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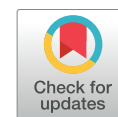
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Summary

The survival benefit of combined radiation therapy and androgen deprivation therapy compared with androgen deprivation therapy alone for clinically lymph node—positive prostate cancer remains controversial. We identified clinically node-positive, nonmetastatic prostate cancer patients from the Veterans Affairs system and compared mortality outcomes between treatment groups. We found that definitive treatment with radiation therapy improved prostate cancer—specific mortality and all-cause

Purpose: The survival benefit of combined radiation therapy (RT) and androgen deprivation therapy (ADT) compared with ADT alone for clinically lymph node—positive prostate cancer remains controversial.

Methods and Materials: We identified patients with clinically node-positive, nonmetastatic prostate cancer diagnosed between 2000 and 2015 and treated with ADT (n = 450) or ADT-RT (n = 198) from a national Veterans Affairs database. We compared prostate cancer—specific mortality (PCSM) and all-cause mortality (ACM) between treatment groups using multivariable competing-risks regression and Cox regression, respectively. An interaction term between ADT-RT and prostate-specific antigen (PSA) level (dichotomized about the median) was included in the multivariable models.

Results: ADT-RT was associated with improved PCSM among patients with PSA levels less than the median of 26 ng/mL (sub-distribution hazard ratio, 0.50; 95% confidence interval [CI] 0.28-0.88; $P = .02$) but not greater than the median (hazard ratio [HR], 1.15; 95% CI 0.67-1.96; $P = .62$) ($P = .038$ for interaction). ADT-RT was also associated with improved ACM among patients with PSA levels less than the median (HR, 0.38; 95% CI 0.25-0.57; $P < .001$) but not greater than the median (HR, 0.91; 95% CI 0.60-1.38; $P = .66$) ($P = .004$ for interaction).

Conclusions: Definitive treatment with ADT-RT is associated with improved PCSM and ACM among patients with clinically node-positive prostate cancer and lower

mortality, though only among patients with lower baseline prostate-specific antigen levels.

baseline PSA levels. Patients with clinically node-positive disease appear to be a heterogeneous cohort, with a subset who may achieve long-term survival with combined RT and ADT. © 2018 Elsevier Inc. All rights reserved.

Introduction

Management of clinically node-positive (cN+) prostate cancer is controversial. Many clinicians consider lymph node involvement to be a marker of systemic disease, whereas others consider the disease to be curable and advocate for definitive locoregional therapy. Therefore, treatment guidelines (1) and practice patterns (2-4) include both palliative therapy with androgen deprivation therapy (ADT) alone and definitive-intent therapy with radiation therapy (RT) and ADT. We sought to test the benefit of RT with ADT using the Veterans Affairs (VA) Informatics and Computing Infrastructure (VINCI) platform.

Methods and Materials

The cohort included veterans with cN+, nonmetastatic prostate cancer diagnosed between 2000 and 2015 and treated with either ADT alone or ADT-RT (Fig. E1; available online at www.redjournal.org). Node-positive status was determined through cancer registry data reflecting the American Joint Committee on Cancer staging criteria (5). We excluded patients who received other treatment modalities (eg, surgery) or no treatment, had >6 months between diagnosis and the start of ADT, had >6 months between the start of ADT and the start of RT, were treated with palliative radiation intent, or had missing covariate data.

Table 1   Characteristics of sample

Covariate	ADT	ADT-RT	P value
Sample size, n (%)	450 (70)	198 (30)	
Age at diagnosis, mean (SD), y	68 (9.4)	65 (8.0)	.001
BMI, mean (SD)	28 (6.7)	30 (6.4)	<.001
Pretreatment PSA level, median (IQR)	33 (15-92)	14 (8-40)	<.001
Race, n (%)			
White	319 (71)	142 (72)	.96
Black	109 (24)	46 (23)	
Other	22 (5)	10 (5)	
Radiation dose, median (range), cGy		7560 (3960-8600)	
Gleason score, n (%)			
≤7	117 (26)	61 (31)	.45
8	114 (25)	46 (23)	
≥9	219 (49)	91 (46)	
Clinical T category, n (%)			
1	98 (22)	52 (26)	.32
2	213 (47)	83 (42)	
3	102 (23)	51 (26)	
4	37 (8)	12 (6)	
Charlson Comorbidity Index, n (%)			
0	324 (72)	152 (77)	.15
1	63 (14)	29 (15)	
≥2	63 (14)	17 (9)	
Year of diagnosis, n (%)			
2000-2003	90 (20)	28 (14)	.22
2004-2007	110 (24)	45 (23)	
2008-2011	135 (30)	64 (32)	
2012-2015	115 (26)	61 (31)	
Employed, n (%)	44 (10)	25 (13)	.28
Married, n (%)	208 (46)	110 (56)	.03
Median income (IQR), $	45,000 (34,000-57,000)	48,000 (39,000-60,000)	.009
% with high school diploma, median (IQR)	86 (78-91)	88 (83-92)	<.001

Abbreviations: ADT = primary androgen deprivation therapy; ADT-RT = androgen deprivation therapy with radiation therapy; BMI = body mass index; IQR = interquartile range; PSA = prostate-specific antigen; SD = standard deviation.

Clinical tumor category, age, race, year of diagnosis, Gleason score, prostate-specific antigen (PSA) level, radiation dose, employment, marital status, and body mass index were obtained via tumor registry data, VA laboratory data, or manual chart review. ZIP code−level education and median income data were obtained through the 2015 American Community Survey. Baseline covariate data were compared between groups using the χ^2 test, t test, or Wilcoxon rank sum test as appropriate. We compared mortality outcomes between treatment groups using Fine-Gray competing-risks regression and Cox regression for prostate cancer−specific mortality (PCSM) and all-cause mortality (ACM), respectively. Vital status and *International Classification of Diseases, Tenth Revision* death certificate cause-of-death codes (6) were obtained through the National Death Index. Patients were censored at last follow-up with a VA physician. An interaction term between ADT-RT and PSA level (dichotomized about the median) was included in the multivariable models.

Results

The cohort included 648 patients overall (450 with ADT and 198 with ADT-RT) (Table 1, Fig. E1; [available online at www.redjournal.org]). The median follow-up period for all patients was 5.2 years. The median duration of ADT use for all patients was 18.0 months (15.4 months for ADT-RT vs 19.4 months for ADT, $P = .004$). The 5-year unadjusted cumulative mortality estimates favored the ADT-RT group (ACM, 24% for ADT-RT vs 42% for ADT; PCSM, 18% vs 27%; noncancer mortality, 6% vs 21%) (Fig. 1, Table E1; [available online at www.redjournal.org]).

In the multivariable regression models, we noted significant interactions between ADT-RT and baseline PSA level stratified by the median of 26 ng/mL for both PCSM ($P = .038$ for interaction) and ACM ($P = .004$ for interaction) indicating heterogeneity of treatment effect according to baseline PSA level. ADT-RT was associated with a significant improvement in PCSM among patients with a pretreatment PSA level less than the median of 26 ng/mL (hazard ratio [HR], 0.50, 95% confidence interval [CI] 0.28-0.88; $P = .02$) (Fig. 2A) but not greater than the median (HR, 1.15; 95% CI 0.67-1.96; $P = .62$) (Fig. 2B, Table 2). Similarly, ADT-RT was associated with a significant improvement in ACM among patients with a pretreatment PSA level less than the median of 26 ng/mL (HR, 0.38; 95% CI 0.25-0.57; $P < .001$) (Fig. 3A) but not greater than the median (HR, 0.91; 95% CI 0.60-1.38; $P = .66$) (Fig. 3B, Table 3).

Discussion

We found that the addition of RT to ADT was associated with substantial improvements in both PCSM and ACM among certain patients with clinically detected lymph
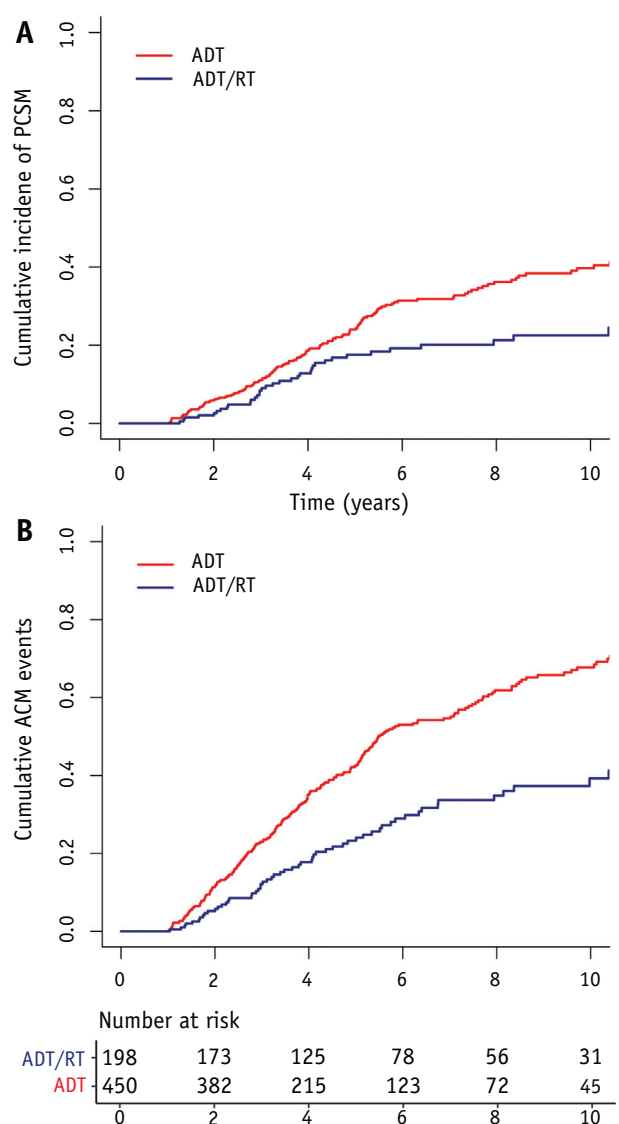

Fig. 1. Unadjusted cumulative incidence of prostate cancer−specific mortality (PCSM) (A) and cumulative all-cause mortality (ACM) events (B) by treatment group. *Abbreviations:* ADT = androgen deprivation therapy; RT = radiation therapy.

node metastases. These data support the growing body of literature that supports definitive therapy in cN+ patients (2-4, 7). An important finding in our study was that RT appears to be beneficial in patients with PSA levels below the median but not in those with PSA levels above the median. We hypothesize that patients with lower PSA levels are more likely to have truly locoregional disease and therefore would be more likely to benefit from locoregional treatment. In contrast, we hypothesize that patients with higher PSA levels are more likely to have subclinical metastases and therefore are less likely to benefit from locoregional RT.

Our study has several additional implications for the management of node-positive prostate cancer. First,
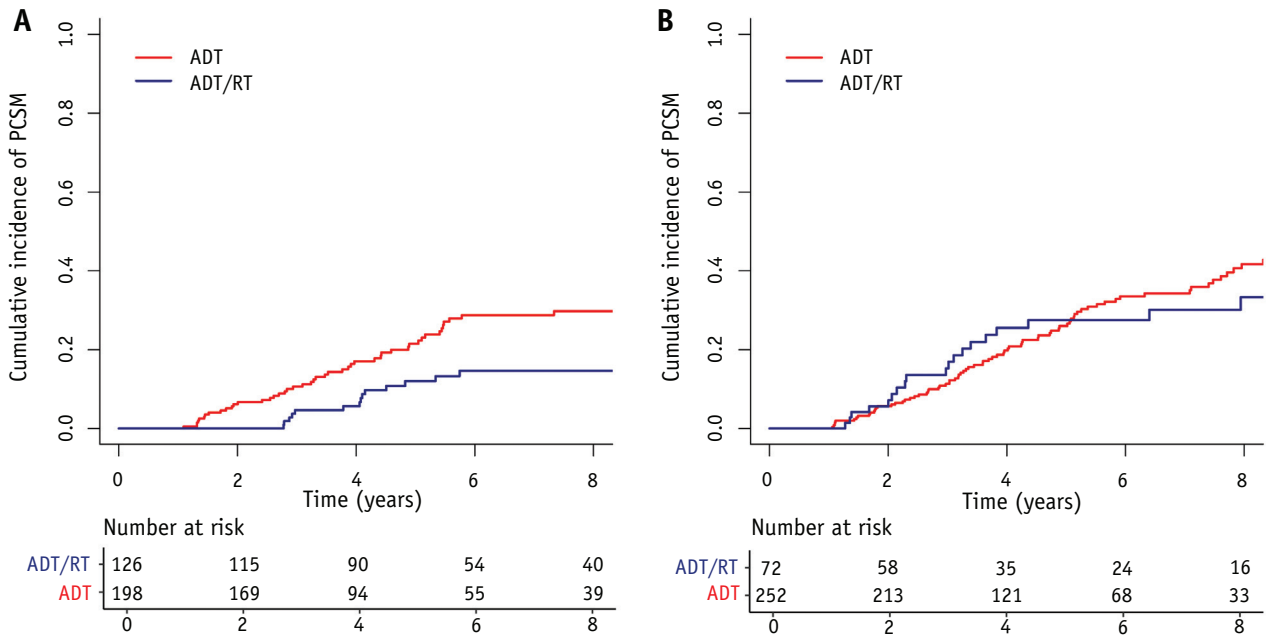
Fig. 2. Unadjusted cumulative incidence of prostate cancer−specific mortality (PCSM) for patients with pretreatment prostate-specific antigen (PSA) levels less than (A) or greater than (B) the median value of 26 ng/mL. *Abbreviations:* ADT = androgen deprivation therapy; RT = radiation therapy.

Table 2 Multivariable competing-risks regression for prostate cancer−specific mortality

Covariate	HR (95% CI)	P value
ADT-RT*		
PSA level < 26 ng/mL	0.50 (0.28-0.88)	.02
PSA level ≥ 26 ng/mL	1.15 (0.67-1.96)	.62
BMI (per 5 kg/m^2)	0.80 (0.69-0.92)	.01
Black race (vs nonblack)	0.69 (0.45-1.04)	.08
Age at diagnosis (per 10 years)	1.09 (0.90-1.31)	.39
Year of diagnosis (per year)	0.93 (0.90-0.97)	<.001
Charlson Comorbidity Index		
0	Reference	
1	1.14 (0.72-1.80)	.57
≥2	0.52 (0.25-1.09)	.08
Gleason score		
≤7	Reference	
8	1.29 (0.80-2.07)	.30
≥9	2.66 (1.77-3.99)	<.001
Tumor category		
T1-T2	Reference	
T3	1.41 (0.99-2.01)	.06
T4	1.78 (1.08-2.93)	.02
Married	0.86 (0.62-1.19)	.36
Employed	1.11 (0.64-1.93)	.71
Median income (per $10,000)	0.96 (0.88-1.05)	.13
Percent with high school diploma (per 10%)	0.90 (0.71-1.15)	.42

Abbreviations: ADT-RT = androgen deprivation therapy and radiation therapy; BMI = body mass index; CI = confidence interval; HR = hazard ratio; PSA = prostate-specific antigen.

* *P* = .038 for interaction.

improved risk stratification is needed to better identify patients who will benefit from locoregional therapy. Additional research should seek to clarify the impact of PSA level and other traditional risk factors on the benefit of definitive therapy. It should be noted that stratification about the median PSA value of 26 ng/mL was chosen rather than an "optimal" threshold to avoid overfitting of the data. As such, the best threshold will need to be clarified in future studies. Second, advances in imaging will likely better differentiate patients with locoregional versus metastatic disease. Bone scanning and computed tomography of the abdomen and pelvis are currently the standard staging studies; however, these tests have poor sensitivity and specificity (8, 9). Novel positron emission tomography tracers (10) or whole-body magnetic resonance imaging (11) should be investigated in this group. Finally, patients with a high risk of PCSM may be a good target for intensification of systemic therapy with advanced hormonal therapy or chemotherapy.

Our study is subject to several limitations. Like all observational studies, selection bias is an important consideration. The VA Informatics and Computing Infrastructure (VINCI) database provides comprehensive information on baseline patient and tumor information, treatment details, and cancer-specific outcomes that is superior to the National Cancer Database or Surveillance, Epidemiology, and End Results analyses that have been published. To our knowledge, no other study has demonstrated improvement in PCSM and ACM while controlling for critical baseline covariates including PSA level and
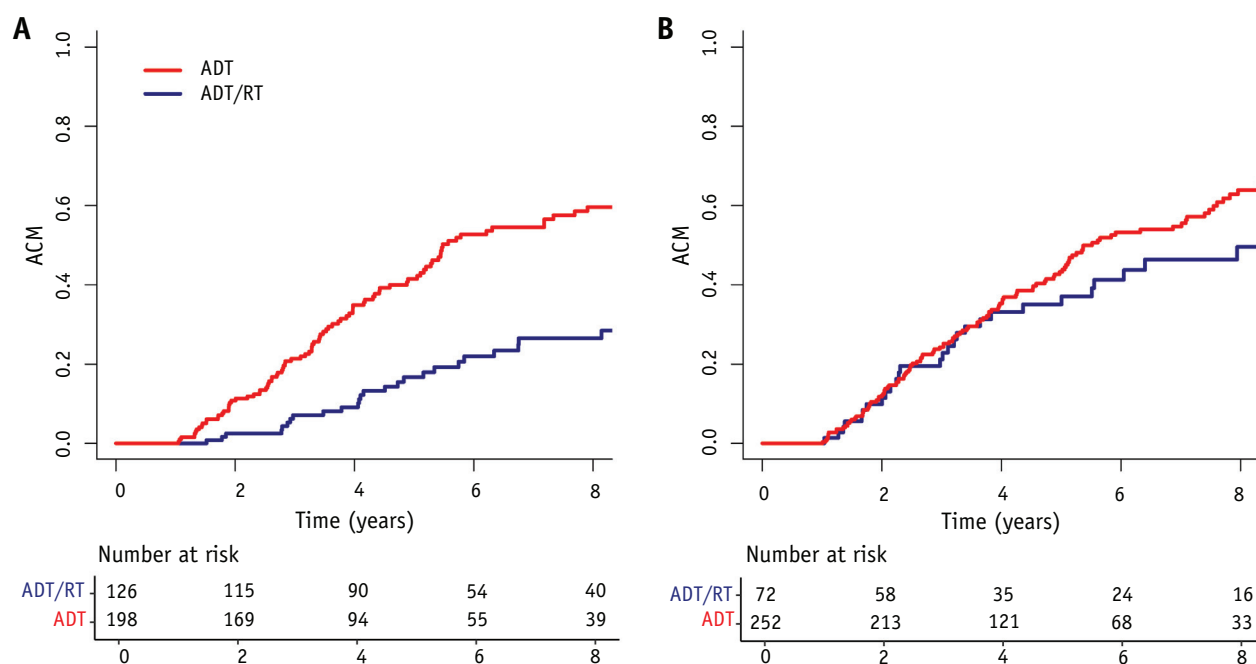
Fig. 3. Unadjusted cumulative all-cause mortality (ACM) events for patients with pretreatment prostate-specific antigen (PSA) levels less than (A) or greater than (B) the median value of 26 ng/mL. *Abbreviations:* ADT = androgen deprivation therapy; RT = radiation therapy.

Table 3 Cox multivariable regression for all-cause mortality

Covariate	HR (95% CI)	P value
ADT-RT*		
PSA level < 26 ng/mL	0.38 (0.25-0.57)	<.001
PSA level ≥ 26 ng/mL	0.91 (0.60-1.38)	.66
BMI (per 5 kg/m^2)	0.95 (0.85-1.06)	.35
Black race (vs nonblack)	0.77 (0.57-1.05)	.10
Age at diagnosis (per 10 years)	1.34 (1.16-1.55)	<.001
Year of diagnosis (per year)	0.95 (0.92-0.98)	.001
Charlson Comorbidity Index		
0	Reference	
1	1.55 (1.12-2.14)	.008
≥2	1.40 (0.96-2.06)	.08
Gleason score		
≤7	Reference	
8	1.14 (0.82-1.57)	.44
≥9	1.51 (1.13-2.01)	.01
Tumor category		
T1-T2	Reference	
T3	1.12 (0.84-1.48)	.44
T4	1.67 (1.10-2.52)	.02
Married	0.80 (0.63-1.02)	.07
Employed	1.21 (0.78-1.87)	.41
Median income (per $10,000)	1.03 (0.96-1.10)	.47
Percent with high school diploma (per 10%)	0.88 (0.75-1.04)	.13

Abbreviations: ADT-RT = androgen deprivation therapy and radiation therapy; BMI = body mass index; CI = confidence interval; HR = hazard ratio; PSA = prostate-specific antigen.
* P = .004 for interaction.

Gleason score. However, there is no way to completely eliminate selection bias. We did note lower noncancer mortality in the ADT-RT group, suggesting the possibility that definitive treatment was chosen for healthier patients. Although we did control for age, comorbidity, and other demographic factors associated with noncancer mortality, it is possible that some residual selection for healthier patients exists. We were also unable to account for the possibility that the treating clinician chose definitive RT based on the PSA level or radiographic response to therapy. This might bias the results to favor the ADT-RT group. Finally, our hypothesis that patients at high risk of subclinical metastases may not benefit from RT conflicts with the possibility of a survival benefit from local therapy in patients with known metastatic disease that has been seen in multiple Surveillance, Epidemiology, and End Results and National Cancer Database studies. Randomized trials will be needed to validate or refute these findings.

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