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Very-high-risk localized prostate cancer: outcomes following definitive radiation

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Abstract

Purpose/Objectives—Existing definitions of high-risk prostate cancer comprise men who experience significant heterogeneity in outcomes. As such, criteria that identify a subpopulation of NCCN high-risk prostate cancer patients who are at very high risk (VHR) for poor survival outcomes following prostatectomy were recently developed at our institution and include the presence of any of the following disease characteristics: multiple NCCN high-risk factors, primary Gleason pattern 5 disease, and/or 5 biopsy cores with Gleason sum 8–10. Whether these criteria also apply to men undergoing definitive radiation is unclear, as is the optimal treatment regimen in these patients.

Methods and Materials—All men consecutively treated with definitive radiation by a single provider from 1993–2006 and who fulfilled criteria for NCCN high-risk disease were identified (n=288), including 99 (34%) patients with VHR disease. Multivariable-adjusted competing risk regression models were constructed to assess associations between the VHR definition and biochemical failure (BF), distant metastasis (DM), and prostate cancer-specific mortality (PCSM). Multivariable-adjusted Cox regression analysis assessed the association of the VHR definition with overall mortality (OM). Cumulative incidences of failure endpoints were compared between VHR men and other NCCN high-risk men.

Results—Men with VHR disease as compared to other NCCN high-risk men experienced higher 10-year incidences of BF (54.0% vs. 35.4%, $p<0.001$), DM (34.9% vs. 13.4%, $p<0.001$), PCSM (18.5% vs. 5.9%, $p<0.001$), and OM (36.4% vs. 27.0%, $p=0.04$). VHR men with a detectable PSA at the end-of-radiation (EOR) remained at high risk of 10-year PCSM, as compared to VHR men with an undetectable EOR PSA (31.0% vs. 13.7%, $p=0.05$).

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Conclusions—NCCN high-risk prostate cancer patients who meet VHR criteria experience distinctly worse outcomes following definitive radiation and long-term androgen deprivation therapy, particularly if an EOR PSA is detectable. Optimal use of local therapies for VHR patients should be further explored, as should novel agents.

Introduction

Balancing the overtreatment of clinically indolent prostate cancer with the high number of prostate cancer deaths per year is a central challenge in the management of this disease.¹ Critical to this task is the accurate risk stratification of men who present with localized disease, such that treatment intensity may be matched to disease severity. In particular, men at high risk of failure following standard therapy represent a population in whom treatment intensification or novel agents may help reduce mortality. However, consistent identification of these patients has been challenging. Despite numerous systems for risk classification,^{2–7} men who fulfill existing definitions of high-risk disease can experience vastly different outcomes following local therapy.^{8–10}

Predicated on these observations, investigators from our institution searched for parameters that could reliably identify a sub-population of men with high-risk disease, as defined by the National Comprehensive Care Network (NCCN), who were at very high risk (VHR) of adverse oncologic outcomes after radical prostatectomy (RP).¹¹ Following a systematic evaluation of multiple permutations of prognostic factors, the presence of any of the following three criteria was found to be associated with significantly elevated hazard ratios for both metastasis-free survival (MFS) and cause-specific survival (CSS): (1) multiple NCCN high-risk factors, (2) primary Gleason pattern 5 disease, and/or (3) 5 biopsy cores with Gleason sum 8–10 disease. Indeed, NCCN high-risk men who met VHR criteria experienced very poor outcomes following RP, including 10-year MFS and CSS of 37% and 62%, respectively.

Whether VHR criteria also identify men with NCCN high-risk prostate cancer who are at very high risk for adverse oncologic outcomes following definitive radiotherapy is unclear, as is the optimal management of these patients. To address these questions, we explored the prognostic utility of the VHR definition in predicting distinctly worse long-term survival in a cohort of NCCN high-risk patients treated with definitive radiation.

Methods

Study design and participants

The study was approved by the institutional review board of our institution. The study cohort included all men who were consecutively treated with definitive radiation by a single provider at our institution between January 1, 1993 and December 31, 2006 and who fulfilled criteria for NCCN high-risk disease (clinical stage T3a, Gleason sum 8–10, and/or pretreatment PSA >20 ng/mL).³ Clinical stage was determined by digital rectal exam and assigned using the American Joint Commission on Cancer, 7th edition.¹² Extraprostatic extension or seminal vesicle invasion noted on biopsy were included in clinical stage determination. Biopsies which were performed at an outside hospital were reviewed by the

genitourinary pathologists at our institution before treatment. Patients without complete clinical or pathologic information were excluded (n=6), as were patients with less than 24 months of follow-up (n=11). The final study population consisted of 288 men with NCCN high-risk disease. Patients were further classified as having VHR disease based on the presence of one of three previously described criteria, namely multiple NCCN high-risk factors, primary Gleason pattern 5 disease, and/or ≥ 5 biopsy cores with Gleason sum 8–10 disease (Table 1).¹¹

Treatment

Patients were treated with definitive radiation using either three dimensional conformal radiation therapy (3D-CRT, 82%) or intensity modulated radiation therapy (IMRT, 18%), with the latter technique increasingly utilized at the end of the study period. Treatment generally consisted of an initial whole pelvis field, which included the prostate, seminal vesicle, and pelvic lymph nodes, followed by a boost field to the prostate. Seminal vesicles were also included in the boost field if there was high suspicion of involvement based on clinical exam. The prescription dose for the initial field was 45–46 Gy, delivered in 1.8–2 Gy fractions. The prescription dose for the boost field varied over the study period, with higher doses administered in more recent years. Median total dose for the cohort was 70.2 Gy (range: 64.8–75.6 Gy).

Additionally, 86% of men received any androgen deprivation therapy (ADT), and 66% of men received neoadjuvant, concurrent, and adjuvant ADT. When administered, neoadjuvant ADT was initiated two months prior to the radiation start date and consisted of a luteinizing hormone-releasing hormone (LHRH) agonist and an oral antiandrogen. The LHRH agonist was continued during the course of radiation and was generally maintained for a goal of two years after completion of radiation, if tolerated without significant toxicities. In our cohort, median total duration of ADT was 28 months (range 0–40 months). Complete information regarding the duration of oral antiandrogen use was unavailable.

Following treatment, patients underwent routine follow-up with serial PSA measurements and digital rectal exam, generally at six month intervals. Frequency of PSA measurements and digital rectal exams was altered based on the PSA trend and clinical symptoms. Similarly, clinical imaging was obtained in the setting of concerning PSA trends or clinical symptoms. Salvage ADT was administered based on the discretion of the treating provider, but was generally influenced by PSA doubling time, co-morbidity, and life expectancy. No patients received salvage local therapy, except for one patient who underwent salvage prostatectomy at an outside institution.

Statistical analysis

The primary endpoint of our study was prostate cancer-specific mortality (PCSM). Death due to prostate cancer was defined as death in a patient with a documented history of hormone-refractory metastatic prostate cancer, evidence of a rising PSA at last follow-up visit, and no other obvious cause of death. Additionally, the National Death Index (NDI) was cross-referenced to confirm cause of death. Patients who were alive were censored at last follow-up. Secondary endpoints included biochemical failure (BF), distant metastasis (DM),

and overall mortality (OM). BF was defined in accordance with the Radiation Therapy Oncology Group – Association of Therapeutic Radiation Oncology Phoenix Consensus Conference definition.¹³ Patients without BF at last follow-up were censored at time of last PSA measurement. Metastasis was defined by a radiographic abnormality on bone scan and/or computed tomography, with biopsy performed as needed for confirmation. Failure endpoints were measured from the last day of radiation.

Differences in patient and treatment characteristics were compared between men with VHR disease and other NCCN high-risk men using the χ^2 test. Thresholds for dichotomous variables were defined in accordance with the literature. For PCSM, DM, and BF, cumulative incidence functions were estimated using the competing risk method to adjust for non-prostate cancer-related death as a competing risk, and Gray's test was used to compare 10-year incidences of PCSM, DM, and BF between men with VHR disease and other NCCN high-risk men.¹⁴ Additionally, multivariable competing risk proportional hazards models were constructed for PCSM, DM, and BF.¹⁵ Hazard ratios for the individual components of the VHR definition as well as for the overall VHR definition were analyzed. Multivariable models adjusted for age at diagnosis, race, perineural invasion on biopsy, radiation prescription dose, use of IMRT, and duration of ADT. For OM, cumulative incidence was estimated using the Kaplan-Meier method and compared between men with VHR and other NCCN high-risk men using the log-rank test. Additionally, multivariable Cox proportional hazards models were constructed for OM, adjusting for the covariates denoted above.

Throughout the analysis, two-sided significance testing was used, and a P-value of 0.05 was considered statistically significant. All statistical analyses were performed with Stata software (Stata/IC10.0).

Results

Of the 288 men with NCCN high-risk disease, 122 patients (42%) died during the study period, including 45 patients (16%) who died due to prostate cancer. Median follow-up was 10.6 years (range: 2.0–20.3 years) for all patients and 13.1 years (3.8–20.3 years) for surviving patients.

Demographic, tumor, and treatment characteristics are outlined in Table 2. At least one of the VHR criteria was fulfilled in 99 patients (34%), including 88 patients (27%) with multiple NCCN high-risk factors, 30 patients (10%) with Gleason sum 8–10 disease in 5 biopsy cores, and 23 patients (8%) with primary Gleason pattern 5 disease. Men with VHR disease were younger, more frequently African-American, and more commonly presented with a higher initial PSA, greater Gleason score, more advanced primary tumor stage, and perineural invasion on biopsy, as compared to other NCCN high-risk men (all $p < 0.05$). While the number of biopsy cores sampled did not differ based on VHR status, men with VHR disease had a higher number and percentage of positive biopsy cores (all $p < 0.01$). Neither radiation dose nor use of IMRT significantly differed based on VHR status. Additionally, median ADT duration was not significantly different between VHR men and other NCCN high-risk men. However, men with VHR disease were more likely to receive any ADT, including neoadjuvant-concurrent ADT and/or long-term ADT (all $p < 0.05$).

We subsequently constructed hazard ratios for the individual components of the VHR definition with respect to all failure endpoints (Supplementary Table 1). The presence of multiple NCCN high-risk factors was significantly associated with a higher incidence of BF ($p<0.001$), DM ($p=0.001$), PCSM ($p=0.001$), and OM ($p=0.01$). Likewise, primary Gleason pattern 5 disease was significantly associated with a higher incidence of DM ($p=0.04$), PCSM ($p=0.02$), and OM ($p=0.03$), although not with BF. Similarly, the presence of 5 biopsy cores with Gleason sum 8–10 disease was also associated with a higher incidence of DM ($p=0.05$), PCSM ($p=0.01$), and OM ($p=0.05$), but not with BF.

Table 3 outlines multivariable-adjusted hazard ratios for men with VHR disease, as compared to other NCCN high-risk men. VHR status was significantly associated with a higher incidence of BF ($p=0.002$), DM ($p=0.002$), PCSM ($p<0.001$), and OM ($p=0.002$). Other prognostic factors included the administration of adjuvant ADT, which was associated with a higher incidence of BF (HR 0.50, 95% CI 0.28 – 0.88, $p=0.02$), DM (HR 0.57, 95% CI 0.30 – 0.88, $p=0.03$), PCSM (HR 0.45, 95% CI 0.22 – 0.94, $p=0.03$), and OM (HR 0.54, 95% CI 0.33 – 0.88, $p=0.01$).

Figure 1 displays cumulative incidence estimates for failure endpoints, stratified by fulfillment of VHR criteria. Despite being more likely to receive adjuvant ADT, men with VHR disease experienced a significantly higher 10-year incidence of BF (54.0% vs. 35.4%, $p<0.001$), DM (34.9% vs. 13.4%, $p<0.001$), PCSM (18.5% vs. 5.9%, $p<0.001$), and 10-year OM (36.4% vs. 27.0%, $p=0.04$), as compared to other NCCN high-risk men.

In patients with VHR disease who experienced biochemical failure, median time to biochemical failure was 34 months (range 3–110 months). As it was routine practice for the treating provider to obtain PSA levels in all men during their last week of radiation, we evaluated whether a detectable end-of-radiation (EOR) PSA, defined as a PSA level during the last week of radiation that was greater than or equal to 0.1 ng/mL, could serve as an early post-treatment metric to segregate men with VHR disease who remain at very high risk of poor outcomes. Since different PSA trajectories would be expected depending on the administration of ADT, we restricted this analysis to men receiving neoadjuvant and concurrent ADT. Amongst these men, the frequency of long-term adjuvant ADT administration did not differ based on whether the EOR PSA was detectable, which was exactly 78.2% in both groups. Notably, a higher proportion of men with VHR disease had detectable EOR PSA levels after completing radiation and neoadjuvant-concurrent ADT, as compared to other NCCN high-risk men (64.2% vs. 47.9%, $p=0.03$). Figure 2 displays cumulative incidence estimates for PCSM in men with VHR disease, stratified by EOR PSA. VHR men with a detectable EOR PSA experienced a significantly higher 10-year incidence of PCSM, as compared to VHR men with an undetectable EOR PSA (31.0% vs. 13.7%, $p=0.05$). Multivariable-adjusted Cox proportional hazards analysis confirmed that a detectable EOR PSA was significantly associated with inferior PCSM in men with VHR disease (HR 4.38, 95% CI 1.77 – 7.37, $p<0.001$).

Of note, practice patterns may vary with respect to the number of biopsy cores removed. In our cohort, for example, the median number of biopsy cores taken was eight but ranged from four to seventeen. Therefore, we analyzed whether the percentage of biopsy cores with

Gleason sum 8–10 disease would provide similar prognostic utility as the absolute number of biopsy cores with high grade disease, using a threshold of 50% involvement. On multivariate analysis, 50% involvement of biopsy cores with high grade disease was associated with inferior DM, PCSM, and OM (all $p < 0.05$, Supplementary Table 2). Additionally, after substituting the percentage of cores with high grade disease into the VHR definition in place of the absolute number of cores with high grade disease, hazard ratios for men with VHR disease remained similarly associated with all endpoints (all $p < 0.01$, Supplementary Table 3).

Although we controlled for duration of ADT in our multivariable competing risk and Cox proportional hazards models, we performed a sensitivity analysis to ensure that the VHR definition was applicable in patients treated with long-term adjuvant ADT, the standard for NCCN high-risk men undergoing definitive radiation based on evidence from randomized trials.^{16, 17} We therefore repeated the analysis, excluding 107 patients (41%) who were treated with less than two years of adjuvant ADT. In the remaining 171 patients, multivariable-adjusted competing risk and Cox proportional hazards analysis showed that VHR disease was significantly associated with all failure endpoints (all $p < 0.01$, Supplementary Table 4). As an example, men that met VHR criteria experienced a significantly higher 10-year incidence of BF (56.6% vs. 25.0%, $p < 0.001$), DM (32.3% vs. 8.4%, $p < 0.001$), PCSM (13.2% vs. 3.9%, $p < 0.001$), and OM (31.0 % vs. 22.9%, $p = 0.02$), as compared to other NCCN high-risk men (Supplementary Figure 1).

Discussion

Using a definition for very-high-risk (VHR) prostate cancer that was developed in a surgical cohort from our institution, we identified a sub-population of NCCN high-risk men who experienced distinctly inferior survival outcomes following definitive radiation and long-term androgen deprivation therapy (ADT). Indeed, men with VHR disease suffered 10-year incidences of prostate cancer-specific mortality (PCSM) and distant metastasis (DM) of 19% and 35% respectively, far worse than NCCN high-risk men who did not meet VHR criteria. Moreover, a PSA level measured at the end-of-radiation (EOR) provided early post-treatment identification of VHR patients who remained at very high risk for PCSM and DM after completing definitive radiation with concurrent ADT. Taken together, our results suggest that prostate cancer patients who meet VHR criteria represent a distinct subgroup of patients, in whom intensification of current therapies or exploration of novel therapies may be warranted, particularly for VHR patients with a detectable PSA at EOR.

Prior studies have illustrated significant variation in outcomes after radical prostatectomy (RP) in men with high-risk disease, according to several common definitions for high-risk disease.^{8–11} Our results extend these findings by also revealing considerable variation in outcomes after definitive radiation in men with NCCN high-risk disease. The heterogeneous nature of this patient population highlights the need for additional risk stratification, both for accurate prognostication and for refinement of treatment recommendations. While the VHR definition represents only one possible combination of prognostic factors, and while a number of other biomarkers are in various stages of analytical and clinical validation,^{18, 19} the VHR definition is attractive for its simplicity and utilization of parameters routinely

collected in clinical practice. Additionally, the VHR definition likely encompasses a non-trivial fraction of NCCN high-risk men, including roughly one in three men in our cohort.

The inferior survival of men with VHR disease also adds to the controversy regarding optimal management of high-risk prostate cancer. A number of studies have reported favorable outcomes in high-risk men treated with RP, including long-term PCSS rates over 90%.^{10, 20–27} However, these cohorts may have been enriched for men with more favorable high-risk disease. For example, in one study of prostate cancer patients with pretreatment PSA levels >20 ng/mL who underwent RP, 10-year PCSS was 91% for patients with no additional risk factors, but dropped to 65% for patients who also had Gleason sum 8–10 disease.²⁶ As summarized in Table 4, a similar decrement in PCSS was seen in RP patients from our institution based on VHR status.¹¹

Also apparent in Table 4 are the nominal differences in survival between treatment modalities among VHR patients treated at our institution. Two key points must be emphasized when interpreting these data, namely that differences in patient characteristics based on treatment modality existed and that nearly 50% of VHR patients in the RP cohort did not undergo postoperative radiation or ADT prior to clinical failure, contrary to modern practice.^{28–31} Nevertheless, the contrast in outcomes supports more formal investigation. While multiple comparisons of RP with definitive RT have been published without clear evidence of one modality's superiority, evaluation within a more restricted patient population, such as men with VHR disease, may yield more illuminating results.^{21, 32–36} Ideally, such a comparison would be conducted in a prospective, randomized setting that includes modern standards for adjuvant/early salvage therapy, but would need to overcome the same accrual obstacles that have hindered prior attempts to do so.^{37–39} Nevertheless, the VHR definition may also aid in patient selection for clinical trials that explore earlier incorporation of newer agents that have proven successful in the metastatic setting.^{40, 41} Incorporation of these agents into the upfront management of VHR men may be worthy of investigation. On the other hand, VHR patients who fail to achieve an undetectable PSA level after completing definitive radiation with concurrent ADT may offer a more restricted population in which to study these therapies. Dose-escalation, perhaps with a brachytherapy boost, offers another method for treatment intensification.^{42–48}

While our study has many strengths, a number of limitations must be acknowledged. Foremost, the retrospective study design is limited by unaccounted biases in patient selection, and the wide study interval may have introduced biases associated with the evolution of treatment techniques and technologies over time. However, we tried to account for such biases by including covariates for the primary treatment variables that may have changed over time, namely radiation dose and planning technique. Notably, the inclusion of patients treated several years ago led to a high proportion of patients with advanced clinical stage, which is less representative of the modern presentation of patients. Nevertheless, the wide study interval allowed for excellent long-term follow-up, which is critical when analyzing long-term endpoints such as PCSM. The fact that all patients were treated by a single provider may have further reduced variation in practice patterns, but it also limits the generalizability of results, and as such, external validation of the VHR definition in a definitive radiation cohort should be pursued. Additionally, the median radiation dose was

70.2 Gy, which is less than common contemporary doses of 78–79.2 Gy. However, while dose-escalated radiotherapy has improved biochemical control, it has yet to be associated with improved PCSS, a more relevant clinical endpoint.^{42–48} Perhaps the most cumbersome aspect of the VHR definition is the criterion of 5 cores with Gleason sum 8–10, which also may be influenced by the number of cores taken at biopsy. However, we showed that substituting the percentage of cores with high grade disease does not appreciably change the utility of the overall VHR definition. Lastly, we should again emphasize that retrospective comparison across modalities is limited by differences in patient populations and should ideally be pursued prospectively using modern treatment practices.

In conclusion, a subpopulation of men with NCCN high-risk prostate cancer who meet VHR criteria experience distinctly worse outcomes following definitive radiation and long-term androgen deprivation therapy, particularly if an EOR PSA is at a detectable level. The VHR definition may therefore serve as a useful tool for identifying patients in whom to reconsider the optimal application of current therapies and to explore novel agents.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Summary

Criteria that identify a subpopulation of NCCN high-risk prostate cancer patients who are at very high risk (VHR) for poor survival outcomes following prostatectomy were recently developed at our institution. Herein, we show that the VHR criteria also identify men with NCCN high-risk disease who experience distinctly inferior long-term survival outcomes following definitive radiation and long-term androgen deprivation. As such, reconsideration of the optimal use of local therapies in men with VHR disease is warranted.

Figure 1.

Cumulative incidence of (a) biochemical failure, (b) distant metastasis, (c) prostate cancer-specific mortality, and (d) overall mortality. Estimates for biochemical failure, distant metastasis, and prostate cancer-specific mortality were calculated using the competing risk method, while estimates for overall mortality were compared using the Kaplan-Meier method. Red curves represent men with very-high-risk (VHR) disease. Blue curves represent other NCCN high-risk men.

Figure 2. Cumulative incidence of prostate cancer-specific mortality in patients receiving radiation with neoadjuvant-concurrent androgen deprivation therapy, stratified by a detectable end-of-radiation PSA level. Blue curve represents men with an undetectable end-of-radiation PSA level. Red curve represents men with a detectable end-of-radiation PSA level.

Table 1

Components of the very-high-risk definition *

Multiple NCCN high-risk factors (two or more)
Primary Gleason pattern 5 disease
5 biopsy cores with Gleason sum 8–10 disease

Abbreviations: National Comprehensive Care Network (NCCN)

* Presence of any of the above factors qualifies a patient for very-high-risk status

Table 2

Demographic, disease, and treatment characteristics

Characteristics	Very-high-risk (N=99)	Other NCCN high-risk (N=189)	P-value
Median age (range), yrs	65 (44–79)	69 (48–83)	0.002
Africa-American race, %	34.3	23.3	0.05
Initial PSA in ng/mL, %			0.001
<10	27.3	38.6	
10–20	13.1	23.8	
>20	59.6	37.6	
Gleason sum, %			<0.001
3+3	9.1	36.0	
3+4	9.1	23.8	
4+3	7.4	8.1	
4+4	37.4	18.5	
4+5	16.2	14.3	
5+4	14.1	---	
5+5	6.1	---	
T-stage, %			<0.001
T1	5.1	21.2	
T2	28.3	48.7	
T3/T4	66.7	30.2	
Perineural invasion on biopsy, %	43.4	31.2	0.04
Biopsy cores			
Median number of sampled cores (range)	10 (4–17)	8 (4–16)	0.54
Median number of positive cores (range)	5 (1–14)	3 (1–12)	0.01
Median percentage of positive cores (range)	67 (8–100)	45 (8–100)	<0.001
Median radiation dose (range), Gy	70.2 (64.8–75.6)	70.2 (66.6–75.6)	0.81
Intensity modulated radiation therapy, %	22.2	15.9	0.18
Median duration of ADT (range), months	28 (0–40)	28 (0–52)	0.11
None	8.1	16.6	0.05
Neoadjuvant and concurrent only	16.2	22.2	0.04
Neoadjuvant, concurrent, and adjuvant	75.8	61.4	0.01

Abbreviations: National Comprehensive Care Network (NCCN); prostate-specific antigen (PSA); androgen deprivation therapy (ADT)

Table 3

Multivariable-adjusted association between very-high-risk status and failure endpoints

	Hazard ratio (95% confidence interval)	P-value
<i>Biochemical failure</i>		
VHR vs. other NCCN high-risk	2.01 (1.29 – 3.11)	0.002
Age 65 years	0.80 (0.52 – 1.24)	0.32
African-American race	0.82 (0.52 – 1.29)	0.39
Perineural invasion on biopsy	1.22 (0.78 – 1.89)	0.39
Use of intensity-modulated radiation	0.75 (0.34 – 1.70)	0.50
Radiation dose 72 Gy	0.73 (0.39 – 1.39)	0.35
Androgen deprivation therapy (ref: none)	---	
Neoadjuvant-concurrent only	0.49 (0.24 – 0.97)	0.04
Neoadjuvant-concurrent and adjuvant	0.50 (0.28 – 0.88)	0.02
<i>Distant Metastasis</i>		
VHR vs. other NCCN high-risk	2.49 (1.40 – 4.45)	0.002
Age 65 years	0.71 (0.61 – 1.21)	0.21
African-American race	1.09 (0.48 – 1.94)	0.77
Perineural invasion on biopsy	1.21 (0.69 – 2.12)	0.51
Use of intensity-modulated radiation	1.08 (0.37 – 1.83)	0.90
Radiation dose 72 Gy	0.82 (0.31 – 2.15)	0.69
Androgen deprivation therapy (ref: none)	---	
Neoadjuvant-concurrent only	0.78 (0.32 – 1.85)	0.57
Neoadjuvant-concurrent and adjuvant	0.57 (0.30 – 0.88)	0.03
<i>Prostate cancer-specific mortality</i>		
VHR vs. other NCCN high-risk	3.19 (1.71 – 5.96)	<0.001
Age 65 years	0.80 (0.43 – 1.48)	0.47
African-American race	1.26 (0.64 – 2.48)	0.50
Perineural invasion on biopsy	0.92 (0.48 – 1.77)	0.81
Use of intensity-modulated radiation	1.06 (0.25 – 4.55)	0.94
Radiation dose 72 Gy	0.60 (0.18 – 1.99)	0.41
Androgen deprivation therapy (ref: none)		
Neoadjuvant-concurrent only	0.57 (0.22 – 1.44)	0.24
Neoadjuvant-concurrent and adjuvant	0.45 (0.22 – 0.94)	0.03
<i>Overall mortality</i>		
VHR vs. other NCCN high-risk	1.87 (1.26 – 2.77)	0.002
Age 65 years	1.97 (1.30 – 2.97)	0.001
African-American race	0.81 (0.54 – 1.21)	0.30
Perineural invasion on biopsy	1.37 (0.93 – 2.01)	0.11
Use of intensity-modulated radiation	0.94 (0.40 – 2.20)	0.89
Radiation dose 72 Gy	0.76 (0.41 – 1.42)	0.39

	Hazard ratio (95% confidence interval)	P-value
Androgen deprivation therapy (ref: none)		
Neoadjuvant-concurrent only	0.66 (0.37 – 1.16)	0.15
Neoadjuvant-concurrent and adjuvant	0.54 (0.33 – 0.88)	0.01

Abbreviations: very-high-risk (VHR); National Comprehensive Care Network (NCCN)

Competing risk regression model was used for biochemical failure, distant metastasis, and prostate cancer-specific mortality. Cox proportional hazards model was used for overall mortality.

Table 4

Outcomes in men with very-high-risk disease and other NCCN high-risk men undergoing definitive radiation and radical prostatectomy*

		VHR	Other NCCN high-risk	
	Definitive RT	RP	Definitive RT	RP
10-year BFFS [†] , %	37.3 (22.8–51.3)	20.6 (9.0–35.6)	55.2 (41.9–66.6)	41.2 (36.0–46.2)
10-year MFS, %	58.7 (44.9–70.3)	36.9 (19.8–54.2)	83.8 (75.3–89.6)	77.9 (72.2–82.6)
10-year PCSS, %	79.4 (69.2–86.6)	62.2 (44.7–75.5)	93.4 (88.4–96.3)	89.5 (85.0–92.8)
10-year OS, %	63.6 (53.0–72.4)	57.9 (41.6–71.1)	73.0 (65.8–78.9)	83.3 (78.2–87.2)

* Outcomes for RP cohort were previously published (Sundi D, Wang VM, Pierorazio PM, et al. Very-high-risk localized prostate cancer: definition and outcomes. *Prostate Cancer and Prostatic Dis.* 2014;17(1):57–63) and had been analyzed using Kaplan-Meier methods and life tables. For the purpose of consistency, we re-analyzed our data using similar methods, which is summarized above.

[†] For patients undergoing definitive radiation, biochemical failure-free survival was defined in accordance with the Radiation Therapy Oncology Group – Association of Therapeutic Radiation Oncology Phoenix Consensus Conference definition.¹³ For patients undergoing radical prostatectomy, biochemical failure was defined as a post-operative increase in PSA (2 ng/mL)

Abbreviations: very-high-risk (VHR); radiation therapy (RT); radical prostatectomy (RP); biochemical failure-free survival (BFFS); metastasis-free survival (MFS); prostate cancer-specific survival (PCSS); overall survival (OS)