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Do all men with pathological Gleason score 8–10 prostate cancer have poor outcomes? Results from the SEARCH database

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Objective

To determine whether there are subsets of men with pathological high grade prostate cancer (Gleason score 8–10) with particularly high or low 2-year biochemical recurrence (BCR) risk after radical prostatectomy (RP) when stratified into groups based on combinations of pathological features, such as surgical margin status, extracapsular extension (ECE) and seminal vesicle invasion (SVI).

Materials and Methods

We identified 459 men treated with RP with pathological Gleason score 8–10 prostate cancer in the SEARCH database. The men were stratified into five groups based on pathological characteristics: group 1, men with negative surgical margins (NSMs) and no ECE; group 2, men with positive surgical margin (PSMs) and no ECE; group 3, men with NSMs and ECE; group 4, men with PSMs and ECE; and group 5, men with SVI. Cox proportional hazards models and the log-rank test were used to compare BCR among the groups.

Results

At 2 years after RP, pathological group was significantly correlated with BCR (log-rank, $P < 0.001$) with patients in group 5 (+SVI) having the highest BCR risk (66%) and those in group 1 (NSMs and no ECE) having the lowest risk (14%). When we compared groups 2, 3, and 4, with each other, there was no significant difference in BCR among the groups (~50% 2-year BCR risk; log-rank $P = 0.28$). Results were similar when adjusting for prostate-specific antigen, age, pathological Gleason sum and clinical stage, or after excluding men who received adjuvant therapy.

Conclusions

In patients with high grade (Gleason score 8–10) prostate cancer after RP, the presence of either PSMs, ECE or SVI was associated with an increased risk of early BCR, with a 2-year BCR risk of ≥50%. Conversely, men with organ-confined margin-negative disease had a very low risk of early BCR despite Gleason score 8–10 disease.

Keywords

prostatic neoplasm, biochemical recurrence, Gleason score 8–10, seminal vesicle invasion, extracapsular extension, positive surgical margin

Introduction

Prostate cancer is projected to account for the largest number of new cancer diagnoses and the second most non-cutaneous cancer-related deaths among men in 2015 [1]. While radical prostatectomy (RP) remains the standard definitive treatment for prostate cancer, not all men achieve complete tumour eradication, with up to one-third of men developing recurrence after surgery [2]. For men who are at increased risk of biochemical recurrence (BCR) after surgery, adjuvant

radiation has been shown to reduce this risk and perhaps even improve overall survival, albeit with the toxicity of radiation [3–5]. As such, the identification of men who are most likely to experience BCR vs those with more indolent disease is crucial.

Gleason score 8–10 on biopsy is considered high-risk disease because of the associated increased risk of BCR and progression of disease, despite treatment [6]. Similarly, Gleason score 8–10 disease at the time of RP also portends an increased risk of BCR [7]. Not all men with Gleason score 8–10 disease, however, are destined to experience BCR. When assessing risk of recurrence after RP, many studies consider pathological features, either individually, as pathological stage, or in various 'favourable' or 'unfavourable' groupings, as risk factors for BCR or other endpoints, such as prostate cancer-specific survival [5,8–17], but while previous studies have examined the relationship between pathological features and BCR in pathological high grade disease [18,19], these studies are >10 years old and, to our knowledge, have not been updated to examine a more racially heterogeneous cohort of men. We therefore used the SEARCH database of men treated with RP [20] to identify men with pathological high grade disease (Gleason score 8–10) and to create groups based on various combinations of pathological features and compare these groups with regard to BCR risk. We hypothesized that men with seminal vesicle invasion (SVI) would have the highest rates of BCR, men with no adverse features would have the lowest rates of BCR and men with positive surgical margins (PSMs) and/or extracapsular extension (ECE) would have intermediate outcomes. In a secondary analysis, we examined how pathological groupings affected time to androgen deprivation therapy (ADT), metastases and prostate cancer death.

Materials and Methods

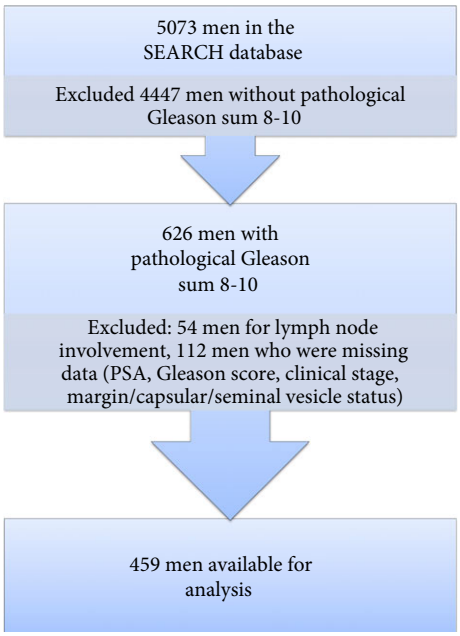
Study Population

After obtaining institutional review board approval, data from men who underwent RP at the Veterans Affairs Medical Centers in West Los Angeles, Palo Alto, and San Diego, California, in Augusta, Georgia and in Durham and Asheville, North Carolina were collected and combined into the SEARCH database [21]. Men treated with preoperative ADT or radiation therapy are excluded from the SEARCH database. As our goal was to examine outcomes among men with high grade disease, from the 5 073 men within the SEARCH database, we selected the subset of men with a pathological Gleason sum of 8–10 on final analysis of the RP specimen for the present analysis. Of the 626 men (12.3%) with pathological Gleason score 8–10 disease, we excluded men with lymph node involvement (n = 54), given the well-known very high risk of recurrence in these men, as well as men with missing data on PSA (n = 16), biopsy Gleason score (n = 13), clinical stage (n = 65), surgical margin status and/or ECE status (n = 17) and SVI (n = 2), resulting in a study population of 459 men (Fig. 1). Men were followed at the attending surgeon's discretion to determine PSA recurrence. BCR was defined as a single PSA value >0.2 ng/mL, two values of 0.2 ng/mL, or secondary treatment for an elevated postoperative PSA level. As a secondary outcome, we also examined prostate cancer death, defined as deaths in men who had metastases who showed progression after hormonal therapy without another obvious cause of death. A total of 15 men with no follow-up data were included in the analysis for evaluating differences in preoperative and pathological characteristics but not BCR.

Statistical Analysis

The men were separated into five groups based on pathological findings: group 1, with negative surgical margins (NSMs) and no ECE, n = 142 (31%); group 2, PSMs but no ECE, n = 89 (19%); group 3, NSMs but ECE, n = 46 (10%); group 4, PSMs and ECE, n = 76 (17%); and group 5, with SVI, n = 106 (23%). Clinical characteristics were compared among the groups using ANOVA for continuous normally distributed variables, Kruskal–Wallis tests for continuous non-normally distributed variables, and chi-squared tests for categorical variables. Fisher's exact test was used for categorical data with cell counts <5. PSA, race, age and year of surgery were examined as continuous variables, while biopsy Gleason score (2–6 vs 7 vs 8–10), pathological Gleason score (8 vs 9–10), and clinical stage (T1 vs T2/T3) were

Fig. 1 Cohort selection flowchart.



examined as categorical variables. The distributions of the relevant clinical and pathological variables were similar among the SEARCH sites, so data from all centres were combined for analyses. Cox proportional hazards models and the log-rank test were used to compare BCR, ADT treatment, development of metastasis, and prostate cancer death among the groups. Survival curves for time to BCR and prostate cancer death were estimated using the Kaplan–Meier method. In a secondary analysis, we repeated the Cox proportional hazards analysis adjusting for PSA, age, pathological Gleason sum and clinical stage. BCR risk was estimated at 2 years, as earlier recurrences are associated with greater risk of metastases and prostate cancer death [22,23]. We also repeated all analyses excluding patients who received adjuvant therapy, defined as treatment after surgery for an undetectable PSA level. All statistical analyses were performed using STATA 13.0 (Stata, Corp., College Station, TX, USA).

Results

Patient Characteristics

The clinical and pathological characteristics of the study subjects, separated into five groups based on pathological findings, including ECE status, surgical margin status and SVI, are shown in Table 1. Overall, 30% of the study cohort was black. There were no statistically significant differences in age, race, biopsy Gleason sum, or clinical stage among the five groups. Men who had worse pathological findings (i.e. were in a higher group) had higher PSA values and a greater proportion of them had pathological Gleason score 9–10 disease (all $P \leq 0.01$). Also, men with worse pathological features were more likely to receive adjuvant therapy, which ranged from <1% in group 1 to 16% in group 5 ($P < 0.001$).

Primary Outcome: Risk of Biochemical Recurrence

The mean (median; interquartile range) follow-up time after surgery among men who did not experience BCR was 50 (29; 9–83) months. During the follow-up period, 218 men (48%) experienced BCR. The risk of BCR was compared among the five groups (Fig. 2, Table 2). At the 2-year mark, men with SVI (group 5) had the highest risk of BCR (66%), while men with no ECE and NSMs (group 1) had the lowest risk of BCR (14%). Furthermore, the median time to BCR was 4.1 months for men with SVI and was not reached (>237 months) for men with no ECE and NSMs. Indeed, group 1 had significantly better outcomes than all other groups (all $P \leq 0.003$), while group 5 had significantly worse outcomes than all other groups (all $P \leq 0.005$). By contrast, among groups 2, 3 and 4, there were no differences in BCR risk among the three groups (all $P \geq 0.113$). When analyses were adjusted for PSA, age, pathological Gleason sum and

Table 1 Clinical and pathological features of men undergoing radical prostatectomy.

	Group 1	Group 2	Group 3	Group 4	Group 5	*P*
No. Patients	142	89	46	76	106	
Age, mean (SD)	62.2 (6.3)	62.8 (6.7)	65.2 (5.4)	62.5 (5.7)	62.3 (6.8)	0.079*
Race, *n* (%)						
White	96 (68)	45 (50)	35 (76)	48 (63)	67 (63)	0.153†
Black	37 (26)	37 (42)	8 (17)	23 (30)	34 (32)	
Other	8 (6)	7 (8)	3 (7)	5 (7)	5 (5)	
Year						
Median	2008	2006	2008	2005	2008	0.010‡
Q1–Q3	2002–2011	2002–2010	2001–2012	2000–2009	2002–2011	
PSA, ng/mL						
Median	6.0	8.3	7.3	8.7	9.5	<0.001‡
Q1–Q3	4.6–8.9	5.7–12.4	5.1–10.0	5.4–15.3	6.1–16.3	
Biopsy Gleason sum, *n* (%)						
2–6	29 (20)	22 (25)	8 (17)	13 (17)	11 (10)	0.275†
7	56 (40)	37 (41)	15 (33)	31 (41)	46 (44)	
8–10	57 (40)	30 (34)	23 (50)	32 (42)	49 (46)	
Pathological Gleason sum, *n* (%)						
8	95 (67)	51 (57)	20 (43)	42 (55)	39 (37)	<0.001†
9–10	47 (33)	38 (43)	26 (57)	34 (45)	67 (63)	
Clinical stage, *n* (%)						
T1	71 (50)	59 (66)	24 (52)	37 (49)	52 (49)	0.089†
T2/T3	71 (50)	30 (34)	22 (48)	39 (51)	54 (51)	
Adjuvant therapy, *n* (%)	1 (0.7)	8 (9.0)	3 (6.5)	13 (17)	17 (16)	<0.001§
No. of metastasis, *n* (%)	5 (3.5)	4 (4.5)	2 (4.3)	12 (16)	23 (22)	<0.001§
No. receiving ADT, *n* (%)	13 (9.1)	27 (30)	13 (28)	34 (45)	54 (51)	<0.001†
No. of recurrences, *n* (%)	37 (26)	50 (56)	19 (43)	42 (55)	70 (67)	<0.001†
No. of deaths, *n* (%)	12 (8)	17 (19)	11 (24)	23 (30)	31 (29)	<0.001†
No. of deaths from prostate cancer, *n* (%)	2 (1)	2 (2)	1 (2)	7 (9)	17 (16)	<0.001§

*ADT, androgen deprivation therapy. Group 1: no extracapsular extension (ECE), negative surgical margins (NSMs); group 2: no ECE, positive surgical margins (PSMs); group 3: ECE, NSMs; group 4: ECE, PSMs; group 5: seminal vesicle invasion. P values calculated using *ANOVA test, †Chi-square test, ‡Kruskal–Wallis test and §Fisher's exact test.*

clinical stage, the conclusions were unchanged, in that group 5 had the highest BCR risk, groups 2–4 were at intermediate risk with no differences among the groups, and group 1 had the lowest risk of BCR as well as the best outcomes. Additionally, results were largely unchanged when analyses were repeated excluding men who received adjuvant therapy (data not shown).

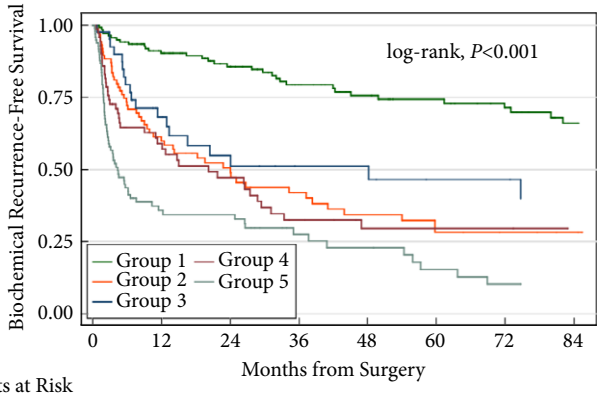
Secondary Outcomes: Androgen Deprivation Therapy, Metastasis and Prostate Cancer Death

As a secondary outcome, we examined the risk of ADT, metastases and prostate cancer death. Overall, 141 men received ADT, 46 developed metastases and 29 men died from prostate cancer over a 60-month median follow-up.

Results for receiving ADT (Table 3) were similar to the results for developing BCR. Specifically, men with SVI were at the highest risk of receiving ADT (all two-way comparisons $P \leq 0.026$), there was no significant difference in risk between groups 2–4, and men with organ-confined margin-negative disease had the lowest risk of receiving ADT (all two-way comparisons $P < 0.001$).

Because of the small number of events and similar risks of BCR and ADT, groups 2, 3 and 4 were combined for analysis. Overall, pathological group was significantly linked with metastases (Table 4) with 9-year risk of metastases of 41, 61 and 90% for group 1, groups 2–4 and group 5, respectively (Fig. 3; log-rank $P < 0.001$). Similarly, pathological group was significantly linked with prostate cancer death. The 9-year risk of prostate cancer death was 0, 6 and 22% for group 1, groups 2–4 and group 5 (Fig. 4; log-rank $P < 0.001$).

Fig. 2 Kaplan–Meier curves for risk of biochemical recurrence of the five groups defined by pathological features. Group 1: no extracapsular extension (ECE), negative surgical margins (NSMs); group 2: no ECE, positive surgical margins (PSMs); group 3: ECE, NSMs; group 4: ECE, PSMs; group 5: seminal vesicle invasion.



Patients at Risk

Group 1	140	111	88	69	59	53	46	32
Group 2	89	42	29	22	18	14	12	10
Group 3	44	22	15	11	11	8	8	6
Group 4	73	31	23	14	10	10	10	8
Group 5	98	24	22	13	10	6	4	3

Discussion

Men with pathological Gleason sum 8–10 prostate cancer at the time of RP are at high risk of BCR and so are good candidates for adjuvant therapy; however, pathological Gleason sum 8–10 as a general category remains heterogeneous and other pathological features, such as surgical margins, ECE and SVI, may also modify the risk of BCR. While many studies have examined pathological features and the risk of BCR [9–17], to our knowledge, only two studies [18,19] have directly compared *combinations* of pathological features as risk factors for BCR and survival outcomes among men with pathological Gleason score 8–10 disease at the time of RP. That said, these studies are >10 years old, and did not examine a heterogeneous cohort of men, whereas in the present study cohort, selected from

Table 2 Hazard ratios and 95% CIs for biochemical recurrence for men, stratified by pathology group.

	Reference group			
	1	2	3	4
Group 2				
HR	3.24 (2.12, 4.97)	–		
P	<0.001	–		
Group 3				
HR	2.34 (1.34, 4.07)	0.72 (0.42, 1.22)	–	
P	0.003	0.224	–	
Group 4				
HR	3.63 (2.32, 5.67)	1.12 (0.74, 1.69)	1.55 (0.90, 2.68)	–
P	<0.001	0.593	0.113	–
Group 5				
HR	6.32 (4.22, 9.47)	1.95 (1.35, 2.81)	2.7 (1.63, 4.50)	1.74 (1.18, 2.56)
P	<0.001	<0.001	<0.001	0.005

HR, hazard ratio. Group 1: no extracapsular extension (ECE), negative surgical margins (NSMs); group 2: no ECE, positive surgical margins (PSMs); group 3: ECE, NSMs; group 4: ECE, PSMs; group 5: seminal vesicle invasion.

Table 3 Hazard ratios and 95% CIs for androgen deprivation therapy for men, stratified by pathology group.

	Reference group			
	1	2	3	4
Group 2				
HR	3.56 (1.86, 6.94)	–		
P	<0.001	–		
Group 3				
HR	3.98 (1.84, 8.61)	1.12 (0.54, 2.18)	–	
P	<0.001	0.742	–	
Group 4				
HR	5.93 (3.13, 11.2)	1.66 (1.00, 2.77)	1.48 (0.78, 2.82)	–
P	<0.001	0.051	0.224	–
Group 5				
HR	9.70 (5.28, 17.8)	2.72 (1.70, 4.36)	2.43 (1.33, 4.64)	1.63 (1.06, 2.52)
P	<0.001	<0.001	0.004	0.026

HR, hazard ratio. Group 1: no extracapsular extension (ECE), negative surgical margins (NSMs); group 2: no ECE, positive surgical margins (PSMs); group 3: ECE, NSMs; group 4: ECE, PSMs; group 5: seminal vesicle invasion.

Table 4 Hazard ratios and 95% CIs for development of metastasis for men by pathology group.

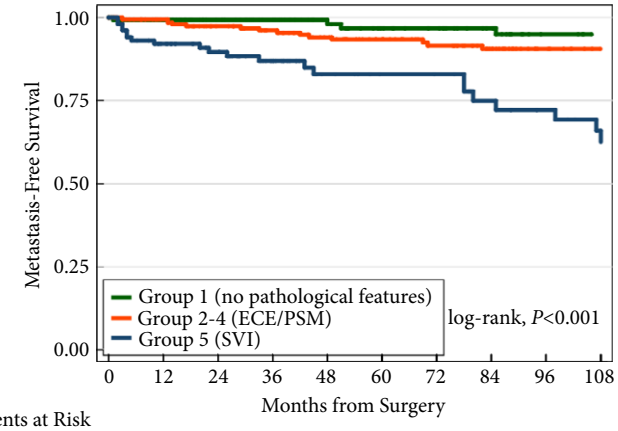
	Reference group			
	1	2	3	4
Group 2				
HR	1.25 (0.33, 4.65)	–		
P	0.741	–		
Group 3				
HR	1.40 (0.27, 7.24)	1.12 (0.20, 6.15)	–	
P	0.687	0.895	–	
Group 4				
HR	3.60 (1.26, 10.2)	2.88 (0.92, 8.98)	2.57 (0.57, 11.5)	–
P	0.016	0.068	0.217	–
Group 5				
HR	7.78 (2.95, 20.5)	6.23 (2.15, 18.0)	5.55 (1.30, 23.6)	2.16 (1.06, 4.37)
P	<0.001	0.001	0.020	0.032

HR, hazard ratio. Group 1: no extracapsular extension (ECE), negative surgical margins (NSMs); group 2: no ECE, positive surgical margins (PSMs); group 3: ECE, NSMs; group 4: ECE, PSMs; group 5: seminal vesicle invasion.

the SEARCH database, 30% of the men were black. Given the heterogeneous outcomes of men with Gleason score 8–10 disease, we sought to determine whether certain subsets of men with pathological Gleason score 8–10 disease were at particularly high or low risk of BCR. We observed that among men with pathological Gleason score 8–10 prostate cancer, specific pathological features were associated with varying risk of BCR: men with SVI had the greatest risk of BCR; men with either ECE, PSMs, or both of these features had intermediate risk; and men without any of these adverse pathological features had a significantly lower risk of BCR. Despite pathological Gleason score 8–10 disease, men with organ-confined margin-negative disease had an overall relatively favourable outcome, with only one man receiving adjuvant therapy (i.e. a 14% recurrence risk at 2 years and <25% recurrence risk at 4 years and 0% prostate cancer mortality at 9 years). If validated in other studies, these findings suggest men with pathological Gleason score 8–10 and organ-confined margin-negative disease will have favourable outcomes and may potentially be spared the toxicity of adjuvant radiation.

Current AUA/American Society for Radiation Oncology (ASTRO) guidelines state that physicians should offer adjuvant radiation to men with adverse pathology at the time of RP because of elevated risk of BCR [24]; however, pathological Gleason score 8–10 disease, a known predictor of poor outcome, is not included as a factor in these guidelines. Although the American Society of Clinical Oncology (ASCO) guidelines, which largely concur with the AUA/ASTRO guidelines, added Gleason score 8–10 disease as a potential criterion for adjuvant radiation, it remains unclear, how adverse pathology interacts with high grade disease [25]; specifically, it remains unclear whether all men with Gleason score 8–10 disease do poorly or whether there are subsets among whom outcomes are better.

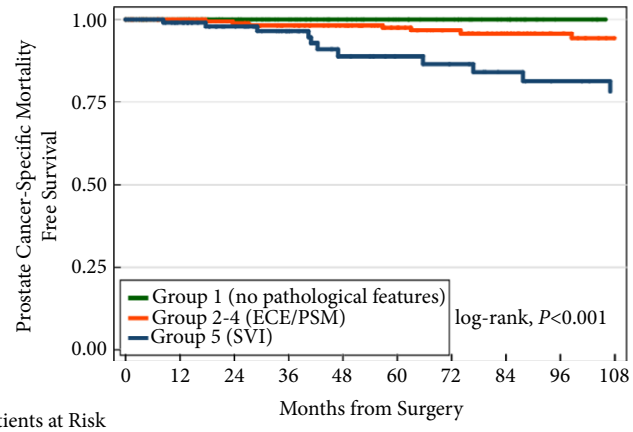
Fig. 3 Kaplan–Meier curves for 9-year risk of metastasis defined by pathologic features. Group 1: no extracapsular extension (ECE), negative surgical margins (NSMs); group 2: no ECE, positive surgical margins (PSMs); group 3: ECE, NSMs; group 4: ECE, PSMs; group 5: seminal vesicle invasion.



Patients at Risk

Group 1	142	135	110	97	81	68	63	54	40	36
Groups 2-4	211	189	163	147	134	117	100	85	69	61
Group 5	106	85	71	56	39	34	33	27	24	20

Fig. 4 Kaplan–Meier curves for 9-year risk of prostate cancer specific mortality defined by pathologic features. Group 1: no extracapsular extension (ECE), negative surgical margins (NSMs); group 2: no ECE, positive surgical margins (PSMs); group 3: ECE, NSMs; group 4: ECE, PSMs; group 5: seminal vesicle invasion.



Patients at Risk

Group 1	142	136	111	98	82	71	64	54	41	37
Groups 2-4	211	190	166	150	140	123	107	91	73	64
Group 5	106	92	77	62	43	38	36	31	28	25

Randomized prospective trials have shown that adjuvant radiation reduces the risk of BCR by ~50% across all strata of patients studied to date [3,24,26–28]. This implies that, regardless of baseline BCR risk, the risk will be cut in half by adjuvant radiation; however, the absolute benefit is highly dependent on the underlying risk of BCR. In other words, if you treat men with very-high-risk disease, in whom failure is nearly guaranteed, you minimize the number of men treated needlessly. Alternatively, if you radiate men with low-risk disease, most of whom were not destined to experience BCR anyway, the absolute benefit is slight. The identification of men with high-risk disease is therefore important to select the appropriate therapy. Equally important is to identify men with low-risk disease in whom the benefits of adjuvant radiation are probably small. To this end, we examined a group of all men with 'high-risk' disease with pathological Gleason score 8–10 in order to identify a potential subset in whom BCR outcomes were favourable and adjuvant radiation would have had less benefit. As a secondary outcome, we then determined whether any of these subsets of men were at lower risk of prostate cancer death.

Our findings showed that among men with pathological Gleason score 8–10 disease, men with any combination of ECE and/or PSMs were at significantly higher risk of BCR compared with men with organ-confined disease. Men with SVI were at the highest risk of BCR. Importantly, given that all men with Gleason score 8–10 disease are typically considered 'high-risk', a key finding in the present study is that men with organ-confined margin-negative high grade disease had quite favourable outcomes with a relatively low risk of BCR. Our results are consistent with those from previous studies. Specifically, Lau et al. [18] examined 407 patients with pathological Gleason score 8–10 at the time of RP. Although they did not examine combinations of pathological features, they did note that with 6.6 years of follow-up, the best outcomes were seen in men with either organ-confined disease (28% BCR risk) or NSMs (35% BCR risk). The rate in men with organ-confined and NSMs was not stated. Similarly, Mian et al. [19] showed that among 188 men with pathological Gleason score 8–10 disease, 6-year BCR risk for those with organ-confined margin-negative disease was ~20%. Both of these results are similar to our findings of ~30% 6-year BCR risk for the men with organ-confined disease with NSMs; however, the present study adds uniquely to the previous studies in that our cohort included 30% of men who were black. While Lau et al. do not report race in their study, Mian et al. report that only 11% of their study population was black.

In contrast to men with organ-confined disease and NSMs, all other groups had poor outcomes, with ≥50% BCR risk. As such, these findings concur with the recent ASCO adjuvant/salvage radiation guidelines that, in the presence of at least one adverse pathological feature, the further presence of Gleason score 8–10 disease indicates a high risk of BCR [25]. We agree, therefore, that such patients remain excellent candidates for adjuvant radiation.

The present study has some limitations. As this was a retrospective study we were not able to control for how attending surgeons followed the men for BCR after RP. Second, given that we collected data from a multi-institutional database, we acknowledge that our analysis is

limited by a lack of central pathological review of RP specimens; however, the population selected from our well established, multi-institutional database includes a racially diverse cohort and thus allows a greater insight into how the findings may relate to the general population. Third, as we excluded men who received preoperative ADT or radiation therapy, there is some selection bias in that men's treatment choices and therefore exclusion from this study were a combination of physician counselling and personal preferences. Given that salvage therapies may influence our secondary outcome of prostate cancer death [29], and many of our patients received these therapies after BCR, it is possible that prostate cancer death rates may have been higher in the absence of such therapies. That being said, the use of the SEARCH database permitted the inclusion of a fairly large group of men with pathological Gleason score 8–10 disease with specific data on each of the pathological variables of interest and PSA follow-up data.

In conclusion, in men with Gleason score 8–10 prostate cancer at the time of RP, the presence of PSMs, ECE, both PSMs and ECE, and SVI was associated with a higher risk of early BCR. While men with SVI were at the highest risk of BCR, the presence of any of those pathological features among men with pathological Gleason score 8–10 prostate cancer may warrant treatment with adjuvant radiation. Conversely, men with organ-confined margin-negative disease have a very low risk of early BCR, despite having Gleason score 8–10 disease.

Conflict of Interest

None declared.

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Abbreviations: BCR, biochemical recurrence; RP, radical prostatectomy; PSM, positive surgical margin; NSM, negative surgical margin; ECE, extracapsular extension; SVI, seminal vesicle invasion; ADT, androgen deprivation therapy; ASTRO, American Society for Radiation Oncology.