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The Impact of Pathologic Staging on the Long-Term Oncologic Outcomes of Patients With Clinically High-Risk Prostate Cancer

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BACKGROUND: In the prostate-specific antigen (PSA) screening era, approximately 15% of US men still present with clinically high-risk prostate cancer (PC). However, high-risk PC may be downgraded/downstaged at radical prostatectomy (RP), making additional therapy unnecessary. The authors tested the oncologic outcomes in men with clinically high-risk disease stratified on RP pathology. **METHODS:** A total of 611 men with high-risk PC (PSA level > 20 ng/mL, biopsy Gleason sum [bGS] ≥ 8, or clinical classification of ≥ T3) underwent RP and pelvic lymphadenectomy between 1998 and 2011. Outcomes included biochemical disease recurrence (BCR), receipt of androgen deprivation therapy (ADT), metastases, and PC-specific and overall survival. RP pathology was classified as unfavorable (pathologic Gleason sum ≥ 8, pathologic classification of ≥ T3, or lymph node-positive disease), or favorable (no unfavorable features). Multivariable analyses tested oncologic outcomes stratified by pathologic classification. **RESULTS:** Overall, 527 men had complete pathologic data and were included in the current analysis. Of the cohort, 206 of 527 men (39%) had favorable pathology. This finding was more common in men with only 1 clinical high-risk feature, and a lower body mass index, PSA level, bGS, and percentage positive biopsy cores. Favorable pathology was associated with decreased BCR (hazards ratio [HR], 0.34), metastases (HR, 0.17), and PC death (HR, 0.17). After a median follow-up of 82 months (range, 49 months-131 months), 193 of the 527 men (37%) received ADT, including only 35 of the 206 men with favorable pathology (17%). Unfavorable pathology was associated with early (≤ 5 years) but not late treatment with ADT. **CONCLUSIONS:** In a large cohort of men with high-risk PC who were managed with RP, 39% had favorable pathology and superior oncologic outcomes. ***Cancer*** **2014;120:1656–62.** *© 2014 American Cancer Society.*

KEYWORDS: prostatic neoplasms, prostatectomy, treatment outcome, pathology.

INTRODUCTION

Prostate cancer (PC) is the second most common cancer in men worldwide.[1] Although there has been a downward stage migration noted in nations in which prostate-specific antigen (PSA) screening is performed, many men are still diagnosed with clinically high-risk disease.[2] Although several definitions of high-risk PC exist, the definition supported by the National Comprehensive Cancer Network and the European Association of Urology is based on serum PSA, clinical stage, and biopsy Gleason sum (bGS).[3] By that definition, approximately 15% of US men will have high-risk disease at the time of diagnosis.[2,4]

Although a clinical low-risk versus intermediate-risk versus high-risk classification scheme is useful for prognosis and structuring treatment paradigms, its accuracy relies on the individual characteristics used to create it. Some high-risk characteristics will be reclassified to lower risk on examination of radical prostatectomy (RP) pathology. For example, men with a bGS of 8 or 9 to 10 will be pathologically downgraded at the time of RP to pathologic Gleason sum (pGS) ≤ 7

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Additional Supporting Information may be found in the online version of this article.

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approximately 50% and 30% of the time, respectively.[5] In addition, up to 27% of men with clinical T3 tumors are found to have organ-confined tumors at the time of RP.[6] Finally, because "high-risk" includes men with 1, 2, or 3 of the clinical high-risk features, this group comprises a heterogeneous population.

There is currently wide variability with regard to how men with clinically high-risk disease are treated. In the United States, approximately 40% of these men do not undergo treatment with curative intent, but rather receive primary or palliative androgen deprivation therapy (ADT).[7] Alternatively, men undergoing radiotherapy (RT) will receive 2 to 3 years of concomitant ADT. Men treated surgically with upfront RP are managed typically with multimodal therapy guided by postoperative PSA and surgical pathology. Due to sampling error of biopsy and imperfections in clinical staging, some men will be expected to have no pathologic high-risk features, thereby reclassifying these men as non-high risk. As such, these men can be provided with a single treatment with a high cure rate and may be spared the toxicity of ADT.

We therefore sought to describe the pathologic features of a large multiethnic cohort of men with clinically high-risk PC who were managed with RP. We hypothesized that despite being clinically considered high risk, men with favorable RP pathology would have superior oncologic outcomes and would have low rates of secondary treatment. To test this, we herein described the long-term outcomes of men with clinical high-risk disease who were treated with RP as primary therapy. We then compared the oncologic outcomes of men stratified by RP pathologic features.

MATERIALS AND METHODS

Study Cohort

After obtaining Institutional Review Board approval from each institution, data from 3930 patients undergoing RP between 1988 and 2011 at the Palo Alto, California; West Los Angeles, California; Augusta, Georgia; Durham, North Carolina; San Diego, California; and Asheville, North Carolina Veterans Affairs medical centers were combined into the Shared Equal Access Regional Cancer Hospital (SEARCH) database. In SEARCH, 611 patients were clinically classified as high risk (clinical disease classification of $\geq$ cT3 or a PSA level $>$ 20 ng/mL or bGS $\geq$ 8) by the National Comprehensive Cancer Network/European Association of Urology definition.[3] Of this cohort, 527 underwent pelvic lymphadenectomy and complete pathologic data and were included in the current analysis.

Treatment

SEARCH does not include patients treated with preoperative ADT or RT. The majority of patients underwent open radical retropubic RP (90%); however, 4% of patients underwent perineal RP, and 5% underwent robotic RP. The extent of pelvic lymphadenectomy was determined by the surgeon. ADT was administered at the discretion of the treating physician. ADT or RT that was initiated in the presence of an undetectable serum PSA was considered adjuvant therapy. The dosimetry of adjuvant or salvage RT was at the discretion of the treating radiation oncologist.

Follow-Up

Because this was a retrospective analysis, follow-up protocols were not predetermined and were left to the discretion of the treating physicians at each of the 5 centers. Surgery date was considered time 0 for all outcomes. Biochemical disease recurrence (BCR) was defined as a single PSA level $>$ 0.2 ng/mL, 2 concentrations at 0.2 ng/mL, or secondary treatment for any detectable postoperative PSA. After RP, a persistent PSA level of $>$ 0.2 ng/mL was considered BCR at the time of the test. Men receiving adjuvant therapy were considered to be nonrecurrent at the time of adjuvant therapy, with follow-up censored at that point for the purposes of BCR. Distant metastases were determined by review of radionuclide bone scans, magnetic resonance imaging, computed tomography, plain radiograph reports, and clinical progress notes. The decision to perform radiographic imaging was at the discretion of the treating physician. PC death was defined as death in any patient with metastases demonstrating PC progression after ADT.

Statistical Analysis

Our primary objective was to compare the oncologic outcomes of patients with clinically high-risk disease stratified by pathologic features. RP pathology was classified as either "favorable" or "unfavorable". Patients with $\geq$ pT3 disease, pN+ disease, or a pGS $\geq$ 8 were classified as having unfavorable RP pathology. All other men were considered to have favorable pathology. As a secondary analysis, the definition of unfavorable was modified to include PSA in the criteria. Specifically, all men with a preoperative PSA level $>$ 20 ng/mL remained unfavorable.

To describe the cohort, preoperative patient characteristics were reported stratified by RP pathology classification. In addition, to characterize the treatment patterns of the cohort, we reported the use of secondary treatment (ADT and/or RT) and its timing (adjuvant or salvage).

TABLE 1. Cohort Characteristics

	Median (IQR) or No. (%)			
	Overall Cohort n = 527	Unfavorable n = 321	Favorable n = 206	*P*
Follow-up, mo	82 (49-131)	81 (49-132)	84 (49-130)	.90
Y of surgery	2001 (1996-2006)	2001 (1996-2006)	2002 (1996-2007)	.31
Age, y	63 (59-68)	63 (59-68)	63 (59-67)	.69
Race				.15
White	311 (59%)	201 (63%)	110 (53%)	
Black	186 (35%)	106 (33%)	80 (39%)	
Other	30 (6%)	14 (4%)	16 (7%)	
BMI, kg/m^2	27.6 (24.8-30.7)	28.1 (25.4-31.1)	26.9 (24.5-30.2)	.03
Preoperative PSA ≥20 ng/mL	239 (46%)	152 (48%)	87 (43%)	.26
Preoperative PSA, ng/mL	16.3 (6.6-27.2)	18.3 (7.0-30.8)	12.6 (6.1-24.7)	.01
Prostate weight, g	43.3 (34.0-55.0)	43.5 (34.5-53.9)	43.0 (33.0-55.8)	.85
No. of biopsy cores obtained	8 (6-12)	8 (6-12)	10 (6-12)	.16
% Biopsy cores positive	42 (25-67)	50 (33-75)	37 (20-50)	<.01
Biopsy Gleason sum				<.01
≤6	93 (18%)	37 (12%)	56 (27%)	
7	93 (18%)	64 (20%)	29 (14%)	
≥8	308 (58%)	196 (61%)	112 (54%)	
Unknown	34 (6%)	24 (7%)	9 (4%)	
Clinical classification				.41
cT1	227 (43%)	133 (41%)	94 (46%)	
cT2	185 (35%)	112 (35%)	73 (35%)	
≥cT3	18 (3%)	8 (2%)	10 (5%)	
cTx	97 (18%)	68 (21%)	29 (14%)	
Positive surgical margins	293 (56%)	212 (67%)	81 (40%)	<.01
Pathologic Gleason sum				<.01
≤6	89 (17%)	21 (7%)	68 (33%)	
7	248 (47%)	110 (34%)	138 (67%)	
≥8	172 (33%)	172 (54%)	0 (0%)	
Unknown	18 (3%)	18 (6%)		
Pathologic classification				<.01
T2	273 (52%)	67 (21%)	206 (100%)	
T3	251 (48%)	251 (78%)	0 (0%)	
Tx	3 (1%)	3 (1%)	0 (%)	
Lymph node stage				<.01
N0	482 (91%)	276 (86%)	206 (100%)	
N+	45 (9%)	45 (14%)	0 (0%)	
Biochemical disease recurrence	288 (56%)	206 (65%)	82 (40%)	<.01
PC death	39 (7%)	36 (11%)	3 (1%)	<.01
Any-cause death	189 (36%)	122 (38%)	67 (33%)	.24
Surgery alone	263 (50%)	119 (37%)	144 (70%)	<.01
Any radiotherapy	158 (30%)	117 (36%)	41 (20%)	<.01
Adjuvant radiotherapy	65 (12%)	56 (17%)	9 (4%)	<.01
Any ADT	193 (37%)	158 (49%)	35 (17%)	<.01
Adjuvant ADT	18 (4%)	15 (5%)	3 (1%)	.03

Abbreviations: ADT, androgen deprivation therapy; BMI, body mass index; IQR, interquartile range, PC, prostate cancer; PSA, prostate-specific antigen.

For ADT, we also described the PSA level at the initiation of therapy and whether ADT was initiated before or after metastases were evident.

Time from RP to BCR, ADT, metastases, PC death, and any-cause death were compared based on RP pathology using Kaplan-Meier plots and the log-rank test. Patients receiving adjuvant ADT were excluded from the BCR and ADT analyses. The hazards ratios (HR) and 95% confidence intervals (95% CIs) associated with favorable pathology were estimated using multivariable Cox models adjusted for age (in years, continuous), race (black, white, or other), center (categorical), and preoperative PSA (in ng/mL, continuous [log-transformed]). Due to concerns that men with unfavorable pathology would receive more ADT and the possibility that ADT increases non-PC deaths, all events after ADT initiation (ie, metastases and PC death) were analyzed using non-PC death as a competing risk and adjusted for the same covariates as above.[8] Proportional hazards assumptions were verified with chi-square tests of Schoenfeld residuals. The model for ADT was found to be significantly nonproportional, necessitating partitioning of the time axis. The cutoff for

TABLE 2. Timing of ADT

		Median (IQR) or No. (%)		
	ADT Recipients n = 193	Unfavorable n = 158	Favorable n = 35	*P*
Adjuvant ADT	18 (9%)	15 (8%)	3 (2%)	.77
PSA at start of ADT, ng/mL	3.0 (0.6-8.6)	2.8 (0.4-7.9)	4.9 (1.1-21.3)	.08
ADT after RT	36 (19%)	29 (15%)	7 (4%)	.99
ADT prior to metastases	180 (93%)	148 (77%)	32 (17%)	.17

Abbreviations: ADT, androgen deprivation therapy; IQR, interquartile range; PSA, prostate-specific antigen; RT, radiotherapy.

partitioning this model was chosen by inspecting the Schoenfeld residual plots for inflection points and reverifying the proportional hazards assumptions.

Bivariable comparisons were performed using the Pearson chi-square or Fisher exact tests as appropriate for categorical variables and Wilcoxon rank sum tests for continuous variables. Continuous variables were reported as median values with interquartile ranges unless otherwise specified. All tests were 2-tailed and P values $< .05$ were considered to be statistically significant. All statistical analyses were performed using R version 3.0.1 (R Foundation for Statistical Computing, Vienna, Austria) with the *survival*, *survplot,* and *cmprsk* packages installed.

RESULTS

Of the 527 patients in the cohort with clinical high-risk disease, 206 (39%) had favorable RP pathology (Table 1). Compared with patients with favorable pathology, those with unfavorable pathology had higher preoperative PSA levels, body mass index, and biopsy tumor volume (percentage of positive biopsy cores). Most patients had only 1 clinical high-risk feature (PSA level > 20 ng/mL, bGS ≥ 8, or clinical classification $\geq$ T3); only 38 (7%) had > 1 feature. Men with only 1 high-risk clinical feature were more likely to have favorable pathology than men with multiple high-risk clinical features (42% vs 8%; $P < .01$). On RP pathology, 48% of men had non–organ-confined tumors ($\geq$ pT3), and 9% had positive lymph nodes. Of the 308 men with a bGS ≥ 8, a total of 166 (54%) were downgraded to a pGS ≤ 7. Of the 18 patients with clinical disease classified as $\geq$ T3, 11 (61%) were downstaged because they had organ-confined disease at the time of RP. After a median follow-up of 82 months, 64% of the cohort was alive. During this time, although 56% had a BCR, only 10% developed metastases and only 7% died of PC. Approximately one-half of the cohort received secondary therapy (ADT or RT) after RP. Notably, 70% of the group with favorable pathology were managed with RP alone, with only 17% receiving ADT. Furthermore, in examining the subset of patients who received ADT (Table 2), it was apparent that having unfavorable RP pathology may influence clinicians to initiate ADT at a lower serum PSA level compared with having favorable pathology (median, 2.8 ng/mL vs 4.9 ng/mL); however, this was not found to be statistically significant ($P = .08$).

To test the importance of pathological classification, grade, and preoperative PSA in predicting oncological outcomes, we determined the risk of the various outcomes for the overall cohort stratified by pGS (see Fig. 1 in online supporting information), pathologic stage (see Fig. 2 in online supporting information), and preoperative PSA (see Fig. 3 in online supporting information). A pGS ≥ 8 was associated with BCR (HR, 2.14; 95% CI, 1.49-3.07 [$P < 0.01$], metastases (HR, 7.44; 95% CI, 2.27-24.34 [$P < .01$]), ADT (HR, 3.88; 95% CI, 2.33-6.47 [$P < .01$]), and PC death (HR, 5.76 95% CI, 1.73-19.22 [$P < .01$]). Pathologic stage (non–organ-confined vs organ-confined disease) was found to have similar associations with the tested outcomes (see online supporting information). However, although a preoperative PSA level > 20 ng/mL was associated with BCR and ADT, it was not found to be associated with metastases or PC death (see online supporting information).

Favorable RP pathology was associated with improved oncologic outcomes (Fig. 1). Landmark survival analyses for the overall cohort and stratified by postoperative risk are shown in Table 3. It is interesting to note that the overall cohort had a PC-specific survival rate of 89%, but only 64% overall survival at 10 years. Although 50% of the patients in the favorable pathology group had a BCR at 10 years, the metastasis-free survival rate was 96% and the PC-specific survival rate was 98%. Similarly, multivariable analysis adjusted for age, race, body mass index, center of treatment, and preoperative PSA confirmed that favorable RP pathology was protective against BCR, metastases, and PC death but not any-cause death (Table 4). When a more stringent definition of "favorable" was used in which

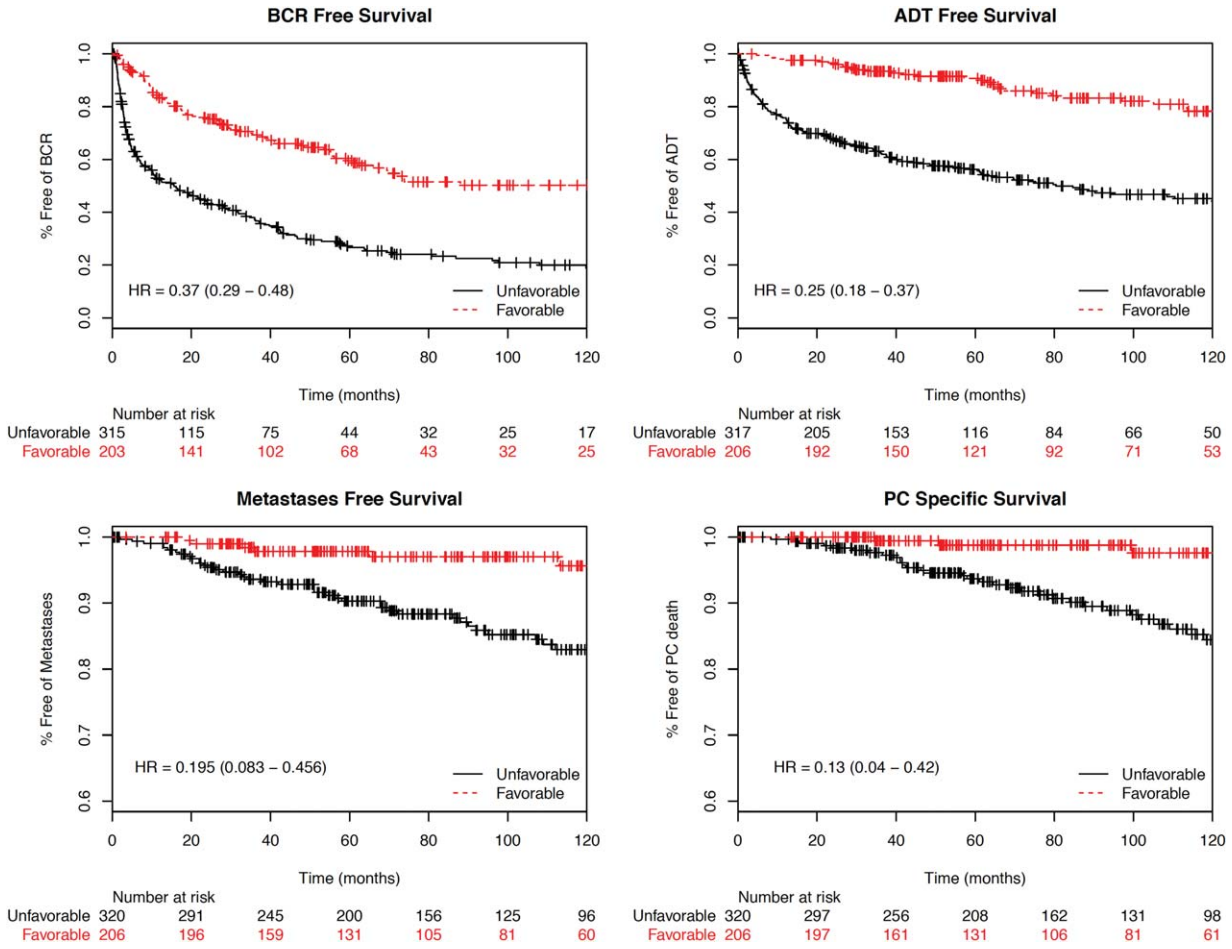

Figure 1. Oncologic outcomes of patients with clinically high-risk disease stratified by pathologic risk group (high-risk vs reclassified): (A) biochemical disease recurrence (BCR), (B) androgen deprivation therapy (ADT), (C) metastases, and (D) prostate cancer (PC)-specific survival. HR indicates hazards ratio.

TABLE 3. Landmark Survival Outcomes

	Overall (n = 527)			Unfavorable (n = 321)			Favorable (n = 206)		
	At 1 Year (95% CI)	At 5 Years (95% CI)	At 10 Years (95% CI)	At 1 Year (95% CI)	At 5 Years (95% CI)	At 10 Years (95% CI)	At 1 Year (95% CI)	At 5 Years (95% CI)	At 10 Years (95% CI)
Overall survival	98 (97-99)	83 (79-86)	64 (60-70)	98 (96-99)	81 (76-85)	62 (56-68)	99 (99-100)	86 (81-91)	69 (61-77)
PC-specific survival	99 (99-100)	96 (94-98)	89 (86-93)	99 (99-100)	94 (91-97)	84 (79-90)	100	99 (97-100)	98 (95-100)
Metastases-free survival	99 (99-100)	93 (91-96)	88 (84-91)	99 (98-100)	90 (87-94)	83 (78-88)	100	98 (96-100)	96 (92-99)
BCR-free survival	65 (61-70)	40 (36-45)	32 (27-37)	53 (47-59)	27 (22-33)	19 (14-26)	83 (78-89)	60 (53-68)	50 (42-60)

Abbreviations: 95% CI indicates 95% confidence interval; BCR, biochemical disease recurrence; PC, prostate cancer.

patients with preoperative PSA levels > 20 ng/mL were excluded, the conclusions were similar. In fact, the 95% CIs of the HRs for each outcome test overlapped, suggesting that a preoperative PSA threshold of 20 ng/mL is less informative than pathologic stage and grade. Time to ADT was examined by dividing the cohort into those with > 5 years or ≤ 5 years of follow-up due to a nonproportional effect of RP pathology on this outcome. It was evident that reclassification was protective from receipt of ADT in the cohort within the first 5 years, but after 5 years this association was found to be weaker and not statistically significant (Table 4).

TABLE 4. RP Pathology and Oncologic Outcomes

	Univariable			Adjusted[a]		
	HR	95% CI	*P*	HR	95% CI	*P*
Favorable pathologic features						
Biochemical disease recurrence[b]	0.38	0.29-0.50	<.01	0.34	0.24-0.48	<.01
ADT ≤5 y	0.24	0.14-0.41	<.01	0.23	0.12-0.44	<.01
ADT >5 y	0.66	0.34-1.29	.23	0.86	0.36-2.05	.73
Metastases	0.14	0.05-0.38	<.01	0.17	0.07-0.43	<.01
PC death	0.09	0.02-0.39	<.01	0.17	0.04-0.75	.02
All-cause death	0.82	0.61-1.11	.20	0.85	0.57-1.28	.44
Favorable pathology and PSA ≤20 ng/mL						
Biochemical disease recurrence[b]	0.42	0.29-0.59	<.01	0.44	0.29-0.68	<.01
ADT ≤5 y	0.20	0.09-0.44	<.01	0.21	0.09-0.52	<.01
ADT >5 y	0.66	0.25-1.70	.39	1.84	0.50-6.72	.36
Metastases	0.27	0.09-0.88	.03	0.30	0.10-0.89	.03
PC death	0.12	0.02-0.90	.04	0.14	0.02-1.16	.07
All-cause death	0.71	0.46-1.10	.12	0.73	0.42-1.27	.26

Abbreviations: 95% CI, 95% confidence interval; ADT, androgen deprivation therapy; HR, hazards ratio; PSA, prostate-specific antigen; PC, prostate cancer; RP, radical prostatectomy.
[a] Adjusted for age, race, body mass index, center, and preoperative PSA (log-transformed).
[b] Patients receiving adjuvant ADT were excluded.

DISCUSSION

To the best of our knowledge, there is no consensus regarding the optimal management of patients with high-risk PC. In men with high-risk disease, competing risks of mortality from comorbid illness are still relevant and in some cases may take precedent over curative therapy for PC.[9] However, a Swedish registry study of more than 12,000 men managed with noncurative intent for clinically high-risk PC found that up to 64% of men will die of PC within 8 years, and concluded that these men may be undertreated.[10] Similarly, the PIVOT (Prostate Cancer Intervention Versus Observation Trial) trial found that men with high-risk PC who were randomized to RP had better PC-specific and overall survival compared with those undergoing observation.[11]

Curative treatment for patients with high-risk PC typically uses either RP (with additional therapy guided by pathology and postoperative PSA) or RT with concomitant ADT. Several centers have reported excellent cancer control with RP in men with high-risk PC.[6,12-17] Despite this, RT with ADT is more commonly used in the United States.[7] Although to our knowledge no prospective comparative data exist for these treatment modalities, observational data from Boorjian et al suggested similar oncologic control for men with high-risk PC who were treated with either RT plus ADT or RP, with both modalities having a 10-year cancer-specific survival rate of 92%, which is similar to that found in the current study.[18]

Several nomograms exist for the prediction of BCR and PC mortality after RP. However, those that have been published have used data sets with a relatively low percentage of clinically high-risk patients.[19-21] Ploussard et al recently published a simplified prediction system for BCR in a large cohort of men defined as having clinically high-risk disease using the criteria of D'Amico et al.[16] In their analysis, each of the clinical factors (stage, Gleason score, and preoperative PSA) were found to be significant predictors of BCR and therefore given equal weight in a scoring system. The authors found that the number of clinical high-risk features discriminated BCR. In contrast to the analysis by Ploussard et al, the results of the current study in a clinically high-risk cohort found that a preoperative PSA level > 20 ng/mL has less prognostic value compared with pathologic stage and grade. Furthermore, we demonstrated that nearly 40% of men with high-risk PC are incorrectly classified as such when compared with RP pathology. In this group, 70% of men required no additional therapy after undergoing RP. Using multivariable analysis adjusted for non-PC death as a competing risk, favorable pathology was found to be associated with a marked reduction in the risk of metastases or PC mortality. This serves to highlight the importance of pathologic staging and grading to determine PC prognosis. Although the current study was not designed specifically to evaluate clinical features associated with RP outcomes, it suggests that men deemed to be at high risk with PSA levels > 20 ng/mL as their only high-risk feature are excellent candidates for RP because many will have favorable pathology, which has more prognostic value. In addition, the results of the current study highlight the need for better clinical

tools such as biomarkers or imaging to identify men who are truly at high risk, because there was an alarming discordance between clinical risk definition and RP pathology. Better clinical staging tools would allow optimal treatment selection for men with high-risk disease, and may aid in selecting those men who will likely require multimodal therapy.

The current study was limited by a lack of central pathologic rereview of biopsy and RP specimens. Despite this, our rates of Gleason downgrading are consistent with those currently undergoing central review in the literature.[5] In addition, the use of adjuvant RT in the current study cohort was low and at the discretion of each treating physician, which may contribute to the differences observed between the pathologically high-risk and reclassified men in the current series. However, although randomized trials have shown oncologic benefit compared with adjuvant RT for patients with non–organ-confined PC, the question of whether this approach is superior to early salvage therapy remains controversial.[22]

Conclusions

High-risk PC based on clinical parameters defines a heterogeneous cohort. In the current study, we found long-term oncologic outcomes of men with clinical high-risk PC managed with RP to be similar to those published by other centers. In the current study, 39% of men believed to be clinically high risk actually had favorable RP pathology. In this favorable subset, oncologic outcomes were excellent and the need for additional therapy was uncommon. Pathologic staging and grading are important data that may be used to more accurately determine prognosis and guide additional therapy after RP, and in the absence of better clinical risk stratification support the use of upfront RP in men with clinically high-risk disease. Moreover, these data highlight that a substantial percentage of men with clinically high-risk disease will be cured with surgery, and that better clinical tools are needed to define high risk preoperatively.

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CONFLICT OF INTEREST DISCLOSURES

Dr. Kane has acted as a consultant for Amgen, Janssen, Dendreon, and Intuitive Inc for work performed outside of the current study.

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