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Testosterone Therapy Does Not Increase the Risks of Prostate Cancer Recurrence or Death After Definitive Treatment for Localized Disease

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Abstract

Background—The safety of testosterone therapy after definitive treatment for localized prostate cancer remains undefined. We sought to analyze the risks of biochemical recurrence and mortality in men receiving testosterone therapy after treatment for localized prostate cancer.

Methods—Cohort analysis using the national U.S. Veterans Affairs Informatics and Computing Infrastructure. We identified 69,984 patients with localized prostate cancer diagnosed from 2001 to 2015 treated with surgery or radiation. We coded receipt of testosterone therapy after treatment as a time-dependent covariate; used the National Death Index to identify cause of death; and defined biochemical recurrence as PSA > 0.2 ng/mL after surgery and nadir + 2 ng/mL after radiation. We analyzed recurrence and mortality using cumulative incidence curves, Fine Gray competing risk regression, and Cox regression.

Results—This cohort included 28,651 surgery patients and 41,333 radiation patients, of whom 469 (1.64%) and 543 (1.31%), respectively, received testosterone therapy with a median follow up of 6.95 years. Comparing testosterone users to non-users, there were no between-group differences in biochemical recurrence, prostate cancer-specific mortality, or overall mortality after surgery [HR 1.07,; HR 0.72 (p=0.43); and HR 1.11 (p= 0.43), respectively] or radiation [HR 1.07, (HR

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Conflicts of Interest

The authors have no competing financial interests in relation to this study.

1.02 (p=0.95); and HR 1.02; (p=0.86) respectively]. Limitations included lack of detailed data on testosterone therapy duration and serum testosterone concentrations.

Conclusions—In this multi-ethnic national cohort, testosterone therapy did not increase the risks of biochemical recurrence or prostate-cancer specific or overall mortality after surgery or radiation. These data suggest that testosterone therapy is safe in appropriate men after definitive treatment of localized prostate cancer.

Keywords

prostate cancer; prostate cancer-specific mortality; radiation therapy; radical prostatectomy; testosterone therapy

INTRODUCTION

Testosterone deficiency affects 30% of men ages 40 to 79 years [1, 2]. Testosterone therapy (TT) may ameliorate testosterone deficiency symptoms including fatigue, decreased libido, erectile dysfunction, depressed mood, and decreased lean body mass [3, 4]. Many patients with localized prostate cancer may benefit from TT. However, the safety of TT in these men remains undefined, even in those who are disease-free after definitive treatment. While clinical data are limited, principles of androgen-driven prostate carcinogenesis [5] and androgen deprivation therapy for advanced prostate cancer [6] have fueled speculation that TT may increase the risks of disease progression and recurrence. These concerns prompted the U.S. Federal Drug Administration (FDA) to issue a black box warning—its most serious advisory—recommending against TT in men with known prostate cancer, regardless of disease status [7].

Still, cohort analyses in prostate cancer patients receiving TT after surgery [8–10] or radiation [10, 11] suggest that TT does not increase the risks of biochemical recurrence, salvage androgen deprivation therapy (ADT), or mortality [12]. Accordingly, the European Association of Urology (EAU) has recommended consideration of TT in patients with symptomatic testosterone deficiencyand localized low-to-intermediate-risk prostate cancer who remain disease-free for more than one year after prostatectomy [13]. The American Urological Association (AUA) has similarly noted that there is insufficient evidence to demonstrate associations of TT with prostate cancer risk [14].

Since randomized clinical trials of TT after definitive prostate cancer treatment would lack equipoise and feasibility, observational studies provide the most robust safety data. Most prior studies of TT in this population involved relatively small cohorts with shorter term follow-up [8, 9, 11]. Additional survival analyses with longer term follow-up in larger and more diverse populations would thus substantively inform care. Using the Veterans Affairs Informatics and Computing Infrastructure (VINCI) database, a national cohort of U.S. military veterans, we assessed associations of TT with biochemical recurrence, prostate cancer-specific mortality, and overall mortality. We hypothesized that there would be no differences between TT users and non-users for recurrence or mortality.

METHODS

Data Source

The VINCI database includes electronic health records of more than 20 million veterans from the years 2000-2015 who sought health care at approximately 1,400 VA outpatient facilities and 152 medical centers in the U.S [15]. VINCI includes tumor registry data collected by registrars who follow protocols issued by the American College of Surgeons. For mortality data, VINCI was linked with the U.S. National Death Index. The San Diego VA Institutional Review Board approved this study. Reith Sarkar, Sunil Patel, Brent Rose, Rishi Deka, and Abhishek Kumar accessed the patient records.

Study Population

A total of 72,083 clinically localized (low, intermediate, high), non-metastatic prostate cancer patients were identified between 2001 and 2015 who received primary treatment with radical prostatectomy or radiation. Of these, 2,099 patients were excluded for unknown information for covariates or cause of death, leaving a final analytic cohort of 69,984 (n = 28,651 surgery and n = 41,333 radiation). Through December 31, 2017, all men were followed until death or last follow-up with a VA provider. Age, year of diagnosis, body mass index (BMI), race, Gleason sum, clinical T stage, ADT, and prostate-specific antigen (PSA) were identified for each patient. Eligible ADT medications included leuprolide, goserelin, triptorelin, histrelin, flutamide, bicalutamide, nilutamide, and degarelix, Patients who initiated ADT of any sort were considered to be exposed to ADT regardless of whether ADT use occurred before or after TT use. Charlson comorbidity index scores were determined using previously described methods [16–18].

Outcomes

Outcomes included biochemical recurrence, prostate-cancer specific mortality, and all-cause mortality. Biochemical recurrence was defined as nadir + 2 ng/ml [19] after radiation PSA ≥ 0.2 ng/ml after surgery [20].

Exposure Ascertainment

TT utilization was ascertained using VA inpatient and outpatient pharmacy records. TT was identified by: 1) testosterone formulation (Testosterone cypionate, Testosterone suspension, Testosterone propionate, Testosterone pellet, Testosterone, Depo-Testosterone, Androgel, Testim, Fortest, Axiron, Vogelxo, Androderm, Testred, Methyltestosterone, Striant, Aveed, Methitest, Natesto, Testopel, Androxy); or Healthcare common procedure coding system codes (HCPCS) (J0900, J1060, J1070, J1080, J2320, J3120, J3030, J3140, J3150, S0189). Androxy and Methitest are synthetic androgens. TT exposure was defined as a binary variable independent of dose or method of therapy.

Statistical Analysis

Differences in covariates between TT users and non-users were assessed using Chi-Square and Wilcoxon rank-sum tests. Surgical patients and radiation patients were analyzed separately. Cumulative incidence curves were used to assess unadjusted estimates of PCSM

and ACM. TT exposure was coded as a time-dependent covariate in multivariable models, to account for the possibility of the immortal time bias. We classified TT exposure beginning with initiation of TT and then continuing for the remainder of the study period: that is, a patient was not considered to be exposed to TT until initiation of TT, and then was considered as exposed for the rest of follow-up. Adjusted estimates of PCSM and NCM were evaluated using multivariable Fine-Gray competing risk regression to account for the competing risk of death and ACM and BCR using multivariable Cox regression. Subdistribution hazard ratios (SHRs) and were estimated for PCSM while hazard ratios (HRs) were estimated for ACM and BCR to quantify the effect a covariate has on the risk of these outcomes. All models adjusted for the covariates listed in the model building section of the methods and started evaluating mortality after RT or RP respectively. All statistical tests were 2-sided, with $P<0.05$ considered significant, and conducted with SAS 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Demographics

For radical prostatectomy, the cohort included 28,651 patients, of whom 469 (1.64%) received TT. Median follow up was 7.36 (95% CI 1.19–15.62) years: 8.74 (95% CI 2.26–16.36) and 7.32 (95% CI 1.18–15.62) years for TT users and non-users, respectively. Median time from surgery to initiation of TT was 3.04 (95% CI 0.025–11.95) years. At baseline, there were no differences in clinical T stage, adjuvant ADT use, or duration of ADT use between TT users and non-users. TT users had higher BMI and Charlson scores; lower median PSA and lower Gleason sum at time of diagnosis; and were more likely to be White (Table 1).

For radiation therapy, the cohort included 41,333 patients, of whom 543 (1.31%) received TT. Median follow up was 6.69 years (95% CI 1.08–14.89 years): 8.79 (95% CI 2.62–15.72 years) and 6.66 years (95% CI 1.08–14.89 years) for TT users and non-users, respectively. Median time from completion of radiation treatment to TT was 3.53 (95% CI 0.39–11.49) years. At baseline, there were no differences in Charlson comorbidity, clinical T stage, median PSA, or—among those who had received it in conjunction with radiotherapy—duration of neoadjuvant androgen deprivation therapy between groups. TT users were younger, more likely to have higher BMI, had lower median Gleason at time of diagnosis, more likely to be diagnosed at a younger age, and more likely to have used neo-adjuvant ADT therapy (Table 1).

Outcomes: Radical Prostatectomy

In unadjusted analyses, TT users had lower 10-year cumulative incidences of prostate-cancer specific (1.1% vs. 3.5%, $p=0.01$) and all-cause (11.7% vs. 20.0%; $p<0.001$) mortality. In adjusted models, there were no differences in biochemical recurrence (HR 1.07; 95% CI 0.84–1.36; $p=0.59$) or prostate-cancer specific (HR 0.72; 95% CI 0.32–1.62; $p=0.43$) or all-cause (HR 1.11; 95% CI 0.85–1.44; $p= 0.43$) mortality between groups (Table 2).

Outcomes: Radiation Therapy

On univariable analysis, TT users had lower 10-year cumulative incidences of prostate cancer-specific (2.7% vs. 4.9%; p=0.05) and all-cause (17.9% vs. 32.7%, p<0.001) mortality. On multivariable analysis, there were no differences in biochemical recurrence (HR 1.07; 95% CI 0.90–1.27; p=0.45) or prostate-cancer specific (HR 1.02; 95% CI 0.62–1.67; p=0.95) or all-cause mortality (HR 1.02; 95% CI 0.84–1.24; p=0.86) between groups (Table 3).

Discussion

In this ethnically diverse, population-based study of nearly 70,000 U.S. veterans, TT therapy did not increase the risks of biochemical recurrence or prostate cancer-specific or all-cause mortality after surgery or radiation for localized prostate cancer. These data suggest that testosterone therapy is safe in appropriate patients after definitive treatment of localized prostate cancer.

To our knowledge, this study is the most comprehensive and diverse comparative analysis to date of the safety of TT after definitive treatment for prostate cancer. In contrast to most other prior studies, it utilized a large, multi-ethnic, nationwide cohort incorporating a broad age range. A substantial strength of this study was the high prevalence of African American men: 24% for radical prostatectomy and 28% for radiotherapy. These results provide reassurance that African-American men, who are at increased risk of death from prostate cancer, may receive TT after definitive treatment for localized disease without increased of cancer specific mortality (HR 0.86, CI 0.77–0.97, p=0.01) or all-cause mortality (HR 0.04, CI 0.9–0.98, p=0.01).

Randomized clinical trials of testosterone in hypogonadal prostate cancer survivors, with incident disease recurrence or death as primary outcomes, would pose substantial ethical challenges. Observational studies such as this one are thus the most feasible method for assessing the safety of therapeutic testosterone in this population. Although testosterone promotes prostate tumor cell growth, there are no definitive data to show that normalization of serum testosterone in hypogonadal men with prostate cancer worsens disease outcomes after definitive treatment with intent to cure. While we were unable to definitely determine whether the men in this study were clinically hypogonadal, our results suggest that testosterone therapy does not worsen cancer outcomes after treatment.

Prior observational studies have demonstrated similar results. In two small cohorts of patients whose received TT after surgery, there was no increased risk of biochemical recurrence [8, 9]. In a study of 149,354 men over age 65 years with prostate cancer from 1992 to 2007 in the U.S. Surveillance, Epidemiology, and End Results-Medicare (SEER)-Medicare registry, 1,181 (0.79%) of whom received TT after diagnosis, there were no associations of TT with post-treatment use of salvage ADT, or in prostate cancer-specific or overall mortality [12]. Similarly, in 38,570 patients in the National Prostate Cancer Register of Sweden identified from 2009 to 2012, of whom 1% initiated TT, there were no increased risk in those who were treated with TT compared to the control, OR 1.03 95% CI 0.90–1.17 [21].

There were two patterns of TT utilization in this cohort which were similar to observations in prior studies, and likely reflect prevailing treatment principles for these patients: time intervals between cancer treatment and TT; and disease characteristics of patients receiving TT. First, the median time from completion of cancer therapy to initiation of TT was 6 months longer for the radiation group—a disparity potentially attributable to verification of an appropriate nadir 12 months after radiotherapy prior to beginning TT [22–24], [11]. Second, in both the surgery and radiation groups, patients with Gleason ≤ 7 (Grade Group 3) were more likely to receive TT than those with Gleason ≥ 8 (Grade Group 4). These patterns, consistent with prior studies, [21] [25] may have reflected reluctance to initiate TT in patients with higher-risk disease. The higher prevalence of TT among radiotherapy (17%) compared to surgery (12%) patients with high-risk disease may have reflected a higher prevalence of persistent post-treatment testosterone deficiency resulting from neoadjuvant ADT.

There are some potential limitations to this study. First, VINCI lacks detailed testosterone therapy duration, dose, and formulation data. Inferences regarding testosterone dose-response and prostate cancer risk, therefore, cannot be drawn. Second, VINCI lacks data on patient blood testosterone concentrations. Thus, testosterone deficiency diagnosis could not be independently verified with serum testosterone, and baseline and on-treatment testosterone data were not available. Yet the prevalence of testosterone therapy in this cohort was similar to other studies in this population [12, 21], suggesting that appropriate, standard-of-care principles were applied for diagnosis and treatment of testosterone deficiency; and that differential misclassification bias was unlikely. Finally, pathologic staging was not consistently available for all patients in VINCI, and could not be incorporated into the analyses. However, since the models adjusted for Gleason sum and clinical stage, it is unlikely that pathologic stage data would have further informed these analyses.

Conclusion

In men with localized prostate cancer who have undergone treatment with surgery or radiation, TT was not associated with increased risks of biochemical recurrence, prostate-cancer specific mortality, or all-cause mortality. These results suggest that testosterone therapy is safe in appropriate patients after definitive management of localized prostate cancer.

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Table 1:

Patient Demographics and Exposure to Testosterone Therapy after Radical Prostatectomy and Radiation Therapy.

	Radiation Therapy						Radical Prostatectomy				
	Testosterone Therapy						Testosterone Therapy				
	No		Yes				No		Yes		
	N	(%)	N	(%)	P value		N	(%)	N	(%)	P value
Median PSA (IQR)	6.7 (4.80–10.30)		6.3 (4.60–10.10)		0.08		5.80 (4.30–8.50)		5 (3.40–7.40)		<.0001
Median Age (IQR)	66 (61–71)		63 (59–68)		<.0001		62 (58–66)		60 (56–65)		<.0001
Median BMI (IQR)	28.10 (24.50–32.20)		30.20 (26.40–34.20)		<.0001		28 (24.80–31.50)		29.40 (26.40–32.90)		<.0001
Median Days ADT Duration (IQR)	186 (90–461)		185 (90–393)		0.76		180 (90–517)		265 (90–691)		0.6139
Androgen Deprivation Therapy					0.0024						0.2078
No	24334	59.7	289	53.2			26092	92.6	427	91	
Yes	16456	40.3	254	46.8			2090	7.4	42	9	
Black Race					0.0036						0.0039
No	29320	71.9	421	77.5			21266	75.5	381	81.2	
Yes	11470	28.1	122	22.5			6916	24.5	88	18.8	
Charlson Comorbidity					0.1308						0.045
0	29379	72	407	75			22508	79.9	357	76.1	
1+	11411	28	136	25			5674	20.1	112	23.9	
Era					<.0001						<.0001
2000–2005	13844	33.9	209	38.5			9374	33.3	182	38.8	
2006–2010	16022	39.3	257	47.3			11065	39.3	222	47.3	
2011–2015	10924	26.8	77	14.2			7743	27.5	65	13.9	
Gleason Score					0.0474						0.0018
6	13095	32.1	177	32.6			7995	28.4	160	34.1	
7	15737	38.6	187	34.4			12406	44	174	37.1	
8+	6818	16.7	91	16.8			3920	13.9	56	11.9	
NA	5140	12.6	88	16.2			3861	13.7	79	16.8	
Clinical T Stage					0.9337						0.9336
T1–2	39687	97.3	528	97.2			27656	98.1	460	98.1	
T3–4	1103	2.7	15	2.8			526	1.9	9	1.9	

Table 2:

Survival and Recurrence in men treated with Radical Prostatectomy

		Prostate Cancer Mortality		All-Cause Mortality		Biochemical Recurrence	
Variable	**Value**	***SHR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Androgen Deprivation Therapy	Yes	2.64 (2.23–3.13)	<0.001	1.46 (1.33–1.59)	<0.001	1.15 (1.05–1.26)	<0.001
	No	ref	ref	ref	ref	ref	ref
Testosterone Use	Yes	0.72 (0.32–1.62)	0.43	1.11 (0.85–1.44)	0.43	1.07 (0.84–1.36)	0.59
	No	ref	ref	ref	ref	ref	ref
Age		1.6 (1.46–1.75)	<0.001	1.86 (1.79–1.94)	<0.001	1.16 (1.11–1.2)	<0.001
Charlson Comorbidity	0	ref	ref	ref	ref	ref	ref
	1+	1.24 (1.05–1.45)	0.01	2.05 (1.93–2.18)	<0.001	1.3 (1.22–1.38)	<0.001
Year of Prostate Cancer Diagnosis	2000–2005	ref	ref	ref	ref	ref	ref
	2006–2010	0.78 (0.66–0.93)	0.01	0.73 (0.68–0.78)	<0.001	0.85 (0.8–0.91)	<0.001
	2011–2015	0.69 (0.53–0.89)	<0.001	0.43 (0.37–0.49)	<0.001	0.76 (0.7–0.82)	<0.001
BMI		0.64 (0.6–0.69)	<0.001	0.72 (0.69–0.74)	<0.001	0.89 (0.87–0.91)	<0.001
Black	Yes	0.9 (0.76–1.07)	0.25	1.02 (0.95–1.09)	0.62	1.12 (1.06–1.19)	<0.001
	No	ref	ref	ref	ref	ref	ref
Log(PSA)		1.37 (1.25–1.5)	<0.001	1.05 (1–1.1)	0.04	1.44 (1.38–1.51)	<0.001
T Stage	1–2	ref	ref	ref	ref	ref	ref
	3–4	2.11 (1.63–2.75)	<0.001	1.49 (1.27–1.74)	<0.001	1.33 (1.12–1.57)	<0.001
Gleason Score	6	0.64 (0.5–0.81)	<0.001	0.94 (0.87–1.02)	0.16	0.68 (0.64–0.72)	<0.001
	7	ref	ref	ref	ref	ref	ref
	8–10	3.36 (2.8–4.04)	<0.001	1.61 (1.47–1.77)	<0.001	1.52 (1.42–1.64)	<0.001
	N/A	1.25 (1.02–1.54)	0.03	1.26 (1.16–1.37)	<0.001	0.98 (0.91–1.05)	0.5

*Subdistribution Hazard Ratio

Table 3:

Survival and Recurrence in Men treated with Radiation Therapy

		Prostate Cancer Mortality		All-Cause Mortality		Biochemical Recurrence	
Variable	**Value**	***SHR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Androgen Deprivation Therapy	Yes	1.12 (1–1.25)	0.05	1.08 (1.03–1.12)	<0.001	0.89 (0.86–0.93)	<0.001
	No	ref	ref	ref	ref	ref	ref
Testosterone Use	Yes	1.02 (0.62–1.67)	0.95	1.02 (0.84–1.24)	0.86	1.07 (0.9–1.27)	0.45
	No	ref	ref	ref	ref	ref	ref
Age		1.18 (1.1–1.26)	<0.001	1.45 (1.41–1.49)	<0.001	1.16 (1.13–1.19)	<0.001
Charlson Comorbidity	0	ref	ref	ref	ref	ref	ref
	1+	1.23 (1.1–1.37)	<0.001	1.98 (1.9–2.06)	<0.001	1.43 (1.38–1.49)	<0.001
Year of Prostate Cancer Diagnosis	2000–2005	ref	ref	ref	ref	ref	ref
	2006–2010	0.85 (0.75–0.96)	0.01	0.72 (0.69–0.76)	<0.001	0.79 (0.76–0.83)	<0.001
	2011–2015	0.74 (0.61–0.91)	<0.001	0.43 (0.39–0.47)	<0.001	0.75 (0.7–0.8)	<0.001
BMI		0.71 (0.67–0.74)	<0.001	0.84 (0.83–0.86)	<0.001	0.91 (0.89–0.92)	<0.001
Black	Yes	0.86 (0.77–0.97)	0.01	0.94 (0.9–0.98)	0.01	1.02 (0.98–1.06)	0.3
	No	ref	ref	ref	ref	ref	ref
Log(PSA)		1.36 (1.27–1.44)	<0.001	1.16 (1.12–1.19)	<0.001	1.35 (1.32–1.38)	<0.001
T Stage	1–2	ref	ref	ref	ref	ref	ref
	3–4	2.03 (1.7–2.43)	<0.001	1.28 (1.17–1.41)	<0.001	1.26 (1.15–1.37)	<0.001
Gleason Score	6	ref	ref	ref	ref	ref	ref
	7	1.57 (1.36–1.82)	<0.001	1.23 (1.17–1.3)	<0.001	1.31 (1.25–1.37)	<0.001
	8–10	3.4 (2.9–3.99)	<0.001	1.56 (1.46–1.67)	<0.001	1.68 (1.58–1.78)	<0.001
	N/A	1.68 (1.43–1.97)	<0.001	1.42 (1.34–1.5)	<0.001	1.35 (1.28–1.42)	<0.001

*Subdistribution Hazard Ratio