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Brief Correspondence

External Validation of the European Association of Urology Biochemical Recurrence Risk Groups to Predict Metastasis and Mortality After Radical Prostatectomy in a European Cohort

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Abstract

The impact of biochemical recurrence (BCR) after radical treatment of prostate cancer on oncological outcomes remains unclear. A new European Association of Urology BCR risk stratification (low and high risk) has been proposed. To validate these risk groups, we retrospectively analyzed data for 1125 post-radical prostatectomy (RP) BCR patients (surgery between 1992 and 2006). Univariable Kaplan-Meier plots and multivariable Cox regression models with time-dependent covariates were used to test the independent predictor status of the risk grouping on metastatic progression (MP) and prostate cancer-specific mortality (PCSM). The 5-yr MP-free and PCSM-free survival rates were significantly higher among patients with low BCR risk compared to their high-risk counterparts. In multivariable analyses, the BCR risk grouping reached independent predictor status for MP (hazard ratio [HR] 3.46; $p < 0.001$) and PCSM (HR 5.12; $p < 0.001$). Salvage radiation therapy, especially when delivered at prostate-specific antigen < 0.5 ng/ml, was highly protective. Our findings corroborate the validity of this novel BCR risk grouping, which is easily applicable in daily practice and could be valuable in decision-making for salvage therapy and clinical trials.

Patient summary: The European Association of Urology grouping for the risk of biochemical recurrence of prostate cancer after radical prostatectomy was valid when applied in a European study cohort.

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Biochemical recurrence (BCR) of prostate cancer (PC) occurs in up to 30% of patients within 10 yr of radical prostatectomy (RP) [1,2]. Only a subgroup of these patients will proceed to metastatic progression (MP), while in others the natural history is indolent. Pound et al. [2] reported a 5-yr MP-free survival rate of 64% among 304 RP BCR patients who were observed until MP. Besides pathological Gleason score (pGS) and prostate-specific antigen doubling time (PSA-DT), the

time from RP to BCR (≤ 2 vs > 2 yr) was an independent predictor of MP in their analysis. These risk factors have been confirmed in several studies since then [1,3].

Van den Broeck et al. [4] recently published a systematic review of the literature on BCR after treatment with curative intent for nonmetastatic PC. The authors confirmed that oncological outcomes differ between groups with and without BCR and found that short PSA-DT and high pGS

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after RP are the main risk factors with a negative impact on survival. On the basis of these analyses, the authors of the systematic review, which was undertaken by the European Association of Urology (EAU) PC guideline panel as part of its guideline update for 2019, proposed a new EAU BCR risk stratification (EAU low-risk BCR: PSA-DT >1 yr and pGS <8 for RP; EAU high-risk BCR: PSA-DT ≤1 yr or pGS 8–10 for RP) [4]. The aim of the present study was to validate the EAU BCR risk grouping.

Using our review-board-approved institutional database, we identified 5509 patients who underwent RP between 1992 and 2006. Of these, 1497 experienced BCR (rising PSA level of ≥0.2 ng/ml on two consecutive measurements). Patients who received neoadjuvant or adjuvant therapies or with PSA persistence after RP were excluded. Risk stratification was performed as proposed by Van den Broeck et al. [4] into low-risk versus high-risk BCR. Univariable Kaplan-Meier plots were used to display MP and prostate cancer-specific mortality (PCSM) and the log-rank test was applied to compare survival between the two groups [5]. Multivariable Cox regression models were used to test the independent predictor status of the EAU BCR risk groups for MP and PCSM [6–8]. The discriminative ability of the EAU BCR risk grouping in predicting MP and PCSM was assessed using the concordance index [9]. To test the sensitivity, all the analyses

were repeated for subsets of patients including those who received neoadjuvant and adjuvant therapies and patients who did receive salvage therapies.

We also assessed the impact of salvage radiation therapy (SRT) delivered early (at PSA <0.5 ng/ml) versus late SRT (at PSA ≥0.5 ng/ml), modeled as a time-dependent covariate that changed at least once during the follow-up period, as previously described [7,8]. Using this method, we were able to distinguish between patients who had SRT at different time points during follow-up. All statistical testing was two-sided with the level of significance set at $p < 0.05$. Analyses were performed using R v.3.3.0 (R Foundation for Statistical Computing, Vienna, Austria).

Table 1 lists demographic and disease characteristics for all patients according to the proposed BCR risk groups. Median follow-up for survivors was 124 mo from RP (interquartile range [IQR] 98–157) and 65 mo from BCR (IQR 31–103). A total of 510 patients were classified as having low-risk and 530 as having high-risk BCR. Low-risk BCR patients had a significantly higher proportion of organ-confined disease at RP and a longer time from RP to BCR when compared to the high-risk BCR group (Table 1). The 5-yr MP-free and PCSM-free survival rates were 97.5% (95% confidence interval [CI] 95.8–99.1%) and 99.7% (95% CI 99.0–100%) for the low-risk BCR group and 86.7% (95% CI

Table 1 – Demographic and disease characteristics of all 1040 study patients according to the European Association of Urology BCR risk groups

Variable	BCR low risk (n = 510)	BCR high risk (n = 530)	p value
Median age at RP, yr (IQR)	63 (60–67)	63 (59–67)	0.5
Median preoperative PSA, ng/ml (IQR)	7.6 (5.1–11.7)	8.4 (5.2–15.1)	0.005
Median PSA-DT, mo (IQR)	25 (17–44)	6 (3–9)	≤0.001
Pathological Gleason score, n (%)			≤0.001
≤6	122 (23.9)	69 (13.0)	
7a	314 (61.6)	276 (52.1)	
7b	74 (14.5)	144 (27.2)	
≥8	0 (0.0)	41 (7.7)	
Pathological ISUP grade group, n (%)			≤0.001
I	122 (23.9)	69 (13.0)	
II	314 (61.6)	276 (52.1)	
III	74 (14.5)	144 (27.2)	
IV	0 (0)	12 (2.3)	
V	0 (0)	29 (5.5)	
Pathological tumor stage, n (%)			≤0.001
pT2	245 (48.0)	190 (35.8)	
≥pT3	265 (52.0)	340 (64.2)	
Surgical margin status, n (%)			0.8
R0	350 (68.6)	369 (69.6)	
R1	160 (31.4)	161 (30.4)	
Lymph node status, n (%)			0.4
N0/Nx	484 (94.9)	495 (93.4)	
N1	26 (5.1)	35 (6.6)	
Time from RP to BCR, n (%)			≤0.001
<12 mo	40 (7.8)	69 (13.0)	
12–35.9 mo	122 (23.9)	183 (34.5)	
≥36 mo	348 (68.2)	278 (52.5)	
Median FU from RP for patients without MP, mo (IQR)	132 (108–160)	120 (89–156)	
Median FU from BCR for patients without MP, mo (IQR)	64 (31–99)	62 (29–102)	
Median FU from RP for survivors, mo (IQR)	131 (108–157)	121 (97–157)	
Median FU from BCR for survivors, mo (IQR)	64 (31–99)	68 (30–109)	

BCR = biochemical recurrence; RP = radical prostatectomy; IQR = interquartile range; PSA = prostate-specific antigen; PSA-DT = PSA doubling time; ISUP = International Society of Urological Pathology; FU = follow-up; MP = metastatic progression.

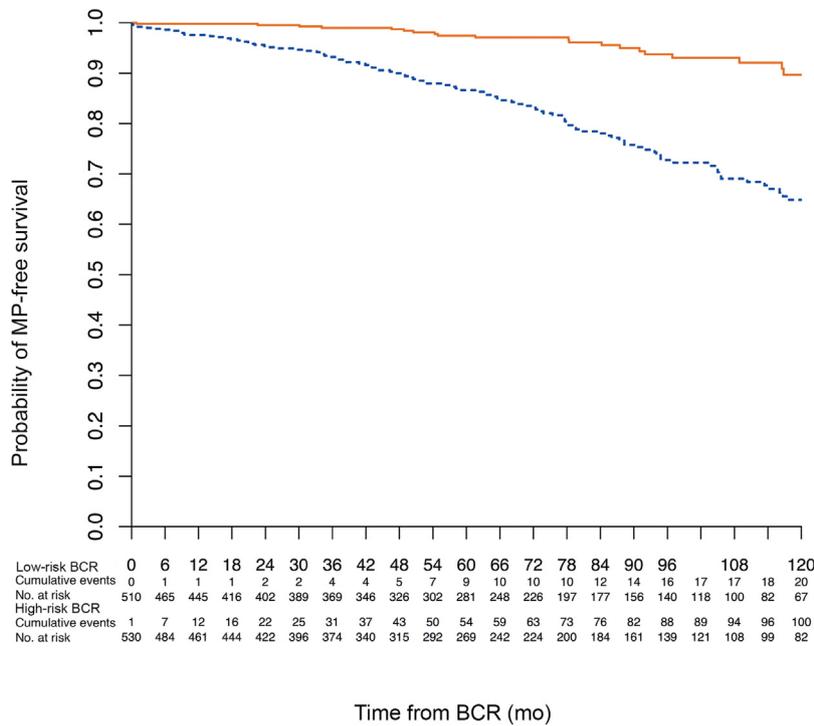


Fig. 1 – Kaplan-Meier plot of metastatic progression (MP)-free survival stratified according to the European Association of Urology biochemical recurrence (BCR) risk groups. The red line denotes low-risk and the blue line high-risk patients.

83.4–90.1%) and 93.8% (95% CI 91.4–96.3%) for the high-risk BCR group (both $p < 0.001$; Figs. 1 and 2). On multivariable Cox regression analyses adjusted for preoperative PSA, pT stage, pathological lymph node status, RP-BCR time, and SRT, the proposed BCR risk grouping reached independent

predictor status for both MP (hazard ratio [HR] 3.46, 95% CI 2.41–4.97; $p < 0.001$) and PCSM (HR 5.12, 95% CI 2.90–9.03; $p < 0.001$; Table 2). However, the discriminative ability of the grouping in predicting MP (c-index 0.67) or PCSM (c-index 0.69) was moderate.

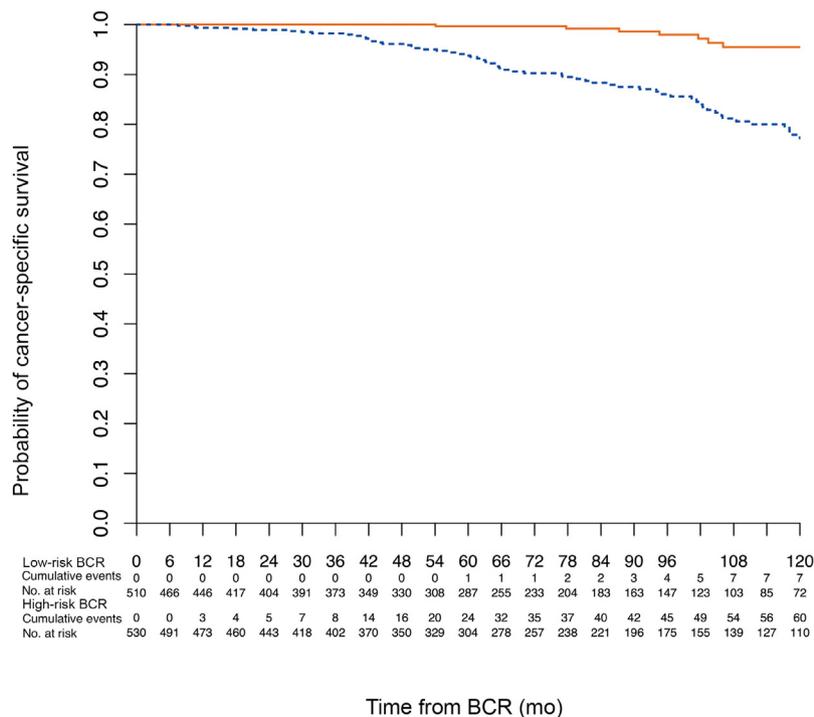


Fig. 2 – Kaplan-Meier plot of prostate cancer-specific survival stratified according to the European Association of Urology biochemical recurrence (BCR) risk groups. The red line denotes low-risk and the blue line high-risk patients.

Table 2 – Multivariable Cox regression models stratified according to the European Association of Urology BCR risk groups predicting MP and PCSM

Variable	MP		PCSM	
	HR (95% CI)	p value	HR (95% CI)	p value
BCR risk group				
Low	1.0 (reference)		1.0 (reference)	
High	3.46 (2.41–4.97)	≤0.001	5.12 (2.90–9.03)	≤0.001
Pathological tumor stage				
≤pT2	1.0 (reference)		1.0 (reference)	
≥pT3	1.33 (0.95–1.86)	0.1	1.21 (0.78–1.88)	0.4
Surgical margin status				
R0	1.0 (reference)		1.0 (reference)	
R1	1.03 (0.76–1.42)	0.8	0.86 (0.56–1.30)	0.5
Pathological lymph node status				
N0/Nx	1.0 (reference)		1.0 (reference)	
N1	1.21 (0.74–1.98)	0.4	0.80 (0.41–1.57)	0.5
Salvage radiation therapy ^a				
No	1.0 (reference)		1.0 (reference)	
Early	0.32 (0.20–0.53)	≤0.001	0.31 (0.15–0.62)	≤0.001
Late	0.56 (0.35–0.88)	0.01	0.58 (0.32–1.04)	0.07
Time from RP to BCR				
<12 mo	1.0 (reference)		1.0 (reference)	
12–35.9 mo	0.54 (0.37–0.79)	≤0.001	0.41 (0.26–0.63)	≤0.001
≥36 mo	0.38 (0.26–0.57)	≤0.001	0.27 (0.17–0.45)	≤0.001
PSA at RP in ng/ml	0.98 (0.97–0.99)	0.006	0.99 (0.98–1.01)	0.3

BCR = biochemical recurrence; PSA = prostate-specific antigen; RP = radical prostatectomy; HR = hazard ratio; CI = confidence interval; MP = metastatic progression; PCSM = prostate cancer-specific mortality.

^a Modeled as time-dependent covariates.

SRT receipt, either early (delivered at PSA <0.5 ng/ml) or late (delivered at PSA ≥0.5 ng/ml), was highly protective, with the maximum effect for early delivery (HR 0.32, 95% CI 0.20–0.53 for MP; HR 0.31, 95% CI 0.15–0.62 for PCSM; both $p < 0.001$; Table 2).

Among a subset of 1125 patients who underwent neoadjuvant or adjuvant therapies, the results were virtually the same as for the entire cohort. Similarly, the results did not change when considering only 398 patients who did not receive salvage therapies before MP.

The main limitation of this retrospective study is that all RPs were performed by high-volume surgeons at a single center, which might have affected the rates of metastases and mortality in our cohort.

In conclusion, our findings corroborate the validity of the novel EAU BCR risk groups, which are easily applicable in daily clinical practice and could be valuable in well-informed decision-making for salvage therapy and clinical trials.

The predictive performance of the EAU BCR risk groups may be refined in the future. Although we observed highly significant results, the accuracy of this two-tier risk stratification remained only moderate. One explanation for the low accuracy might be the inclusion of pGS 4 + 3 in the low-risk BCR group. Previous publications have shown that for pGS 7 there are large differences in outcomes between pGS 3 + 4 and pGS 4 + 3 [10,11]. Furthermore, predictive accuracy may be improved by using a nomogram with more levels. However, we know from daily experience that clinical applicability remains best with the simplest solution. Further validation of the EAU BCR risk groups is warranted.

Author contributions: Derya Tilki had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Tilki.

Acquisition of data: Tilki, Preisser, Graefen, Huland, Pompe.

Analysis and interpretation of data: Tilki, Pompe.

Drafting of the manuscript: Tilki, Pompe.

Critical revision of the manuscript for important intellectual content: Tilki, Preisser, Graefen, Huland, Pompe.

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References

- [1] Pompe RS, Gild P, Karakiewicz PI, et al. Long-term cancer control outcomes in patients with biochemical recurrence and the impact of time from radical prostatectomy to biochemical recurrence. *Prostate* 2018;78:676–81.
- [2] Pound CR, Partin AW, Eisenberger MA, et al. Natural history of progression after PSA elevation following radical prostatectomy. *JAMA* 1999;281:1591–7.

- [3] Freedland SJ, Humphreys EB, Mangold LA, et al. Risk of prostate cancer-specific mortality following biochemical recurrence after radical prostatectomy. *JAMA* 2005;294:433–9.
- [4] Van den Broeck T, Van den Bergh RCN, Arfi N, et al. Prognostic value of biochemical recurrence following treatment with curative intent for prostate cancer: a systematic review. *Eur Urol* 2019;75:967–87.
- [5] Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457–81.
- [6] Scrucca L, Santucci A, Aversa F. Regression modeling of competing risk using R: an in depth guide for clinicians. *Bone Marrow Transpl* 2010;45:1388–95.
- [7] Lévesque LE, Hanley JA, Kezouh A, et al. Problem of immortal time bias in cohort studies: example using statins for preventing progression of diabetes. *BMJ* 2010;340:5087.
- [8] Therneau T, Crowson C, Atkinson E. Using time dependent covariates and time dependent coefficients in the Cox model. *Mayo Clinic* 2013.
- [9] Heagerty PJ, Lumley T, Pepe MS. Time-dependent ROC curves for censored survival data and diagnostic marker. *Biometrics* 2000;56:337–44.
- [10] Epstein JI, Zelefsky MJ, Sjoberg DD, et al. A contemporary prostate cancer grading system: a validated alternative to the Gleason score. *Eur Urol* 2016;69:428–35.
- [11] Pompe RS, Davis-Bondarenko H, Zaffuto E, et al. Population-based validation of the 2014 ISUP Gleason grade groups in patients treated with radical prostatectomy, brachytherapy, external beam radiation or no local treatment. *Prostate* 2017;77:686–93.

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