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Survival after Radical Prostatectomy versus Radiation Therapy in High-Risk and Very High-Risk Prostate Cancer

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Abbreviations and Acronyms

CRR [competing risks regression
CSM [cancer-specific mortality
EBRT [external beam radiotherapy
GGG [Gleason Grade Group
GS [Gleason score
HR [high risk
JH [Johns Hopkins University
NCCN□ [National Comprehensive Cancer Network□
OCM [other cause mortality
PCa [prostate cancer
PSA [prostate specific antigen
PSM [propensity score matching
RP [radical prostatectomy
SEER [Surveillance, Epidemiology, and End Results
VHR [very high risk

Purpose: Our goal was to compare cancer-specific mortality (CSM) rates between radical prostatectomy (RP) vs external beam radiotherapy (EBRT) in National Comprehensive Cancer Network□ (NCCN□) high risk (HR) patients, as well as in Johns Hopkins University (JH) HR and very high risk (VHR) subgroups.

Materials and Methods: Within the Surveillance, Epidemiology, and End Results database (2010e2016), we identified 24,407 NCCN HR patients, of whom 10,300 (42%) vs 14,107 (58%) patients qualified for JH HR vs VHR, respectively. Overall, 9,823 (40%) underwent RP vs 14,584 (60%) EBRT. Cumulative incidence plots and competing-risks regression addressed CSM after 1:1 propensity score matching (according to age, prostate specific antigen, clinical T and N stages, and biopsy Gleason score) between RP and EBRT patients. All analyses addressed the combined NCCN HR cohort, as well as in JH HR and JH VHR subgroups.

Results: In the combined NCCN HR cohort 5-year CSM rates were 2.3% for RP vs 4.1% for EBRT and yielded a multivariate hazard ratio of 0.68 (95% CI 0.54e0.86, p <0.001) favoring RP. In VHR patients 5-year CSM rates were 3.5% for RP vs 6.0% for EBRT, yielding a multivariate hazard ratio of 0.58 (95% CI 0.44e0.77, p <0.001) favoring RP. Conversely, in HR patients no significant difference was recorded between RP vs EBRT (HR 0.7, 95% CI 0.39e1.25, p [0.2).

Conclusions: Our data suggest that RP holds a CSM advantage over EBRT in the combined NCCN HR cohort, and in its subgroup of JH VHR patients.

Key Words: prostatic neoplasms, prostatectomy, radiotherapy, risk

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A total of 17% to 31% of newly diagnosed clinically localized prostate cancers (PCas) will be classified as high risk (HR; defined as Gleason sum 8–10, or prostate specific antigen [PSA] >20 ng/ml, or clinical stage ≥T3) according to the National Comprehensive Cancer Network® (NCCN®) definition.[1,2] Within NCCN HR patients, respectively 85% and 15% will be classified as HR (presence of at least 1 of the following criteria: cT3a or Gleason Grade Group [GGG] IV/V or PSA >20ng/ml) vs very high risk (VHR; presence of at least 1 of the following criteria: cT3b-cT4 and/or primary Gleason pattern 5 and/or 2–3 HR features and/or ≥5 positive biopsy cores with GGG IV/V), according to the original Johns Hopkins University (JH) classification and its adaptations.[3,4]

It is of note that, when JH criteria are used, VHR patients displayed worse oncologic outcomes (biochemical recurrence, metastasis-free survival and cancer-specific mortality [CSM]) independently of all other features when compared with their HR counterparts.[4,5] Both JH HR and VHR patients qualify for either radical prostatectomy (RP) or external beam radiotherapy (EBRT) when curative intent is sought.[6] However, to the best of our knowledge no large-scale, population-based analyses tested which treatment modality may hold an advantage regarding CSM, especially in JH HR or VHR patients. We addressed this data gap. We hypothesized that no CSM difference exists between RP vs EBRT. Our analyses addressed the entire HR population, according to NCCN definition. Moreover, we repeated all analyses in 2 separate subgroups, namely 1) JH HR and 2) JH VHR. Our analyses distinguished themselves from previous reports by propensity score matching (PSM) and competing risks regression (CRR) to address if biases exist between RP vs EBRT patients.

MATERIAL AND METHODS

Study Population

Within Surveillance, Epidemiology, and End Results (SEER) database (2010–2016),[7] we identified and included all RP or EBRT-treated patients ≥18 years old with histologically confirmed adenocarcinoma of the prostate, diagnosed at biopsy (ICD-O-3 code 8140, site code C61.9) who fulfilled HR NCCN PCa criteria. Patients with missing vital status, unknown PSA, unknown clinical T, N, M stages, unknown biopsy Gleason score (GS) and autopsy or death certificate only cases were excluded (fig. 1). Subsequently, we stratify NCCN HR patients between 1) JH HR and 2) JH VHR. Since biopsy GGG characteristics are unavailable for each separate biopsy core in the SEER database, we relied on ≥5 positive biopsy cores with biopsy pathology of GGG IV/V as proxy, according to previously defined methodology.[8] 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.

Within the SEER database that focuses on PCa, CSM was defined as deaths attributable to PCa. Conversely, other cause mortality (OCM) was defined as deaths attributable to other causes than PCa.[9] The exact cause of death was obtained from death certificates, which are coded by the state health department or state vital records.[10]

Followup was defined as time from diagnosis to CSM, OCM, loss to followup or end of study. These criteria equally applied to RP and EBRT patients. In both groups censoring occurred at end of the available observation, unless the event of interest (CSM or OCM) occurred. Censoring was applied nondifferentially to both RP and EBRT patients.

Statistical Analyses

Descriptive statistics included medians and interquartile ranges, as well as frequencies and proportions for continuous and categorical variables, respectively. The statistical significance of differences in medians and proportions was evaluated with the Wilcoxon and chi-square tests.

The primary objective of the analyses was to test for differences in CSM between RP and EBRT in the entire cohort of NCCN HR patients. The secondary objective of the analyses was to repeat survival analyses within JH HR and JH VHR subgroups. Formal interaction testing was performed to statistically validate the subgroup approach that distinguished between JH HR vs JH VHR.

In all analyses, we relied on 1:1, nearest neighbor PSM[11] with a caliper of 0.1 to match RP patients with similar EBRT patients according to age, biopsy GS, clinical T and N stages, and PSA (in 1 ng/ml intervals). The final matched data sets were analyzed without any control or adjustment for matched pairs. Second, cumulative incidence plots to illustrated CSM rates. Third, multivariable CRR (Fine-Gray) tested for CSM differences between matched RP vs EBRT patients, after adjustment for OCM, age and race. In the analyses of the matched NCCN HR cohort, we also added to the CRR model JH risk category, as well as the interaction term defined by JH risk groups (HR vs VHR) and treatments (RP vs EBRT).

For all statistical analyses R software environment for statistical computing and graphics (version 3.4.3, The R Foundation, Vienna, Austria) was used. All tests were 2-sided with a level of significance set at $p < 0.05$.

RESULTS

Study Population

We identified 24,407 NCCN HR PCa patients. Of those, 9,823 (40%) underwent RP vs 14,584 (60%) EBRT. Of those, 10,300 (42%) harbored JH HR vs 14,107 (58%) harbored JH VHR PCa. Of JH HR patients, 4,863 (47%) were treated with RP vs 5,437 (53%) with EBRT. Of JH VHR patients, 4,960 (35%) were treated with RP and 9,147 (65%) with EBRT.

In general, EBRT patients were older (median age 71 [IQR 65, 76] vs 64 [59, 68] years), harbored higher PSA values (median 13 [IQR 7, 27] vs 8 [IQR 6, 20] ng/ml) and higher clinical T and N stages (table 1). Similarly, 5-year OCM rates were higher in EBRT (12%, 95% CI 12–13) vs RP patients (3.4%, 95% CI 2.9–3.9).

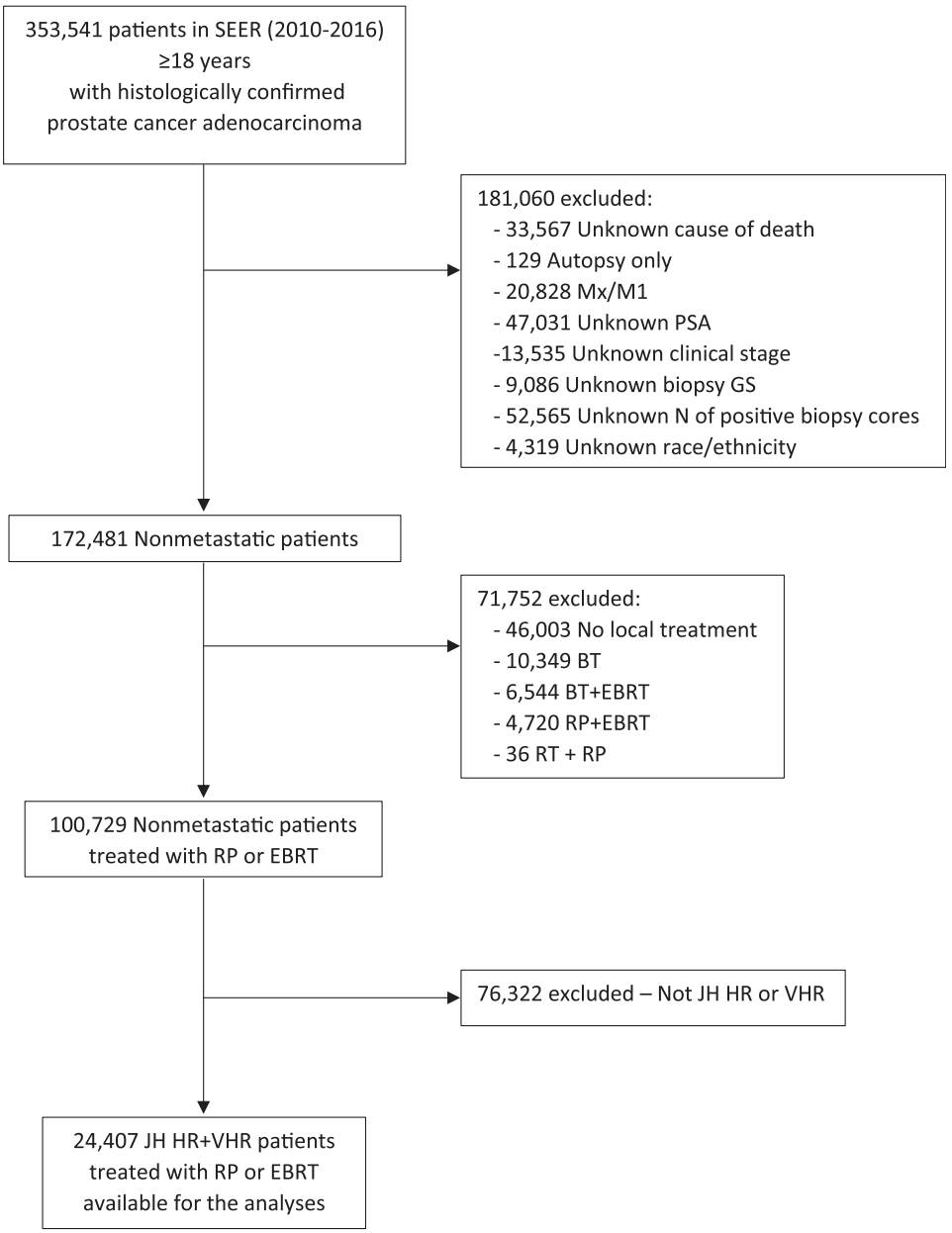

Figure 1. Patient selection flowchart. BT, brachytherapy.

PSM (1:1) and CRR Models in the Overall NCCN HR Cohort

One-to-one PSM was applied to the entire cohort of NCCN HR patients (24,407), of whom 9,823 were treated with RP vs 14,584 with EBRT. PSM resulted in 2 equally sized groups of 7,363 RP vs 7,363 EBRT patients, with no residual statistically significant differences in age, PSA, biopsy GS, and clinical T and N stages (supplementary table 1, A, and supplementary fig. 1, https://www.jurology.com). The median followup durations of patients without an event were 41 vs 35 months for RP vs EBRT. The number of patients followed for at least 60 months without an event was 1,745 for RP vs 1,588 for EBRT.

In cumulative incidence plots depicting CSM at 5 years of followup, rates were 2.3% (95% CI 1.9e2.9) for RP vs 4.1% (95% CI 3.4e4.8) for EBRT ($p < 0.01$, fig. 2). The latter translated into a multivariate competing-risks hazard ratio of 0.68 (95% CI 0.54e0.86, $p < 0.001$) favoring RP, after adjustment for OCM, race and JH risk category. It is noteworthy that JH VHR group exhibited independent predictor status for higher CSM (HR 4.2, 95% CI 3.12e5.67, $p < 0.001$, table 2) relative to JH HR group. However, no statistically significant interaction was identified between JH risk groups and treatment type for CSM (HR 0.71, 95% CI 0.39e1.31, p [0.27).

Table 1. Descriptive characteristics of 24,407 nonmetastatic NCCN HR PCa patients within SEER database (2010e2016) stratified according to treatment type and JH risk groups

Characteristic	Treatment Type					JH Risk Group				
	RP		EBRT		p Value*	HR		VHR		p Value*
Total No. pts	9,823		14,584			10,300		14,107		
Median yrs age at diagnosis (IQR)	64	(59, 68)	71	(65, 76)	<0.001	67	(61, 72)	68	(62, 74)	<0.001
Median ng/ml PSA (IQR)	8	(6, 20)	13	(7, 27)	<0.001	11	(6, 26)	10	(6, 22)	
No. race/ethnicity (%):					<0.001					
African American	1,390	(14)	2,775	(19)		1,944	(19)	2,221	(16)	
Asian	662	(6.7)	940	(6.4)		708	(6.9)	894	(6.3)	
Caucasian	6,878	(70)	9,472	(65)		6,634	(64)	9,716	(69)	
Hispanic	893	(9.1)	1,397	(9.6)		1,014	(9.8)	1,276	(9.0)	
No. clinical T stage (%):					<0.001					
cT1	5,211	(53)	7,482	(51)		6,338	(62)	6,355	(45)	
cT2	3,370	(34)	5,138	(35)		3,185	(31)	5,323	(38)	
cT3a	824	(8.4)	1,006	(6.9)		777	(7.5)	1,053	(7.5)	
cT3b	377	(3.8)	776	(5.3)		0	(0)	1,153	(8.2)	
cT4	41	(0.4)	182	(1.2)		0	(0)	223	(1.6)	
No. clinical N stage (%):					<0.001					
cN0	8,728	(89)	13,819	(95)		9,883	(96)	12,664	(90)	
cN1	1,068	(11)	572	(3.9)		341	(3.3)	1,299	(9.2)	
cNX	27	(0.3)	193	(1.3)		76	(0.7)	144	(1.0)	
No. biopsy GS (%):					<0.001					
3þ3	642	(6.5)	587	(4.0)		1,142	(11)	87	(0.6)	
3þ4	983	(10)	1,254	(8.6)		1,980	(19)	257	(1.8)	
3þ5	460	(4.7)	522	(3.6)		252	(2.4)	730	(5.2)	
4þ3	755	(7.7)	1,239	(8.5)		1,708	(17)	286	(2.0)	
4þ4	4,369	(44)	5,915	(41)		4,027	(39)	6,257	(44)	
4þ5	2,043	(21)	3,552	(24)		1,191	(12)	4,404	(31)	
5þ3	90	(0.9)	140	(1.0)		0	(0)	230	(1.6)	
5þ4	363	(3.7)	930	(6.4)		0	(0)	1,293	(9.2)	
5þ5	118	(1.2)	445	(3.1)		0	(0)	563	(4.0)	
No. JH risk group (%):					<0.001					
HR	4,863	(50)	5,437	(37)			-		-	
VHR	4,960	(50)	9,147	(63)			-		-	
No. treatment (%):										<0.001
RP		-		-		4,863	(47)	4,960	(35)	
EBRT		-		-		5,437	(53)	9,147	(65)	

* Wilcoxon rank sum-test; Pearson's chi-squared test.

PSM (1:1) and CRR Models in Johns Hopkins VHR Group

One-to-one PSM was applied to JH VHR patients (14,107), of whom 4,960 were treated with RP vs 9,147 with EBRT. PSM resulted in 2 equally sized groups of 4,020 RP vs 4,020 EBRT, with no residual statistically significant differences in age, PSA, biopsy GS, and clinical T and N stages (supplementary table 1, B, and supplementary fig. 2, https://www.jurology.com). The median followup durations of patients without an event were 39 vs 33 months for RP vs EBRT. The number of patients followed for at least 60 months without an event was 847 for RP vs 788 for EBRT.

In cumulative incidence plots depicting CSM at 5 years of followup, rates were 3.5 (95% CI 2.7e4.4) vs 6.0% (95% CI 4.9e7.2, p <0.001, fig. 3) which translated into a competing-risks multivariate hazard ratio of 0.58 (95% CI 0.44e0.77, p <0.01, table 2) favoring RP, after adjusting for OCM and race.

PSM (1:1) and CRR Models in JU HR Group

One-to-one PSM was applied to JH HR patients (10,300), of whom 4,863 were treated with RP vs 5,437 with EBRT. PSM resulted in 2 equally sized groups of 3,207 RP vs 3,207 EBRT, with no residual statistically significant differences in age, PSA, biopsy GS, and clinical T and N stages (supplementary table 1, C, and supplementary fig. 3, https://www.jurology.com). The median followup durations of patients without an event were 44 vs 38 months for RP vs EBRT. The number of patients followed for at least 60 months without an event was 888 for RP vs 784 for EBRT.

In cumulative incidence plots depicting CSM at 5 years of followup, rates were 0.7% (95% CI 0.4e1.2) vs 1.2% (95% CI 0.7e1.8, p [0.1, fig. 4) for RP vs EBRT, respectively, which translated into a multivariate competing risks statistically insignificant hazard ratio of 0.7 (95% CI 0.39e1.25, p [0.2, table 2).

DISCUSSION

We hypothesized that no difference exists in CSM rates of NCCN HR patients treated with RP vs EBRT. Moreover, we hypothesized that no difference exists in CSM rates between RP vs EBRT patients after further stratification according to JH HR vs VHR definitions. We tested these 3 hypotheses

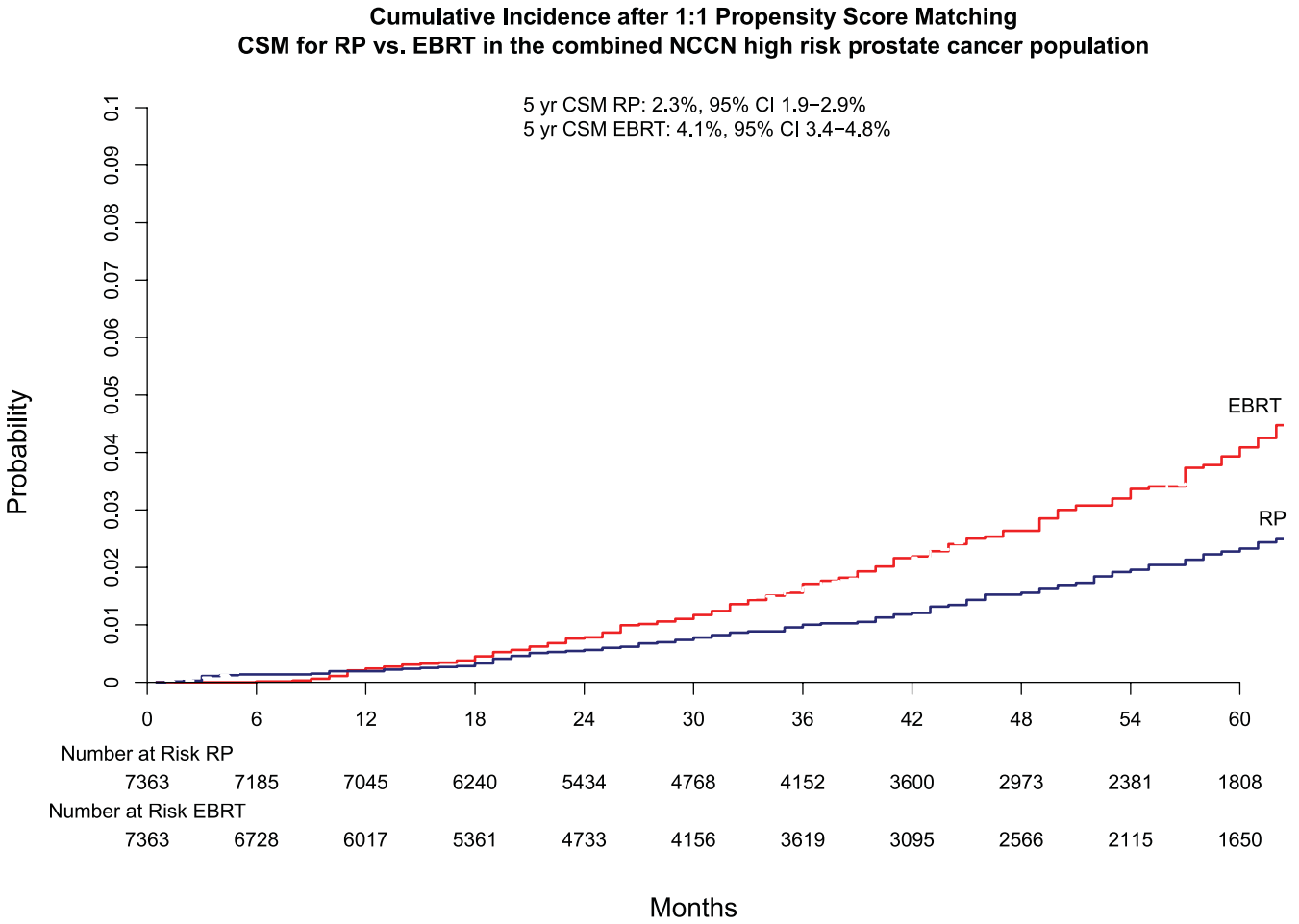

Figure 2. Cumulative incidence plots after 1:1 PSM depicting CSM after adjusting for OCM in RP vs EBRT in NCCN HR PCa patients.

within a large, population-based sample of JH HR and VHR patients treated with RT vs EBRT. Our study resulted in several noteworthy observations.

First, we observed very important differences in age, PSA, clinical stage and biopsy GS characteristics of RP patients, relative to their EBRT

Table 2. Multivariable CRR models testing for difference in CSM between RP vs EBRT after 1:1 PSM (according to age, biopsy GS, clinical T and N stages, PSA) within SEER database (2010e2016)

	CSM		OCM	
	HR (95% CI)	p Value	HR (95% CI)	p Value
		Combined NCCN HR (14,726 pts)		
RP vs EBRT	0.68 (0.54e0.86)	<0.001	0.37 (0.31 - 0.45)	<0.001
Race/ethnicity:				
African Americans	1.18 (0.89e1.57)	0.26	1.11 (0.92e1.34)	0.29
Asians	0.39 (0.18e0.83)	0.01	0.64 (0.43e0.96)	0.03
Hispanic/Latinos	0.89 (0.58e1.36)	0.58	0.71 (0.52e0.97)	0.03
VHR vs HR	4.2 (3.12e5.67)	<0.001	1.13 (0.97e1.33)	0.12
		JH HR (6,414 pts)		
RP vs EBRT	0.7 (0.39e1.25)	0.22	0.36 (0.28e0.47)	<0.001
Race/ethnicity:				
African Americans	1.66 (0.86e3.21)	0.13	0.94 (0.7e1.26)	0.68
Asians	0.74 (0.18e3.13)	0.68	0.53 (0.28e1)	0.05
Hispanic/Latinos	1.53 (0.63e3.7)	0.35	0.9 (0.59e1.37)	0.63
		JH VHR (8,040 pts)		
RP vs EBRT	0.58 (0.44e0.77)	<0.001	0.41 (0.33e0.52)	<0.001
Race/ethnicity:				
African Americans	1.1 (0.78e1.55)	0.58	1.25 (0.97e1.62)	0.08
Asians	0.4 (0.16e0.98)	0.04	0.61 (0.34e1.1)	0.1
Hispanic/Latinos	0.88 (0.54e1.44)	0.62	0.68 (0.45e1.04)	0.08

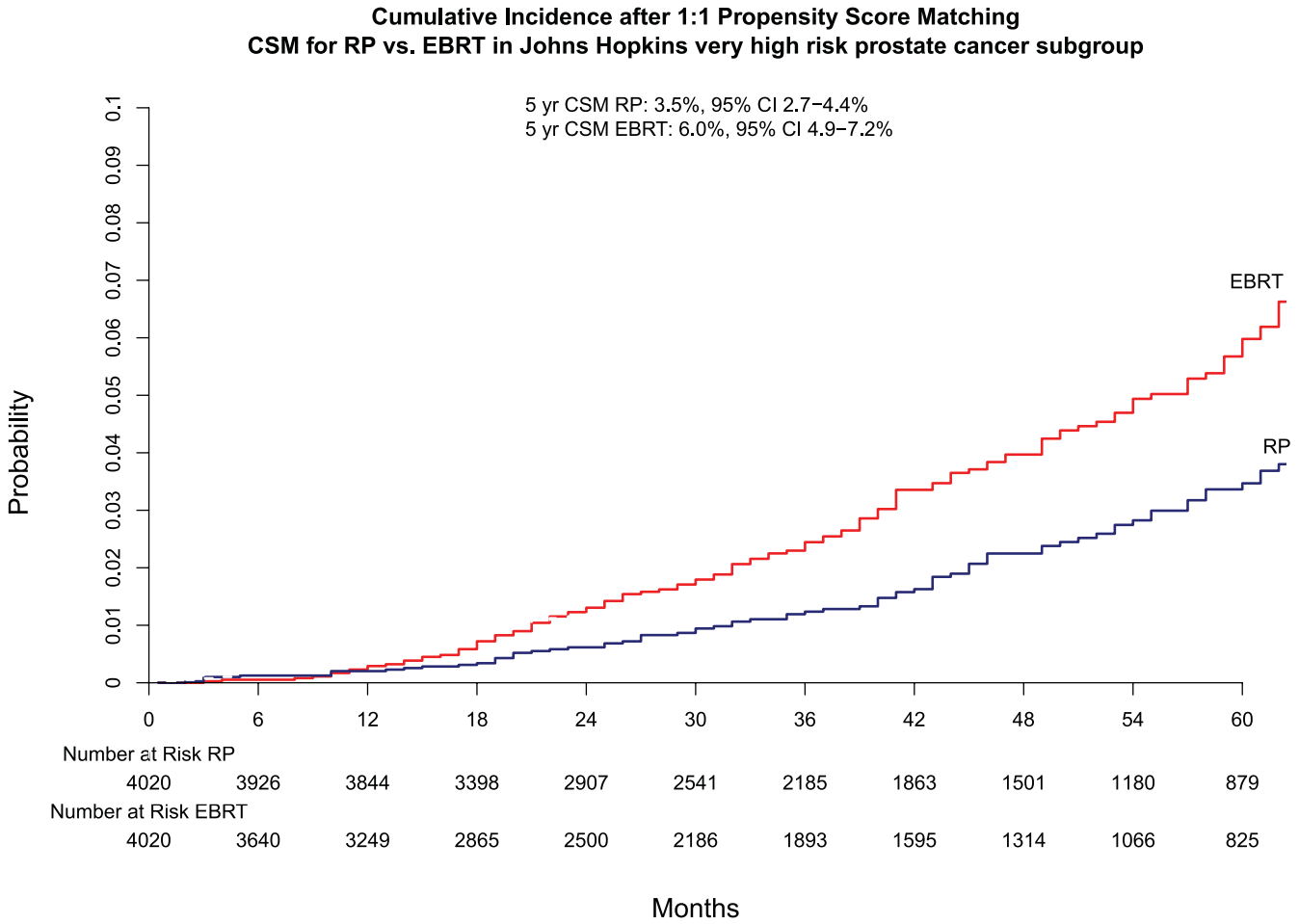

Figure 3. Cumulative incidence plots after 1:1 PSM depicting CSM after adjusting for OCM in RP vs EBRT in JH VHR PCa patients.

counterparts (table 1). In consequence, we applied PSM and additional multivariable adjustments to control for such differences. Similar methodology was previously applied in comparisons between RP vs EBRT. However, these comparisons did not specifically focus on NCCN HR patients, neither did they stratify between HR vs VHR according to JH criteria.[12,13]

Second, we observed very important differences in OCM between RP and EBRT patients. In consequence, we relied on CRR, where CSM rates are adjusted for OCM rates. This approach was not used in previous analyses of HR and/or VHR patients. However, even the strictest and most detailed adjustment methods (PSM, CRR etc) cannot fully account for potential residual differences between compared groups.[14]

Third, after PSM, we tested for CSM differences in the entire cohort of NCCN HR patients, which includes JH HR and VHR. Here, we observed 5-year CSM rates of 2.3% vs 4.1% for RP vs EBRT, respectively, which yielded a highly statistically significant protective hazard ratio of 0.68 (95% CI 0.54e0.86, p <0.001) favoring RP. In consequence, in NCCN HR patients, RP holds a CSM advantage over EBRT.

Fourth, despite lack of statistically significant interaction between risk groups (HR vs VHR) and treatments (RP vs EBRT), based on clinical considerations we also tested for CSM differences between RP vs EBRT patients in JH HR and VHR groups. In VHR patients, we identified clinically meaningful and statistically significant CSM rate differences (3.5% vs 6.0%) favoring RP, which translated into a multivariate hazard ratio of 0.58 (95% CI 0.44e0.77, p <0.001) favoring RP. In consequence, in JH VHR patients RP holds a CSM advantage over EBRT. Conversely, no statistically significant CSM difference between RP vs EBRT was recorded in JH HR patients. It is noteworthy that the number of CSM events in the JH HR cohort (48) was insufficient to fulfill 80% power and 0.05, 2-sided alpha requirements that called for approximately 247 CSM events. In consequence, within JH HR patients valid conclusions about CSM differences between RP vs EBRT cannot be made. Nonetheless, our analysis revealed a higher CSM rate in JH VHR vs JH HR patients, which validates the clinical pertinence of JH classification.

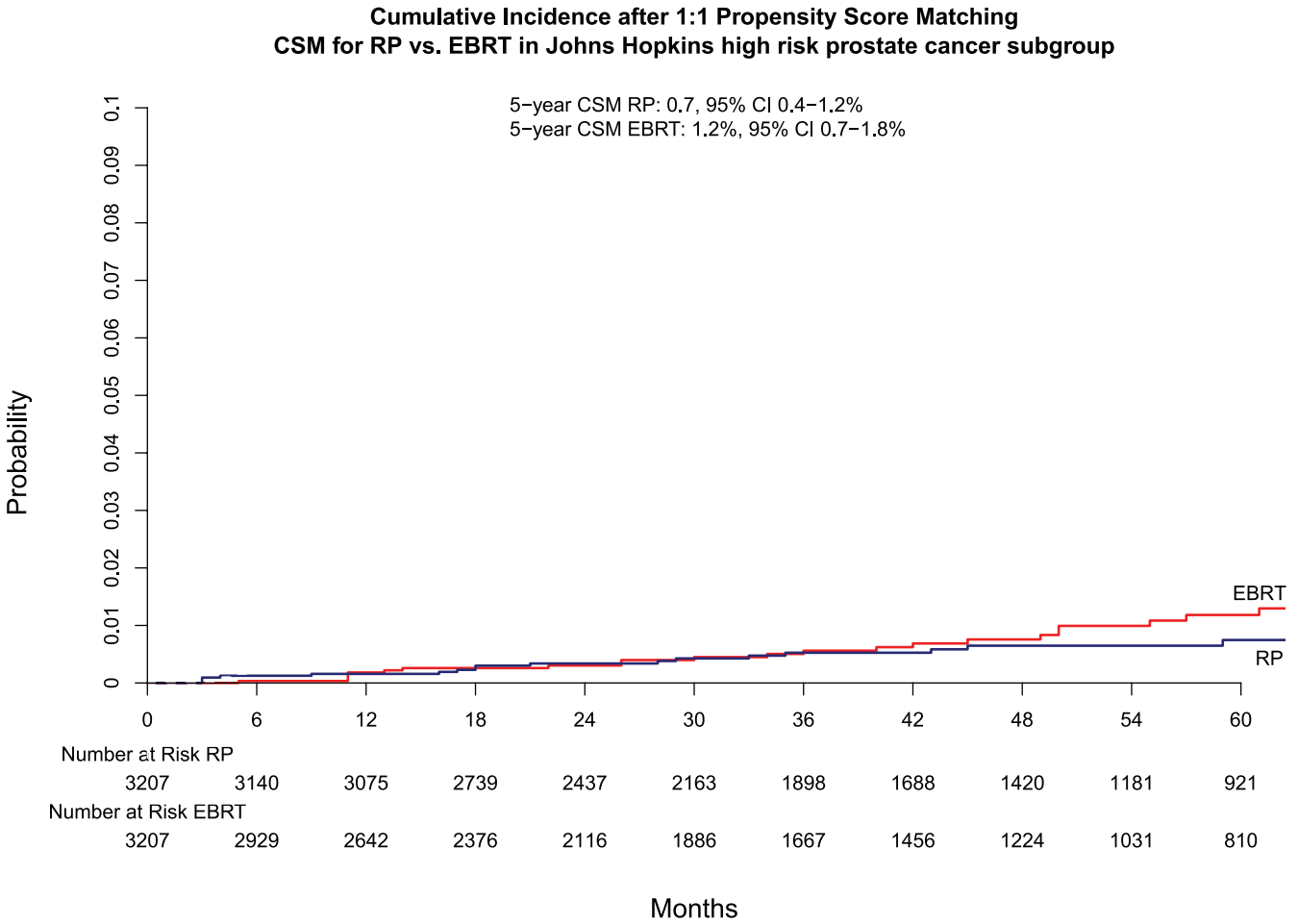

Figure 4. Cumulative incidence plots after 1:1 PSM depicting CSM after adjusting for OCM in RP vs EBRT in JH HR PCa patients.

Previous studies only partially or indirectly addressed similar hypotheses to our study.[12,15e18] For example, Knipper et al observed a CSM difference favoring RP vs EBRT in biopsy GS 9e10 patients, that represents a fraction of the current study population.[12,15] To the best of our knowledge, we are the first to test for CSM differences after stratification between JH HR and VHR in a large-scale, population-based cohort. In consequence, our findings cannot be directly compared with other studies.

Several limitations of our study need to be mentioned. First, since SEER is an observational database, data are retrospective. However, this also applies to other institutional studies, which previously addressed RP vs EBRT in NCCN HR patients.[17,18] This limitation should be considered in the context of currently unavailable randomized, controlled trials comparing RP vs EBRT in the combined NCCN HR population. The ongoing prospective trial comparing RP vs EBRT in locally advanced PCa (SPCG-15)[19] will not be able to stratify between JH HR vs VHR, due to the rarity of the latter. Moreover, its sample size of 1,200 patients may be underpowered based on the observed 1.8% (in the combined NCCN HR population) or 2.5% (in JH VHR population) absolute difference in 5-year CSM rates, which may require some 3,500 patients per arm within a prospective randomized trial powered at 80% with 2-sided alpha of 0.05.[20] Second, the SEER database does not include information regarding comorbidities, which could affect treatment assignment. However, we relied on adjustment for OCM, which represents a well-established proxy of significant comorbidities.[12,21,22] Unfortunately, only the SEER-Medicare database allows the concomitant use of comorbidities and OCM. However, it only holds a fraction (approximately 30%) of the SEER database population used in the current analyses.[23] In consequence, SEER-Medicare derived observations may be more precise, but less robust. Conversely, the National Cancer Database does not allow assessment of CSM, since only OSM is available in that database.[24] Regional and multi-institutional databases hold even smaller number of patients and in consequence are even less

well-suited for the comparison at hand. For example, the North American database that was used to define the JH criteria of HR and VHR PCa included 753 NCCN HR patients, of which 15% were VHR.[3] The JH stratification was later validated within a North American multi-institutional cohort of 1,091 NCCN HR patients (of whom 30.4% were VHR), as well as within a single-center European database of 4,041 NCCN HR patients (of whom 33.9% were VHR).[4,5] Additionally, absence of earlier cancer-control outcomes such as biochemical recurrence, progression-free survival or metastatic progression may also be criticized. However, these end points are clearly not as definitive and not as established as the ultimate end point of CSM. Unfortunately, post-procedure complications, side effects, quality of life and other important variables are not included in the SEER database and therefore cannot be assessed. Finally, the absence of central pathology review and the lack of information on the type and duration of androgen deprivation and type and dosage of radiation therapy may represent additional limitations. All SEER-based analyses share these limitations.

CONCLUSIONS

After adjustment for OCM and baseline PCa clinical characteristics, our data show that RP is associated with lower CSM in NCCN HR patients when compared to EBRT. Moreover, our analyses provide evidence of a benefit for RP vs EBRT in the JH VHR subgroup.

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EDITORIAL COMMENTS

Management of HR PCa centers on local therapy with either RP or EBRT, but there is a lack of knowledge regarding relative survival benefits of these modalities. Using the retrospective SEER database (2010–2016), Chierigo et al assessed CSM in men undergoing RP (9,823) vs EBRT (14,584) for HR disease. To better address potential biases, subjects were propensity score matched by age, clinical stage, PSA and GS prior to analysis using CRR. Overall, the authors observed a protective effect of RP relative to EBRT (CSM HR 0.68, 95% CI 0.54–0.86). Interestingly, this finding was observed in the subgroup of patients meeting Johns Hopkins' VHR criteria (HR 0.58, 95% CI 0.44–0.77) but not those that only met HR criteria (HR 0.7, 95% CI 0.39–1.25).

The current study provides a uniquely large-scale comparison that appropriately considers confounding factors and competing risks. Nonetheless, it is important our conclusions remain measured in light of the known limitations of these retrospective, population-based data. While statistical approaches such as PSM help adjust for known confounders, these methods are unlikely to fully account for the disparate nature of the study populations.[1] Moreover, as the authors acknowledge, information regarding androgen deprivation therapy use was not available for the current analysis—a notable limitation in light of the study outcome.

Thus, these data contribute to a developing picture, but solving this puzzle will ultimately require rigorous prospective trials in line with the ongoing SPGC-15 (reference 19 in article). Until these trials are performed, it is critical that we carefully consider the strengths, limitations and applicability of the clinical data shared in the course of counseling.

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In a comparative outcomes study, Chierigo et al examined the impact of RP vs EBRT on the outcome of 24,407 patients with PCa in the SEER database who are classified as HR by NCCN guidelines. They observed that RP was associated with more favorable cancer-specific mortality in these individuals, especially in men who were further classified as VHR by the JH criteria.

The authors are aware of the limitations of the SEER data and did an excellent job trying to mitigate these using PSM and competing risk regression, which distinguishes their work from previous reports (references 12 and 13 in article). However, due to the presence of unobserved confounders, there is inevitably some residual bias associated with using retrospective registry data that cannot be accounted for. Such a limitation can be only overcome using randomized clinical trials data, such as the SPCG-15. Unfortunately, conducting such trials is difficult, expensive and takes a long time. Thus, in the meanwhile, and especially for specific subgroups such as the JH VHR, which are unlikely to be addressed separately in a trial, retrospective reports such as the one by Chierigo et al represents the highest level of evidence available.

Interestingly, Chierigo et al show encouraging outcomes for patients with HR PCa treated surgically, which corroborate other recent reports and refute the historical belief that such patients are inappropriate surgical candidates and cannot be cured surgically (references 12 and 15 in the article). Such information is very helpful in counseling patients, while keeping in mind the limitations of retrospective data.

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