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Assessment of the optimal number of positive biopsy cores to discriminate between cancer-specific mortality in high-risk versus very high-risk prostate cancer patients

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Abstract

Background: Number of positive prostate biopsy cores represents a key determinant between high versus very high-risk prostate cancer (PCa). We performed a critical appraisal of the association between the number of positive prostate biopsy cores and CSM in high versus very high-risk PCa.

Methods: Within Surveillance, Epidemiology, and End Results database (2010–2016), 13,836 high versus 20,359 very high-risk PCa patients were identified. Discrimination according to 11 different positive prostate biopsy core cut-offs (≥2–≥12) were tested in Kaplan–Meier, cumulative incidence, and multivariable Cox and competing risks regression models.

Results: Among 11 tested positive prostate biopsy core cut-offs, more than or equal to 8 (high-risk vs. very high-risk: $n = 18,986$ vs. $n = 15,209$, median prostate-specific antigen [PSA]: 10.6 vs. 16.8 ng/ml, <.001) yielded optimal discrimination and was closely followed by the established more than or equal to 5 cut-off (high-risk vs. very high-risk: $n = 13,836$ vs. $n = 20,359$, median PSA: 16.5 vs. 11.1 ng/ml, $p < .001$). Stratification according to more than or equal to 8 positive prostate biopsy cores resulted in CSM rates of 4.1 versus 14.2% (delta: 10.1%, multivariable hazard ratio: 2.2, $p < .001$) and stratification according to more than or equal to 5 positive prostate biopsy cores with CSM rates of 3.7 versus 11.9% (delta: 8.2%, multivariable hazard ratio: 2.0, $p < .001$) in respectively high versus very high-risk PCa.

Conclusions: The more than or equal to 8 positive prostate biopsy cores cutoff yielded optimal results. It was very closely followed by more than or equal to 5 positive prostate biopsy cores. In consequence, virtually the same endorsement may

Abbreviation: HR, high-risk; VHR, very high-risk.

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be made for either cutoff. However, more than or equal to 5 positive prostate biopsy cores cutoff, based on its existing wide implementation, might represent the optimal choice.

KEYWORDS
biopsy cores, high risk, NCCN, prostate cancer, very high risk

1 | INTRODUCTION

NCCN guidelines recommend distinguishing high-risk prostate cancer (PCa) patients according to the Johns Hopkins subclassifications that discriminates between high-risk versus very high-risk features.[1] This recommendation is based on a study by Sundi et al.,[2] where Kaplan–Meier methodology showed that very high-risk PCa patients treated with radical prostatectomy (RP) have worse biochemical-free, metastasis-free, cancer-specific, and overall survival, than their high-risk PCa counterparts.[2] Moreover, several publications investigated oncological outcomes in different treatment modalities of very high-risk PCa patients.[3–12]

One of the key features of the Johns Hopkins subclassifications rests on the number of positive prostate biopsy cores with Gleason grade group (GGG) pattern 4–5. Other features consist of cT-stage 3b-4, primary Gleason pattern 5 or two to three high-risk PCa features (pT3a, GGG 4/5, and prostate-specific antigen [PSA] ≥ 20 ng/ml). Of all features, the number of positive prostate biopsy cores represents the most contentious component, since relatively restricted data were used to determine the optimal number of positive prostate biopsy cores cutoff. Specifically, the original Johns Hopkins study relied on relatively small RP patient population (high-risk: $n = 639$, very high-risk: $n = 114$). The subsequent European validation relied on a larger sample (high-risk: $n = 2672$, very high-risk: $n = 1369$.[2,13] However, the proportion of patients with very high-risk PCa features was also limited in size ($n = 1369$). Similar limitations applied to two additional studies that relied on samples of 1981 (high-risk: $n = 1,379$, very high-risk: $n = 602$), and 203 (high-risk: $n = 100$, very high-risk: $n = 103$) patients.[14,15] In consequence, it is possible that within a larger epidemiological cohort of high and very high-risk PCa patients, a different cutoff for the number of positive prostate biopsy cores may be identified to better discriminate between high and very high-risk PCa. We tested this hypothesis within the Surveillance, Epidemiology and End Results (SEER) database (2010–2016).

2 | MATERIAL AND METHODS

2.1 | Study population

Within SEER database 2010–2016, we identified all patients more than or equal to 18 years old with histologically confirmed adenocarcinoma of the prostate, diagnosed at biopsy (International Classification of Disease for Oncology [ICD-O-3] code 8140 site code C61.9).[16] Cases identified through death certificate or at autopsy, as well as patients with or with unknown PSA, unknown histology, unknown cT-stage, unknown biopsy GGG, or metastatic prostate cancer and those without information about number of prostate biopsy cores or unknown number of positive prostate biopsy cores were excluded.

Only individuals that fulfilled high-risk NCCN PCa criteria were included, since high-risk PCa patients may then be classified as either high or very high-risk, according to the Johns Hopkins criteria.[1,2] In NCCN high-risk PCa patients, Johns Hopkins high-risk PCa was defined according to the presence of at least one of the following criteria: cT3a or GGG 4/5 or PSA more than 20 ng/ml. Johns Hopkins very high-risk PCa was defined according to the presence of at least one of the following criteria: cT3b–cT4 and/or primary Gleason pattern 5 and/or 2–3 high-risk features and/or more than or equal to 5 positive biopsy cores and biopsy pathology of GGG 4/5. Since biopsy GGG characteristics are unavailable for each separate biopsy core in the SEER database, we relied on more than or equal to 5 positive biopsy cores and biopsy pathology of GGG 4/5, as proxy, as previously reported.[17]

2.2 | Statistical analyses

The primary endpoint of the current analysis consisted of testing whether the current number of positive prostate biopsy cores cutoff of more than or equal to 5 may be replaced by a higher or lower value with better discriminant properties, based on cancer-specific mortality (CSM). To address this hypothesis, we defined 11 separate cutoffs for the number of positive prostate biopsy cores. These ranged from ≥2 to ≥12. Each of the 11 cut-offs was then integrated along with all other Johns Hopkins criteria to define high versus very high-risk PCa subgroups. Subsequently, the 11 different scenarios were tested in Kaplan–Meier and in multivariable Cox regression models with the objective of identifying the cutoff that optimally discriminates between high versus very high-risk PCa, according to CSM. Finally, the 11 different scenarios were retested in cumulative incidence plots and in multivariable competing risks regression (CRR) models, to expand the testing for the best CSM cutoff, after additional consideration and adjustment for other cause mortality (OCM), as previously reported.[18] All tests were two-sided with a level of significance set at $p < .05$ and R software environment for statistical computing and graphics (version 3.4.3) was used for all analyses.

TABLE 1 Descriptive characteristics of 34,195 high-risk prostate cancer patients, stratified according to high-risk versus very-high risk including either ≥5 or ≥8 positive cores per biopsy with Gleason grade group IV or V, diagnosed within the Surveillance, Epidemiology, and End Results database from 2010 to 2016

Variable		High-risk <5 cores *n* = 13,836 (40.5%)	Very high-risk ≥5 cores *n* = 20,359 (59.5%)	*p* value	High-risk <8 cores *n* = 18,986 (55.5%)	Very high-risk ≥8 cores *n* = 15,209 (44.5%)	*p* value
Age at diagnosis	Median (IQR)	67 (61–73)	68 (62–75)	<.001	67 (62–73)	68 (62–75)	<.001
PSA at diagnosis, ng/ml	Median (IQR)	16.5 (6.8–29.7)	11.9 (6.9–27.5)	<.001	10.6 (6.3–24.3)	16.8 (8.0–37.0)	<.001
PSA at diagnosis, ng/ml	<20	7253 (52.4)	13412 (65.9)	<.001	12383 (65.2)	8282 (54.5)	<.001
	≥20	6583 (47.6)	6947 (34.1)		6603 (34.8)	6927 (45.5)	
Number of biopsy cores	Median (IQR)	12 (12–12)	12 (12–13)	<.001	12 (12–12)	12 (12–13)	<.001
Number of positive biopsy cores	Median (IQR)	3 (2–6)	8 (6–11)	<.001	4 (3–6)	9 (6–12)	<.001
Percentage of positive cores per biopsy	Median (IQR)	30 (20–60)	70 (50–90)	<.001	40 (20–60)	80 (60–100)	<.001
cTstage	cT1	8577 (62.0)	9094 (44.7)	<.001	11502 (60.6)	6169 (40.6)	<.001
	cT2	4345 (31.4)	7643 (37.5)		6570 (34.6)	5418 (35.6)	
	cT3a	914 (6.6)	1465 (7.2)		914 (4.8)	1465 (9.6)	
	cT3b	0 (0)	1659 (8.1)		0 (0)	1659 (10.9)	
	cT4	0 (0)	498 (2.4)		0 (0)	498 (3.3)	
Gleason Grade group at biopsy	1	1913 (13.8)	110 (0.5)	<.001	1913 (10.1)	110 (0.7)	<.001
	2	2923 (21.1)	362 (1.8)		2923 (15.4)	362 (2.4)	
	3	2635 (19)	442 (2.2)		2635 (13.9)	442 (2.9)	
	4	4967 (35.9)	9875 (48.5)		8411 (44.3)	6431 (42.3)	
	5	1398 (10.1)	9570 (47.0)		3104 (16.3)	7864 (51.7)	
cN stage	cN0	13172 (95.2)	17878 (87.8)	<.001	18011 (94.9)	13039 (85.7)	<.001
	cN1	492 (3.6)	2127 (10.4)		751 (4)	1868 (12.3)	
	cNx	172 (1.2)	354 (1.7)		224 (1.2)	302 (2)	
Treatment	RP	4060 (29.3)	4333 (21.3)	<.001	5636 (29.7)	2757 (18.1)	<.001
	EBRT	4870 (35.2)	8472 (41.6)		7004 (36.9)	6338 (41.7)	
	BT	315 (2.3)	374 (1.8)		411 (2.2)	278 (1.8)	
	No local treatment	2765 (20.0)	3836 (18.8)		3321 (17.5)	3280 (21.6)	
	BT + EBRT	718 (5.2)	1201 (5.9)		1079 (5.7)	840 (5.5)	
	RP + EBRT	688 (5.0)	1560 (7.7)		1009 (5.3)	1239 (8.1)	
	RT + RP	2 (0)	6 (0)		2 (0)	6 (0)	
	Unknown	418 (3.0)	577 (2.8)		524 (2.8)	471 (3.1)	
pT	pT2	2368 (58.3)	1511 (34.9)	<.001	3139 (55.7)	740 (26.8)	<.001
	pT3	1625 (40.0)	2701 (62.3)		2402 (42.6)	1924 (69.8)	
	pT4	11 (0.3)	60 (1.4)		16 (0.3)	55 (2.0)	
	pTx	56 (1.4)	61 (1.4)		79 (1.4)	38 (1.4)	

(Continues)

TABLE 1 (Continued)

Variable		High-risk <5 cores *n* = 13,836 (40.5%)	Very high-risk ≥5 cores *n* = 20,359 (59.5%)	*p* value	High-risk <8 cores *n* = 18,986 (55.5%)	Very high-risk ≥8 cores *n* = 15,209 (44.5%)	*p* value
Gleason score at RP	6	282 (6.9)	49 (1.1)	<.001	301 (5.3)	30 (1.1)	<.001
	7	2598 (64)	1932 (44.6)		3440 (61)	1090 (39.5)	
	8–10	1088 (26.8)	2229 (51.4)		1763 (31.3)	1554 (56.4)	
	Unknown	92 (2.3)	123 (2.8)		132 (2.3)	83 (3.0)	
pN stage	pN0	3161 (77.9)	3205 (74)	<.001	4434 (78.7)	1932 (70.1)	<.001
	pN1	225 (5.5)	709 (16.4)		364 (6.5)	570 (20.7)	
	pNx	674 (16.6)	419 (9.7)		838 (14.9)	255 (9.2)	
Race/ethnicity	Caucasian	8374 (60.5)	13397 (65.8)	<.001	11897 (62.7)	9874 (64.9)	<.001
	African American	2824 (20.4)	3383 (16.6)		3588 (18.9)	2619 (17.2)	
	Hispanic	1375 (9.9)	1870 (9.2)		1803 (9.5)	1442 (9.5)	
	Unknown/Other	1263 (9.1)	1709 (8.4)		1698 (8.9)	1274 (8.4)	

Abbreviations: EBRT, external beam radiation therapy; IQR, Interquartile range; RP, radical prostatectomy.

3 | RESULTS

3.1 | Descriptive characteristics of the established high and very high-risk PCa study population

According to the established, Johns Hopkins criteria that relied on more than or equal to 5 positive prostate biopsy cores with GGG 4/5, 20,359 (59.5%) patients were classified as very high-risk PCa and 13,836 as high-risk PCa, among the total population of 34,195.

Here, high-risk PCa patients harbored significantly higher PSA (16.5 vs. 11.1 ng/ml, $p < .001$), more frequently underwent RP (29.3 vs. 21.3%, $p < .001$), less frequently underwent external beam radiation therapy ([EBRT], 35.2 vs. 41.6%, $p < .001$). In the RP subgroup ($n = 8393$), at final pathology, very high-risk PCa patients more frequently harbored more than or equal to pT3-stage (63.7 vs. 40.3%, $p < .001$) and Gleason 8–10 (51.4 vs. 26.8%, $p < .001$, Table 1).

3.2 | Descriptive analyses of the application of 11 different number of positive prostate biopsy cores cut-offs

When more than or equal to 2 positive prostate biopsy cores were used as cutoff, the proportions of very high-risk PCa patients were 75.0% (Table 2). When cutoffs of more than or equal to 3 up to more than or equal to 12 were applied, the proportion of very high-risk PCa decreased from: 70.2% to 35.1%. According to the 11 different cutoffs for the number of positive prostate biopsy cores, the distribution of median PSA values also demonstrated a variation that ranged from 10.1 (cutoff ≥ 2) to 23.1 (cut-off ≥ 12) in very high-risk PCa patients. Conversely, in the subgroup of RP patients, more than or equal to pT3-stage demonstrated less variability that ranged from 18.0 (cutoff ≥ 12) to 19.3% (cutoff ≥ 6) in very high-risk patients.

In Kaplan–Meier plots, 6-year CSM rate for the established more than or equal to 5 positive prostate biopsy cores cutoff was 3.9 versus 12.9% (delta: 9.0%) in respectively high versus very high-risk PCa (Figure 1A). The application of the alternative 10 cutoffs that ranged from ≥2 to ≥12 positive prostate biopsy cores resulted in respectively 6-year CSM rates that were 4.1 versus 10.8% (delta: 6.7%), 4.1 versus 11.3% (delta: 7.2%), 4.0 versus 12.0% (delta: 8.0%), 4.1 versus 13.7% (delta: 9.6%), 4.3 versus 14.8% (delta: 10.5%), 4.4 versus 15.5% (delta: 11.1%), 4.7 versus 15.9% (delta: 11.2%), 4.8 versus 16.4% (delta: 11.6%), 4.9 versus 16.9% (delta: 12.0%), and 5.0 versus 17.3% (delta: 12.3%).

In multivariable Cox regression models, the application of the established Johns Hopkins more than or equal to 5 positive prostate biopsy cores cutoff resulted in a hazard ratio [HR] of 2.0 for very high-risk versus high-risk PCa (Figure 1B). The application of the alternative 10 cutoffs resulted into HRs that were respectively 1.5, 1.7, 1.8, 2.1, 2.2, 2.1, 2.1, 2.1, and 2.1 for cutoffs from more than or equal to 2, up to more than or equal to 12 positive prostate biopsy cores. Virtually identical findings were recorded for CSM rates in cumulative incidence plots and in multivariable CRR models, where additional adjustment for OCM was made (Table 3 and Figure 2-4).

4 | DISCUSSION

Previous studies that created and validated the definition of high and very high-risk prostate cancer were based on relatively small patient samples.[2,13–15] Specifically, those studies had limited ability to test the number of positive prostate biopsy cores as a discriminating

TABLE 2 Univariable and multivariable Cox regression models, after adjustment for cT-stage, cN-stage, age at diagnosis, year at diagnosis, PSA, and Gleason grade group (GGG) predicting cancer-specific mortality for eleven different positive biopsy core cutoffs with GGG 4/5

	Univariable			Multivariable			
	HR	95% CI	*p* value	HR	95% CI	*p* value	Very high-risk sample size
High-risk (Ref.)	1	–	–	1	–	–	
≥2 cores and GGG 4–5	2.75	2.33-3.24	<0.001	1.50	1.12–2.02	.006	75.0%
≥3 cores and GGG 4–5	3.03	2.59-3.54	<0.001	1.72	1.36–2.18	<.001	70.2%
≥4 cores and GGG 4–5	3.19	2.76-3.69	<0.001	1.77	1.44–2.16	<.001	65.1%
≥5 cores and GGG 4–5	3.56	3.10-4.09	<0.001	2.00	1.67–2.40	<.001	59.5%
≥6 cores and GGG 4–5	3.73	3.27-4.26	<0.001	2.05	1.74–2.43	<.001	54.3%
≥7 cores and GGG 4–5	3.91	3.45-4.43	<0.001	2.12	1.82–2.48	<.001	48.4%
≥8 cores and GGG 4–5	4.04	3.59-4.56	<0.001	2.17	1.86–2.52	<.001	44.5%
≥9 cores and GGG 4–5	4.00	3.56-4.50	<0.001	2.08	1.79–2.41	<.001	41.5%
≥10 cores and GGG 4–5	4.06	3.62-4.56	<0.001	2.09	1.81–2.42	<.001	39.2%
≥11 cores and GGG 4–5	4.11	3.67-4.60	<0.001	2.12	1.83–2.45	<.001	36.8%
≥12 cores and GGG 4–5	4.12	3.68-4.60	<0.001	2.10	1.81–2.42	<.001	35.1%

Note: Very high-risk definition consisted of primary Gleason score pattern 5 or cT3b-4, or ≥ below stated of positive cores and GGG 4–5 or multiple high-risk features.

Abbreviations: HR, hazard ratio, CI, confidence interval; PSA, prostate-specific antigen.

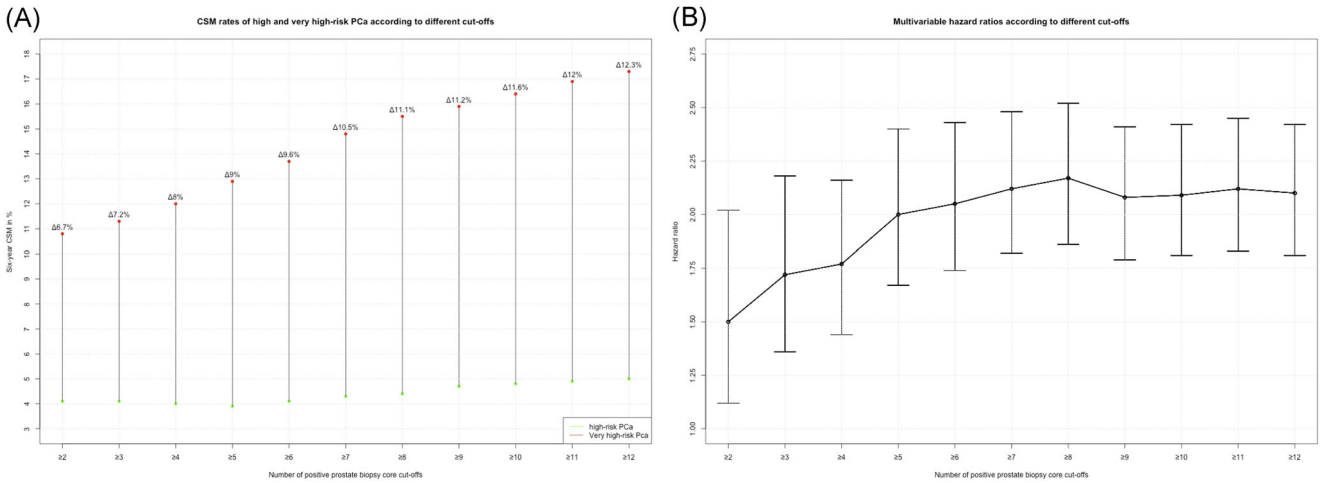

FIGURE 1 Plots depicting (A) 6-year cancer-specific mortality (CSM) rates of high-risk versus very high-risk prostate cancer (PCa) derived from Kaplan–Meier methodology for 11 tested cutoffs of number of prostate biopsy cores and (B) Cox regression derived multivariable hazard ratios for all tested cut-offs

feature between high and very high-risk PCa, since few study subjects harbored more than or equal to 5 positive prostate biopsy cores, in addition to a limited sample size of very high-risk PCa, in general. In consequence, it could be postulated that testing of alternative values more than or equal to 5 positive prostate biopsy cores in the definition of very high-risk PCa may result in better CSM discrimination. We tested this hypothesis in a large epidemiological cohort of 34,195 high-risk PCa patients that qualified for stratification between high versus very high-risk, according to Johns Hopkins criteria. Our patients were identified within the SEER 2004–2016 database, regardless of administered treatment type. Our study resulted in several noteworthy observations).

First, high and very high-risk PCa patients exhibited important differences regarding PSA at diagnosis, but not for pT-stage, when 11 tested cut-offs for positive prostate biopsy cores were applied and compared. These differences validate the need to adjust for these baseline prostate cancer characteristics, such as PSA at diagnosis, in analyses such as ours.[19,20] Multivariable adjustment is also indirectly

TABLE 3 Univariable and multivariable competing risk regression models, after adjustment for cT-stage, cN-stage, age at diagnosis, year at diagnosis, PSA, Gleason grade group (GGG), and other-cause mortality, predicting cancer-specific mortality for eleven different positive biopsy core cutoffs with GGG 4/5

	Univariable			Multivariable			
	HR	95% CI	*p* value	HR	95% CI	*p* value	Very high-risk sample size
High-risk (Ref.)	1	–	–	1	–	–	
≥2 cores and GGG 4–5	2.73	2.31–3.22	<.001	1.50	1.15–1.95	.002	75.0%
≥3 cores and GGG 4–5	3.01	2.57–3.51	<.001	1.72	1.39–2.13	<.001	70.2%
≥4 cores and GGG 4–5	3.16	2.73–3.66	<.001	1.76	1.46–2.13	<.001	65.1%
≥5 cores and GGG 4–5	3.51	3.06–4.03	<.001	1.99	1.67–2.37	<.001	59.5%
≥6 cores and GGG 4–5	3.67	3.22–4.18	<.001	2.04	1.73–2.40	<.001	54.3%
≥7 cores and GGG 4–5	3.83	3.38–4.43	<.001	2.10	1.80–2.45	<.001	48.4%
≥8 cores and GGG 4–5	3.96	3.51–4.46	<.001	2.15	1.85–2.49	<.001	44.5%
≥9 cores and GGG 4–5	3.92	3.49–4.40	<.001	2.06	1.78–2.39	<.001	41.5%
≥10 cores and GGG 4–5	3.97	3.54–4.55	<.001	2.08	1.80–2.41	<.001	39.2%
≥11 cores and GGG 4–5	4.01	3.58–4.49	<.001	2.11	1.83–2.43	<.001	36.8%
≥12 cores and GGG 4–5	4.01	3.59–4.49	<.001	2.08	1.80–2.41	<.001	35.1%

Note: Very high-risk definition consisted of primary Gleason score pattern 5 or cT3b-4, or ≥ below stated of positive cores and GGG 4–5 or multiple high-risk features.

Abbreviations: HR, hazard ratio, CI, confidence interval; PSA, prostate-specific antigen.

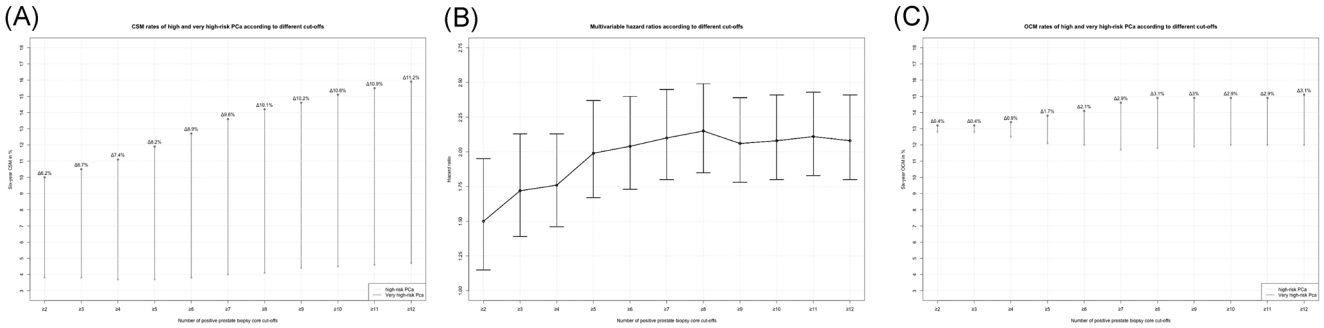

FIGURE 2 Plots depicting (A) 6-year cancer-specific mortality (CSM) rates of high-risk versus very high-risk prostate cancer (PCa), derived from cumulative incidence methodology, for 11 tested cutoffs of number of prostate biopsy cores, after adjustment for other cause mortality (OCM) and (B) competing risks regression model derived multivariable hazard ratios for all tested cutoffs and (C) 6-year OCM rates of high-risk versus very high-risk PCa for all tested cutoffs, after adjustment for CSM

performed in clinical decision making, where the distinction between high versus very high-risk is made based on simultaneous input from multiple variables.

In the second part of the analyses, we tested 11 positive prostate biopsy core cutoffs to discriminate between high versus very high-risk PCa patients, according to CSM. In multivariable Cox regression, as well as in multivariable competing risks regression models, a number of positive prostate biopsy core cutoff ≥8 yielded optimal findings. Specifically, a plateau was observed, when multivariable HRs from Cox regression, as well as from multivariable competing risks regression models were recorded, tabulated, and plotted (Figures 1 and 2 and Tables 2 and 3). The plateau-effect resulted in HRs that ranged from 2.17 (≥8) to 2.12 (≥12), using both modeling techniques, where Cox regression modeling does not account for OCM, but competing risks regression models does. The use of number of positive prostate biopsy core cutoff more than or equal to 5 ranked close, based on the consideration of the same criteria. In consequence, ideally a cutoff based on more than or equal to 8 positive prostate biopsy cores should be recommended. However, the marginal difference that separates the cutoff more than or equal to 8 relative to more than or equal to 5 positive prostate biopsy cores in addition to the established status of more than or equal to 5 cutoff

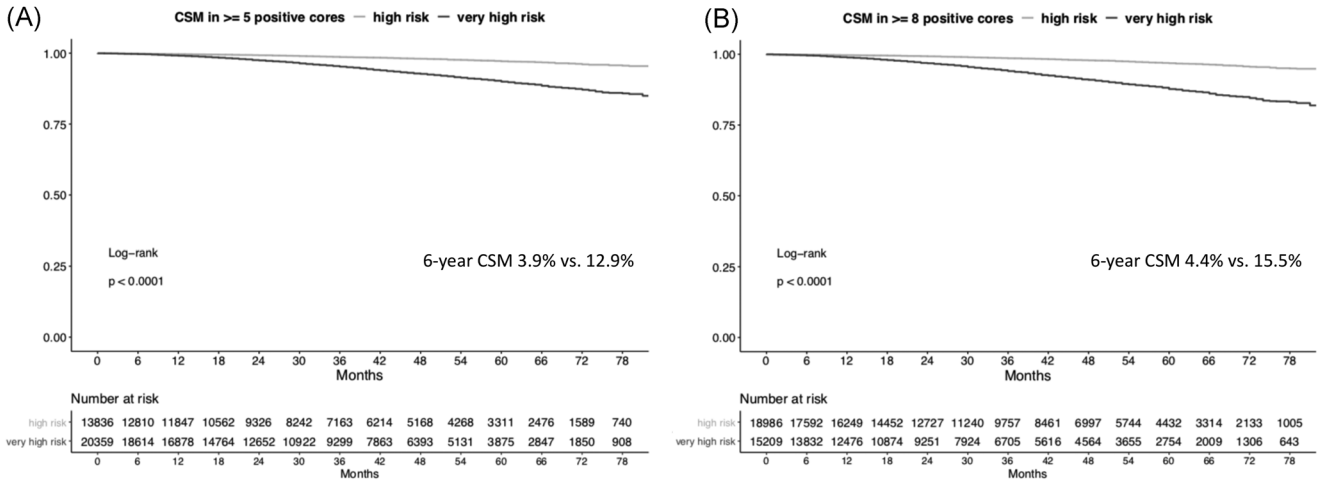

FIGURE 3 Kaplan–Meier plots depicting cancer-specific mortality (CSM) in high-risk versus very high-risk prostate cancer for ≥5 (A) or ≥8 (B) positive biopsy cores with Gleason grade group IV/V

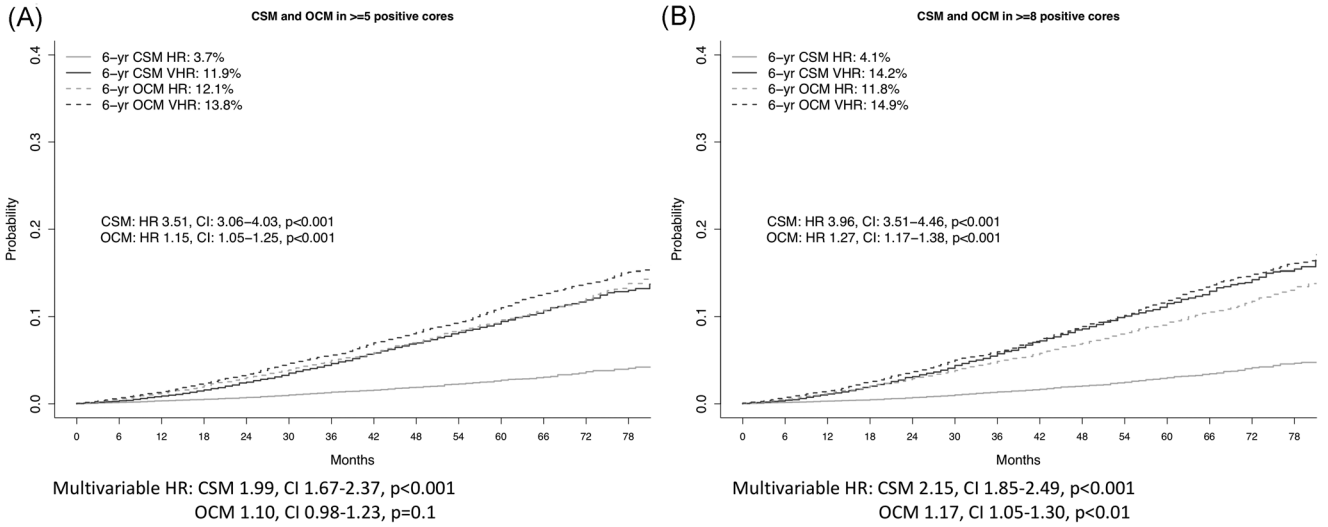

FIGURE 4 Cumulative incidence plots depicting cancer-specific mortality (CSM) after adjusting for other cause mortality (OCM) in high-risk versus very high-risk prostate cancer for ≥5 (A) or ≥8 (B) positive biopsy cores with Gleason grade group IV/V

both argue in favor of preferentially endorsing the more than or equal to 5 cutoff. This endorsement is based on its established role and use in clinical practice. Moreover, validation of an established cutoff, obviates the need for introducing a new cutoff that many clinicians may not be familiar with. Moreover, it obviates the need for further testing and confirmatory studies of a new cutoff of more than or equal to 8 positive prostate biopsy core. Such studies may be difficult to complete due to the relative rarity of very high-risk PCa, even in multi-institutional and/or epidemiological databases. Bases on the rarity of high-risk and even greater rarity of very high-risk PCa, it is difficult to directly compare our cohort to other previous cohorts of high versus very high-risk PCa patients that were used to devise the cut-off based on more than or equal to 5 positive prostate biopsy cores, in the original Johns Hopkins study, as well as in subsequent validation studies.[2,13,14] However, the current study patients clearly share prostate cancer characteristics (e.g., higher PSA in high-risk vs. very high-risk PCa patients with the established ≥5 positive prostate biopsy core cutoff) with those from previous studies. However, unlike most previous studies, the current cohort included a larger proportion of EBRT patients. In consequence, the current findings are more generalizable to EBRT patients than in previous publications. To better validate our findings, we relied on competing risks regression models that adjusted CSM for OCM and yielded virtually the same results as Cox methodology. This is particularly important, since OCM needs to be considered in survival analyses of localized PCa patients, where most die of OCM.[21,22]

However, unlike previous studies that relied on smaller sample sizes from predominately single- or multi-institutional databases, our study provided less detail and granularity regarding PCa characteristics. For example, we relied on the number of positive prostate

biopsy cores in patients with biopsy GGG 4/5 as a proxy for number of positive prostate biopsy core with GGG 4/5. This limitation is noteworthy. However, the agreement between our observations regarding the ideal positive prostate biopsy cores' cutoff and that recorded in previous studies suggests that this limitation is far from being rate limiting. However, the applied proxy does not ideally account for tumor volume of high grade PCa biopsy cores. Other large-scale databases should therefore ideally be used for additional validations of the number of positive prostate biopsy cores. Unfortunately, some of very high-quality databases, such as the National Cancer Database do not provide CSM rates. Instead, they only provide overall mortality rates. Additionally, alternative databases that ideally include observations from outside of North America should be also sought. Moreover, other PCa characteristics such as molecular markers will also help in the future to further distinguish patients into high and very high-risk PCa.

Taken together, our findings validated the current NCCN classification according to high-risk versus very high-risk PCa that is based on the number of positive prostate biopsy cores cutoff of more than or equal to 5. However, we also found that a cutoff of more than or equal to 8 positive biopsy cores discriminates CSM rates between high-risk versus very-risk PCa marginally better. In consequence, despite marginally better performance of the more than or equal to 8 positive biopsy core cutoff, the current cutoff of more than or equal to 5 positive prostate biopsy cores appears ideal based on its established role and familiarity. These observations are important and represent a significant contribution. Nonetheless, they should be interpreted in the context of some limitations. These consist of retrospective and population-based design of our database. Moreover, the distinction between high-risk and very high-risk prostate cancer can only be made in SEER database since the year 2010, when number of positive prostate biopsy cores became available. This fact unfortunately restricts CSM rate calculations to maximal follow-up of 6 years. Moreover, important information regarding lesions and number of biopsy cores obtained from magnet resonance imaging targeted biopsy are unavailable in the SEER database and could not be assessed in the current study.[23–25] Moreover, no central review of prostate biopsies was performed.

5 | CONCLUSION

The more than or equal to 8 positive prostate biopsy cores cutoff yielded optimal results. It was very closely followed by more than or equal to 5 positive prostate biopsy cores. In consequence, virtually the same endorsement may be made for either cutoff. However, more than or equal to 5 positive prostate biopsy cores cutoff, based on its existing wide implementation, might represent the optimal choice.

CONFLICT OF INTERESTS

The research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

ETHICS STATEMENT

All analyses and their reporting followed the SEER reporting guidelines. Due to the anonymously coded design of the SEER database, study-specific Institutional Review Board ethics approval was not required. Patient consent statement, permission to reproduce material from other sources and clinical trial registration: Not applicable.

DATA AVAILABILITY STATEMENT

Data will be made available for bona fide researchers on request.

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