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ORIGINAL ARTICLE

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Non-cancer mortality in elderly prostate cancer patients treated with combination of radical prostatectomy and external beam radiation therapy

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Abstract

Background: To test for rates of other cause mortality (OCM) and cancer-specific mortality (CSM) in elderly prostate cancer (PCa) patients treated with the combination of radical prostatectomy (RP) and external beam radiation therapy (EBRT) versus RP alone, since elderly PCa patients may be over-treated.

Methods: Within the Surveillance, Epidemiology and End Results database (2004–2016), cumulative incidence plots, after propensity score matching for cT-stage, cN-stage, prostate specific antigen, age and biopsy Gleason score, and multivariable competing risks regression models (socioeconomic status, pathological Gleason score) addressed OCM and CSM in patients (70–79, 70–74, and 75–79 years) treated with RP and EBRT versus RP alone.

Results: Of 18,126 eligible patients aged 70–79 years, 2520 (13.9%) underwent RP and EBRT versus 15,606 (86.1%) RP alone. After propensity score matching, 10-year OCM rates were respectively 27.9 versus 20.3% for RP and EBRT versus RP alone ($p < .001$), which resulted in a multivariable HR of 1.4 ($p < .001$). Moreover, 10-year CSM rates were respectively 13.4 versus 5.5% for RP and EBRT versus RP alone. In subgroup analyses separately addressing 70–74 year old and 75–79 years old PCa patients, 10-year OCM rates were 22.8 versus 16.2% and 39.5 versus 24.0% for respectively RP and EBRT versus RP alone patients (all $p < .001$).

Conclusion: Elderly patients treated with RP and EBRT exhibited worrisome rates of OCM. These higher than expected OCM rates question the need for combination therapy (RP and EBRT) in elderly PCa patients and indicate the need for better patient selection, when combination therapy is contemplated.

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KEYWORDS
other cause mortality, overtreatment, radiation, radical prostatectomy, survival

1 | INTRODUCTION

After radical prostatectomy (RP), radiation therapy may be administered either in adjuvant or salvage settings. Four prospective randomized controlled trials (RCT) showed significantly lower 10-year rates of biochemical recurrence (BCR) after RP and adjuvant external beam radiation therapy (EBRT), relative to RP alone.[1–4] However, only one of these four RCTs showed higher rates of 10-year overall survival after RP and EBRT versus RP alone.[1] In all four studies, the majority of patients were aged less than 70 years (median age range: 61–65 years). Moreover, only one of these four studies stratified overall survival analyses according to patients' age.[2] Here, patients ≥70 years exhibited significantly higher overall mortality after RP and EBRT versus RP alone (hazard ratio [HR]: 2.9). In consequence, guidelines only recommend adjuvant EBRT in highly select RP patients: Namely in those with positive surgical margins and/or Gleason score 8–10, ≥pT3 or pN1-stage.[5,6]

To add to the above controversy, no prospective data demonstrated a survival benefit after salvage EBRT, regardless of age, including elderly patients.[7,8] To address these knowledge gaps that particularly apply to elderly patients (70–79 years), we examined other cause mortality rates (OCM) in elderly prostate cancer patients treated with RP and EBRT, relative to elderly prostate cancer patients treated with RP alone. We postulated that equally favorable and equally low OCM rates should apply to RP and EBRT treated elderly patients, as to their elderly counterparts treated with RP alone. We further stratified the population of interest (70–79 years) between 70 and 74 and 75–79 age groups to provide more age-specific results. We tested this hypothesis within the 2004–2016 Surveillance, Epidemiology, and End Results (SEER) database.

2 | MATERIALS AND METHODS

2.1 | Study population

The current SEER database samples over one-third of the US population and approximates it in demographic composition and cancer incidence.[9] Within SEER database 2004–2016, we identified all National Comprehensive Cancer Network (NCCN) intermediate and high risk patients aged 70–79 years with biopsy diagnosed and histologically confirmed adenocarcinoma of the prostate (International Classification of Disease for Oncology [ICD-O-3] code 8140 site code C61.9), treated with RP or RP + EBRT.[10] Low risk prostate cancer patients were excluded since the preferred treatment strategy in those patients is active surveillance or observation, according to NCCN guidelines.[6] Cases only identified at autopsy or death certificate were excluded. Moreover, patients with unavailable prostate specific antigen (PSA) or metastatic prostate cancer were excluded. Finally, patients treated with brachytherapy were excluded. All analyses focused either on treatment with EBRT after RP versus RP alone. These selection criteria resulted in a cohort of 18,126 elderly prostate cancer patients.

2.2 | Statistical analyses

Descriptive statistics included frequencies and proportions for categorical variables. Means, medians, and interquartile ranges (IQRs) were reported for continuously coded variables. The χ^2 tested the statistical significance in proportions' differences. The *t* test and Kruskal–Wallis test examined the statistical significance of means' and distributions' differences.

Treatment rates with RP or RP + EBRT were tabulated before and after full adjustment for baseline PCa characteristics (PSA, cT-stage, biopsy Gleason grade groups [GGG]) in a multinomial model.[11] Here, a predicted treatment probability was calculated for each patient. Afterwards, treatment probabilities of each patient in the age categories 70–79 years were averaged for both treatment types.

We relied on propensity score matching for age at diagnosis, T-stage, N-stage, PSA, and biopsy Gleason score for comparisons between RP and EBRT versus RP alone, aged 70–79 years (1:2 matching). Subsequently, matching was repeated for purpose of the same comparisons in patients aged 70–74 years (1:2 matching), as well as in patients aged 75–79 years (1:1 matching). The aim of propensity score matching was to maximally reduce differences between differences that are due to age and/or prostate cancer characteristics. Cumulative incidence plots were applied to the matched populations and depicted OCM and cancer-specific mortality (CSM) rates. Additional multivariable competing risks regression models were fitted after further adjustment for socioeconomic status and pathological Gleason score, in addition to providing OCM rates that are adjusted for CSM and vice-versa. 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.[12]

3 | RESULTS

3.1 | Descriptive characteristics of the study population

Of 18,126 eligible elderly prostate cancer (70–79 years aged) patients, 2520 (13.9%) underwent RP and EBRT versus 15,606 (86.1%) RP alone (Table 1). Median age was respectively

TABLE 1 Descriptive characteristics of 18,126 prostate cancer patients aged 70–79, stratified according treatment with radical prostatectomy (RP) versus RP and external beam radiotherapy (EBRT) diagnosed within the surveillance, epidemiology, and end results database between 2004 to 2016

Variable		Overall, *n* = 18,126	RP, *n* = 15,606 (86.1%)	RP + EBRT, *n* = 2520 (13.9%)	*p* Value
Age at diagnosis	Median (IQR)	72 (71–74)	72 (71–74)	73 (71–75)	<.001
PSA, ng/ml	Median (IQR)	7.0 (5.1–10.8)	6.9 (5.0–10.3)	8.8 (5.5–16.1)	<.001
Follow-up, months	Median (IQR)	69 (35–103)	70 (37–104)	59 (29–95)	<.001
Biopsy GGG	1	2022 (11.2)	1856 (11.9)	166 (6.6)	<.001
	2	6653 (36.7)	6080 (39)	573 (22.7)	
	3	3298 (18.2)	2884 (18.5)	414 (16.4)	
	4	2800 (15.4)	2280 (14.6)	520 (20.6)	
	5	2021 (11.1)	1373 (8.8)	648 (25.7)	
	Unknown	1332 (7.3)	1133 (7.3)	199 (7.9)	
D'Amico risk	intermediate	10976 (60.6)	9988 (64.0)	988 (39.2)	<.001
	High risk	7150 (39.4)	5618 (36.0)	1532 (60.8)	
cT-stage	cT1	9513 (52.5)	8214 (52.6)	1299 (51.5)	<.001
	cT2	7231 (39.9)	6357 (40.7)	874 (34.7)	
	cT3	618 (3.4)	431 (2.8)	187 (7.4)	
	cT4	77 (0.4)	14 (0.1)	63 (2.5)	
	cTx	687 (3.8)	590 (3.8)	97 (3.8)	
cN-stage	cN0	17084 (94.3)	14859 (95.2)	2225 (88.3)	<.001
	cN1	862 (4.8)	613 (3.9)	249 (9.9)	
	cNx	180 (1)	134 (0.9)	46 (1.8)	
pT-stage	pT2	10494 (57.9)	10255 (65.7)	239 (9.5)	<.001
	pT3	5826 (32.1)	4943 (31.7)	883 (35.0)	
	pT4	144 (0.8)	108 (0.7)	36 (1.4)	
	pTx	1662 (9.2)	300 (1.9)	1362 (54.0)	
pN-stage	pN0	11132 (61.4)	10255 (65.7)	877 (34.8)	<.001
	pN1	815 (4.5)	593 (3.8)	222 (8.8)	
	pNx	6179 (34.1)	4758 (30.5)	1421 (56.4)	
Pathological Gleason	6	952 (5.3)	940 (6.0)	12 (0.5)	<.001
	7	6108 (33.7)	5790 (37.1)	318 (12.6)	
	8–10	2194 (12.1)	1803 (11.6)	391 (15.5)	
	Unknown	8872 (48.9)	7073 (45.3)	1799 (71.4)	
Race/ethnicity	Caucasian	13587 (75.0)	11739 (75.2)	1848 (73.3)	<.001
	African American	1308 (7.2)	1078 (6.9)	230 (9.1)	
	Hispanic	1785 (9.8)	1536 (9.8)	249 (9.9)	
	Unknown/Oother	1446 (8.0)	1253 (8.0)	193 (7.7)	
Marital status	Married	14323 (79.0)	12405 (79.5)	1918 (76.1)	<.001
	Unmarried	2875 (15.9)	2393 (15.3)	482 (19.1)	
	Unknown	928 (5.1)	808 (5.2)	120 (4.8)	

TABLE 1 (Continued)

Variable		Overall, *n* = 18,126	RP, *n* = 15,606 (86.1%)	RP + EBRT, *n* = 2520 (13.9%)	*p* Value
Region	West	11470 (63.3)	10099 (64.7)	1371 (54.4)	<.001
	Midwest	1785 (9.8)	1500 (9.6)	285 (11.3)	
	North-East	1957 (10.8)	1532 (9.8)	425 (16.9)	
	South	2914 (16.1)	2475 (15.9)	439 (17.4)	
Socioeconomic status	First quartile	4833 (26.7)	4180 (26.8)	653 (25.9)	.4
	Second–fourth quartile	13293 (73.3)	11426 (73.2)	1867 (74.1)	

Abbreviations: GGG, Gleason grade group; IQR, inter quartile range; PSA, prostate specific antigen.

73 versus 72 ($p < .001$). RP and EBRT patients exhibited higher PSA at diagnosis (8.8 [IQR: 5.5–16.1] vs. 6.9 ng/ml [IQR 5.0–10.3]), higher rates of biopsy GGG IV and V (20.6 vs. 14.6% and 25.7 vs. 8.8%), higher rates of cT3-stage (7.4 vs. 2.8%), higher rates of cN1-stage at diagnosis (9.9 vs. 3.3%), higher rates of pT3-stage (35.0 vs. 31.7%), higher rate of pN1-stage (8.8 vs. 3.8%), and higher rate of pathological Gleason score 8–10 (15.5 vs. 11.6%), than RP alone patients (all $p < .001$). No differences were observed according to socioeconomic status ($p = .4$). Median follow-up duration was 69 months (IQR: 35–103) in the overall cohort.

After stratification according to age category 70–74 versus 75–79, the rates of RP and EBRT were 12.0 versus 21.7%. After stratification according to each year of age, the rate of combination of RP and EBRT ranged from 11.2% to 31.0% ($p < .001$, Figure 1A). After further adjustment for PSA, cT-stage, and biopsy GGG, this range became narrower: 13.0% to 19.0% in for patients aged 70–79 ($p < .001$, Figure 1B).

3.1.1 | OCM and CSM rates in prostate cancer patients aged 70–79 years: RP and EBRT versus RP alone

After 1:2 propensity score matching, 2540 RP and EBRT versus 5040 RP alone patients aged 70–79 years were assessable. Ten-year OCM rates were respectively 27.9 versus 20.3% for RP and EBRT versus RP alone (Figure 2). Univariable and multivariable OCM HRs were respectively 2.1 and 1.4 (both $p < .001$, Table 2). Ten-year CSM rates were respectively 13.4 versus 5.5% for RP and EBRT versus RP alone ($p < .001$). Univariable and multivariable CSM HRs were respectively 2.3 and 2.1 (both $p < .001$).

3.1.2 | OCM and CSM rates in prostate cancer patients aged 70–74 years: RP and EBRT versus RP alone

After 1:2 propensity score matching, 1754 RP and EBRT versus 3508 RP alone patients aged 70–74 years were assessable. Ten-year OCM

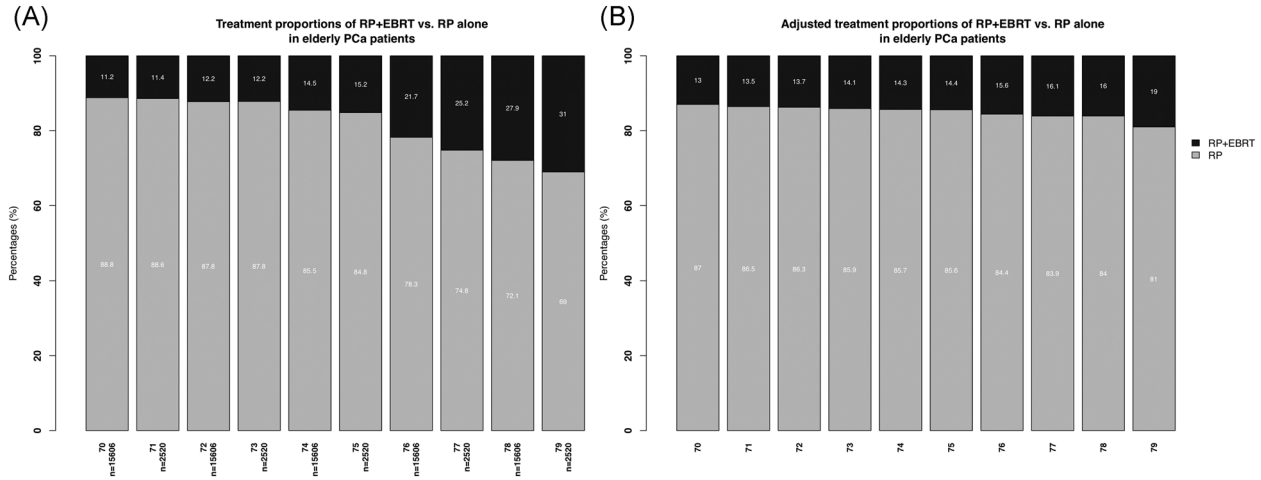

FIGURE 1 Barplots depicting (A) observed rates of radical prostatectomy (RP) and external beam radiation therapy (EBRT) versus RP alone for each year of age between 70 and 79 years and (B) adjusted rates (PSA, cT-stage, biopsy Gleason grade group) of RP and EBRT versus RP alone. PSA, prostate specific antigen

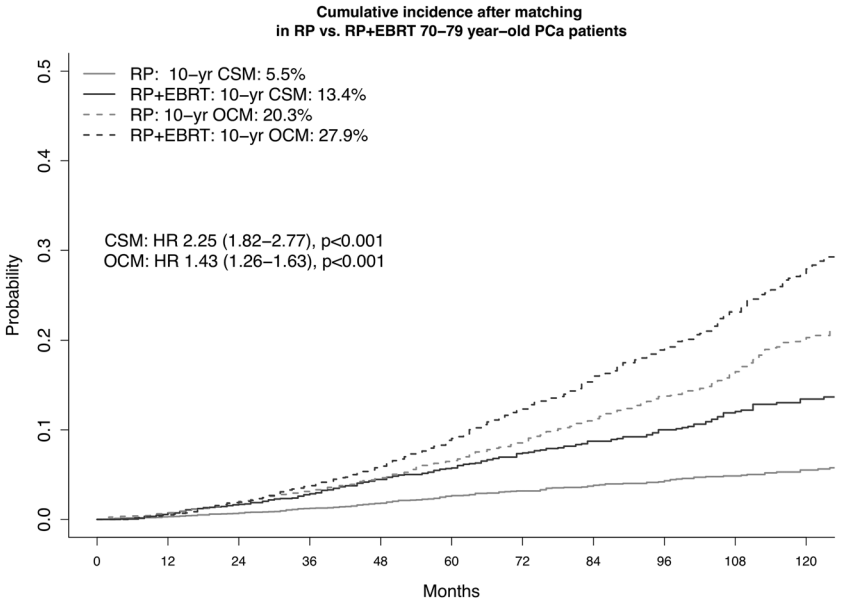

FIGURE 2 Cumulative incidence plots illustrating cancer specific mortality (CSM) and other cause mortality (OCM) after 2:1 propensity score matching for age, cT-stage, cN-stage, PSA, biopsy Gleason score in in prostate cancer (PCa) patients aged 70–79 years, treated with RP ($n = 5080$) versus RP + EBRT ($n = 2540$). EBRT, external beam radiation therapy; HR, hazard ratio; PSA, prostate specific antigen; RP, radical prostatectomy

TABLE 2 Univariable and multivariable competing-risks regression models for RP versus RP EBRT treated patients, classified for age categories 70–79, 70–74, and 75–79

	CSM				OCM			
	Univariable		Multivariable		Univariable		Multivariable	
	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value
Age 70–79								
RP	1.00 (Ref.)	-	1.00 (Ref.)	-	1.00 (Ref.)	-	1.00 (Ref.)	-
RP + EBRT	2.25 (1.82–2.77)	<.001	1.43 (1.26–1.63)	<.001	2.05 (1.67–2.53)	<.001	1.42 (1.24–1.62)	<.001
Age 70–74								
RP	1.00 (Ref.)	-	1.00 (Ref.)	-	1.00 (Ref.)	-	1.00 (Ref.)	-
RP + EBRT	2.30 (1.78–2.97)	<.001	1.51 (1.27–1.8)	<.001	2.10 (1.63–2.71)	<.001	1.47 (1.23–1.75)	<.001
Age 75–79								
RP	1.00 (Ref.)	-	1.00 (Ref.)	-	1.00 (Ref.)	-	1.00 (Ref.)	-
RP + EBRT	1.47 (0.99–2.19)	.06	1.74 (1.35–2.24)	<.001	1.33 (0.89–1.99)	.2	1.68 (1.28–2.19)	<.001

Note: Univariable and multivariable competing-risks regression models for RP versus RP + EBRT treated prostate cancer patients, matched for T-stage, N-stage, PSA, biopsy Gleason score and age and subsequently adjusted in multivariable models for pathological Gleason score and socioeconomic status.

Abbreviations: CI, confidence interval; CSM, cancer specific mortality; EBRT, external beam radiation therapy; HR, hazard ratio; OCM, other cause mortality; PSA, prostate specific antigen; RP, radical prostatectomy.

rates were respectively 22.8 versus 13.4% for RP and EBRT versus RP alone (Figure 3). Univariable and multivariable OCM HRs were respectively 1.5 and 1.5 (both $p < .001$). Ten-year CSM rates were respectively 13.4 versus 5.2% for RP and EBRT versus RP alone ($p < .001$). Univariable and multivariable CSM HRs were respectively 2.3 and 2.1 (both $p < .001$).

3.1.3 | OCM and CSM rates in prostate cancer patients aged 75–79 years: RP and EBRT versus RP alone

After 1:1 propensity score matching, 766 RP + EBRT versus 766 RP alone patients aged 75–79 years were assessable. Ten-year OCM rates were respectively 39.5 versus 24.0% for RP and EBRT versus RP alone (Figure 4, $p < .001$). Univariable and multivariable OCM HRs were respectively 1.7 and 1.7 (both $p < .001$). Ten-year CSM rates were respectively 13.9 versus 8.8% for RP and EBRT versus RP alone ($p < .001$). Univariable and multivariable CSM HRs were respectively 1.5 and a HR of 1.3 (both $p < .001$).

4 | DISCUSSION

Adjuvant or salvage EBRT is guideline recommended and delivered between 6% and 12% of RP treated patients.[13,14] The use of combination therapy is meant to reduce CSM in select, particularly high-risk

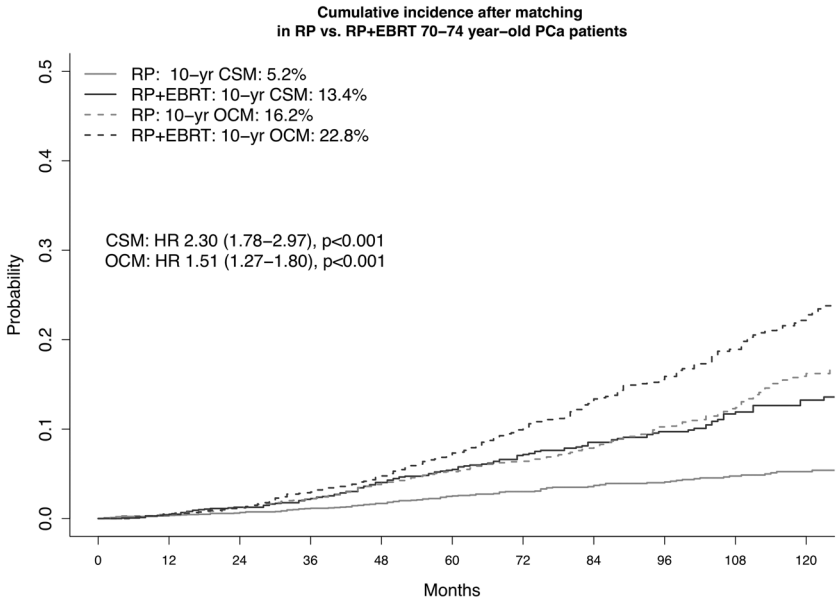

FIGURE 3 Cumulative incidence plots illustrating CSM and OCM after 2:1 propensity score matching for age, cT-stage, cN-stage, PSA, biopsy Gleason score in in PCa patients aged 70–74 years, treated with RP ($n = 3508$) versus RP + EBRT ($n = 1754$). CSM, cancer specific mortality; EBRT, external beam radiation therapy; HR, hazard ratio; OCM, other cause mortality; PCa, prostate cancer; PSA, prostate specific antigen; RP, radical prostatectomy

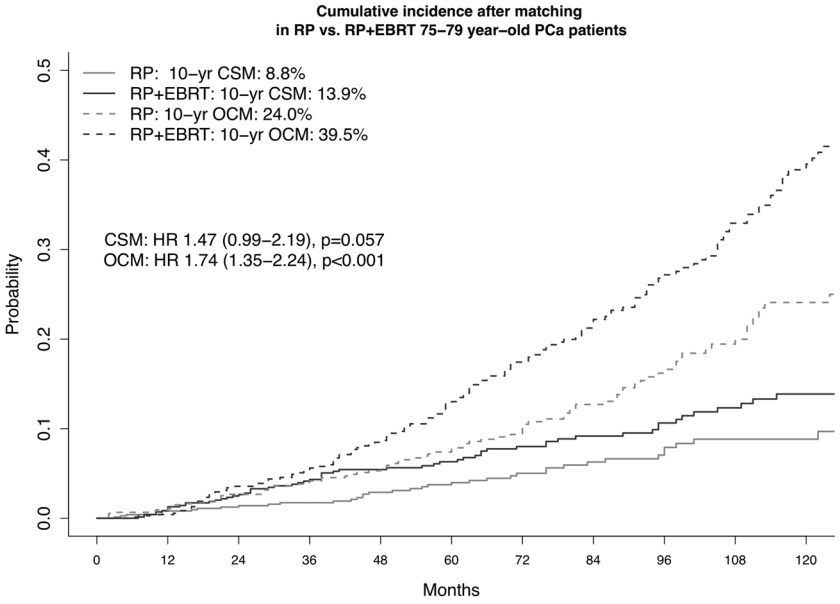

FIGURE 4 Cumulative incidence plots illustrating CSM and OCM after 1:1 propensity score matching for age, cT-stage, cN-stage, PSA, biopsy Gleason score in in PCa patients aged 75–79 years, treated with RP ($n = 766$) versus RP + EBRT ($n = 766$). CSM, cancer specific mortality; EBRT, external beam radiation therapy; HR, hazard ratio; OCM, other cause mortality; PCa, prostate cancer; PSA, prostate specific antigen; RP, radical prostatectomy

individuals. Despite, clear guideline recommendations regarding cancer characteristics (positive surgical margins and/or Gleason score 8–10, ≥pT3 or pN1-stage), for individuals that should be considered for salvage or adjuvant EBRT, specific selection criteria regarding life expectancy of combination therapy candidates have not been elaborated. Nonetheless, since combination therapy candidates have been selected as surgical candidates, it may be postulated that their rate of OCM should be very similar to that of their RP alone counterparts. We tested this hypothesis in elderly prostate cancer patients (70–79 years) treated with RP and EBRT, relative to RP alone. We repeated all analyses in individuals aged 70–74 years, as well as 75–79 years, to provide more age-specific comparisons. Our study yielded several noteworthy findings.

First, we made important observations regarding patient and tumor characteristics in elderly (aged 70–79 years) prostate cancer patients with treatment of RP and EBRT and RP alone. First, we recorded older median age in RP and EBRT patients versus RP alone (73 years, IQR: 71–75 vs. 72, IQR: 71–74). Conversely, RP and EBRT patients harbored significantly worse baseline prostate cancer characteristics (cT-stage, cN-stage, grade and PSA), as well as worse pathological prostate cancer characteristics (pT-stage, pN-stage). These differences represent the basis for propensity score matched analyses, that were aimed to maximally reduce potential selection biases related to these baseline differences.[15–17]

Second, in the overall population aged 70–79 years, we observed a 14% rate of combined RP and EBRT, which is higher than previously reported, despite significantly higher age distribution, relative to the two previous reports.[13,14] After stratification according to age category 70–74 versus 75–79 the respectively rates of RP and EBRT were 13.5% and 21.7%. These rates were counterintuitive,

since lower rates of combination of RP and EBRT would be expected in the older age category, based on shorter life expectancy. To further examine this unexpected observation, we tabulated the rates of combination of RP and EBRT according to each year of age. Here, we also recorded an age-related direct increase in combined RP and EBRT rates that ranged from 11.2% to 31.0%. Since that increase may have been artificially related to more adverse prostate cancer characteristics of elderly patients, we further adjusted for PSA, cT-stage and biopsy Gleason grade group within each year of age category. Despite this most stringent adjustment, we still observed an increase from 13% to 19% ($p < .001$) from youngest (70 years) to oldest age (79 years) strata. These observations are not only counterintuitive but suggest a possibility of combination RP and EBRT overuse in elderly patients.

Third, we also made important observations regarding mortality rates in patients aged 70-79 treated either with RP and EBRT versus RP alone. Specifically, we observed significantly higher ten-year OCM rates in RP and EBRT patients than after RP alone (27.9 vs. 20.3%). After multivariable adjustment, RP and EBRT patients were at 1.4-fold higher risk of OCM than their RP alone counterparts. This observation is worrisome. The explanation for the OCM rates may originate from suboptimal selection of individuals with baseline comorbidity profiles that eventually result in higher OCM. Conversely, it is also possible that the effect of EBRT and of androgen deprivation therapy (ADT) that accompanies EBRT in those individuals, may also contribute to higher OCM. Finally, a combination of both scenarios must also be considered. Unfortunately, the etiological cause, which cannot be validly ascertained using retrospective data. Nonetheless, the objective within the urological community involved in the care of these patients, should be considered both scenarios with the intend of reducing OCM rates either at the time of RP and EBRT selection, based on OCM risk and/or susceptibility to ADT plus EBRT and ADT toxicity.[18–24]

Fourth, based on subgroup analyses of elderly prostate cancer patients, we also made important observations in patients treated with either RP and EBRT versus RP alone. Specifically, the proportions of RP and EBRT were higher in patient 75–79 years versus 70–74 years. This observation may originate from the fact that in patients aged 75–79 years only very aggressive prostate cancer patients are selected for surgical treatment and high risk for recurrent prostate cancer. Nonetheless, these observations also indicate that the urologic community should consider the use of combination therapy according to patient age and life expectancy. Finally, subgroup analyses further corroborated significantly higher OCM in RP and EBRT versus RP alone. Specifically, OCM disadvantage was more pronounced in RP and EBRT 75–79 year subgroup, relative to 70–74 year subgroup. Specifically, in the 75–79 year subgroup, as many as 39.5% of patients died of other causes within ten years of prostate cancer diagnosis. These observations are in an agreement with previous prostate cancer studies, where age also was the strongest predictor of OCM.[25–27] This alarmingly high OCM rate in the current study resonates the urgent need to study its origin.

Taken together, we observed that RP and EBRT treated patients are older than their counterparts treated with RP alone, even though we focused on a very specific and relatively narrow age interval (70–79 years). Second, we observed that a relative minority of patients with baseline intermediate and high risk prostate cancer are treated with RP and EBRT (14%). Finally and most important, we recorded unexpectedly elevated OCM rates in RP and EBRT treated patients, relative to RP alone patients. The OCM disadvantage was particularly important in the older half of the age distribution, namely 75–79 year old. Here, as many as 39.5% died of other causes within 10 years of diagnosis. This observation is very worrisome and raises questions about appropriate selection criteria for RP and EBRT, based on comorbidities and life expectancy. It also raises questions about potential increase in OCM related to the use of EBRT and/or ADT. Both concerns require urgent focus in future studies.

Our study has limitations and should firstly be interpreted in the context of its retrospective and population-based design. Secondly, no distinction could be made according to adjuvant or salvage EBRT after RP. Moreover, we could not account for BCR rates in this study. However, since the study was focused on OCM rates, this limitation does not affect its primary outcome. Third, no information was available about the dose of EBRT and its extent and about type and duration of concomitant androgen deprivation therapy. Finally, no matching for pathological characteristics could be performed, due to high rates of missing values in the combination therapy group. However, higher rates of more unfavorable pathological characteristics were observed in the group of combination therapy and translated into higher CSM rates, than elderly patients treated with RP only.

5 | CONCLUSION

Elderly patients treated with RP and EBRT exhibited worrisome rates of OCM. These higher than expected OCM rates question the need for combination therapy (RP and EBRT) in elderly PCa patients and indicate the need for better patient selection, when combination therapy is contemplated.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

DATA AVAILABILITY STATEMENT

All data generated for this analysis were from the SEER 18 database. The code for the analyses will be made available after request.

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.

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