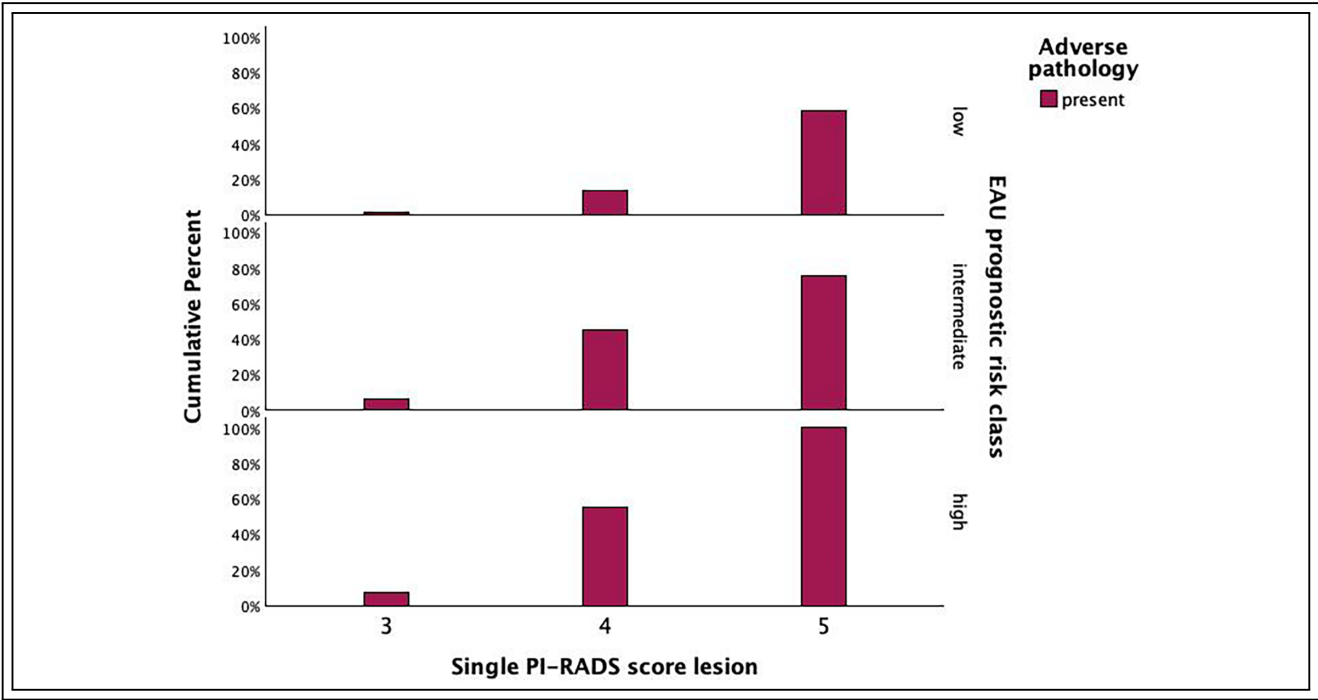


FIGURE 2. Cumulative incidence of one visible PI-RADS index lesion with adverse pathology in the surgical specimen stratified by EAU prognostic risk classes. Accordingly, single PI-RADS index lesions positively associated with adverse pathology allowing patient stratification within EAU risk classes, as well. See results and discussion for details

radiologist and surgeons; moreover, it was also outperformed by standard nomograms suggesting that mpMRI findings on index lesions were not sufficient for predicting the event of PLNI; accordingly several limitations biased this multicenter trial because of the operator dependency of such finding.^{1,2,11,12} Likewise, our study demonstrated specifically that

single visible index lesions positively associated with adverse pathology findings including all possible unfavorable events occurring in surgical specimens; conversely, significant rates of favorable pathology parameters fall into the adverse pathology category which was a multidimensional variable because of its algorithm pattern; conversely, decreasing PI-RADS

index lesions were less likely to associate with unfavorable clinical parameters modelling the prognostic EAU risk classes which were then further stratified by the index lesions, as well.

Our results are sustained by studies having biological basis foundations of associations between visible mpMRI lesions and aggressive cancer biology showing metastatic patterns. Accordingly, two investigational studies have both shown that index lesions phenotypes positively associated with risk scores features of genes expressing patterns of aggressive cancer biology leading to early metastases; conversely, decreasing scores expressing index lesions associated with low MRI index lesions, as well; furthermore, even low risk disease may exhibit high adverse gene scores indicating that the risk category is heterogenous with clusters exhibiting aggressive biology, accordingly.^{13–15} Likewise, our results showed that as significant index lesions increased, so patients were more likely to have adverse pathology defining an multidimensional cluster expressing the most adverse prognosis for combining the worst pathology patterns; so far, single visible index lesions associated with cancers which were high grade and/or large with ECE or SVI as well as with metastases to pelvic lymph nodes, as well.

The natural history of managed PCa is long with mortality rates at 15 years varying from 2.7% to 3.2%; accordingly, prognostic risk groups are defined by adverse prognostic factors which mainly include high tumor grade (ISUP 4/5) a both biopsy or pathology and short PSA dynamics (PSA doubling time), as well; moreover, disease mortality is lowered by PSA screening; as a result, adverse tumor grade at both biopsy or specimen pathology and short PSA dynamics are important for assessing managed prognostic groups; likewise, overtreatment toxicities may be mitigated by active surveillance or active monitoring, as well.^{1–7,14–18} Likewise, our study has shown that a single visible index PI-RADS lesion not only associated with high-grade cancers but also with overall adverse pathology which is to be considered as a multidimensional variable for including all pathology algorithms leading to the most adverse patterns involving an unfavorable PCa natural history with early biochemical recurrence, metastatic progression and disease specific mortality; interestingly, these patterns allowed further stratification of patients with prognostic risk groups which do not consider parameters related to significant PI-RADS lesions, as well. Accordingly, our study has implications for daily practice, as well. When a patient is diagnosed with PCa, mpMRI may show a single PI-RADS index lesion which may vary from 3 to 5; accordingly, the

risk of adverse pathology is increased for index lesion ranking from 3 to 5; conversely, patients presenting with PI-RADS lesion 3 or 4 are less likely to have adverse pathology as well as to belong to the high EAU risk class when compared to high grade index lesions; furthermore, subjects presenting with grade 3 lesions compared with those ranked as 4 are also less likely to associate with intermediate and high-risk prognostic groups, as well; however, confirmatory studies are required.

Although genomic testing was not performed in the present cohort, our findings support the hypothesis that imaging characteristics of a single visible PI-RADS index lesion may reflect underlying tumor biology. Future prospective studies should directly correlate mpMRI findings with validated genomic classifiers, such as Decipher, Prolaris, or similar molecular assays, to determine whether PI-RADS score independently predicts genomic risk. Such integrated imaging-genomic approaches may improve biological risk stratification and support more personalized management of patients with localized prostate cancer.

The present study focused on patients presenting with a single visible PI-RADS index lesion, which represented 76.1% of the population undergoing mpMRI in our surgical cohort, whereas multifocal MRI-visible disease was observed in 23.9% of patients and was excluded. This selection was intended to minimize staging ambiguity and allow a more precise evaluation of the prognostic impact of a single dominant lesion. Although multifocal disease may reflect more aggressive tumor biology or improved MRI detection sensitivity, single visible lesions may still harbor adverse pathological features, as observed in our cohort. Therefore, characterization of a single index lesion provides clinically relevant prognostic information and may improve risk stratification in patients with localized prostate cancer.

Our study has limitations due to its retrospective design and the heterogeneity of the mpMRI procedure, which involves several hospitals and different radiologists. Likewise, the use of different PI-RADS versions may represent an additional limitation, since they differ in criteria for transitional zone lesions; nevertheless, PI-RADS criteria are continuously updated in successive versions and were consistently applied by dedicated radiologists. Furthermore, surgical procedures were performed by several surgeons. Not all prostate biopsies were performed at our institution; therefore, detailed data on MRI-targeted biopsy cores corresponding to the visible PI-RADS index lesions were not consistently available for all patients and could not be analysed.

In addition, MRI scans were not centrally reviewed and inter-reader variability was not assessed; nevertheless, MRI readings were consistently performed by dedicated radiologists and all surgical specimens were evaluated by a dedicated pathologist. Moreover, sub-analyses of individual adverse pathological features according to PI-RADS categories were not performed due to the limited number of events, and larger multicenter studies are needed to clarify the contribution of specific adverse components. Likewise, our study has strengths, including being a single-center study, and all specimens were evaluated by a dedicated pathologist. Moreover, the analysis focused on a single significant PI-RADS lesion in a large population stratified according to adverse pathology and EAU prognostic risk groups.

Conclusions

In clinical PCa patients, single visible PI-RADS index lesions positively associated adverse pathology features which allowed patient stratification within prognostic risk classes; conversely, as PI-RADS index lesions decreased, so patients were less likely to have adverse cancer parameters; nevertheless, one third of subjects presenting with one visible lesion classified PI-RADS associate with the risk of adverse pathology, which needs to be excluded by re-biopsy and/or close monitoring in order to elect subjects to active surveillance; accordingly, genomic tests focused on single PI-RADS lesions may represent the way forward for prognostic classification of such lesions.

Acknowledgement

The authors would like to thank all collaborators and clinical staff involved in patient care and data collection.

Funding Statement

The authors received no specific funding for this work.

Author Contributions

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Sonia Costantino, Matteo Brunelli, Salvatore Siracusano, and Alessandro Antonelli contributed to study conception and design, data acquisition, analysis, and interpretation. Antonio Benito Porcaro drafted the manuscript. Riccardo Bertolo and Alessandro Antonelli critically revised the manuscript for important intellectual content. All authors reviewed and approved the final version of the manuscript.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval

The study was conducted in accordance with ethical standards and the principles of the Declaration of Helsinki. The local ethics committee (Comitato Etico Territoriale Area Sud-Ovest Veneto–CET-ASOV) did not require a formal application for the present data evaluation, as all data were routinely collected and recorded by the institution in the context of close follow-up for this specific clinical condition. Written informed consent was obtained from each of the patients.

Conflicts of Interest

The authors declare no conflicts of interest.

Supplementary Materials

The supplementary material is available online at <https://www.techscience.com/doi/10.32604/cju.2026.076673/s1>.

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