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Identification of men with the highest risk of early disease recurrence after radical prostatectomy

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Abstract

Background—Men destined to have early biochemical recurrence (BCR) following radical prostatectomy (RP) may be optimal candidates for multimodal treatment. Here we identified pre-operative predictors of early BCR within a surgical cohort who recurred.

Methods—An institutional prostate cancer (PCa) database containing over 20,000 patients was queried to identify 1471 men who had BCR after RP, and pre-operative predictors of early versus late BCR were assessed. Early BCR was defined as recurrence within one year after RP. Within the recurrence cohort, those with National Comprehensive Cancer Network (NCCN) high-risk features were more likely to experience early BCR. Therefore, in all NCCN high-risk men in the database, we abstracted detailed pathologic biopsy data. Among 753 high-risk men, 41 alternate multivariable criteria were assessed for their ability to predict early BCR in crude and adjusted logistic regression models.

Results—The criteria that best identified those likely to experience early BCR are primary Gleason pattern 5 on biopsy or ≥4 cores containing pattern 4 (odds ratio 3.17, p <0.001). These criteria included 26.7% of NCCN high-risk men. Additionally, these criteria selected for men within the high-risk classification who were at significantly higher risk of subsequent metastasis (adjusted hazard ratio 3.04, p<0.001) and cancer-specific death (adjusted hazard ratio 3.27, p<0.001).

Conclusions—In men with PCa who present with high-risk features, pre-operative criteria have the ability to discriminate the subgroup most likely to experience early BCR after RP. Men at risk for early disease recurrence may be the most suitable candidates for multimodal therapy.

Keywords

prostate cancer; early biochemical recurrence; multimodal therapy; intraoperative therapy

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Introduction

Many men with prostate cancer (PCa) who undergo radical prostatectomy (RP) are not cured by surgical treatment alone, particularly those with high-risk features pre-operatively. For example, high-risk men undergoing RP have a 55–70% rate of biochemical recurrence (BCR) 3–5 years after RP [1,2]. Further, up to 32% will experience BCR and 16% will experience metastasis at 10 years [3].

Therefore there is a need to identify men with aggressive disease features who will benefit from multimodal therapy. For example, three prospective trials have shown that men with aggressive pathologic features [extracapsular extension or seminal vesicle invasion or positive surgical margins (PSM)] derive oncologic benefit from adjuvant external beam radiotherapy (RT) [4–8]. Because of the benefit associated with adjuvant therapy in men with adverse pathology, other investigators have explored the use of even earlier multimodality approaches: intra-operative radiotherapy [9,10] and neoadjuvant clinical trials (clinicaltrials.gov, NCT 00430183, 01542021, 01696877, 01088529, and 01547299). However, these studies' cohorts and inclusion criteria are quite heterogeneous and often include men with low- or intermediate-risk PCa. Instead, it may be important to select men with quite aggressive PCa phenotypes in order to detect a real benefit and determine if novel multimodal treatment approaches can alter a rapidly progressive disease course.

The oncologic benefits of multimodal therapies for selected high-risk men can be definitively evaluated only in prospective controlled trials, and here we hypothesize that men with early BCR may be ideal trial candidates. First, early BCR may be a consequence of particularly aggressive cancers or retained cancer cells in the surgical bed (a concept that is echoed by the inclusion criteria of the prior adjuvant RT trials). Second, it has been shown that initiation of salvage RT after RP is associated with improved cancer-specific survival specifically when administered early after BCR [11,12]. Third, men with elevated PSA immediately after RP predominantly experience local failures, suggesting that multimodal local treatments are appropriate in men at risk for early BCR [13]. Therefore men with early recurrence despite extirpative therapy may represent the subset of men who are most likely to benefit from a curative multimodal treatment approach at the time of prostatectomy. Here we retrospectively evaluated systematic permutations of pre-operative criteria that best identify men who experience early BCR (within one year) after RP.

Materials and methods

Cohort

The IRB-approved Johns Hopkins prostate cancer database containing 20735 men was used to identify men who experienced BCR (defined as post-operative PSA ≥0.2 ng/ml) after undergoing RP with extended pelvic lymph node dissection [14]. Men who were treated in the pre-PSA era (prior to 1992) and who received neoadjuvant therapies were excluded, leaving 18320 men. Men with incomplete pre-operative risk-stratification data (n=307) and unknown follow-up (n=6359) were excluded, leaving 11636 men. Of these, 1471 experienced BCR. This recurrence cohort formed the basis for early BCR (n=520) and late

BCR (n=951) comparison groups. Early BCR was defined as recurrence within one year of RP.

Study Design

Clinicopathologic variables, rates of post-operative treatments, and oncologic outcomes were compared between groups. Within the recurrence cohort, univariate and multivariable logistic regression analyses were performed to assess pre-operative predictors of early BCR, the strongest of which were high-risk features as defined by the National Comprehensive Cancer Network (NCCN) [15].

Therefore, in order to identify which of the high-risk men are likely to experience BCR, we subsequently analyzed men who met NCCN high-risk criteria (biopsy Gleason sum 8–10 and/or PSA >20 ng/ml, and/or clinical stage >T2) [15]. In this cohort (n=753), we performed detailed review of pre-operative prostate biopsy reports: primary versus secondary Gleason scores, volume of every Gleason pattern present, and features such as perineural invasion). Because BCR is quite common after RP among high-risk men [1,3], comparison groups for analyses among the NCCN high-risk men were 1) men who had early BCR (n=174) and 2) men who did not recur or experienced delayed BCR (n=579).

Using criteria sets comprised of 41 distinct permutations of adverse pre-operative prognostic variables, we evaluated the unadjusted odds ratios of each set of criteria to predict early BCR. We only tested criteria sets that could be easily identified from universally available pre-operative variables (PSA, clinical stage, and biopsy characteristics) but which did not require any calculation, as when using nomograms.

We selected all criteria sets associated with early BCR that had unadjusted odds ratios ≥3. The odds ratio cut-off point was arbitrarily selected after noting that the most adverse quintile of predictive criteria clustered above early BCR odds ratios of 3. These candidate criteria were subsequently analyzed by multivariable models in order to identify the set of criteria with the highest adjusted odds ratio for early BCR among NCCN high-risk men.

A sensitivity analysis was conducted in order to further control for variations in treatment year and extent of biopsy sampling. The modern Gleason grading system was adopted at our center in 2004. According to the modern schema set forth by the International Society of Urological Pathologists, Gleason patterns with poor-formation, ill-defined lumina, or cribriform features, which had prior been classified as pattern 3, are now classified as pattern 4 [16]. Extended biopsy sampling was defined as 10 or more cores taken at the diagnostic biopsy.

Statistical Analysis

Means, medians, and proportions were compared using t-, Wilcoxon-Mann-Whitney rank-sum-, and, chi-squared tests, respectively. The association of pre-operative criteria with early BCR was assessed with univariate and multivariable logistic models. Rates of time-dependent events (metastasis and cancer-specific mortality) were compared using log-rank tests, and hazard ratios were calculated with univariate and multivariable Cox models. The

two-tailed level of statistical significance was set at 0.05. Analyses were computed with Stata 11.0 (College Station, Texas, USA).

Results

Among those who experienced BCR after RP, men who recurred early had higher PSA, biopsy Gleason sum, and NCCN risk classification (Table I). Baseline and pathologic characteristics of men excluded for unknown follow-up and those with follow-up data were similar. With follow-up, men with early BCR were at increased risk of subsequent distant metastasis (33.1% vs 18.1%, log-rank $p<0.001$) and cancer-specific mortality (24.0% vs 13.1%, log-rank $p<0.001$), despite equivalent rates of RT and higher rates of androgen deprivation therapy (ADT) administered before detection of metastasis (Table I). Of men with late BCR, 390/579 (3%) had no PSA recurrence at last follow-up (median 3.0, mean 5.0 years).

Comparing early and late BCR cohorts, the early group was enriched with NCCN high-risk men (Table I and Figure 1). In a multivariable logistic adjusting for age and year of surgery, higher biopsy Gleason sum and PSA>20 ng/ml were associated with early recurrence (Table II, multivariable model 1). Because year of surgery had a strong association with early BCR, we tested whether the proportion of men with high-risk disease increased in more recent years. In 2002–2012, compared to 1992–2001, the proportion with NCCN high-risk disease was 27.4% vs 22.7% ($p=0.044$). Therefore, to appropriately control for era and pre-operative risk, we included the interaction year-of-surgery*high-risk in the final model (Table II). The men most likely to experience early BCR included those with increasing biopsy Gleason sums (≥8 in particular), followed by increasing PSA (>20 ng/ml in particular), and to a lesser extent, higher clinical stage. Thus the strongest predictors of early BCR were NCCN high-risk features.

Accordingly, we focused further study (detailed prostate biopsy characterization) on the cohort with NCCN high-risk features, specifically exploring pre-operative criteria that identify sub-populations of high-risk men who are likely to experience early BCR after RP. Among high-risk men, those who experienced early BCR presented with more aggressive disease features (higher clinical stage, biopsy Gleason sum, and multiple NCCN high-risk characteristics) (Table III). Men with early BCR were nearly twice as likely to have perineural invasion noted on biopsy (36.7% vs 22.3%, $p<0.001$) and were at markedly higher risk of distant metastasis (48.1% vs 8.6%, log-rank $p<0.001$) and cancer-specific mortality (24.1% vs 4.0%, log-rank $p<0.001$). Among men who progressed to distant metastasis, 16/124 (12.9%) did so within one year. Median follow-up was shorter in the early BCR group (4.0 vs 6.0 years, $p<0.001$).

Using alternate permutations of adverse pre-treatment prognostic variables, 41 test criteria sets were assessed for strength of association with early BCR in the high-risk cohort. Criteria sets with unadjusted odds ratios ≥3 (bolded in Table IV) were selected for further evaluation in models that controlled for factors not already incorporated into the test criteria: patient age, year of surgery, and perineural invasion. Among the eight test criteria in this final analysis, the criteria that had the strongest association with early BCR was presence of

primary Gleason pattern 5 or ≥4 cores containing pattern 4 on biopsy (odds ratio 3.17, 95% C.I. 2.11–4.76, p <0.001). These criteria included 26.7% of the NCCN high-risk cohort (Table V).

318 of 753 men (42.4%) were treated in the modern Gleason era, and 351 of 566 men with known total core information (62.0%) underwent extended sampling. Among men meeting both criteria, or the modern era/extended sampling cohort (n=275), the final criteria (primary Gleason pattern 5 or ≥4 cores containing pattern 4 on biopsy) remained significantly associated with early BCR (crude odds ratio 3.60, 95% C.I. 2.00–6.49, p<0.001; adjusted odds ratio 2.73, 95% C.I. 1.46–5.09, p=0.002).

The association of this top-ranking early BCR criteria set (primary pattern 5 or ≥4 cores with pattern 4) with freedom from metastasis and cancer-specific mortality was also studied (Figure 1). Controlling for age, year of surgery, and perineural invasion, the adjusted hazard ratios of this criteria set for subsequent metastasis was 3.04 (95% C.I 1.93–4.80, p<0.001) and 3.27 for subsequent cancer-specific mortality (95% C.I. 1.79–5.99, p<0.001).

In the NCCN high-risk cohort, lymph node positivity was four times more common in men with early BCR (31.6% vs 7.1%, p<0.001). Therefore we tested whether the early BCR prediction criteria retained significant associations with outcomes after excluding men with pN1 disease. In this setting the prediction criteria remained significantly associated with early BCR (adjusted O.R. 3.35, 95% C.I. 2.09–5.39, p<0.001). Likewise, the adjusted hazard ratios of these criteria for subsequent metastasis was 2.66 (95% C.I 1.44–4.91, p=0.002) and 3.16 for cancer-specific mortality (95% C.I. 1.44–6.95, p=0.004).

607/753 men (80.6%) had an initially undetectable PSA after RP; these men were less likely to have pathologically positive pelvic nodes (7.2% vs 35.6%, p<0.001). In an analysis excluding men who had detectable PSA immediately after RP, the early BCR prediction criteria remained significantly associated with early BCR among high-risk men (crude O.R. 2.81, 95% C.I. 1.29–6.10, p=0.009) and approached statistical significance in the adjusted model (O.R. 2.30, 95% C.I. 0.97–5.46, p=0.058). Of 16 men who experienced metastasis in the first post-operative year, 7/16 had pathologically positive lymph nodes at radical prostatectomy and only 3/16 achieved undetectable PSA after surgery.

Discussion

Here we identify pre-operative criteria that identify the subgroup within NCCN high-risk who are mostly likely to experience early BCR (within 1 year) after RP: primary Gleason pattern 5 or ≥4 cores containing pattern 4 on biopsy. General risk stratification tools and BCR after local therapy has been studied at length, but prior to this study, the unique oncologic implications of early BCR have not been fully evaluated. In the present study we demonstrate that early BCR is associated with significantly lower freedom from metastasis and cancer-specific survival.

Identifying the group mostly likely to experience early BCR may guide the selection of optimal candidates for curative multimodal therapy at prostatectomy. Prior prospective trials have shown that early RT after RP improves freedom from biochemical progression and/or

metastasis in men with adverse pathologic features [4,6,8]. In these trials, rates of freedom from BCR in the observation arms ranged from 35–54%, suggesting that improved adjuvant selection criteria may reduce over-treatment. Further, in the event of rapid BCR after RP, timely RT provides clear oncologic benefits [11]. Stephenson et al showed that men who had the best progression-free survival after salvage RT were those with pre-RT PSA ≤0.5 ng/ml, suggesting the best timing for RT is “the earliest sign of recurrence” [12]. Interestingly, recent evidence suggests this benefit may actually be limited to a subset of patients with multiple adverse risk features [17,18].

We defined early BCR as the primary outcome, rather than metastasis or cancer-related death, because identification of men prone to early BCR after RP may select men susceptible to local failure with surgery who may experience oncologic cure with multimodal local therapy. In this study we included men with pN1 disease. It is unknown how men with subclinical nodal metastasis at RP will fare with IORT or other adjunct treatments; this is best assessed with a prospective trial. Importantly, even after excluding men who had positive nodes at surgery, the early BCR predictive criteria derived from the inclusive cohort of high-risk men remained strongly associated with early BCR, metastasis, and cancer-specific mortality.

Some believe that early BCR is a harbinger for metastatic disease that was already present at RP [19], though in our high-risk cohort, only 16/124 (12.9%) of men who progressed to clinical metastasis did so within one year of RP. When we sub-analyzed men who achieved undetectable PSA after RP, the early BCR prediction criteria, again, remained strongly associated with early BCR, subsequent metastasis, and cancer-related mortality.

Supporting the notion that early BCR is not synonymous with unrecognized metastatic disease, Swanson et al, reported in SWOG 8794 that in men with immediately detectable post-prostatectomy PSA (up to 1.0 ng/ml), recurrences were predominantly local [13]. Thus, the key goal of multimodality treatment at the time of RP in selected high-risk men is to optimize local control. As suggested by Coen et al, excellent initial local control at the time of curative treatment can improve 15-year freedom from metastasis by up to 35%, whereas local persistence of disease has the potential to give “rise to a late wave of metastases” [20].

Recognizing the potential significance of predicting early BCR using pre-operative variables, Borque et al constructed a nomogram incorporating four single nucleotide polymorphisms (SNPs) in order to yield a continuous probability estimate of early BCR [19]. While demonstrative of the future potential of genetic markers to guide prognosis, a limitation of this study is that it analyzed predominantly lower-risk men: 76% had Gleason sum ≤6 and 50% had clinical stage T1c.

Here we present pre-operative predictors that are easily recalled, readily applied in any clinical encounter, and universally available from standard risk stratification and biopsy information. These criteria were derived from a high-risk population because high-risk features were identified as most strongly associated with early versus delayed BCR in the broader cohort inclusive of all risk-categories. The final pre-operative criteria (primary

Gleason pattern 5 on biopsy or ≥4 cores containing pattern 4) dichotomize men with NCCN high-risk features into a select group that has a 3.17 adjusted odds ratio for early BCR.

There are several limitations to this study. The study was retrospective and single-institution, thus introducing potential selection bias and limited generalizability: of20735 patients, 6359 were excluded for unknown follow-up. Though men lost to follow-up had similar characteristics to the analyzed cohort, external validation is required to confirm these findings. Follow-up was shorter in men with early BCR; reasons for this were not documented and may be related to transfer of care from the surgeon primarily to a different oncologic discipline. A known contributing factor for the follow-up discrepancy, however, is the increased mortality in the early

BCR cohort. Despite shorter follow-up, metastasis and cancer-related death were detected more frequently in the early BCR group, which is significant in that this study may underestimate adverse oncologic sequelae after early BCR. This study did not evaluate the role of prostate imaging, which may have a role in staging and prognosis [21]. This study focused on high-risk men because NCCN high-risk features conferred the greatest overall risk of early BCR among all risk categories. Still, the majority of early (and delayed) BCR men were intermediate-risk. Though this is partially related to surgical selection, a subset of intermediate-risk men prone to early BCR may thus also be appropriate for multimodal treatments at RP; efforts to identify this cohort are ongoing. Finally this study analyzed predictors of early BCR. It is unknown if men with delayed BCR would be ideal candidates for curative multimodal trials. Though we extrapolate prior findings to suggest that men who are likely to experience early BCR are the best potential candidates for adjunctive treatment at surgery, this hypothesis is unproven and must be prospectively tested.

Conclusions

Men with high-risk features experience BCR frequently after RP. Prospective data demonstrate that adverse pathologic features predict response to adjuvant RT. Adjunct treatments at RP (such as IORT) may represent the best chance for local cure for men predicted to have early BCR based on pre-operative variables. Here we identify the pre-operative criteria that best identify men within the NCCN high-risk cohort who will experience early BCR within one year of RP: those with primary Gleason pattern 5 or ≥4 cores containing pattern 4 on biopsy.

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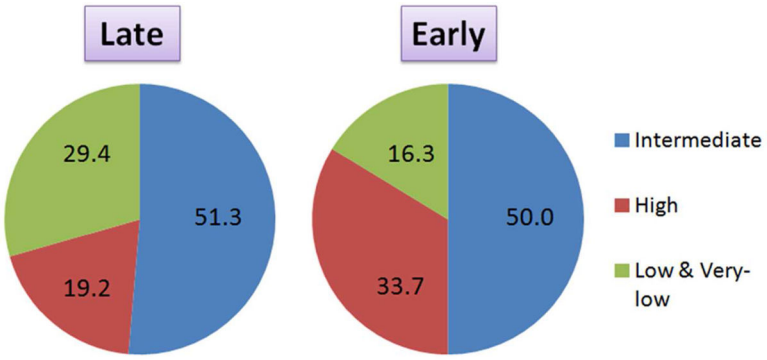

Figure 1.

NCCN risk-category distribution of men who experienced late & early BCR, among the entire BCR cohort, n=1471

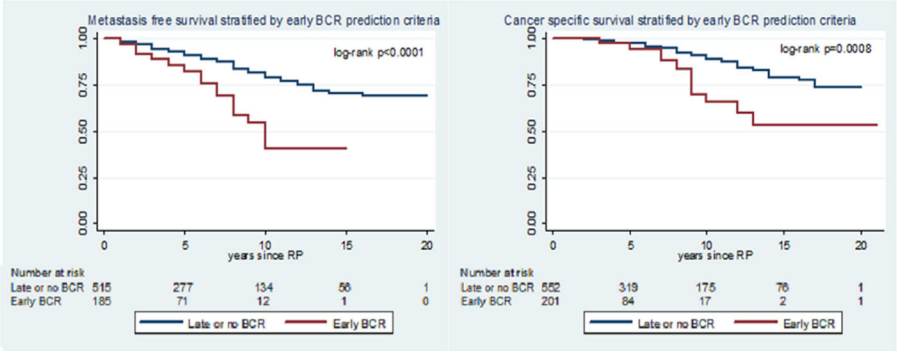

Figure 2.

Adverse prognostic significance of early BCR prediction criteria

Table I

Men who recur, late versus early, 1992–2012, Hopkins radical prostatectomy cohort

	Late BCR (>1 year)	Early BCR (≤1 year)	p
N	951	520	
Median age (IQR)	59.0 (55.0, 64.0)	58.0 (54.0, 63.0)	**0.0223***
Race			**0.002**
Caucasian	848 (89.2%)	431 (82.9%)	
African American	80 (8.4%)	64 (12.3%)	
Other	23 (2.4%)	20 (3.8%)	
Pre-op PSA			**0.028**
0–4	88 (9.3%)	47 (9.0%)	
4.1–10	553 (58.1%)	268 (51.5%)	
10.1–20	226 (23.8%)	138 (26.5%)	
>20	84 (8.8%)	67 (12.9%)	
Median PSA density (IQR)	0.17 (0.12, 0.26)	0.20 (0.13, 0.32)	**<0.001***
Clinical Stage			0.280
T1	478 (50.3%)	251 (48.3%)	
T2a–T2b	418 (44.0%)	228 (43.8%)	
T2c–T3a	55 (5.8%)	41 (7.9%)	
Biopsy Gleason sum			**<0.001**
6	483 (50.8%)	160 (30.8%)	
7 (3+4)	243 (25.6%)	134 (25.8%)	
7 (4+3)	124 (13.0%)	115 (22.1%)	
8	75 (7.9%)	74 (14.2%)	
9–10	26 (2.7%)	37 (7.1%)	
NCCN risk category			**<0.001**
Low or very low	280 (29.4%)	85 (16.3%)	
Intermediate	488 (51.3%)	260 (50.0%)	
High	183 (19.2%)	175 (33.7%)	
ECP	655/948 (69.1%)	430/519 (82.9%)	**<0.001**
pT3b	160 (16.8%)	181 (34.5%)	**<0.001**
pN1	77 (8.1%)	125 (24.0%)	**<0.001**
PSM	277/950 (29.2%)	233/519 (44.9%)	**<0.001**
Median follow-up (years) (IQR)	9.0 (6.0, 13.0)	4.0 (2.0, 8.0)	**<0.001***
Radiation after RP (excluding treatment at or after metastasis)	417/913 (45.7%)	211/474 (44.5%)	0.681

	Late BCR (>1 year)	Early BCR (≤1 year)	p
Androgen deprivation after RP (excluding treatment at or after metastasis)	214/801 (26.7%)	210/405 (51.9%)	**<0.001**
Subsequent metastasis	162/896 (18.1%)	157/474 (33.1%)	**<0.001**^
Median time to metastasis (years) (IQR)	7.0 (5.0, 11.0)	3.0 (2.0, 6.0)	**<0.001***
Subsequent cancer-related mortality	24/183 (13.1%)	42/175 (24.0%)	**<0.001**^
Median time to cancer-related mortality (years) (IQR)	10.0 (8.0, 13.0)	7.0 (4.0, 10.0)	**<0.001***

*Wilcoxon-Mann-Whitney rank-sum p-value

^log-rank p-value

Table II

Logistic regression models to assess predictors of early biochemical recurrence

	UNIVARIATE		MULTIVARIABLE model 1		MULTIVARIABLE model 2	
Variable	**O.R.**	**p**	**O.R.**	**p**	**O.R.**	**p**
Biopsy Gleason sum						
6	Referent		Referent		Referent	
7 (3+4)	1.66	**<0.001**	1.42	**0.018**	1.35	**0.045**
7 (4+3)	2.80	**<0.001**	2.18	**<0.001**	1.91	**<0.001**
8	2.98	**<0.001**	2.35	**<0.001**	2.64	**<0.001**
9–10	4.30	**<0.001**	3.05	**<0.001**	3.29	**0.001**
PSA						
0–4	Referent		Referent		Referent	
4.1–10	0.91	0.619	1.02	0.936	1.09	0.675
10.1–20	1.14	0.525	1.43	0.116	1.70	**0.022**
>20	1.49	0.100	1.91	**0.013**	2.77	**0.001**
Clinical stage						
T1	Referent		Referent		Referent	
T2a–T2b	1.04	0.737	1.04	0.764	1.13	0.352
T2c–T3	1.42	0.112	1.44	0.123	1.79	**0.019**
Age ≥60	0.83	0.098	0.83	0.112	0.84	0.151
Year of surgery ≥2002	2.93	**<0.001**	2.75	**<0.001**		
Year of surgery*NCCN high risk interaction					0: 1.15 1: 1.13	**<0.001**

Table III

Men who recur, late versus early, 1992 – 2012, Hopkins high-risk prostatectomy cohort

	Late or no BCR	Early BCR (≤1 year)	p
N	579	174	
Median Age (years) (IQR)	60.0 (54.0, 64.0)	58.0 (53.0, 62.0)	**0.007***
African American race	65 (11.2%)	19 (10.9%)	0.910
Pre-op PSA			0.128
0–4	64 (11.1%)	12 (6.9%)	
4.1–10	218 (37.7%)	65 (37.4%)	
10.1–20	67 (11.6%)	30 (17.2%)	
>20	230 (39.7%)	67 (38.5%)	
Median PSA density (ng/ml/cc) (IQR)	0.23 (0.12, 0.52)	0.28 (0.17, 0.52)	**0.014***
Clinical Stage			**0.003**
T1	324 (56.0%)	72 (41.4%)	
T2a–T2b	216 (37.3%)	87 (50.0%)	
T2c–T3a	39 (6.7%)	15 (8.6%)	
Biopsy Gleason sum			**<0.001**
6	148 (25.6%)	19 (10.9%)	
7	93 (16.1%)	45 (25.9%)	
8	258 (44.6%)	70 (40.2%)	
9	79 (13.6%)	36 (20.7%)	
10	1 (0.2%)	4 (2.3%)	
Perineural invasion	129 (22.3%)	69 (39.7%)	**<0.001**
NCCN high risk features			**0.006**
1	552 (95.3%)	156 (89.7%)	
2 or 3	27 (4.7%)	18 (10.3%)	
Extracapsular penetration	243 (42.0%)	134 (77.0%)	**<0.001**
Seminal vesicle invasion	74 (12.8%)	76 (43.7%)	**<0.001**
Lymph node invasion	41 (7.1%)	55 (31.6%)	**<0.001**
Positive surgical margin	125 (21.7%)	87 (50.0%)	**<0.001**
Median/mean follow- up (years) (IQR)	7.1, 6.0 (2.0, 11.0)	4.5, 4.0 (2.0, 6.0)	**<0.001**^
Radiation after RP (excluding treatment at or after metastasis)	93/559 (16.6%)	69/153 (45.1%)	**<0.001**
Androgen deprivation after RP (excluding treatment at or after metastasis)	54/524 (10.3%)	82/121 (67.8%)	**<0.001**

	Late or no BCR	Early BCR (≤1 year)	p
Subsequent metastasis	48/557 (8.6%)	76/158 (48.1%)	**<0.001**^
Median time to metastasis (years) (IQR)	8.0 (4.0, 10.0)	3.0 (2.0, 6.0)	**<0.001***
Subsequent cancer-related mortality	23 (4.0%)	42 (24.1%)	**<0.001**^
Median time to cancer-related mortality (years) (IQR)	8.0 (3.0, 10.0)	4.0 (2.0, 7.0)	**0.0151***
Subsequent all-cause mortality	61 (10.5%)	54 (31.0%)	**<0.001**^
Median time to all- cause mortality (years) (IQR)	6.0 (0.0, 9.0)	7.5 (5.0, 11.0)	0.1182

^log-rank p-value

Table IV

Predictive criteria for early BCR after radical prostatectomy within high-risk cohort

	Criteria tested for association with early BCR	O.R.	p	%
1	Any pattern 5 or pattern 4 + PSA >20 or pattern 4 + ≥cT3a	2.08	<0.001	43.6
2	Any pattern 5 or Gleason 8 + PSA >20 or Gleason 8 + ≥cT3a	1.52	0.028	25.2
3	Any pattern 5 or PPC with pattern 4 ≥50	2.45	<0.001	30.9
4	Any pattern 5 or PPC with pattern 4 ≥50 or multiple high-risk features	2.43	<0.001	33.5
5	Multiple high-risk features	2.36	0.007	6.0
6	Any pattern 5	1.41	0.081	22.7
7	Primary pattern 5	2.03	0.019	6.9
8	Any pattern 5 or multiple high-risk features	2.25	0.025	26.2
9	Any pattern 5 or ≥4 cores with pattern 4	2.52	<0.001	38.0
10	Any pattern 5 or ≥4 cores with pattern 4 or multiple high-risk feat	2.41	<0.001	40.4
11	Primary pattern 5 or multiple high-risk features	2.27	0.001	12.0
12	**Primary pattern 5 or PPC with pattern 4 ≥50**	**3.41**	**<0.001**	**17.5**
13	**Primary pattern 5 or PPC with pattern 4 ≥50 or mult high-risk feat**	**3.23**	**<0.001**	**21.4**
14	**Primary pattern 5 or ≥4 cores with pattern 4**	**3.12**	**<0.001**	**26.7**
15	Primary pattern 5 or ≥4 cores with pattern 4 or multiple high-risk feat	2.94	<0.001	30.2
16	Any pattern 5 or max pattern 4 or 5 per core >50%	2.21	<0.001	48.9
17	Any pattern 5 or max pattern 4 or 5 per core >50% or mult hi risk feat	2.17	<0.001	51.0
18	**Primary pattern 5 or PPC with pat 4/5 ≥50 or mult high-risk feat**	**3.00**	**<0.001**	**22.2**
19	**Primary pattern 5 or ≥4 cores with pattern 4/5**	**3.02**	**<0.001**	**27.1**
20	Primary pattern 5 or ≥4 cores with pattern 4/5 or mult high-risk feat	2.86	<0.001	30.5
21	Primary pattern 5 or PPC with pat 4/5 ≥50 or PNI	2.64	<0.001	36.7
22	Primary pattern 5 or ≥4 cores with pattern 4/5 or PNI	2.65	<0.001	40.9
23	Primary pattern 5 or PNI	2.50	<0.001	31.1
24	Primary pattern 5 or ≥1 core with sum 8–10 or multiple high-risk features	1.24	0.226	60.4
25	Primary pattern 5 or ≥2 cores with sum 8–10 or multiple high-risk features	1.68	0.003	35.5
26	Primary pattern 5 or ≥3 cores with sum 8–10 or multiple high-risk features	2.26	<0.001	23.4
27	Primary pattern 5 or ≥4 cores with sum 8–10 or multiple high-risk features	1.98	0.001	18.3
28	Primary pattern 5 or ≥5 cores with sum 8–10 or multiple high-risk features	2.14	<0.001	15.1
29	Primary pattern 5 or ≥6 cores with sum 8–10 or multiple high-risk features	2.25	<0.001	13.6
30	Primary pattern 5 or ≥7 cores with sum 8–10 or multiple high-risk features	2.34	<0.001	12.5
31	**Primary pattern 5 or PPC with sum 8–10 ≥50 or multiple high- risk features**	**4.08**	**<0.001**	**13.9**
32	Primary pattern 5 or mult hi risk features or PNI	2.41	<0.001	34.1
33	Primary pattern 5 or mult hi risk features or PNI+ ≥1 cores with Gleason sum 8–10	2.00	<0.001	25.4
34	Primary pattern 5 or mult hi risk features or PNI+ ≥2 cores with Gleason sum 8–10	1.89	0.002	20.2
35	Primary pattern 5 or mult hi risk features or PNI+ ≥3 cores with Gleason sum 8–10	2.38	<0.001	16.6
36	**PPC with pattern 4 ≥50**	**3.18**	**<0.001**	**19.8**
37	≥4 cores with pattern 4	3.07	<0.001	22.3

	Criteria tested for association with early BCR	O.R.	p	%
38	≥4 cores with pattern 4/5	2.90	<0.001	23.4
39	**PPC with pattern 4 ≥50 or multiple high-risk features**	**3.19**	**<0.001**	**16.3**
40	PPC with pat 4/5 ≥50 or multiple high-risk features	2.97	<0.001	17.7
41	PPC with sum 8–10 ≥50 or multiple high-risk features	2.49	<0.001	10.6

Table V

Adjusted odds ratios of criteria with crude odds ratio ≥3.0 - adjusted for age, year of surgery, and perineural invasion

	Criteria tested for association with early BCR	O.R.	p	%
12	Primary pattern 5 or PPC with pattern 4 ≥50	3.15	<0.001	17.5
13	Primary pattern 5 or PPC with pattern 4 ≥50 or mult high-risk feat	2.91	<0.001	21.4
14	**Primary pattern 5 or ≥4 cores with pattern 4**	**3.17**	**<0.001**	**26.7**
18	Primary pattern 5 or PPC with pat 4/5 ≥50 or mult high-risk feat	1.92	<0.001	22.2
19	Primary pattern 5 or ≥4 cores with pattern 4/5	3.07	<0.001	27.1
31	Primary pattern 5 or PPC with sum 8–10 ≥50 or multiple high-risk features	2.37	<0.001	13.9
36	PPC with pattern 4 ≥50	2.56	<0.001	19.8
37	≥4 cores with pattern 4	3.08	<0.001	22.3
39	PPC with pattern 4 ≥50 or multiple high-risk features	2.71	<0.001	16.3