ORIGINAL PAPER

UROLOGICAL ONCOLOGY

Radiation after radical prostatectomy in elderly patients – a SEER database-derived competing-risk survival analysis of propensity score-matched age groups

Piotr Zapała[1], Aleksander Ślusarczyk[1], Łukasz Zapała[1], Tomasz Borkowski[1], Paweł Rajwa[2,3], Grzegorz Niemczyk[1], Piotr Radziszewski[1]

[1]Department of General, Oncological, and Functional Urology, Medical University of Warsaw, Warsaw, Poland
[2]Department of Urology, Medical University of Silesia, Zabrze, Poland
[3]Department of Urology, Comprehensive Cancer Centre, Medical University of Vienna, Vienna, Austria

Citation: Zapała P, Ślusarczyk A, Zapała Ł, et al. Radiation after radical prostatectomy in elderly patients – a SEER database-derived competing-risk survival analysis of propensity score-matched age groups. Cent European J Urol. 2023; 76: 293-299.

Article history
Submitted: July 14, 2023
Accepted: Sept. 21, 2023
Published online: Nov. 13, 2023

Corresponding author
Aleksander Ślusarczyk
Department of General, Oncological, and Functional Urology
Medical University of Warsaw,
Lindleya 4, 02-005 Warsaw, Poland
phone +48 22 502 1702
slusarczyk.aleksander@gmail.com

Introduction This study aimed to evaluate cancer-specific (CSM) and other-cause mortality (OCM) in elderly patients with prostate cancer treated with radical prostatectomy (RP) and postoperative radiotherapy (RT).

Material and methods The Surveillance, Epidemiology, and End Results (SEER) database was searched for clinically non-metastatic prostate cancer (PCa) treated with RT after RP between 2010 and 2015. Patients were stratified according to age groups and underwent propensity score (PS) matching. The Kaplan-Meier method and competing-risk Cox regression (CRR) were used for survival analysis.

Results In total, 5385 patients were analysed, including 738 (13.7%) elderly patients (≥70 years old) and 4647 (86.29%) younger individuals. A total of 54 (7.32%) and 69 (9.35%) patients aged ≥70 years died due to PCa and competing reasons, respectively. Among younger patients these included 275 (5.92%) and 208 (4.48%) deaths, respectively. At a median follow-up of 80 months, patients ≥70 years old had significantly shorter OCM ($p < 0.0001$) than PS-matched younger controls without significant impairment of cancer-specific survival when compared to controls ($p = 0.19$). In CRR analysis older patients were at significantly higher risk of OCM (HR = 2.24, $p = 0.0002$ and HR = 3.3, $p = 0.011$ for patients aged ≥70 and ≥75 years, respectively). Simultaneously, the CRR revealed no increased risk of CSM for patients older than 70 and 75 years (HR = 1.2, $p = 0.33$ and HR = 1.53, $p = 0.29$, respectively).

Conclusions Elderly patients with PCa are at high risk of dying due to competing reasons, which might prevent the survival benefit of RT after RP. Selection for salvage and adjuvant RT in these individuals should be cautious.

Key Words: radical prostatectomy ‹› radiotherapy ‹› survival ‹› competing risk ‹› elderly ‹› prostate cancer

INTRODUCTION

Prostate cancer (PCa) remains the second most common cancer in men, with a total of 1.4 million individuals diagnosed yearly according to recent CLOBOCAN reports [1]. In non-metastatic disease, surgical treatment with curative intent provides excellent long-term cancer control with a significant rate of PCa eradication both in organ-confined [2] and non-organ-confined settings [3]. According to previous population-based studies, even patients with poorly differentiated PCa are more likely to die from competing reasons during the first decade, which facilitated a 10-year life expectancy as mandatory when selecting candidates for active treatment [4]. However, adverse pathology after radical prostatectomy (RP) remains strongly associated with biochemical

recurrence (BCR), which inevitably precedes metastatic progression. It is estimated that even half of the patients with locally advanced disease and/or positive surgical margins will progress during the first 5 years [5], whereas 10-year BCR-free rates in individuals with local lymph node metastasis (pN1) range from 28% to 56% [6]. To delay the metastatic disease onset, most patients with adverse pathological features (APF) will be treated with subsequent radiation (RT). In elderly men, however, BCR might never affect overall survival or never present as clinical progression. This study aimed at evaluating cancer-specific (CSM) and other-cause mortality (OCM) in elderly patients treated with RP and postoperative radiation. The secondary aim of this study was to define the population of elderly patients who benefit most from combined treatment.

MATERIAL AND METHODS

Analysed cohort

The National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) database (2000–2015) imported with SEER*Stat software was used for this population-based analysis. Individuals with clinically nonmetastatic PCa (ICD-10 code C61.9) treated with RP and subsequent radiotherapy were included. Chemotherapy, lack of postprostatectomy pathological report or pathology defined on autopsy, as well as missing survival status constituted exclusion criteria. Patients were stratified according to age using a cut-off age of 70 years (individuals <70 and ≥ 70 years old).

Statistical analysis

Categorical variables are presented as numbers with percentages, and continuous variables are presented as medians accompanied by the interquartile range (IQR). Factors likely to confound the survival outcome, including race, year of diagnosis, pathological Gleason score (available from 2010), and pathological local and nodal staging, were then used for propensity score matching (PSM) of the age groups (matching 1:1). Differences between age groups before and after PSM were tested with the U-Mann-Whitney test for continuous variables and with the exact Fisher test for categorized variables. Kaplan-Meier curves illustrated the cancer-specific and other-cause-specific survival. Cox proportional hazards competing risk regression was performed to estimate

Table 1. *Baseline characteristics of the age-stratified cohort (2010–2015)*

	Variable	Before PSM			After PSM		
		≥70 years n = 722	<70 years n = 4615	P value	≥70 years n = 722	<70 years n = 722	P value
pT staging	T2	133 (18.42%)	1105 (23.94%)	0.0044	133 (18.42%)	129 (17.87%)	0.96
	T3	506 (70.08%)	2993 (64.85%)		506 (70.08%)	509 (70.50%)	
	T4	83 (11.50%)	517 (11.20%)		83 (11.50%)	84 (11.63%)	
pN staging	N0	608 (84.21%)	3888 (84.20%)	0.95	608 (84.21%)	611 (84.63%)	0.94
	N1	112 (15.51%)	713 (15.45%)		112 (15.51%)	111 (15.37%)	
	Nx	2 (0.28%)	16 (0.35%)		2 (0.28%)	0 (0%)	
Race	White	624 (86.43%)	3674 (79.61%)	<0.0001	624 (86.43%)	625 (86.57%)	0.95
	African descent	36 (4.99%)	631 (13.67%)		36 (4.99%)	36 (4.99%)	
	American Indian/Alaska native	0 (0%)	17 (0.37%)		0 (0%)	0 (0%)	
	Asian or Pacific Islander	60 (8.31%)	278 (6.02%)		60 (8.31%)	60 (8.31%)	
	Unknown	2 (0.28%)	15 (0.33%)		1 (0.14%)	2 (0.28%)	
Grade Group	I	18 (2.49%)	193 (4.18%)	<0.0001	18 (2.49%)	16 (2.22%)	0.99
	II	136 (18.84%)	1281 (27.76%)		136 (18.84%)	143 (19.81%)	
	III	203 (28.12%)	1346 (29.17%)		203 (28.12%)	201 (27.84%)	
	IV	111 (15.37%)	569 (12.33%)		111 (15.37%)	111 (15.37%)	
	V	254 (35.18%)	1226 (26.57%)		254 (35.18%)	251 (34.76%)	
PSA (mean/ IQR)		11.69 / 7.7	13.42 / 9.3	0.64	11.69 / 7.7	14.61 / 10.5	0.012

PSM – propensity score matching; PSA – prostate-specific antigen [ng/mL]

the risk of cancer-specific and other-cause-specific mortality. The log-rank test was used to discriminate the survival differences between age groups. To assess differences in survival outcomes in different clinical settings a subgroup analysis was performed. For statistical analyses a 2-sided p-value <0.05 was considered statistically significant. Statistical analyses were performed in SAS software version 9.4.

RESULTS

Baseline characteristics

A total of 5337 patients treated in 2010–2015 were selected for this analysis including 722 patients aged ≥70 years (13.53%) and 4615 patients aged <70 years (86.47%). A cut-off of 75 years was also tested, but due to the limited number of individuals stratification for further analysis defined elderly patients as aged ≥70 years. After propensity score matching the elderly cohort and younger cohort included 722 patients each. Baseline characteristics of the age-stratified cohort before and after propensity score matching are presented in Table 1.

Survival analysis

Median follow-up was 82 months (95%CI 81–83) and 80 months (95%CI 78–82) before and after PSM, respectively.

During this period a total of 326 (6.11%) and 275 (5.15%) patients died due to cancer and competing reasons, respectively. Among elderly patients, 52 (7.20%) and 67 (9.28%) individuals died due to cancer and competing reasons, respectively. Among patients aged <70 years, 274 (5.94%) and 208 (4.51%) individuals died due to cancer and competing reasons, respectively. After propensity score matching a total of 52 (7.20%) and 48 (6.65%) patients died due to cancer in the <70 and ≥70 years old PS-matched cohorts, respectively, whereas 78 (10.80%) and 119 (16.48%) died due to competing reasons.

Elderly patients matched with younger individuals presented the same cancer-specific survival (p = 0.52), although significantly worse (p <0.0001) other-cause-specific survival (Figure 1). In competing-risk Cox regression analysis elderly patients were more likely to die due to competing reasons than PS-matched younger patients (HR 2.34, 95%CI 1.52–3.58; p <0.0001), whereas the risk of dying due to cancer did not differ significantly (HR 1.09, 95%CI 0.74–1.61; p = 0.65) between cohorts. When using a second cut-off of 75 years, older patients were at even higher risk of OCM (HR = 3.3, p = 0.011) but still with no increased risk of CSM (HR = 1.53, p = 0.29).

In multivariable competing-risk Cox regression in the entire cohort after PSM, only the age group constituted a predictor of other-cause-specific survival, whereas locally advanced disease, higher grading group, and African race constituted independent predictors of cancer-specific mortality (Table 2).

Survival subgroup analysis

To estimate the impact of the age group on survival outcomes in the presence of particular adverse features, subgroup survival analysis was performed on PS-matched cohorts (Figure 2).

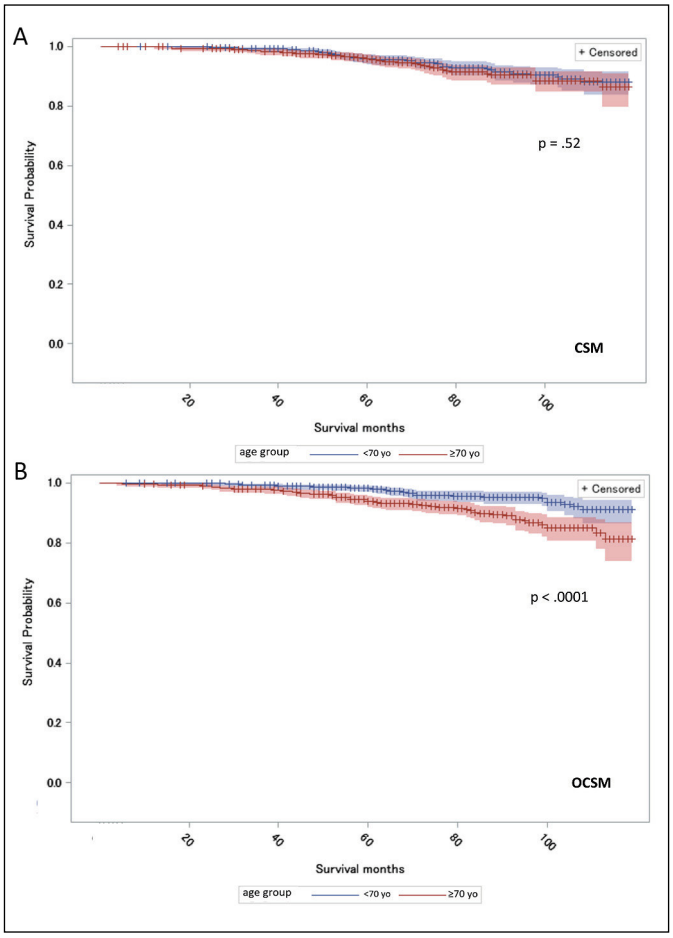

Figure 1. *Kaplan-Meier curves depicting cancer-specific survival* **(A)** *and other-cause-specific survival* **(B)** *in propensity score-matched cohorts.*

yo – years old; CSM – cancer-specific mortality; OCSM – other-cause-specific mortality

Age remained significantly (p = 0.0004) associated with OCM in the T3¬–T4 subgroup, but it did not impact other-cause-specific survival in patients with N1 (p = 0.11) and grade group V (p = 0.18). Simultaneously, in subgroups bearing N1, grade group V, or T3–T4, cancer-specific survival did not differ significantly (p = 0.39, p = 0.31, p = 0.47, respectively) between patients aged ≥70 and <70 years. In subgroups with grade group V and nodal involvement, no significant differences in OCM-free survival between age groups was found (p = 0.99). Of note, elderly patients presenting both N1 and GG V revealed noticeably worse cancer-specific survival than PS-matched younger individuals (HR = 2.56, 95%CI 0.92–7.14; p = 0.08), whereas OCM-free survival remained similar for both age groups (p = 0.99).

DISCUSSION

This population-based study indicates potentially limited cancer-specific survival benefits in elderly prostate cancer patients who are considered for beam radiation after radical prostatectomy. The main finding of our analysis is that patients aged ≥70 years are at high risk of dying due to competing reasons. Simultaneously, the probability of dying due to prostate cancer after adjustment for adverse features remains comparable for patients aged ≥70 and <70 years. To determine the elderly individuals who might benefit from postoperative radiation we performed a subgroup analysis, which revealed that patients ≥70 years old bearing grade group V or nodal involvement do not differ from younger individuals in terms of cancer-specific survival as well as other-cause-specific survival. Finally, the highest grade (Gleason score 9 or 10) elderly patients simultaneously bearing N1 might present an even worse oncological prognosis than younger individuals. Because in this subgroup overall survival seems not to be compromised due to high competing cancer-specific mortality, the rationale of radiation in pN1 and grade group V elderly patients should be sustained, particularly in individuals presenting both features.

Men with a life expectancy shorter than 10 years are unlikely to benefit from radical treatment [7, 8, 9]. Although external-beam radiotherapy (EBRT) has been suggested to bring similar cancer control in different age groups [10], older age might be associated with adverse functional outcomes regarding the lower urinary tract [11] and its survival yield [12, 13] as well as consumption of medical resources [14].

However, estimating the necessary threshold of life expectancy when addressing salvage treatment is more challenging. At 10 years, CSS after salvage radical prostatectomy (SRP) is estimated between 70 and 83% [15], which supports surgical selection using a conservative 10-year life expectancy threshold. However, in the adjuvant ra-

Table 2. *Competing-risk multivariable Cox regression analysis*

Variable		CSM		OCSM	
		HR	p-value	HR	p-value
T stage	T2	1 (ref)		1 (ref)	
	T3	1.71	0.15	1.11	0.70
	T4	4.08	0.0009	0.47	0.13
N stage	N0	1 (ref)		1 (ref)	
	N1	1.45	0.12	1.03	0.91
Grade group	I–II*	1 (ref)		1 (ref)	
	III	2.07	0.17	1.61	0.10
	IV	4.04	0.0079	0.79	0.55
	V	8.98	<0.0001	1.19	0.55
Race	White	1 (ref)		1 (ref)	
	African descent	2.67	0.0057	1.02	0.97
	Asian or Pacific Islander	0.375	0.094	0.55	0.17
Age group	<70 years	1 (ref)		1 (ref)	
	≥70 years	1.12	0.55	2.39	<0.0001

CSM – cancer-specific mortality; OCSM – other-cause-specific mortality; HR – hazard ratio; ref – reference;
*grade groups I and II were analysed in one stratum due to the low number of events in grade group I

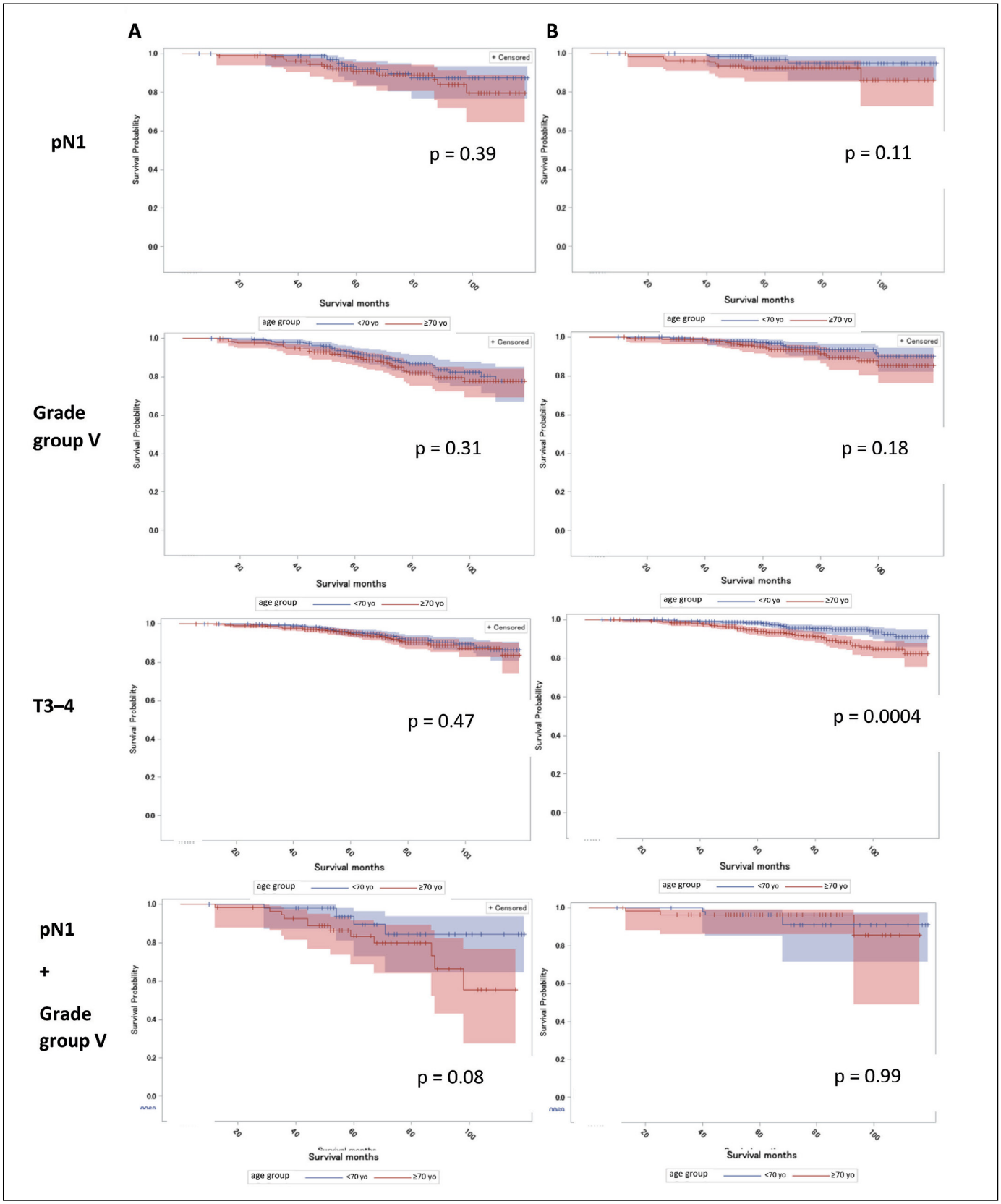

Figure 2. *Kaplan-Meier curves depicting cancer-specific survival* **(A)** *and other-cause-specific survival* **(B)** *in propensity score-matched cohorts – subgroup analysis.*

yo – years old

diotherapy scenario, survival benefits in patients aged >70 years might become apparent only in patients with unfavourable postprostatectomy pathology [16]. In the SEER cohort presented in this study, more than 80% of patients aged >70 years remained alive after a median follow-up of 7 years, which suggests a generally fit profile of the population analysed. For comparison, the population-based study by Jeldres et al. revealed that as much as 70% of patients >70 years old treated in the primary setting with EBRT fail to reach the 10-year survival mark [13]. However, even considering strong selection bias, both this study and the previous SEER analysis [12] suggest worrisome other-cause mortality (OCM). The study by Wenzel et al. reported 10-year OCM rates of 22.8% and 39.5% for patients aged 70–74 and 75–79 years, respectively [12].

The rationale for the use of radiotherapy after RP comes from 3 randomized clinical trials, but only one of them (SWOG 8794) provided evidence on the overall survival benefit of RT compared to observation (10-year OS 74% vs. 66%) [17, 18, 19]. The other 2 RCTs only showed benefit in biochemical progression-free survival from post-RP radiotherapy. Importantly, the SWOG 8794 and ARO 96-02 trials permitted only patients 75 years old or younger, whereas in EORTC 22911 the median age was 64 years in the RT cohort. In the EORTC 22911 trial, radiotherapy in patients aged 70 years and more did not improve biochemical or clinical RFS but appeared to worsen OS [17]. This raises questions regarding the evidence of RT use in patients older than 75 years. Our results suggest a higher OCM in patients >70 years of age compared to younger counterparts. This implies that elderly patients might not benefit from additional radiotherapy after RP. Such treatment might decrease the quality of life and increase the burden of local symptoms. In current cutting-edge hormone therapy, the wait-and-see approach might render RT intervention unnecessary and limit the burden of social and economic costs without compromising survival. On the other hand, avoiding postoperative radiotherapy might be challenging in elderly patients without significant comorbidities and relatively long life expectancy despite advanced age.

Identification of patients bearing the highest grade (Gleason score 9 or 10) and pN1 feature as clear candidates for postoperative irradiation is among the main outcomes of our analysis. Based on previous cohort studies, EBRT provided better cancer control than surgery in grade group V patients, with radical dose escalation improving CSS [20]. In the adjuvant scenario, CSS benefit in patients aged >70 years becomes apparent only in individuals bearing 2 or more adverse pathological features (GG IV - V, pT3b/4, pN1) [16]. Our analysis revealed that older age (>70 years) did not impact other-cause-specific survival in patients with N1 ($p = 0.11$) and grade group V ($p = 0.18$). In fact, elderly patients presenting both N1 and GG V revealed noticeably worse cancer-specific survival than PS-matched younger individuals, whereas OCM-free survival remained similar for both age groups.

The limitations of this study are related to its retrospective and population-based character. Some viable information contributing to baseline treatment was not available for analysis. This includes biochemical follow-up, biochemical recurrence, type of radiation (adjuvant vs. salvage), and type of recurrence (local, nodal, systemic). We were not able to determine the status of comorbidities, which constituted an uncontrolled confounder and might have contributed to significant selection bias. Based on the existing literature, comorbidities might be a stronger determinant of life expectancy than age. In patients treated with EBRT the comorbidity index and performance score seem to decline the OS independently of the baseline PCa characteristics [21]. We were also not able to track the impact of ADT on other-cause mortality. Based on previous series, supplementing RT with androgen deprivation in patients aged >75 years might additionally contribute to increasing OCM [22]. Due to the population-based character of this analysis, we suspect that a significant amount of confounding remained undiagnosed. Finally, the analysis was not aimed at a head-to-head comparison of postoperative radiation with the prostatectomy followed by conservative treatment, which prevents the drawing of direct conclusions.

CONCLUSIONS

To conclude, our study indicates that PCa patients > 70 years of age who underwent radiation after RP are characterized by a significant burden of non-PCa-specific mortality. To avoid overtreatment and increase the cost-effectiveness, RT should be reserved for highly selected individuals accepting the risks of excessive mortality. Indications for RT after RP should be further prospectively verified, especially in the context of novel effective hormone therapy.

CONFLICTS OF INTEREST
The authors declare no conflicts of interest.

FUNDING
The authors declare that no funds, grants, or other financial support were received during the preparation of this manuscript.

DATA AVAILABILITY
The datasets analysed during the current study are available from the US National Cancer Institute upon request.

ETHICS APPROVAL
Due to the study character no Ethics Committee approval was required.

References

1. Culp MB, Soerjomataram I, Efstathiou JA, Bray F, Jemal A. Recent Global Patterns in Prostate Cancer Incidence and Mortality Rates. Eur Urol. 2020; 77: 38-52.
2. Hamdy FC, Donovan JL, Lane JA, et al. 10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer. N Engl J Med. 2016; 375: 1415-1424.
3. Zapała P, Kozikowski M, Dybowski B, Zapała Ł, Dobruch J, Radziszewski P. External validation of a magnetic resonance imaging-based algorithm for prediction of side-specific extracapsular extension in prostate cancer. Cent Eur J Urol. 2021; 74: 327-333.
4. Albertsen PC, Moore DF, Shih W, Lin Y, Li H, Lu-Yao GL. Impact of comorbidity on survival among men with localized prostate cancer. J Clin Oncol Off J Am Soc Clin Oncol. 2011; 29: 1335-1341.
5. Würnschimmel C, Wenzel M, Wang N, et al. Radical prostatectomy for localized prostate cancer: 20-year oncological outcomes from a German high-volume center. Urol Oncol. 2021; 39: 830.e17-830.e26.
6. Marra G, Valerio M, Heidegger I, et al. Management of Patients with Node-positive Prostate Cancer at Radical Prostatectomy and Pelvic Lymph Node Dissection: A Systematic Review. Eur Urol Oncol. 2020; 3: 565-581.
7. Bill-Axelson A, Holmberg L, Garmo H, et al. Radical prostatectomy or watchful waiting in early prostate cancer. N Engl J Med. 2014; 370: 932-942.
8. Wilt TJ, Brawer MK, Jones KM, et al. Radical Prostatectomy versus Observation for Localized Prostate Cancer. N Engl J Med. 2012; 367: 203-213.
9. Zapała P, Garbas K, Lewandowski Z, et al. The Clinical Utility of Systemic Immune-Inflammation Index Supporting Charlson Comorbidity Index and CAPRA-S Score in Determining Survival after Radical Prostatectomy-A Single Centre Study. Cancers. 2022; 14: 4135.
10. Kupelian PA, Elshaikh M, Reddy CA, Zippe C, Klein EA. Comparison of the efficacy of local therapies for localized prostate cancer in the prostate-specific antigen era: a large single-institution experience with radical prostatectomy and external-beam radiotherapy. J Clin Oncol Off J Am Soc Clin Oncol. 2002; 20: 3376-3385.
11. Lemanska A, Dearnaley DP, Jena R, Sydes MR, Faithfull S. Older Age, Early Symptoms and Physical Function are Associated with the Severity of Late Symptom Clusters for Men Undergoing Radiotherapy for Prostate Cancer. Clin Oncol R Coll Radiol G B. 2018; 30: 334-345.
12. Wenzel M, Würnschimmel C, Chierigo F, et al. Non-cancer mortality in elderly prostate cancer patients treated with combination of radical prostatectomy and external beam radiation therapy. The Prostate. 2021; 81: 728-735.
13. Jeldres C, Suardi N, Walz J, et al. Poor overall survival in septa- and octogenarian patients after radical prostatectomy and radiotherapy for prostate cancer: a population-based study of 6183 men. Eur Urol. 2008; 54: 107-116.
14. Wu SY, Effendi FF, Peng JY, Huang CC. Long-Term Medical Resource Consumption of Radical Prostatectomy vs. Intensity-Modulated Radiotherapy for Old Patients With Prostate Cancer: A Nationwide Population-Based Cohort Study. Front Med. 2022; 9: 843709.
15. Chade DC, Eastham J, Graefen M, et al. Cancer control and functional outcomes of salvage radical prostatectomy for radiation-recurrent prostate cancer: a systematic review of the literature. Eur Urol. 2012; 61: 961-971.
16. Abdollah F, Karnes RJ, Suardi N, et al. Impact of adjuvant radiotherapy on survival of patients with node-positive prostate cancer. J Clin Oncol Off J Am Soc Clin Oncol. 2014; 32: 3939-3947.
17. Bolla M, van Poppel H, Tombal B, et al. Postoperative radiotherapy after radical prostatectomy for high-risk prostate cancer: long-term results of a randomised controlled trial (EORTC trial 22911). Lancet Lond Engl. 2012; 380: 2018-2027.
18. Wiegel T, Bartkowiak D, Bottke D, et al. Adjuvant radiotherapy versus wait-and-see after radical prostatectomy: 10-year follow-up of the ARO 96-02/AUO AP 09/95 trial. Eur Urol. 2014; 66: 243-250.
19. Thompson IM, Tangen CM, Paradelo J, et al. Adjuvant radiotherapy for pathological T3N0M0 prostate cancer significantly reduces risk of metastases and improves survival: long-term followup of a randomized clinical trial. J Urol. 2009; 181: 956-962.
20. Kishan AU, Cook RR, Ciezki JP, et al. Radical Prostatectomy, External Beam Radiotherapy, or External Beam Radiotherapy With Brachytherapy Boost and Disease Progression and Mortality in Patients With Gleason Score 9-10 Prostate Cancer. JAMA. 2018; 319: 896-905.
21. Lehtonen M, Heiskanen L, Reinikainen P, Kellokumpu-Lehtinen PL. Both comorbidity and worse performance status are associated with poorer overall survival after external beam radiotherapy for prostate cancer. BMC Cancer. 2020;20: 324.
22. Yamazaki H, Masui K, Suzuki G, et al. Effect of Androgen Deprivation Therapy on Other-Cause of Mortality in Elderly Patients with Clinically Localized Prostate Cancer Treated with Modern Radiotherapy: Is There a Negative Impact? J Clin Med. 2019; 8: 338. ■