Journal of Nuclear Medicine, published on July 29, 2021 as doi:10.2967/jnumed.121.262411

The European Association of Urology Biochemical Recurrence Risk Groups Predict Findings on PSMA PET in Patients with Biochemically Recurrent Prostate Cancer after Radical Prostatectomy

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Abstract

Purpose: To evaluate the association of a new biochemical recurrence (BCR) risk stratification system with PSMA-targeted PET/CT findings.

Methods: Two prospective studies that included patients with BCR were pooled. Findings on PSMA PET were catalogued. Patients were characterized according to the European Association of Urology (EAU) BCR risk categories. Univariable and multivariable analyses were carried out by logistic regression.

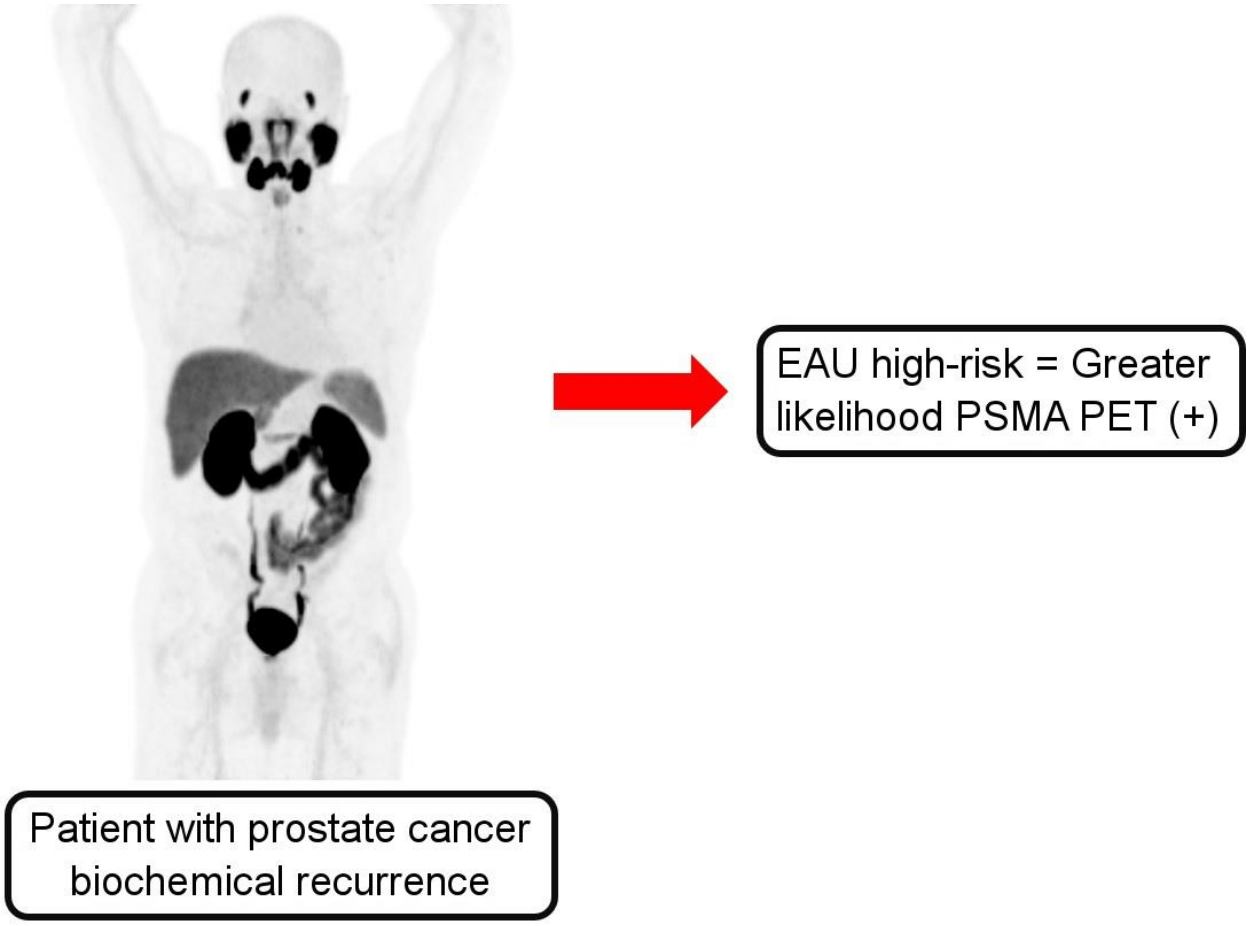
Results: 145 patients were included (45 low-risk and 100 high-risk). High-risk BCR patients had a higher positive rate when compared to low-risk (82.0% vs. 48.9%; $P < 0.001$), and reached independent predictor status for positive PSMA PET/CT scan on multivariable logistic regression (OR 6.73, 95% CI 2.41-18.76; $P < 0.001$). The AUC using the combination of BCR risk group and PSA was higher than PSA alone (0.834 vs. 0.759, $P = 0.015$).

Conclusion: The EAU BCR risk group defines the best candidates who can benefit from a PSMA PET/CT scan when BCR occurs.

Key words

Prostate cancer; BCR; prostate-specific membrane antigen; positron emission tomography

Graphical Abstract



Introduction

Prostate cancer (PCa) is the second most common cancer type and the fifth leading cause of cancer death in men worldwide [1]. In patients who receive either radical prostatectomy (RP) or radiotherapy to treat their primary tumors, approximately 30% will develop biochemical recurrence (BCR) [2]. Since, by definition, PCa at this stage is invisible on conventional imaging, it is of importance to stratify BCR patients into different risk groups in order to give intensive treatment to patients with aggressive disease phenotypes.

The European Association of Urology (EAU) BCR risk stratification system was proposed by the EAU PCa Guideline Update, which defines low-risk BCR after RP as patients with prostate-specific antigen doubling time (PSADT) >12 months and Gleason score (GS) <8; and high-risk BCR after RP as patients with PSADT ≤12 months or GS ≥8 [3]. Validation of this risk stratification system in 1125 patients demonstrated that the 5-year metastatic progression (MP)-free and PCa-specific mortality (PCSM)-free survival rates were significantly higher among patients with low-risk BCR. Multivariable analysis confirmed the EAU risk stratification as an independent predictor of MP and PCSM [4].

With the recent advances in prostate-specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET/CT), our current definition of BCR may soon be obsolete. We may need to begin re-phrasing our clinical questions in the context of PSMA-positivity. We previously reported more than 60% of post-RP BCR patients had positive findings on PSMA PET/CT scan, and according to a meta-analysis, the positive predictive value (PPV) of PSMA PET/CT was 0.99 based on a histopathologic gold standard [5-7].

The aim of the current study was to compare the detection rates and the localization of PSMA-avid lesions in low-risk versus high-risk BCR patients after RP, and to evaluate the association of this new risk stratification system with PSMA PET/CT findings.

Methods

Patients

We pooled cohorts of patients with BCR from two prospective studies at tertiary referral centers (Johns Hopkins Hospital, JHU and Renji Hospital, RJH). The inclusion criteria of the patients in each cohort, as well as technical details of the PSMA PET/CT scan (scanner, scan protocol, scan interpretation, etc.) have been previously reported, respectively [5, 6]. Risk stratification was performed as proposed by Van den Broeck and colleagues [3].

Pelvic-confined disease was defined by uptake of the radiotracer in the prostate bed (PB), pelvic soft tissue, and/or pelvic lymph nodes. PSADT was calculated as previously described [6], using the three most recent PSA values prior to PSMA PET/CT scan. If the slope of the linear regression was 0 (elevated but constant PSA) or negative (decreasing PSA after initial increase), the PSADT was set as ≥12 months.

Statistical Analysis

Logistic regression models were conducted for univariable and multivariable analyses, calculating odds ratios (ORs) with 95% confidence intervals (CIs) to estimate the associations between BCR risk stratification and outcomes, adjusting for potential confounders. The predictive value of BCR risk stratification was assessed using the receiver operating characteristic (ROC)

curve and the area under the curve (AUC). Statistical testing was based on the two-sided tests at the 5% level of significance. SAS 9.4 (SAS Institute, Cary, NC, USA) software was used.

Results

Patients

145 patients were enrolled; 94 were scanned with ^{18}F-DCFPyL PET/CT (JHU), and 51 were scanned with ^{68}Ga-PSMA-11 PET/CT (RJH). 45 patients had low-risk and 100 had high-risk BCR. Table 1 summarizes the clinical and pathological characteristics of these patients.

Imaging Findings

104/145 (71.7%) patients had at least one PSMA-positive lesion on the PSMA PET/CT scan. High-risk BCR patients had a significantly higher positive rate when compared to the low-risk BCR group (82.0% vs. 48.9%; $P < 0.001$; Figure 1A). On multivariable logistic regression analyses adjusted for age, PSA at time of scan, disease-free time, pathological tumor stage (pT stage), and cohort (JHU or RJH), the BCR risk group was an independent predictor for a positive PSMA PET/CT scan (OR 6.73, 95% CI 2.41-18.76; $P < 0.001$; Table 2). The median number (interquartile range) of PSMA-positive lesions is 0 (0-1) for low-risk BCR and 1 (1-3) for high-risk BCR. Multivariable linear regression model was used to estimate the associations between BCR risk group and lesion number. The model parameter β is 0.85 with statistical significance ($P = 0.037$).

In PSA subgroups, the positive rates of patients with low-risk BCR remained the same (40%) in groups of PSA< 0.5 ng/mL and 0.5-1.0 ng/mL, while higher positive rates were observed with increasing PSA values in patients with high-risk BCR. Nearly 95% of patients with a PSA

greater than 1.0 ng/mL in the high-risk group had detectable disease on PSMA PET/CT, while the positive rate was 66.7% for low-risk patients in the same PSA subgroup (Figure 1B).

Of the 104 scan-positive patients, fifty-six (53.8%) had pelvic-confined disease. The BCR risk group was not associated with pelvic-confined disease (Table 2; Figure 1C). ROC curves were generated to demonstrate the ability of the BCR risk group and PSA to predict positive PSMA PET/CT imaging. The AUCs using the BCR risk group or PSA alone were comparable (0.761 vs. 0.759, $P = 0.96$; Figure 1D), while the AUC using the combination of BCR risk group and PSA was higher than PSA alone (0.834 vs. 0.759, $P = 0.015$; Figure 1D).

68/145 (46.9%) patients had recurrence/metastasis in lymph nodes (LN), 28/145 (19.3%) patients had bone metastasis, and 31/145 (21.4%) patients had PB recurrence. On multivariable logistic regression analyses, the BCR risk group was independently associated with LN involvement on PSMA PET/CT in all patients including those with a negative scan (OR 2.38, 95% CI 1.04-5.49; $P = 0.041$; Table 2). However, in 104 patients with a positive scan, the BCR group was not associated with the location of PSMA-avid lesions (Figure 2; Table 2).

Discussion

We demonstrated that patients with EAU high-risk BCR were more likely to have PSMA PET/CT-detectable disease, suggesting that tumor volume and distribution may help to explain the worse prognosis of those patients. Notably, even patients with low-risk BCR had relatively high detection rates on PSMA PET/CT and the rates of extra-pelvic disease on positive scans was similar between high- and low-risk, suggesting that patients across the BCR spectrum may be good candidates for PSMA PET/CT imaging.

Previously, PSA has been reported as the strongest predictor of a positive PSMA PET/CT scan [8]. In this study, the added value of the EAU BCR risk groups has been demonstrated in a diverse population. It further stratifies the patients in each PSA subgroup, defining the patients who are most likely to have a positive PSMA PET/CT scan. Use of EAU risk groups can serve as a simple and clinically applicable nomogram for predicting if patients will have a positive scan. The survival benefits from salvage pelvic radiation or focal treatment of oligometastases in different BCR risk groups in the context of PSMA PET/CT should be further explored.

The EAU BCR risk groups are associated with meaningful oncologic outcomes such as MP-free and PCSM-free survival rates [4], suggesting that PSMA-targeted PET imaging will yield imaging biomarkers. Imaging specialists, urologists, and oncologists working with PSMA imaging should focus their attention on the design of prospective trials that can discover and validate the prognostic significance of findings.

The limitations of this work include the relatively small number of cases, the *post hoc* evaluation of prospectively acquired data, the use of more than one PSMA-targeted radiotracer, and lack of central review or a specific read paradigm. Future work is needed to confirm these findings in multi-center, larger prospective cohorts.

Declarations

Funding: We acknowledge funding from Progenics Pharmaceuticals, the Prostate Cancer Foundation Young Investigator Award, National Institutes of Health grants (CA134675, CA183031, CA184228, and EB024495), Program of Shanghai Subject Chief Scientist (19XD1402300) and Program for Outstanding Medical Academic Leader (2019LJ11). We thank Meghan Pienta and Morgan D. Kuczler for their kind help in data collection.

Conflicts of Interest: M.G.P. is a co-inventor on a US patent covering ^{18}F-DCFPyL and as such is entitled to a portion of any licensing fees and royalties generated by this technology. This arrangement has been reviewed and approved by the Johns Hopkins University in accordance with its conflict of interest policies. M.A.G. has served as a consultant to Progenics Pharmaceuticals, the licensee of ^{18}F-DCFPyL. S.P.R. is a consultant to Progenics Pharmaceuticals. K.J.P., M.G.P., M.A.G., and S.P.R. have all received research funding from Progenics Pharmaceuticals. No other authors have declared any relevant conflicts of interest.

Key Points

Question: Are the EAU BCR risk groups associated with findings on PSMA PET?

Pertinent Findings: In men with BCR after RP, the EAU high-risk group is more likely to have visible sites of recurrent disease on PSMA PET. However, low-risk and high-risk men have the same likelihood of having non-pelvic-confined disease.

Implications for Patient Care: Risk stratification using the EAU BCR risk groups can help select men who are most likely to benefit from imaging with PSMA PET.

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Table 1. Demographics and clinical data for the study cohort

	BCR low risk N (%)	BCR high risk N (%)	*P* value
Age (year)			0.426
Median (IQR)	71 (65-76)	69 (63-73)	
Cohort			0.288
JHU	32 (71.1)	62 (62.0)	
RJH	13 (28.9)	38 (38.0)	
Disease free time (year)			0.012
Median (IQR)	5.1 (3-8)	2.2 (1.3-5.3)	
Adjuvant therapy	44 (97.8)	86 (86.0)	0.242
Salvage therapy	36 (80.0)	85 (85.0)	0.688
PSA (ng/mL) at time of scan			0.195
<0.5	20 (44.4)	31 (31.0)	
0.5-1	10 (22.2)	22 (22.0)	
>1	15 (33.4)	47 (47.0)	
PSADT (month)*			< 0.001
<12	0 (0.0)	87 (89.7)	
≥12	45 (100.0)	10 (10.3)	
Gleason score			< 0.001
<8	45 (100.0)	54 (54.0)	
≥8	0 (0.0)	46 (46.0)	
pT stage			0.005
< pT3	33 (73.3)	48 (48.0)	
≥ pT3	12 (26.7)	52 (52.0)	

BCR: Biochemical recurrence; IQR: Interquartile range; PSA: Prostate specific antigen; PSADT: PSA doubling time

* The PSADT data of 3 JHU patients are not available, however all were high-risk based on Gleason scores.

Table 2. Univariable and multivariable Logestic regression models stratified according to the European Association of Urology BCR risk groups predicting positive findings, pelvic-confined disease, and disease location on PSMA PET/CT imaging

	EAU BCR risk groups			**EAU BCR risk groups**		
	Univariable analysis			Mutivariable analysis		
Outcome	OR	95% CI	P	OR*	95% CI	P
Positive PSMA PET/CT scan	4.76	2.19-10.35	0.000	6.73	2.41-18.76	0.000
Pelvic-confined disease	0.96	0.38-2.48	0.941	1.31	0.43-3.96	0.631
LN involvement in all patients	2.60	1.24-5.47	0.012	2.38	1.04-5.49	0.041
Bone metastasis in all patients	3.24	1.05-9.96	0.041	2.50	0.76-8.24	0.133
PB recurrence in all patients	1.71	0.68-4.33	0.255	1.91	0.69-5.32	0.216
LN involvement in PSMA-positive patients	1.10	0.41-2.94	0.846	0.97	0.31-3.01	0.960
Bone metastasis in PSMA-positive patients	1.86	0.57-6.08	0.303	1.44	0.38-5.48	0.594
PB recurrence in PSMA-positive patients	0.89	0.32-2.45	0.816	0.93	0.29-3.02	0.902

EAU: European Association of Urology; BCR: Biochemical recurrence; PSMA PET/CT: prostate-specific membrane antigen-targeted positron emission tomography/computerized tomography; LN: lymph nodes (s); PB: prostate bed

*Adjusted for age, PSA, disease-free time, pT stage and cohort.

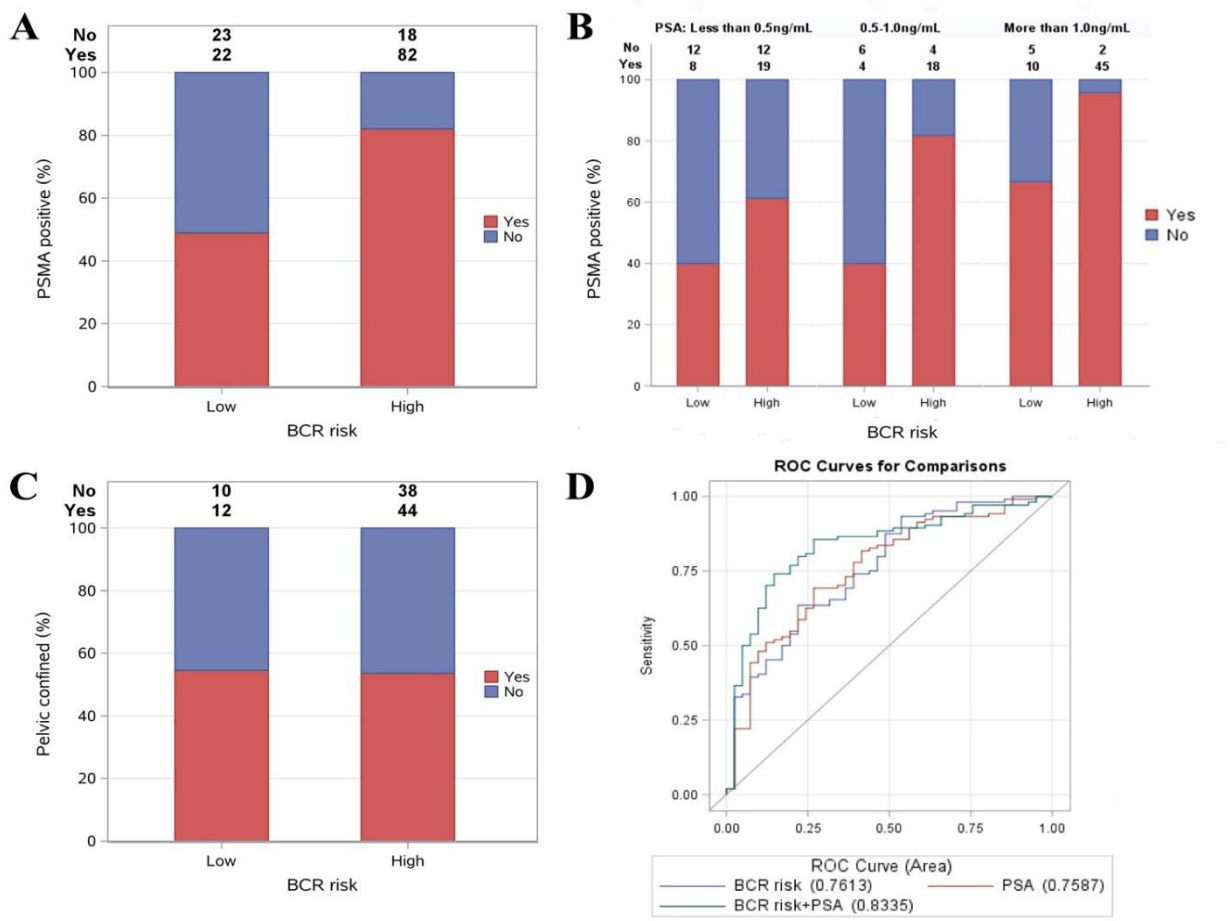

Figure 1. Prostate cancer detection and prevalence of pelvic-confined disease by PSMA PET/CT imaging in patients with low-risk versus high-risk biochemically recurrent prostate cancer. Percentage of patients with positive PSMA PET/CT scans in all patients (A) and PSA subgroups (B). Prevalence of pelvic-confined disease in each risk group (C). AUC for detection of prostate cancer stratified by the BCR risk group (blue), PSA (red) and the combination of the BCR risk group and PSA (green) (D). Each ROC multivariable analysis models also include age, disease-free time and pT stage.

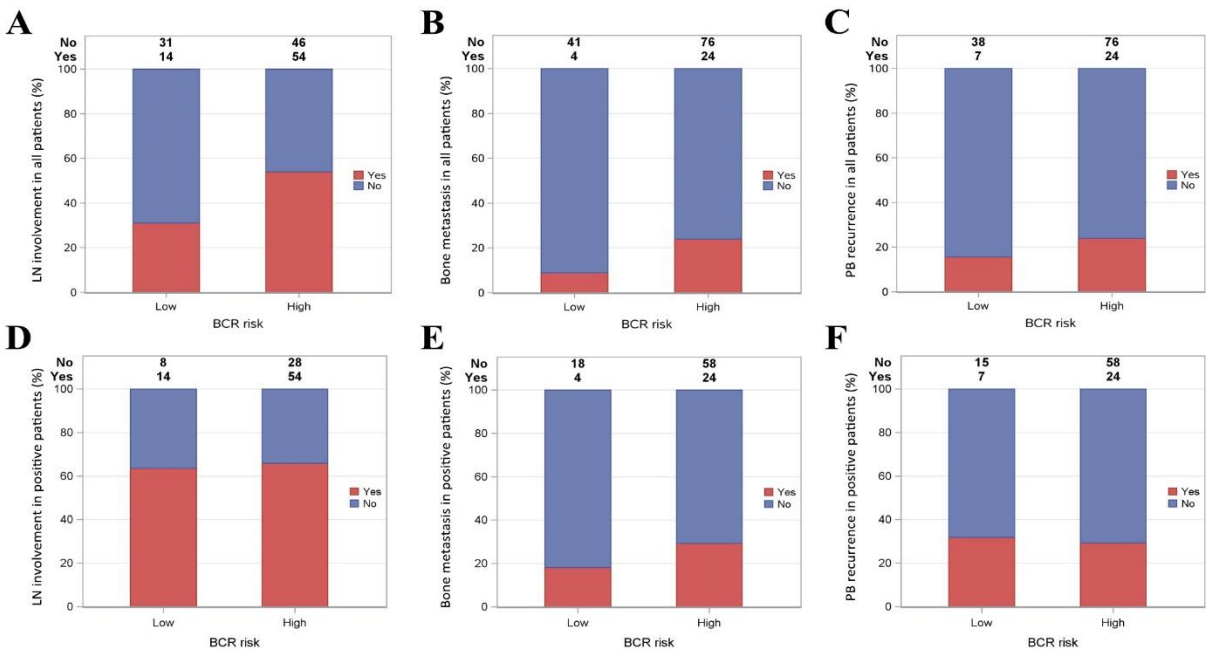

Figure 2. Localization of PSMA-avid lesions in patients with low-risk versus high-risk biochemically recurrent prostate cancer. Percentage of patients with lymph nodes (LN) involvement (A), bone metastasis (B) and prostate bed (PB) recurrence (C) in all patients (n=145). Percentage of patients with LN involvement (D), bone metastasis (E) and PB recurrence (F) in PSMA scan-positive patients (n=104).