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Androgen Deprivation With or Without Radiation Therapy for Clinically Node-Positive Prostate Cancer

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Abstract

Background: Clinically lymph node–positive (cN+) prostate cancer (PCa) is an often-fatal disease. Its optimal management remains largely undefined given a lack of prospective, randomized data to inform practice. We sought to describe modern practice patterns in the management of cN+ PCa and assess the effect of adding radiation therapy (RT) to androgen deprivation therapy (ADT) on survival using the National Cancer Data Base.

Methods: Patients with cN+ PCa and without distant metastases diagnosed between 2004 and 2011 were included. Five-year overall survival for patients diagnosed between 2004 and 2006 and treated with ADT alone or ADT+RT were compared. Propensity score (PS) matching was used to balance baseline characteristics, and Cox multivariate regression analysis was used to estimate hazard ratios (HRs) for all-cause mortality.

Results: Of 3540 total patients, 32.2% were treated with ADT alone and 51.4% received ADT+RT. Compared with ADT alone, patients treated with ADT+RT were younger and more likely to have private insurance, lower comorbidity scores, higher Gleason scores, and lower PSA values. After PS matching, 318 patients remained in each group. Compared with ADT alone, ADT+RT was associated with a 50% decreased risk of five-year all-cause mortality (HR = 0.50, 95% CI = 0.37 to 0.67, two-sided $P < .001$; crude OS rate: 71.5% vs 53.2%).

Conclusions: Using a large national database, we have identified a statistically significant survival benefit for patients with cN+ PCa treated with ADT+RT. These data, if appropriately validated by randomized trials, suggest that a substantial proportion of such patients at high risk for prostate cancer death may be undertreated, warranting a reevaluation of current practice guidelines.

While there is ongoing concern regarding overdiagnosis and overtreatment of prostate cancer, there remain subsets of this disease with a high propensity for distant metastatic spread and cancer-specific death. Clinically lymph node–positive (cN+) prostate cancer, determined by radiographic staging with or without biopsy confirmation, is one such subset where management remains controversial given the paucity of data and lack of completed randomized trials to inform practice (1). Notably, patients with cN+ prostate cancer are placed in the same stage grouping as those with distant metastases, though they are often considered as a separate entity (2–4). Despite this, some providers may have the impression that prostate cancer outside of the prostate cannot be cured and therefore should not receive local therapy. Instead, providers may favor noncurative treatment with androgen deprivation therapy (ADT) alone. Indeed, clinical practice guidelines (5–7) for patients with cN+ prostate cancer and no distant metastases recommend both ADT alone or combined with radiation therapy (RT).

RT is a common treatment for prostate cancer, and recent randomized data support its addition to ADT in high-risk and locally advanced disease (8,9). Retrospective data also exist supporting the addition of RT to ADT in patients with pathologically

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positive lymph nodes (pN+) discovered after prostatectomy and/or lymphadenectomy (10,11). However, limited data exist supporting the role for the addition of RT to ADT in patients with cN+ disease identified using modern staging techniques. Using a large national cancer outcomes database, we sought to define current practice patterns for patients with cN+ prostate cancer and compare survival of patients treated with ADT alone vs ADT+RT.

Methods

Data Sources

The National Cancer Data Base (NCDB), a nationwide hospital-based cancer registry jointly sponsored by the American College of Surgeons (ACoS) and the American Cancer Society, collects data from more than 1400 hospitals accredited by the ACoS Commission on Cancer (CoC). The NCDB captures approximately 70% of all newly diagnosed cancer cases in the United States (12). It contains standardized data on patient demographic and disease characteristics, insurance status, American Joint Committee on Cancer (AJCC) staging, treatment, and comorbidities. Patient demographic and clinical characteristics captured in the NCDB are comparable with those reported in the Surveillance, Epidemiology, and Ends Results (SEER) database (13). Additionally, the NCDB collects information on systemic therapy (eg, hormone therapy) and hospital characteristics necessary to understand patterns of care. The NCDB has previously been used to explore trends in cancer treatment, address disparities, and examine outcomes (14).

Study Population

Male patients aged 18 to 90 years with a new diagnosis of prostate adenocarcinoma (*International Classification of Disease for Oncology, 3rd Edition* [ICD-O-3] site code: C61.9), diagnosed between 2004 and 2011, who were diagnosed or received part or all of their first course treatment at a CoC-accredited facility, were identified. The study cohort was then restricted to include patients with regional lymph node metastasis identified before treatment (cN+) and no proven distant metastases (M0 or Mx). Patients treated with radical prostatectomy were also excluded. Patients who had missing information in cancer diagnosis date (n = 13), treatment (n = 21), census region (n = 23), or insurance (n = 109) or had government-sponsored insurance other than Medicaid and Medicare (eg, Bureau of Indian Affairs, Public Health Service) (n = 38) were excluded from the study (Figure 1).

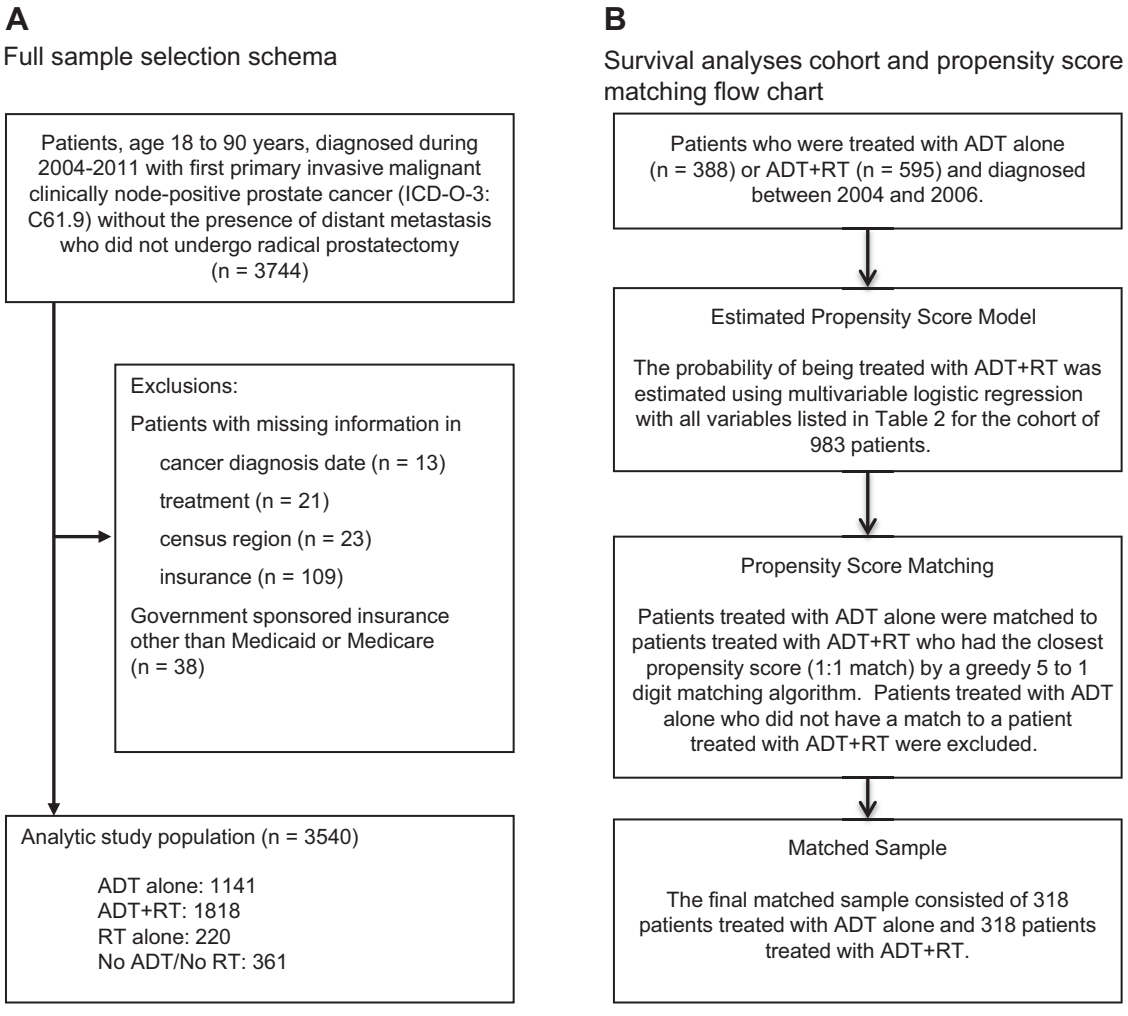

Figure 1. Patient selection schema. **A)** Full sample selection schema. **B)** Survival analyses study cohort and propensity score matching flow chart. ADT = androgen deprivation therapy; ICD-O-3 = *International Classification of Disease for Oncology, 3rd Edition*; RT = radiation therapy.

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Measurement

The primary outcome of this study was five-year overall survival in the subcohort diagnosed between 2004 and 2006. The end date of follow-up was December 31, 2011. Patients who were lost to follow-up or still alive at the end of the study period were censored. ADT indicates receipt of medications to suppress testosterone, while RT indicates administration of regional (pelvic) radiotherapy. Patients were thus categorized as ADT alone, combined ADT+RT, RT alone, and no ADT/no RT.

Patient insurance status was defined as private, uninsured, Medicaid, younger Medicare (age 18–64 years) and older Medicare (age 65+ years). Race/ethnicity was categorized as non-Hispanic white, black, Hispanic, other, and missing. Comorbidity was measured by Charlson-Deyo Comorbidity Score. Median income level in the ZIP code of a patient's residence was derived from 2000 US Census data. Gleason Score and prostate-specific antigen (PSA) level were collected as site-specific factors, while clinical T-stage was directly coded by cancer registrars based on available medical records. Missing data on Gleason score, PSA, and clinical T-stage were infrequent (<10%).

Statistical Analyses

Descriptive analyses were conducted for all patients included in the study population diagnosed between 2004 and 2011. A linear trend test was conducted to examine changes in practice patterns over time. To assess the effect of adding RT to ADT on five-year overall survival (OS), the study population was further restricted to those diagnosed between 2004 and 2006, as full five-year follow-up data was only available for this subcohort. Propensity score matching of patients receiving ADT alone or with RT was performed via the greedy-matching technique to create a subsample adjusted for all available potential confounders (15). Covariate balance was checked before and after adjustment with chi-square tests. Crude five-year OS rates were estimated for the two treatment modalities using the Kaplan-Meier approach. Log-rank *P* values under .05 were considered statistically significant. The assumption of proportionality was tested by Proc Phreg in SAS. If a specific covariate violated the assumption of proportionality, in-strata adjustment was performed in the Cox proportional regression analyses. All other reported *P* values have a statistical significance level set at *P* values of less than .05 (two-sided). As the number of involved lymph nodes could potentially affect the choice of treatment, a sensitivity analysis including number of positive lymph nodes as a clinical factor was performed. To further understand whether including cases with missing data would introduce additional confounding, a sensitivity analysis was conducted by excluding patients with missing key clinical characteristics. An additional sensitivity analysis was performed by including patients diagnosed between 2004 and 2011 and censoring those who were still alive at last follow-up. Statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC).

Results

Patient Characteristics and Patterns of Practice

A total of 3540 patients were included (Table 1). Median age was 66 years. Median follow-up time was 5.2 years for patients diagnosed between 2004 and 2006 and 2.7 years for patients diagnosed between 2004 and 2011. The majority of patients were non-Hispanic white (65.8%) and were insured by Medicare (50.0%) or private insurance (41.2%). Approximately half of patients were treated at community-based centers. Most patients had at least one high-risk feature, including Gleason scores of 8 to 10 (61.7%), PSA levels of 20 ng/mL or higher (46.2%), and clinical T-stage T3 or T4 (39.4%). Overall, 1141 (32.2%) were treated with ADT alone, 1818 (51.4%) with ADT+RT, 220 (6.2%) with RT alone, and 361 (10.2%) with neither ADT nor RT. Receipt of ADT alone decreased from 36.6% in 2004 to 32.2% in 2011, while ADT+RT increased from 45.2% to 54.1%; however, a trend test for the use of ADT+RT over the study period was not statistically significant (*P* = .36). For patients who received ADT+RT, 97% received external beam radiotherapy with median doses of 50.4 Gy to the pelvis and 75.6 Gy total.

Factors Associated With Treatment and Propensity Score Matching

The analysis was then restricted to patients diagnosed between 2004 and 2006 receiving guideline-supported care (ADT alone or ADT+RT). Prior to propensity score matching, the study cohort comprised 388 patients treated with ADT alone and 595 patients treated with ADT+RT. Patients who received combined treatment tended to be younger (*P* < .001) and were more likely to have private insurance (*P* < .001), lower comorbidity score (*P* = .002), higher Gleason grade (*P* < .001), lower PSA values (*P* < .001), and clinical T-stage T2 or T3 (*P* < .001). After propensity score matching, 318 patients remained in each group. The two cohorts were well balanced with no statistically significant differences in the matched factors (Table 2).

Survival Analyses

Prior to propensity score matching, 47.1% of patients treated with ADT alone and 25.0% of patients treated with ADT+RT died within the five-year follow-up period. The loss-to-follow-up rate was 10.3% and 16.8%, respectively. The crude five-year OS rate was 49.4% for patients treated with ADT alone vs 72.4% for patients treated with RT and ADT (log-rank *P* <.001) (Figure 2A). Combined ADT+RT was associated with a 49.2% decreased risk of five-year all-cause mortality (hazard ratio [HR] = 0.51, 95% confidence interval [CI] = 0.40 to 0.65, *P* < .001) compared with ADT alone after adjustment for confounding variables. Among the propensity score–matched subgroups, the crude five-year OS rate among patients treated with ADT alone was still statistically significantly lower than those treated with combined therapy (53.2% vs 71.5%, log-rank *P* <.001) (Figure 2B). After adjusting for patient demographic and clinical characteristics, combined ADT+RT was associated with a statistically significant 50.3% reduction in the risk of five-year all-cause mortality (HR = 0.50, 95% CI = 0.37 to 0.67, *P* < .001) compared with ADT alone. In addition, patients who were age 75 years and older (*P* = .05), and those treated at non-NCI-designated cancer centers (*P* < .05) also had an increased risk of five-year all-cause mortality (Table 3). To further understand whether the association of treatment and survival varied by age at diagnosis, clinical T-stage, Gleason score, and PSA level, stratified analyses were conducted (Table 4). Regardless of age at diagnosis, ADT+RT was associated with statistically significant reduction in the risk of five-year all-cause mortality compared with ADT alone (age <65 years: HR = 0.25, 95% CI = 0.14 to 0.45, *P* < .001; age ≥65 years: *HR* = 0.64, 95% CI = 0.44 to 0.95, *P* = .03). ADT+RT was associated with decreased overall mortality among patients with T1-T2 stage, with a trend among those with T3-T4 disease (T1-T2:

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Table 1. Patient demographic and clinical characteristics of the total study population*

	Total	ADT+RT	ADT only	RT only	no ADT/no RT	
	3540 (100)	1818 (51.4)	1141 (32.2)	220 (6.2)	361 (10.2)	
Characteristics	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	P†
Age, y						
<50	103 (2.9)	57 (3.1)	30 (2.6)	6 (2.7)	10 (2.8)	<.001
50–59	745 (21.1)	429 (23.6)	219 (19.2)	38 (17.3)	59 (16.3)	
60–64	646 (18.3)	357 (19.6)	184 (16.1)	45 (20.5)	60 (16.6)	
65–69	740 (20.9)	396 (21.8)	229 (20.1)	47 (21.4)	68 (18.8)	
70–74	562 (15.9)	297 (16.3)	165 (14.5)	44 (20.0)	56 (15.5)	
75–90	744 (21.0)	282 (15.5)	314 (27.5)	40 (18.2)	108 (29.9)	
Race/ethnicity						
Non-Hispanic white	2330 (65.8)	1236 (68.0)	735 (64.4)	149 (67.7)	210 (58.2)	<.001
Hispanic	183 (5.2)	91 (5.0)	47 (4.1)	12 (5.5)	33 (9.1)	
Black	635 (17.9)	284 (15.6)	228 (20.0)	35 (15.9)	88 (24.4)	
Other	108 (3.1)	67 (3.7)	26 (2.3)	6 (2.7)	9 (2.5)	
Missing	284 (8.0)	140 (7.7)	105 (9.2)	18 (8.2)	21 (5.8)	
Insurance						
Uninsured	161 (4.6)	52 (2.9)	69 (6.1)	11 (5.0)	29 (8.0)	<.001
Medicaid	152 (4.3)	69 (3.8)	60 (5.3)	6 (2.7)	17 (4.7)	
Younger Medicare‡	160 (4.5)	94 (5.2)	41 (3.6)	10 (4.6)	15 (4.2)	
Older Medicare§	1609 (45.5)	771 (42.4)	559 (49.0)	102 (46.4)	177 (49.0)	
Private	1458 (41.2)	832 (45.8)	412 (36.1)	91 (41.4)	123 (34.1)	
Diagnosis year						
2004	385 (10.9)	174 (9.6)	141 (12.4)	27 (12.3)	43 (11.9)	.31
2005	368 (10.4)	188 (10.3)	103 (9.0)	26 (11.8)	51 (14.1)	
2006	438 (12.4)	233 (12.8)	144 (12.6)	24 (10.9)	37 (10.3)	
2007	428 (12.1)	225 (12.5)	131 (11.5)	29 (13.2)	43 (11.9)	
2008	456 (12.9)	230 (12.7)	143 (12.5)	29 (13.2)	54 (15.0)	
2009	494 (14.0)	247 (13.6)	163 (14.3)	33 (15.0)	51 (14.1)	
2010	477 (13.5)	254 (14.0)	157 (13.8)	28 (12.7)	38 (10.5)	
2011	494 (14.0)	267 (14.7)	159 (13.9)	24 (10.9)	44 (12.2)	
Census region						
Northeast	841 (23.8)	443 (24.4)	284 (24.9)	52 (23.6)	62 (17.2)	<.001
Midwest	962 (27.2)	509 (28.0)	334 (29.3)	47 (21.4)	72 (19.9)	
South	1068 (30.2)	514 (28.3)	321 (28.1)	80 (36.4)	153 (42.4)	
West	669 (18.9)	352 (19.4)	202 (17.7)	41 (18.6)	74 (20.5)	
Median income, USD						
<30 000	504 (14.2)	233 (12.8)	168 (14.7)	35 (15.9)	68 (18.8)	.07
30 000–34 999	571 (16.1)	287 (15.8)	174 (15.3)	40 (18.2)	70 (19.4)	
35 000–45 999	921 (26.0)	473 (26.0)	307 (26.9)	57 (25.9)	84 (23.3)	
46 000+	1398 (39.5)	753 (41.4)	444 (38.9)	76 (34.6)	125 (34.6)	
Missing	146 (4.1)	72 (4.0)	48 (4.2)	12 (5.5)	14 (3.9)	
Facility type						
Community Cancer Program	349 (9.9)	176 (9.7)	109 (9.6)	27 (12.3)	37 (10.3)	<.001
Comprehensive Community Cancer Center	1520 (42.9)	811 (44.6)	441 (38.7)	110 (50.0)	158 (43.8)	
Teaching/research	844 (23.8)	387 (21.3)	314 (27.5)	45 (20.5)	98 (27.2)	
NCI Program/Network	509 (14.4)	280 (15.4)	191 (16.7)	19 (8.6)	19 (5.3)	
Other	318 (9.0)	164 (9.0)	86 (7.6)	19 (8.6)	49 (13.6)	
Charlson Comorbidity Score						
0	2951 (83.4)	1560 (85.8)	916 (80.3)	187 (85.0)	288 (79.8)	<.001
1	429 (12.1)	206 (11.3)	156 (13.7)	21 (9.6)	46 (12.7)	
2+	160 (4.5)	52 (2.9)	69 (6.1)	12 (5.5)	27 (7.5)	
GLS						
2–6	188 (5.3)	71 (3.9)	39 (3.4)	45 (20.5)	33 (9.1)	<.001
7	789 (22.3)	440 (24.2)	214 (18.8)	55 (25.0)	80 (22.2)	
8–10	2185 (61.7)	1220 (67.1)	723 (63.4)	87 (39.6)	155 (42.9)	
Missing	378 (10.7)	87 (4.8)	165 (14.5)	33 (15.0)	93 (25.8)	
PSA						
<10 ng/mL	947 (26.8)	554 (30.5)	209 (18.3)	93 (42.3)	91 (25.2)	<.001
10-<20 ng/mL	719 (20.3)	416 (22.9)	214 (18.8)	36 (16.4)	53 (14.7)	
20+ ng/mL	1636 (46.2)	803 (44.2)	627 (55.0)	64 (29.1)	142 (39.3)	
Missing	238 (6.7)	45 (2.5)	91 (8.0)	27 (12.3)	75 (20.8)	

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Table 1. Continued

Characteristics	Total 3540 (100) No. (%)	ADT+RT 1818 (51.4) No. (%)	ADT only 1141 (32.2) No. (%)	RT only 220 (6.2) No. (%)	no ADT/no RT 361 (10.2) No. (%)	P†
Clinical T stage						
T1	811 (22.9)	367 (20.2)	272 (23.8)	71 (32.3)	101 (28.0)	<.001
T2	1175 (33.2)	634 (34.9)	359 (31.5)	72 (32.7)	110 (30.5)	
T3	1002 (28.3)	634 (34.9)	257 (22.5)	48 (21.8)	63 (17.5)	
T4	393 (11.1)	160 (8.8)	167 (14.6)	24 (10.9)	42 (11.6)	
Missing	159 (4.5)	23 (1.3)	86 (7.5)	5 (2.3)	45 (12.5)	

* All statistical tests were two-sided. Because of rounding, percentages presented throughout this table may not add up precisely to 100%. ADT = androgen deprivation therapy; GLS = Gleason Score; PSA = prostate-specific antigen; RT = radiation therapy; USD = U.S. dollars.
† *P* values were calculated using Pearson's chi-squared test.
‡ Younger Medicare: patients aged 18 to 64 years eligible for Medicare.
§ Older Medicare: patients eligible for Medicare aged 65 years or older.

HR = 0.40, 95% CI = 0.26 to 0.62, $P < .001$; T3-T4: HR = 0.62, 95% CI = 0.38 to 1.01, $P = .05$). ADT+RT was associated with improved survival among patients with Gleason Scores of 8 to 10, with a trend among those with Gleason Scores of 7 or less (GLS ≤ 7: HR = 0.49, 95% CI = 0.23 to 1.01, $P = .05$; GLS ≥ 8: HR = 0.55, 95% CI = 0.38 to 0.79, $P = .001$). ADT+RT was also associated with improved survival among patients with PSA levels of 20 ng/mL or higher but not among those with PSA levels of less than 20 ng/mL (PSA <20 ng/mL: HR = 0.60, 95% CI = 0.35 to 1.04, $P = .07$; PSA ≥ 20 ng/mL: HR = 0.44, 95% CI = 0.28 to 0.68, $P < .001$).

As the number of involved lymph nodes could also potentially affect the choice of treatment, we sought to include this factor in our model. Unfortunately these data were only available for 30% of the cohort. We conducted a sensitivity analysis for those patients without missing data for number of involved lymph nodes, and the results were similar to our primary analysis (data not shown). A sensitivity analysis on the subset of patients without missing data for Gleason Score, PSA level, and clinical T-stage was also performed, as was an analysis that included patients diagnosed between 2004 and 2011. Results of both analyses were similar to our original findings (Supplementary Tables 1 and 2, available online).

Discussion

Using propensity score matching of patient data derived from a large US cancer database, we have identified that the addition of RT to ADT for patients with cN+ prostate cancer decreases five-year all-cause mortality by 50%. Our data also suggest that nearly half of patients with this presentation may not receive optimal therapy with the potential for durable disease control.

Between 2004 and 2011, we found no statistically significant changes in the utilization of ADT or RT in patients with cN+ prostate cancer. This may be because of the paucity of data to inform practice and guidelines that support both ADT alone or along with RT for these patients (5–7). Many physicians use lymph node status as a dividing line between what they consider a curative and noncurative patient, an approach tacitly supported by the current AJCC staging system, which groups node-positive patients along with those known to have distant metastatic disease (2). Despite this, numerous studies exist, suggesting that patients with isolated lymph node involvement can be long-term survivors and have outcomes approaching those of patients with locally advanced disease (16–19). While randomized data exist to support the use of ADT+RT in locally advanced prostate cancer, the ability to extrapolate these results to patients with nodal involvement is limited, as such patients were typically excluded from these trials (4,9,20). The rationale for such therapy remains the same; that is, disease confined to the pelvis can potentially be sterilized by radiotherapy allowing for durable disease control.

There are few previous reports that address the role of a combined modality approach in patients with cN+ prostate cancer. In an unplanned subgroup analysis of cN+ patients included in RTOG 8531, a randomized trial of RT alone vs RT plus ADT for patients with locally advanced prostate cancer, the addition of ADT to RT resulted in a substantial improvement in progression-free and overall survival (nine-year OS rate = 62% vs 38%) (21). While these data indicated a benefit for combined modality therapy, patient numbers were small (98 receiving ADT+RT and 75 receiving RT alone) and all patients in this trial received RT. Another population-based cancer registry study found that cN+ prostate cancer patients treated with RT had improved overall survival (HR = 0.57, $P < .001$) and prostate cancer–specific survival (HR = 0.58, $P < .001$) compared with those not treated with RT (22). This study, however, cannot comment on the benefit of adding RT to ADT, given that the SEER database lacks information on the use of ADT.

The use of RT alone is an uncommon practice in the modern era (6.2% in our study). Therefore, these data cannot inform the potential differences between ADT alone and ADT+RT, which are the dominant modern management strategies supported by clinical practice guidelines (5–7). RTOG 9608 made an attempt to address this question (ADT +/- RT) in a randomized fashion; however, this trial failed to accrue and was closed.

In another retrospective unmatched single-institution study, Zagars et al. compared outcomes for 255 node-positive prostate cancer patients, 183 of whom received ADT alone and 72 of whom received ADT+RT between 1984 and 1998 (11). Patients treated with combined modality therapy had superior overall survival on univariate and multivariate analysis compared with those treated with ADT alone (five-year OS: 92% vs 83%). All of the patients in this study, however, had subclinical node-positive disease discovered only at the time of staging lymphadenectomy. As patients with bulky radiographically positive lymph nodes may be at higher risk of harboring concomitant but undetectable micrometastatic disease, the relative benefit of adding local treatment with RT was not adequately assessed by this study.

Recent data has also emerged suggesting a role for adjuvant RT for patients with lymph node metastases discovered at the time of radical prostatectomy (10,23). In an updated retrospective

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Table 2. Demographic and clinical characteristics at baseline for patients diagnosed between 2004 and 2006 treated with ADT alone or combined ADT+RT*

	Before propensity matching			After propensity matching		
	ADT alone	ADT+RT	P†	ADT alone	ADT+RT	P†
	(n = 388)	(n = 595)		(n = 318)	(n = 318)	
Characteristics	No. (%)	No. (%)		No. (%)	No. (%)	
Age, y						
<50	12 (3.1)	22 (3.7)	<.001	10 (3.1)	15 (4.7)	.83
50–59	79 (20.4)	145 (24.4)		69 (21.7)	71 (22.3)	
60–64	60 (15.5)	127 (21.3)		53 (16.7)	60 (18.9)	
65–69	71 (18.3)	124 (20.8)		61 (19.2)	55 (17.3)	
70–74	65 (16.8)	90 (15.1)		53 (16.7)	47 (14.8)	
75–90	101 (26.0)	87 (14.6)		72 (22.6)	70 (22.0)	
Race/ethnicity						
Non-Hispanic white	265 (68.3)	396 (66.6)	.16	215 (67.6)	223 (70.1)	.56
Hispanic	14 (3.6)	25 (4.2)		9 (2.8)	15 (4.7)	
Black	61 (15.7)	89 (15.0)		52 (16.4)	45 (14.2)	
Other	5 (1.3)	24 (4.0)		5 (1.6)	3 (0.9)	
Missing‡	43 (11.1)	61 (10.3)		37 (11.6)	32 (10.1)	
Insurance						
Uninsured	20 (5.2)	9 (1.5)	<.001	7 (2.2)	6 (1.9)	.36
Medicaid	17 (4.4)	18 (3.0)		15 (4.7)	10 (3.1)	
Younger Medicare	13 (3.4)	32 (5.4)		13 (4.1)	15 (4.7)	
Older Medicare	195 (50.3)	238 (40.0)		153 (48.1)	134 (42.1)	
Private	143 (36.9)	298 (50.1)		130 (40.9)	153 (48.1)	
Facility type						
Community Cancer Program	40 (10.3)	60 (10.1)	.17	33 (10.4)	39 (12.3)	.21
Comprehensive Community Cancer Center	172 (44.4)	281 (47.2)		137 (43.1)	153 (48.1)	
Teaching/research	104 (26.8)	122 (20.5)		84 (26.4)	62 (19.5)	
NCI Program/Network	45 (11.6)	76 (12.8)		42 (13.2)	36 (11.3)	
Other	27 (7.00)	56 (9.4)		22 (6.9)	28 (8.8)	
Charlson Comorbidity Score						
0	321 (82.7)	522 (87.7)	.002	272 (85.5)	278 (87.4)	.78
1	47 (12.1)	65 (10.9)		38 (12.0)	33 (10.4)	
2+	20 (5.2)	8 (1.3)		8 (2.5)	7 (2.2)	
GLS						
2–6	21 (5.4)	32 (5.4)	<.001	19 (6.0)	17 (5.4)	.84
7	86 (22.2)	162 (27.2)		80 (25.2)	76 (23.9)	
8–10	226 (58.3)	373 (62.7)		196 (61.6)	206 (64.8)	
Missing‡	55 (14.2)	28 (4.7)		23 (7.2)	19 (6.0)	
PSA						
<10 ng/mL	78 (20.1)	194 (32.6)	<.001	73 (23.0)	83 (26.1)	.67
10-<20 ng/mL	77 (19.9)	141 (23.7)		72 (22.6)	61 (19.2)	
20+ ng/mL	192 (49.5)	237 (39.8)		154 (48.4)	155 (48.7)	
Missing‡	41 (10.6)	23 (3.9)		19 (6.0)	19 (6.0)	
Clinical T stage						
T1	79 (20.4)	121 (20.3)	<.001	67 (21.1)	66 (20.8)	.97
T2	131 (33.8)	216 (36.3)		117 (36.8)	115 (36.2)	
T3	98 (25.3)	207 (34.8)		93 (29.3)	90 (28.3)	
T4	55 (14.2)	43 (7.2)		33 (10.4)	39 (12.3)	
Missing‡	25 (6.4)	8 (1.3)		8 (2.5)	8 (2.5)	

* All statistical tests were two-sided. Propensity matching adjusted all variables listed in Table 2, including age at diagnosis, race/ethnicity, insurance, comorbidity, clinical T stage, Gleason Score, PSA level, and facility type. Even though race/ethnicity and facility type were not shown to be statistically significantly different between the groups, previous reports have suggested possible differences in practice patterns by these factors. Thus, they were included in the final propensity score model (26–30). ADT = androgen deprivation therapy; GLS = Gleason Score; NCI = National Cancer Institute; PSA = prostate-specific antigen; RT = radiation therapy.

† *P* values were calculated using Pearson's chi-squared test.

‡ To reduce incomplete propensity score matching, missing data was assigned as a category to be calculated in the propensity score.

study of two cohorts matched for relevant clinical characteristics, Briganti et al. found that the addition of RT to ADT for patients with pathologic lymph node involvement improved eight-year overall survival from 65% to 84% (10). This improvement remained statistically significant, even for patients with more extensive lymph node involvement. While these data are compelling, they are again not directly applicable to patients with cN+ prostate cancer, who are treated definitively with primary RT/ADT and no

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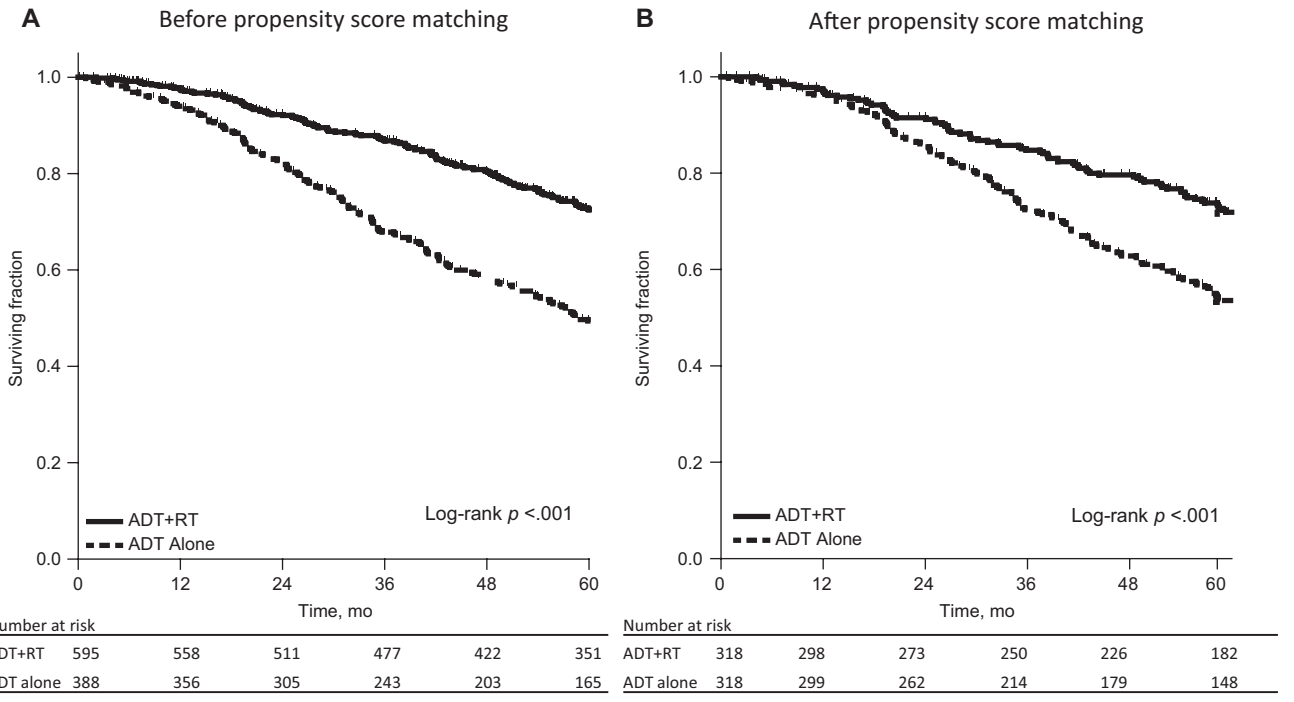

Figure 2. Kaplan-Meier survival curves for patients treated with androgen deprivation therapy (ADT) alone and combined ADT+ radiation therapy (RT). **A)** Kaplan-Meier survival curves for patients treated with ADT alone and combined ADT+RT before propensity score matching. **B)** Kaplan-Meier survival curves for patients treated with ADT alone and combined ADT+RT after propensity score matching. Log-rank *P* value was two-sided. ADT = androgen deprivation therapy; RT = radiation therapy.

surgery. Additionally, patients undergoing radical prostatectomy tend to be younger and healthier than prostate cancer patients on the whole, which may increase any potential benefit seen for more aggressive adjuvant therapy in this study. It is important to note, however, that the studies by Briganti et al. and Da Pozzo et al. were not randomized and so may be subject to substantial selection bias. Regardless, the role of surgery in the multimodal management of cN+ prostate cancer warrants further investigation (1).

Our study has several limitations. First, the NCDB is a hospital-based cancer registry that captures only patients who are diagnosed or treated in CoC-accredited facilities. Our results, therefore, may not fully represent the entire cancer population in the United States, though the NCDB does capture approximately 70% of incident cancers each year and previous studies show similar patient characteristics in the NCDB compared with other population-based cohorts (12,13,24,25). Indeed, our cohort would include a more diverse sample of patients and comorbidities than would be present in a strictly controlled randomized trial or prospective single-institution database. As such, these results may be more generalizable overall and represent "real-world" outcomes for patients with this condition. Second, we are unable to comment on cancer-specific mortality, as such data was not collected. However, overall survival remains the gold standard endpoint relevant to a disease state such as cN+ prostate cancer, which has many events within a few years of diagnosis. Indeed, a recent publication with just over seven years of follow-up demonstrated a statistically significant survival benefit for patients with locally advanced disease when RT was added to ADT (9). As cN+ prostate cancer is a disease state with an even higher likelihood of leading to lethal prostate cancer, a five-year endpoint is reasonable, though longer follow-up will no doubt improve the conclusions from this study. Third, as this is a retrospective study, we have included all relevant clinical factors associated with disease outcome that are contained in the NCDB to control for possible confounding factors. However, there may still exist some residual unmeasurable confounding factors that we failed to identify and control for, despite the use of propensity score matching and multivariate modeling (such as lymph node size which is not recorded in the NCDB). Though including a larger study population might help to overcome this concern, our study was limited to include only patients having adequate data on prognostic risk factors and five-year follow-up in hopes of providing more accurate and generalizable conclusions. Finally, we are unable to comment on toxicity and quality-of-life differences between the different management strategies.

While prostate cancer patients with lymph node involvement are at high risk for developing distant metastases and death because of prostate cancer, a benefit for local therapy to the pelvis may yet exist. Using data from a large national cancer database, we identify a statistically significant survival benefit for the addition of RT to ADT in cN+ prostate cancer patients. These data also suggest that up to 50% of such patients in the United States are potentially being undertreated. As aggressive local management of cN+ prostate cancer may lead to durable disease control or even cure, these data have important implications for clinical practice guidelines and staging systems. Validation of these data by future prospective and randomized studies is, however, required.

Notes

This study used the National Cancer Data Base (NCDB). The interpretation and reporting of these data are the sole responsibility of the authors. The data used in the study are derived from a deidentified NCDB file. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology employed or the conclusions drawn from these data by the authors.

An abstract based on these results was accepted for presentation at the Academy Health Annual Research Meeting, June

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Table 3. Multivariable Cox proportional hazards analyses of five-year overall mortality*

	Before PS matching		After PS matching	
	ADT alone: n = 388; ADT+RT: n = 595		ADT alone: n = 318; ADT+RT: n = 318	
Variables	HR (95%CI)	P	HR (95%CI)	P
Treatment				
ADT alone	Ref		Ref	
ADT+RT	0.51 (0.40 to 0.65)	<.001	0.50 (0.37 to 0.67)	<.001
Age, y				
<50	Ref		Ref	
50–59	1.74 (0.68 to 4.40)	.25	1.16 (0.44 to 3.03)	.77
60–64	1.82 (0.71 to 4.66)	.21	1.09 (0.41 to 2.91)	.87
65–69	2.80 (1.07 to 7.36)	.04	1.63 (0.60 to 4.49)	.34
70–74	2.19 (0.82 to 5.81)	.12	1.27 (0.46 to 3.55)	.65
75–90	4.01 (1.53 to 10.53)	.005	2.69 (0.98 to 7.37)	.05
Race/ethnicity				
Non-Hispanic white	Ref		Ref	
Hispanic	1.11 (0.57 to 2.16)	.76	1.09 (0.46 to 2.61)	.84
Black	0.87 (0.61 to 1.26)	.46	0.88 (0.55 to 1.40)	.59
Others	1.40 (0.70 to 2.80)	.34	1.71 (0.50 to 5.80)	.39
Missing†	0.92 (0.63 to 1.33)	.65	1.00 (0.64 to 1.56)	.99
Insurance				
Private	Ref		Ref	
Uninsured	1.11 (0.57 to 2.16)	.76	2.30 (0.87 to 6.04)	.09
Medicaid	0.87 (0.61 to 1.26)	.46	0.67 (0.28 to 1.60)	.37
Young Medicare	1.40 (0.70 to 2.80)	.34	1.76 (0.90 to 3.47)	.10
Old Medicare	0.92 (0.63 to 1.33)	.65	1.02 (0.65 to 1.61)	.94
Diagnosis year				
2004	Ref		Ref	
2005	0.98 (0.74 to 1.31)	.91	1.00 (0.68 to 1.47)	.99
2006	1.03 (0.79 to 1.34)	.83	1.08 (0.76 to 1.53)	.68
Census Region				
Northeast	Ref		Ref	
Midwest	0.95 (0.70 to 1.29)	.73	0.85 (0.58 to 1.25)	.41
South	1.03 (0.74 to 1.42)	.87	0.97 (0.65 to 1.47)	.90
West	0.87 (0.61 to 1.23)	.42	0.79 (0.51 to 1.22)	.29
Median income, USD				
<30 000	Ref		Ref	
30 000–34 999	1.20 (0.79 to 1.85)	.39	0.86 (0.50 to 1.47)	.58
35 000–45 999	1.09 (0.73 to 1.63)	.68	0.86 (0.52 to 1.42)	.55
46 000+	1.12 (0.76 to 1.65)	.57	0.85 (0.52 to 1.38)	.50
Missing†	0.86 (0.42 to 1.76)	.67	0.65 (0.28 to 1.50)	.31
Charlson Comorbidity Score				
0	Ref		---§	---§
1	1.41 (1.02 to 1.94)	.04	---§	---§
2+	2.09 (1.28 to 3.41)	.003	---§	---§
Facility type				
NCI Program/Network	Ref		Ref	
Community Cancer Program	1.66 (0.97 to 2.84)	.07	1.78 (0.89 to 3.54)	.10
Comprehensive Community Cancer Center	1.84 (1.20 to 2.84)	.006	2.33 (1.32 to 4.12)	.004
Teaching/research	1.70 (1.07 to 2.70)	.03	2.17 (1.19 to 3.96)	.01
Others	2.35 (1.37 to 4.03)	.002	3.13 (1.56 to 6.29)	.001
GLS				
2–6	---‡	---‡	Ref	
7	---‡	---‡	0.88 (0.46 to 1.71)	.71
8–10	---‡	---‡	1.57 (0.87 to 2.84)	.13
Missing†	---‡	---‡	1.43 (0.66 to 3.10)	.36
PSA				
<10 ng/mL	Ref		Ref	
10-<20 ng/mL	1.22 (0.87 to 1.70)	.25	1.35 (0.88 to 2.07)	.18
20+ ng/mL	1.31 (0.98 to 1.73)	.07	1.58 (1.10 to 2.26)	.01
Missing†	1.16 (0.71 to 1.91)	.55	1.57 (0.81 to 3.05)	.18

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Table 3. Continued

Variables	Before PS matching: ADT alone: n = 388; ADT+RT: n = 595		After PS matching: ADT alone: n = 318; ADT+RT: n = 318	
	HR (95%CI)	P	HR (95%CI)	P
Clinical T stage				
T1	Ref		Ref	
T2	0.84 (0.60 to 1.17)	.30	0.78 (0.52 to 1.16)	.22
T3	1.27 (0.91 to 1.76)	.16	1.15 (0.77 to 1.72)	.49
T4	1.62 (1.10 to 2.40)	.02	1.65 (1.02 to 2.66)	.04
Missing†	1.58 (0.87 to 2.85)	.13	1.70 (0.68 to 4.22)	.25

* All statistical tests were two-sided. ADT = androgen deprivation therapy; GLS = Gleason Score; NCI = National Cancer Institute; PS = propensity score; PSA = prostate-specific antigen; Ref = referent; RT = radiation therapy; USD = U.S. dollars.
† To reduce incomplete propensity score matching, missing data was assigned as a category to be calculated in the propensity score.
‡ Because Gleason score violated the assumption of proportionality in cases before propensity matching (diagnosed between 2004 and 2006), in-strata adjustment was performed.
§ Because Charlson Comorbidity Score violated the assumption of proportionality in cases after propensity matching (diagnosed between 2004 and 2006), in-strata adjustment was performed.

Table 4. Multivariable Cox proportional hazards analyses of five-year overall mortality, stratifying by age at diagnosis, clinical T stage, Gleason Score, and PSA level*

Stratified subset	ADT alone, No. (%) dead within 5 y	ADT plus RT, No. (%) dead within 5 y	Adjusted HR (95% CI) †	P‡
Age < 65 y	50 (37.9)	24 (16.4)	0.25 (0.14 to 0.45)	<.001
Age ≥ 65 y	89 (47.9)	59 (34.3)	0.64 (0.44 to 0.95)	.03
T1-T2	74 (38.5)	37 (19.6)	0.40 (0.26 to 0.62)	<.001
T3-T4	65 (51.6)	46 (35.7)	0.62 (0.38 to 1.01)	.05
GLS ≤7	33 (33.3)	16 (17.2)	0.49 (0.23 to 1.01)	.05
GLS ≥8	94 (48.0)	63 (30.6)	0.55 (0.38 to 0.79)	.001
PSA < 20 ng/mL	56 (38.6)	35 (24.3)	0.60 (0.35 to 1.04)	.07
PSA ≥ 20 ng/mL	74 (48.1)	45 (29.0)	0.44 (0.28 to 0.68)	<.001

* All statistical tests were two-sided. Stratified subset derived from propensity matched study cohort (n = 636). ADT = androgen deprivation therapy; CI = confidence interval; GLS = Gleason Score; HR = hazard ratio; PSA = prostate-specific antigen; RT = radiation therapy.
† Reference = ADT alone; hazard ratios are adjusted for age at diagnosis, sex, race/ethnicity, insurance status, diagnosis year, median income level, Gleason score, Clinical T stage, PSA level, census region, and facility type, in-strata adjusted by comorbidity score.
‡ *P* values were derived from multivariate Cox proportional hazards analyses.

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All authors participated in the concept and design of the study, interpretation of the data, and drafting of the manuscript. CL also contributed to the data analyses.

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References

1. Mitin T, Blute M, Lee R, et al. Management of lymph node-positive prostate cancer: the role of surgery and radiation therapy. *Oncology (Williston Park)*. 2013;27(7):647–655.
2. AJCC. *American Joint Committee on Cancer: Cancer Staging Manual*. In. Sixth ed; 2002.
3. American Joint Committee on Cancer. Prostate Cancer Staging, https://cancerstaging.org/references-tools/quickreferences/Documents/ProstateSmall.pdf. Accessed April 22, 2014.
4. AJCC: American Joint Committee on Cancer: Cancer Staging Manual. *Prostate*. 7th ed: Springer; 2010.
5. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines for Prostate Cancer. http://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf.
6. Heidenreich A, Bastian PJ, Bellmunt J, et al. EAU Guidelines on Prostate Cancer. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent—Update 2013. *Eur Urol*. 2014;65(1):124–137.
7. Horwich A, Parker C, de Reijke T, et al. Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2013;24(Suppl 6):vi106-vi114.
8. Warde P, Mason M, Ding K, et al. Combined androgen deprivation therapy and radiation therapy for locally advanced prostate cancer: a randomised, phase 3 trial. *Lancet*. 2011;378(9809):2104–2111.
9. Widmark A, Klepp O, Solberg A, et al. Endocrine treatment, with or without radiotherapy, in locally advanced prostate cancer (SPCG-7/SFUO-3): an open randomised phase III trial. *Lancet*. 2009;373(9660):301–308.
10. Briganti A, Karnes RJ, Da Pozzo LF, et al. Combination of adjuvant hormonal and radiation therapy significantly prolongs survival of patients with pT2-4 pN+ prostate cancer: results of a matched analysis. *Eur Urol*. 2011;59(5):832–840.
11. Zagars GK, Pollack A, von Eschenbach AC. Addition of radiation therapy to androgen ablation improves outcome for subclinically node-positive prostate cancer. *Urol*. 2001;58(2):233–239.
12. Lerro CC, Robbins AS, Phillips JL, et al. Comparison of cases captured in the national cancer data base with those in population-based central cancer registries. *Ann Surg Oncol*. 2013;20(6):1759–1765.
13. Fedewa SA, Etzioni R, Flanders WD, et al. Association of insurance and race/ethnicity with disease severity among men diagnosed with prostate can-

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cer, National Cancer Database 2004–2006. *Cancer Epidemiol Biomarkers Prev*. 2010;19(10):2437–2444.
14. Winchester DP, Stewart AK, Phillips JL, et al. The national cancer data base: past, present, and future. *Ann Surg Oncol*. 2010;17(1):4–7.
15. Parsons L. Reducing Bias in a Propensity Score Matched-Pair Sample Using Greedy Matching Techniques. SAS Institute Inc. *SUGI26*. West Sacramento, CA; 2001.
16. Cheng L, Zincke H, Blute ML, et al. Risk of prostate carcinoma death in patients with lymph node metastasis. *Cancer*. 2001;91(1):66–73.
17. Boorjian SA, Thompson RH, Siddiqui S, et al. Long-term outcome after radical prostatectomy for patients with lymph node positive prostate cancer in the prostate specific antigen era. *J Urol*. 2007;178(3 Pt 1):864–870; discussion 870–871.
18. Bader P, Burkhard FC, Markwalder R, et al. Disease progression and survival of patients with positive lymph nodes after radical prostatectomy. Is there a chance of cure? *J Urol*. 2003;169(3):849–854.
19. Daneshmand S, Quek ML, Stein JP, et al. Prognosis of patients with lymph node positive prostate cancer following radical prostatectomy: long-term results. *J Urol*. 2004;172(6 Pt 1):2252–2255.
20. Bolla M, Van Tienhoven G, Warde P, et al. External irradiation with or without long-term androgen suppression for prostate cancer with high metastatic risk: 10-year results of an EORTC randomised study. *Lancet Oncol*. 2010;11(11):1066–1073.
21. Lawton CA, Winter K, Grignon D, et al. Androgen suppression plus radiation versus radiation alone for patients with stage D1/pathologic node-positive adenocarcinoma of the prostate: updated results based on national prospective randomized trial Radiation Therapy Oncology Group 85-31. *J Clin Oncol*. 2005;23(4):800–807.
22. Rusthoven CG, Carlson JA, Waxweiler TV, et al. The impact of definitive local therapy for lymph node-positive prostate cancer: a population-based study. *Int J Radiat Oncol Biol Phys*. 2014;88(5):1064–1073.
23. Da Pozzo LF, Cozzarini C, Briganti A, et al. Long-term follow-up of patients with prostate cancer and nodal metastases treated by pelvic lymphadenectomy and radical prostatectomy: the positive impact of adjuvant radiotherapy. *Eur Urol*. 2009;55(5):1003–1011.
24. Bilimoria KY, Bentrem DJ, Stewart AK, et al. Comparison of Commission on Cancer–Approved and –Nonapproved Hospitals in the United States: Implications for Studies That Use the National Cancer Data Base. *J Clin Oncol*. 2009;27(25):4177–4181.
25. Mohanty S, Bilimoria KY. Comparing national cancer registries: The national cancer data base (NCDB) and the surveillance, epidemiology, and end results (SEER) program. *J Surg Oncol*. 2014;109(7):629–630.
26. Bekelman JE, Zelefsky MJ, Jang TL, et al. Variation in adherence to external beam radiotherapy quality measures among elderly men with localized prostate cancer. *Int J Radiat Oncol Biol Phys*. 2007;69(5):1456–1466.
27. Schroeck FR, Kaufman SR, Jacobs BL, et al. Regional variation in quality of prostate cancer care. *J Urol*. 2014;191(4):957–962.
28. Ziehr DR, Mahal BA, Aizer AA, et al. Income inequality and treatment of African American men with high-risk prostate cancer. *Urol Oncol*. 2015;33(1):18 e7-e13.
29. Underwood W, De Monner S, Ubel P, et al. Racial/ethnic disparities in the treatment of localized/regional prostate cancer. *J Urol*. 2004;171(4):1504–1507.
30. Hamilton AS, Fleming ST, Wang D, et al. Clinical and Demographic Factors Associated With Receipt of Non Guideline-concordant Initial Therapy for Nonmetastatic Prostate Cancer. *Am J Clin Oncol*. 2014 Jan1 [Epub ahead of print].

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