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Clinical Investigation

Definition and Validation of "Favorable High-Risk Prostate Cancer": Implications for Personalizing Treatment of Radiation-Managed Patients

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Summary

In our study we developed and validated a novel classification system for patients with high-risk prostate cancer. We define favorable high-risk prostate cancer as

Purpose: To define and validate a classification of favorable high-risk prostate cancer that could be used to personalize therapy, given that consensus guidelines recommend similar treatments for all radiation-managed patients with high-risk disease.

Methods and Materials: We studied 3618 patients with cT1-T3aN0M0 high-risk or unfavorable intermediate-risk prostate adenocarcinoma treated with radiation at a single institution between 1997 and 2013. Favorable high-risk was defined as T1c disease with either Gleason $4 + 4 = 8$ and prostate-specific antigen <10 ng/mL or Gleason 6 and prostate-specific antigen >20 ng/mL. Competing risks regression was used to

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T1c with Gleason 4 + 4 = 8 and PSA <10 ng/mL or Gleason 6 and PSA >20 ng/mL. This subset has better outcomes than others with high-risk disease and similar outcomes as those with unfavorable intermediate-risk disease. These results might be used to individualize the duration of androgen deprivation therapy for high-risk prostate cancer patients.

determine differences in the risk of prostate cancer–specific mortality (PCSM) after controlling for baseline factors and treatment. Our results were validated in a cohort of 13,275 patients using the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database.

Results: Patients with favorable high-risk disease had significantly better PCSM than other men with high-risk disease (adjusted hazard ratio [AHR] 0.42, 95% confidence interval [CI] 0.18-0.996, $P = .049$) and similar PCSM as men with unfavorable intermediate-risk disease (AHR 1.17, 95% CI 0.50-2.75, $P = .710$). We observed very similar results within the SEER-Medicare cohort (favorable high-risk vs other high-risk: AHR 0.21, 95% CI 0.11-0.41, $P < .001$; favorable high-risk vs unfavorable intermediate-risk: AHR 0.67, 95% CI 0.33-1.36, $P = .268$).

Conclusions: Patients with favorable high-risk prostate cancer have significantly better PCSM than other patients with high-risk disease and similar PCSM as those with unfavorable intermediate-risk disease, who are typically treated with shorter-course androgen deprivation therapy. This new classification system may allow for personalization of treatment within high-risk disease, such as consideration of shorter-course androgen deprivation therapy for favorable high-risk disease.

Introduction

Patients with prostate cancer are generally considered to have high-risk disease if they have a serum prostate-specific antigen (PSA) level of >20 ng/mL, Gleason score 8 to 10, or clinical stage T3a (1-3). Local therapy typically consists of radical prostatectomy or radiation therapy, and patients may be treated with neoadjuvant, concurrent, or adjuvant androgen deprivation therapy (ADT) (1). Based on the results of randomized trials (4-6), current guidelines recommend similar treatment for all radiation-managed patients with high-risk disease, including long-course (2 to 3 years) ADT (1, 2). On the other hand, short-course (4-6 months) ADT is considered standard for radiation-managed patients with intermediate-risk disease (1, 7).

Although ADT has been shown to prolong cancer-specific and overall survival in randomized trials, it has also been associated with significant toxicity, such as weight gain, decreased libido, fatigue, acute kidney injury, psychiatric illness, diabetes, and possibly an increased risk of cardiovascular events (8-10). Therefore, it is desirable to identify patients with high-risk disease who might be adequately treated with a shorter course of ADT than is typically recommended for this risk group. Conversely, because there is increasing interest in trials of novel systemic agents for high-risk prostate cancer, it would be useful to limit enrollment to subsets of high-risk patients who might be able to derive the most benefit from additional therapy.

Although the randomized trials that established 2 to 3 years of ADT as standard included mostly patients with cT3 or T4 disease, stage T1c (PSA-detected) is currently the most commonly detected form of prostate cancer (11), and many patients with high-risk disease are diagnosed with only 1 high-risk feature (12). In this study we used an institutional cohort to determine whether the subset of high-risk patients with nonpalpable prostate cancer (T1c) and either Gleason 4 + 4 = 8 disease or PSA >20 ng/mL (but not both) represent a favorable subset. We excluded patients with any Gleason grade 5 disease, including patients with Gleason score 5 + 3 = 8, 3 + 5 = 8, or 9 to 10, from this potentially favorable subset of patients owing to their significantly worse outcomes in prior work (13). We validated our findings within a large, national cohort linked to Medicare insurance claims data.

Methods and Materials

Patient population

We studied 3618 men with N0M0 prostate adenocarcinoma who were consecutively treated with brachytherapy with or without supplemental external beam radiation therapy (EBRT) at a single institution between 1997 and 2013 and were deemed to have unfavorable intermediate-risk or high-risk prostate cancer according to consensus guidelines (1) and the definitions described recently by Zumsteg et al (14). Specifically, patients were considered to have high-risk disease if they had stage T3a disease, Gleason score 8 to 10, or PSA >20 ng/mL (1). Favorable high-risk disease was defined as stage T1c with Gleason 4 + 4 = 8 and PSA <10 ng/mL or stage T1c with Gleason 6 and PSA >20 ng/mL. Per the Zumsteg definition, patients were considered to have unfavorable intermediate-risk disease if they had intermediate-risk disease (T2b-c, Gleason score 7, or PSA 10-20 ng/mL with no high-risk features) with more than 1 intermediate-risk feature, primary Gleason pattern 4, or percentage of positive biopsy cores ≥50% (14). Patients received ultrasound-guided brachytherapy with preloaded isotopes and preplanned dosimetry. When patients were treated with brachytherapy alone, the doses were 144 Gy

(iodine), 108 Gy (palladium), or 132 Gy (cesium); when patients were treated with combination therapy, the EBRT dose was 45 Gy to the prostate and seminal vesicles, and the brachytherapy boost dose was 108 Gy (iodine), 90 Gy (palladium), or 100 Gy (cesium). This population comprised our derivation cohort. Androgen deprivation therapy was given at the discretion of the treating clinician for a median duration of 4 months (interquartile range, 3-6 months) and consisted of a luteinizing hormone−releasing hormone agonist with or without an antiandrogen.

To validate our findings, we also identified a national cohort of radiation-managed prostate cancer patients with unfavorable intermediate- or high-risk disease from the Surveillance, Epidemiology, and End Results (SEER) database linked with Medicare claims data. The SEER-Medicare dataset combines patient data regarding cancer diagnostic information and outcomes from 18 SEER cancer registries covering 28% of the US population with administrative data for patients enrolled in Medicare (15, 16). Because of limitations in the availability of data within SEER, we could not include percentage of positive biopsy cores when determining whether patients had favorable or unfavorable intermediate-risk disease. Otherwise, the definitions for risk stratification match the definitions used by consensus guidelines (1) and described by Zumsteg et al (14). Because of recently reported possible inaccuracies in the recording of PSA in the SEER database, in which some values may have had a misplaced decimal point (17, 18), we excluded 588 of 13,863 initial patients (4.2%) who had discordant values for PSA and PSA interpretation (eg PSA <4.0 ng/mL recorded as "positive/elevated" or PSA >4.0 ng/mL recorded as "negative/normal"), giving us a final cohort size of 13,275. This approach to identifying possibly incorrectly coded PSA values was based on the observations of Schymura et al (19). Using Medicare claims data, we determined which patients in the SEER database received ADT (codes C9216, C9430, J0128, J1950, J9202, J1675, J9217-19, J9225-26, J3315, S0133, S0165, and Q2020). This study was approved by the institutional review board.

Statistical analyses

Statistical analyses were conducted using SAS version 9.3 (SAS Institute, Cary, NC), R version 3.0.1 (The R Foundation, Vienna, Austria), and Stata/MP 13.1 (StataCorp, College Station, TX). Fine and Gray competing risks regression (20) was used to determine differences in the risk of prostate cancer−specific mortality (PCSM) between groups of patients after controlling for age at diagnosis, year of treatment, and receipt of ADT. For the institutional cohort, all of whom received brachytherapy, we additionally controlled for receipt of EBRT. In a sensitivity analysis, we also controlled for duration of ADT received (in months) when comparing patients with favorable high-risk disease and unfavorable intermediate-risk disease. We reported estimates of 8-year PCSM in the institutional cohort and 5-year PCSM in the SEER cohort owing to differences in follow-up. Median values were compared using the Kruskall-Wallis test, and proportions were compared using the χ^2 test or t test, as appropriate. P values were reported as statistically significant if less than $\alpha = 0.05$.

Finally, we conducted 2 sensitivity analyses to test the possible effect of PSA recording errors on our results. Patients with discordant values for PSA and PSA interpretation were (*1*) included in the analyses with their recorded values or (*2*) had their PSA level adjusted by a factor 10 to account for possible misplacement of the implied decimal point in SEER PSA values (18).

Results

Baseline patient characteristics

In our institutional cohort of 3618 patients, there were 2433 (67.2%) who had unfavorable intermediate-risk disease, 267 (7.4%) who had favorable high-risk disease, and 918 other men (25.4%) who had high-risk disease. Their baseline characteristics are shown in Table 1. Median follow-up was 8.4 years (interquartile range, 5.7-11.1 years) in the entire cohort. Patient demographic characteristics were not significantly different among the 3 groups. Patients with favorable high-risk disease were more likely to receive ADT than those with unfavorable intermediate-risk disease, and less likely to receive ADT than other men with high-risk disease ($P<.001$).

In our validation cohort of 13,275 patients from the SEER-Medicare database, 6059 (45.6%) had unfavorable intermediate-risk disease, 1290 (9.7%) had favorable high-risk disease, and 5926 other men (44.6%) had high-risk disease. Their baseline characteristics are shown in Table 2.

Favorable high-risk prostate cancer is associated with relatively low PCSM

Figure 1 and Table 3 show comparisons of PCSM for patients with unfavorable intermediate-risk, favorable high-risk, and other high-risk prostate cancer. Patients with favorable high-risk prostate cancer had a much lower risk of 8-year PCSM than other patients with high-risk disease (2.1% vs 7.1%; adjusted hazard ratio [AHR] 0.42; 95% confidence interval [CI] 0.18-0.996; $P=.049$). In contrast, patients with favorable high-risk prostate cancer had approximately the same risk of 8-year PCSM as patients with unfavorable intermediate-risk disease (2.1% vs 2.5%; AHR 1.17; 95% CI 0.50-2.75; $P=.710$).

Results from our nation wide SEER-Medicare validation cohort are shown in Figure 2 and Table 4. Similar to those in our derivation cohort, patients with favorable high-risk disease had a much lower risk of 5-year PCSM than other men with high-risk disease (1.3% vs 7.2%; AHR 0.21; 95% CI 0.11-0.41; $P<.001$) and similar 5-year PCSM as those with unfavorable intermediate-risk disease (1.3% vs 2.0% AHR

Table 1 Baseline patient characteristics for the institutional cohort

	Patients						
	Unfavorable intermediate-risk (n=2433)		Favorable high-risk (n=267)		Other high-risk (n=918)		
Characteristic	n	%	n	%	n	%	*P*
Follow-up (y), median (IQR)	8.5 (6.0-11.2)		7.7 (5.6-10.5)		8.1 (5.5-11.1)		.049
Year of treatment							.019
1997-2005	1523	62.6	146	54.7	546	59.5	
2006-2013	910	37.4	121	45.3	372	40.5	
Patient age (y)							.18
≤65	581	23.9	52	19.5	202	22.0	
>65	1852	76.1	215	80.5	716	78.0	
Race							.19
White	1510	62.1	173	64.8	602	65.6	
Black	213	8.8	26	9.7	69	7.5	
Other	143	5.9	7	2.6	50	5.4	
Unknown	567	23.3	61	22.8	197	21.5	
PSA (ng/mL)							<.001
<10	1331	54.7	133	49.8	308	33.6	
10-20	1102	45.3	-	-	213	23.2	
>20	-	-	134	50.2	397	43.2	
Median PSA (ng/mL)	9.0		20.0		15.2		<.001
Gleason score							<.001
≤6	532	21.9	134	50.2	88	9.6	
7	1901	78.1	-	-	259	28.2	
8	-	-	133	49.8	359	39.1	
9-10	-	-	-	-	212	23.1	
T stage							<.001
T1	1331	54.7	267	100.0	248	27.0	
T2	1102	45.3	-	-	476	51.9	
T3	-	-	-	-	194	21.1	
Received ADT							<.001
No	1674	68.8	146	54.7	302	32.9	
Yes	759	31.2	121	45.3	616	67.1	
Duration of ADT (y)							<.001
<2	2292	94.2	234	87.6	729	79.4	
≥2	12	0.5	2	0.7	47	5.1	
Unknown	129	5.3	31	11.6	142	15.5	
% Positive biopsies							<.001
<50%	813	33.4	183	68.5	372	40.5	
≥50%	1581	65.0	78	29.2	519	56.5	
Unknown	39	1.6	6	2.2	27	2.9	

Abbreviations: ADT = androgen deprivation therapy; IQR = interquartile range.

0.67; 95% CI 0.33-1.36; $P=.268$). In a sensitivity analysis to determine the possible effects of coding errors of PSA in the SEER database, when we included 588 patients whose PSA value and recorded PSA interpretation were discordant, the hazard ratios changed only minimally (favorable high-risk vs other high-risk: AHR 0.24, $P<.001$; favorable high-risk vs unfavorable intermediate-risk: AHR 0.76, $P=.406$). When we adjusted their PSA values by a factor of 10 to account for a possible misplaced decimal point, the hazard ratios were also similar to those in the original analysis (AHR 0.18, $P<.001$ and AHR 0.61, $P=.161$, respectively).

Finally, although use of long-course ADT was rare in both cohorts and was similar between the favorable high-risk and unfavorable intermediate-risk groups, we performed a sensitivity analysis adjusting for ADT duration and confirmed our results demonstrating similar PCSM between the favorable high-risk and the unfavorable intermediate-risk groups (institutional cohort: AHR 1.20, $P=.680$; SEER-Medicare cohort: AHR 0.66, $P=.256$).

Discussion

In this study we defined a subset of patients with "favorable high-risk prostate cancer" (T1c, Gleason 4 + 4 = 8, and PSA <10 ng/mL or T1c, Gleason 6, and PSA >20 ng/mL)

Table 2 Baseline patient characteristics for the SEER-Medicare cohort

Characteristic	Patients						
	Unfavorable intermediate-risk (n=6059)		Favorable high-risk (n=1290)		Other high-risk (n=5926)		
	n	%	n	%	n	%	*P*
Follow-up (y), median (IQR)	2.8 (1.5-4.2)		2.8 (1.5-4.2)		2.8 (1.5-4.1)		.003
Year of treatment							.947
2004-2006	3119	51.5	653	50.6	3061	51.7	
2007-2009	2940	48.5	637	49.4	2865	48.3	
Patient age (y)							<.001
≤75	3315	54.7	711	55.1	2985	50.4	
>75	2744	45.3	579	44.9	2941	49.6	
Race							.008
White	4998	82.5	1028	79.7	4757	80.3	
Black	636	10.5	169	13.1	714	12.0	
Other	425	7.0	93	7.2	455	7.7	
PSA (ng/mL)							<.001
<10	3492	57.6	852	66.0	2114	35.7	
10-20	2567	42.4	-	-	1376	23.2	
>20	-	-	438	34.0	2436	41.1	
Median PSA (ng/mL)	8.4		7.9		14.3		<.001
Gleason score							<.001
≤6	189	3.1	438	34.0	282	4.8	
7	5870	96.9	-	-	1294	21.8	
8	-	-	852	66.0	2388	40.3	
9-10	-	-	-	-	278	4.7	
T stage							<.001
T1	2725	45.0	1290	100.0	2302	38.8	
T2	1102	45.3	-	-	3346	56.5	
T3	-	-	-	-	278	4.7	
Received ADT							<.001
No	2351	38.8	382	29.6	917	15.5	
Yes	3708	61.2	908	70.4	5009	84.5	
Duration of ADT (y)							<.001
<2	5685	93.8	1171	90.8	5018	84.7	
≥2	374	6.2	119	9.2	908	15.3	

Abbreviations as in Table 1.

who represented approximately 20% of the high-risk group. We showed that they have very similar 8-year PCSM compared with those with unfavorable intermediate-risk disease: 2.1% and 2.5%, respectively. In competing risks regression adjusting for age, year of treatment, receipt of EBRT, and receipt of ADT, there was no significant difference in PCSM between favorable high-risk and unfavorable intermediate-risk patients (AHR 1.17; $P=.710$). In contrast, patients with favorable high-risk disease had much lower 8-year PCSM than others with high-risk disease (2.1% vs 7.1%; AHR 0.42; $P=.049$). These findings were also validated within a large, national cancer database of radiation-managed patients and were robust to any potential differences in the duration of ADT received.

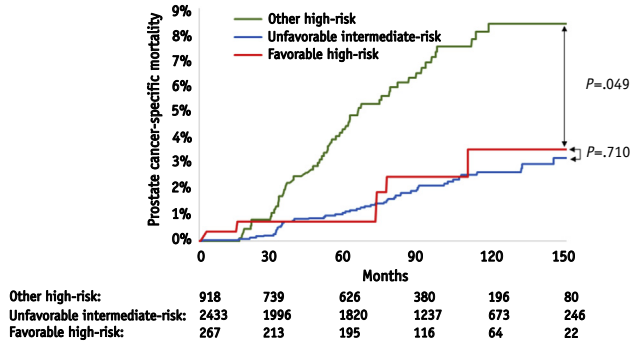

Fig. 1. Prostate cancer–specific mortality for the patients in the institutional cohort by risk group. The numbers of patients at risk are shown below the chart.

These findings suggest that men with favorable high-risk prostate cancer have significantly better outcomes than others with high-risk prostate cancer, which might allow for increased personalization of therapy. This personalization could be most relevant when determining the appropriate duration of ADT. Long-course ADT, consisting of 2 to 3 years of androgen suppression, is currently recommended for all men with high-risk disease by National

Table 3 Prostate cancer–specific mortality (PCSM) at 8 years for patients with unfavorable intermediate-isk, favorable high-risk, and other high-risk prostate cancer in the institutional cohort

Risk group	8-year PCSM (%)	HR (95% CI)	*P*
Unfavorable intermediate-risk disease	2.1		
Favorable high-risk disease	2.5		
Other high-risk disease	7.1		
MVA comparison			
Favorable high vs unfavorable intermediate		1.17 (0.50-2.75)	.710
Favorable high vs other high		0.42 (0.18-0.996)	.049
Unfavorable intermediate vs other high		0.36 (0.23-0.56)	<.001

Abbreviations: CI = confidence interval; HR = hazard ratio; MVA = multivariate analysis.
MVA includes adjustment for age, year of treatment, receipt of external beam radiation therapy, and receipt of androgen deprivation therapy.

Comprehensive Cancer Network and European Association of Urology guidelines (1, 2) based on the results of large randomized trials, including the European Organization for Research and Treatment of Cancer (EORTC) 22961 trial, the Radiation Therapy Oncology Group (RTOG) 9202 trial, and the Grupo de Investigación Clínica en Oncología Radioterápica (GICOR) DART 01/05 trial (4-6). All 3 trials showed improvements in cancer-specific outcomes or overall survival with long-course ADT compared with short-course ADT in patients with high-risk prostate cancer. However, the EORTC and RTOG trials included mostly patients with locally advanced (T3/T4) prostate cancer and did not include any patients with nonpalpable (T1c) disease, which is becoming a more common presentation for modern high-risk patients. Although the GICOR trial did include T1c patients, published data from the trial are not available to determine outcomes for the favorable high-risk subgroup. Therefore, it is not clear that the benefits of long-term versus short-term ADT would also apply to the favorable high-risk cohort identified in this study. Further, given their low 2.5% risk of PCSM at 8 years using radiation and mainly short-course ADT, the absolute magnitude of any potential benefit of long-course ADT would likely be small and would need to be weighed against the additional toxicity of longer-duration ADT (8-10).

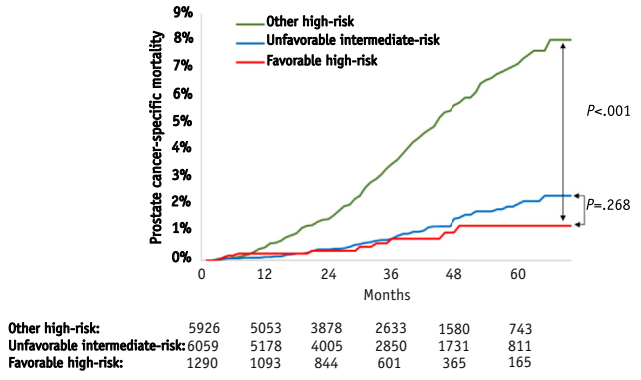

Fig. 2. Prostate cancer–specific mortality for the patients in the Surveillance, Epidemiology, and End Results–Medicare cohort by risk group. The numbers of patients at risk are shown below the chart.

On the other hand, for intermediate-risk disease, several trials have established short-course (4-6 months) ADT as beneficial and sufficient (21-23), and recent work suggests that this benefit may be limited to those with unfavorable intermediate-risk disease (14, 24-26). Because of their similar PCSM in this study, it is possible that patients with favorable high-risk disease and those with unfavorable intermediate-risk disease might be adequately treated with similar hormonal therapy.

Alternatively, one might consider favorable high-risk patients for treatment with 18 months of ADT given the preliminary results of a study that failed to prove the superiority of 36 months over 18 months of ADT for high-risk disease, but which has not been fully adopted owing to it being underpowered as a noninferiority trial (27). Although only a prospective, randomized, controlled noninferiority trial can definitively show that the duration of ADT can be safely shortened in the favorable high-risk subgroup, the low PCSM rates seen in this group make it unlikely that there would be a difference in such a trial.

Our findings also have implications for the design of clinical trials testing the marginal benefit of novel systemic therapies for men with high-risk disease. Given the low prostate cancer mortality rate in men with favorable high-risk disease, such patients are unlikely to significantly benefit from the addition of novel systemic therapies to long-term ADT. Therefore, future studies of additional agents are more likely to be successful if they exclude patients with favorable high-risk disease in favor of focusing on other high-risk patients, where a bigger benefit is likely to be seen.

These results highlight that patients with high-risk prostate cancer are a heterogeneous group. Other series that have subclassified patients with high-risk prostate cancer have focused on surgically managed patients. Recent data suggest that some patients with pathologic high-risk disease due to occult extracapsular extension (ie pT3a) may have better outcomes than those presenting with clinical T3 disease and similar outcomes as those with pathologic organ-confined disease (28). Three recent studies have shown that the presence of fewer high-risk features may predict for better cancer-specific outcomes among patients with high-risk prostate cancer treated with

Table 4 Prostate cancer–specific mortality (PCSM) at 5 years for patients with unfavorable intermediate-risk, favorable high-risk, and other high-risk prostate cancer

Risk group	5-year PCSM (%)	HR (95% CI)	*P*
Unfavorable intermediate-risk disease	2.0		
Favorable high-risk disease	1.3		
Other high-risk disease	7.2		
MVA comparison			
Favorable high vs unfavorable intermediate		0.67 (0.33-1.36)	.268
Favorable high vs other high		0.21 (0.11-0.41)	<.001
Unfavorable intermediate vs other high		0.31 (0.23-0.41)	<.001

Abbreviations as in Table 3.
MVA includes adjustment for age, year of diagnosis, and receipt of androgen deprivation therapy.

radical prostatectomy (3, 29, 30). Compared with prior work, the strengths of our study are that we demonstrate the presence of a favorable subgroup of high-risk disease within a radiation-managed cohort and show similar outcomes between favorable high-risk and unfavorable intermediate-risk disease. Importantly, unlike prior studies, our findings might be applied to personalize therapy for radiation-managed patients with favorable high-risk disease, particularly with regard to the duration of ADT to be used.

There are some potential limitations to our study. First, our results suggesting similar PCSM between patients with favorable high-risk and unfavorable intermediate-risk prostate cancer are based on retrospective data and therefore should be interpreted cautiously. We attempted to control for differences in treatment between the 2 groups, including duration of ADT, but it is possible that a third factor is responsible for the similar PCSM of these 2 groups of patients. Only a large randomized trial can account for all possible sources of selection bias.

Second, our classification system might not apply at the extremes of presentation. For example, a very young patient with favorable high-risk disease but 12 of 12 biopsy cores positive with nearly 100% involvement of each core would likely require aggressive therapy, including long-course ADT, owing to their relatively poor prognosis and long life expectancy. Therefore, clinical judgement should be exercised when applying our results.

Third, our derivation cohort consisted of patients treated at a single institution specializing in brachytherapy, which may represent a biased sample of radiation-managed patients. We attempted to address this limitation by validating our initial findings in a more general national cohort from the SEER-Medicare database and found very similar results.

Fourth, our validation cohort depended on the recorded values of PSA in the SEER database, which may contain a number of errors (18), possibly due to misplacement of an implied decimal point. However, in preliminary investigations by the SEER program, only 5% of PSA values led to incorrect classification of PSA among the 3 categories of values relevant to the present study (<10 ng/mL, 10-20 ng/mL, and >20 ng/mL) (17). Based on the observations in a recent quality analysis of the SEER database (19), we tried to account for this possible source of error by excluding patients who had discordant PSA values and recorded PSA interpretations (eg, PSA <4 ng/mL recorded as "positive/elevated," 4.2% of our initial cohort). In addition, we conducted sensitivity analyses in which these originally excluded patients were included in the analysis with or without adjustment for a presumed misplacement of the implied decimal point. Though our approach likely did not account for all possible errors in the SEER dataset, we observed similar results in the sensitivity analyses as in our main analysis. Although our results should be interpreted with caution given the possibility of erroneous data points, the low rate of incorrect categorization of PSA values combined with the results of our sensitivity analyses may be interpreted to support the validity of our findings.

Fifth, it is possible that there is a true, clinically significant difference in the risk of PCSM between patients with unfavorable intermediate-risk or favorable high-risk disease, but that we failed to detect it owing to inadequate power. This possibility is not likely given that our validation cohort had 13,275 patients and that the estimated adjusted hazard ratio was <1 (favoring patients with favorable high-risk disease) in that cohort.

Conclusion

Patients with favorable high-risk disease (T1c, Gleason 4 + 4 = 8, and PSA <10 ng/mL or T1c, Gleason 6, and PSA >20 ng/mL) have significantly better PCSM than other patients with high-risk disease and similar PCSM as those with unfavorable intermediate-risk disease. This new classification system may allow for personalization of treatment within high-risk disease.

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