National Trends in the Utilization of Androgen Deprivation Therapy for Very Low Risk Prostate Cancer

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OBJECTIVE To analyze national trends using the National Cancer Database (NCDB) in use of androgen deprivation therapy (ADT), outside of standard of care, in patients with very low risk prostate cancer.

METHODS We identified 52,797 men in the NCDB from 2010 to 2015 diagnosed with very low risk prostate cancer as defined (cT1cM0, PSA <10, Gleason ≤6, <3 biopsy cores positive). We evaluated the treatment trends and the proportion of men treated with ADT based on race, income, insurance status, treatment facility volume, and Charlson comorbidity.

RESULTS From 2010 to 2015, prevalence of primary ADT use in patients with very low risk prostate cancer remained 0.7%. Patients treated at low-volume facilities were more likely to receive primary ADT (hazard ratio [HR] 1.29, P <.001) as were black patients (HR 1.47, P <.001). When evaluated over time, the proportion of men treated with primary ADT who were white decreased while the proportion of men who were black increased.

CONCLUSION The use of primary ADT in men with very low risk prostate cancer has not changed over time, and may be over utilized, particularly among black men and those treated at low-volume facilities. UROLOGY 130: 79–85, 2019. © 2019 Published by Elsevier Inc.

Approximately 240,000 men are diagnosed with prostate cancer each year, with 80% of new diagnoses representing localized disease.[1] Several nomograms exist for risk stratification of treatment and survival outcomes.[2,3] For example, National Comprehensive Cancer Network (NCCN) includes very low risk (T1c, PSA <10 ng/mL, Gleason score ≤6, ≤2 cores positive, ≤50% of each core positive, PSA density <0.15), low risk (T1c, PSA ≤10 ng/mL, Gleason score ≤6), intermediate (PSA 10-20 ng/mL, or Gleason score 7, or clinical stage T2b), or high risk (PSA > 20 ng/mL, or Gleason score 8-10, or clinical stage ≥ T2c).[2] The majority of very low and low-risk prostate cancers are clinically insignificant, slow growing, and very unlikely to progress to metastasis.[4,5] Therefore, active surveillance is often recommended for very low and low-risk prostate cancer patients in order to avoid harmful side effects of overtreatment.[6]

Androgen deprivation therapy (ADT) is typically used for metastatic prostate cancer but may also be used in conjunction with radiation therapy for intermediate- or high-risk disease. ADT centers on reducing the effects of circulating testosterone and is associated with substantial side effects, including hot flashes, sexual dysfunction, skeletal morbidity, metabolic syndrome, cardiovascular morbidity, and psychological and cognitive effects. ADT use as primary treatment or in conjunction with radiation has not been shown to improve survival in patients with very low or low-risk disease. Thus, AUA and NCCN guidelines do not recommend ADT in very low or low-risk localized cancers.[7,8] Without guideline support, the use of ADT in low-risk disease remains nonstandard of care treatment. We sought to analyze national trends in ADT treatment for a subset of very low risk prostate cancer and evaluate whether any racial or socioeconomic disparities exist.

METHODS

Data Source

The National Cancer Database (NCDB) is a nationwide oncology outcomes database containing information regarding cancer treatment and outcome patterns. Approximately 70% of new cancer cases each year in the United States are treated and reported to the NCDB from more than 1500 facilities accredited by the Commission on Cancer.[9] Standardized coding definitions are utilized, and the data are freely available to participating institutions after application for projects are submitted and accepted by the NCDB. 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

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employed, or the conclusions drawn from these data by the investigator.

In this study, the NCDB prostate cancer participant user file was queried for all patients treated for very low risk prostate cancer, defined as clinical stage T1cM0, PSA <10 ng/mL, Gleason score ≤6, and <3 cores positive, from 2010 to 2015. Patient treatments were categorized into active surveillance (which began coding within the NCDB in 2010), surgery, radiation, radiation with ADT, and primary ADT. Within the NCDB, surgical treatment was defined as radical prostatectomy, prostatectomy, or prostatectomy not otherwise specified. Radiation therapy included external beam and brachytherapy modalities. Covariable data included age, race, comorbidity, income status, facility type, and insurance status. Race was reported as white, black, or other. Comorbidity was evaluated by Charlson comorbidity index with values of 0, 1, 2, or 3+. Income status is reported as median household income in categories of <$38,000, $38,000-47,999, $48,000-62,999, and $63,000+. Facilities reporting to the NCDB were classified as low or high volume. Facilities reporting more than 500 new cancer cases per year were classified as high volume, while those with less than 500 new cases were considered low volume. Insurance status is reported as uninsured, private insurance, Medicaid, Medicare, other government insurance, or unknown.

Statistical Analysis

Using the cohort from 2010 to 2015, we compared trends in treatment over time. Fisher's exact test was used to compare proportion of treatment types from the first year of study (2010) to the final year of study (2015). Estimated annual percentage change was performed for each treatment modality. We compared demographic and clinical data between patients treated with ADT vs other treatments. Wilcoxon rank sum test and Kruskal-Wallis test were used to compare PSA and age and Student's *t* test was utilized for comparison of all other continuous variables. Analysis of variance (ANOVA) or Fisher's exact test was performed for categorical variables. We evaluated the correlation between ADT treatment and covariates using multivariate logistic regressions adjusting for stage, age, race, comorbidity, income, facility type, and insurance status. We utilized SPSS v24 (New York, NY) for all analyses, with *P* value of <.05 denoting statistical significance.

RESULTS

A total of 52,797 patients were identified in the NCDB from 2010 to 2015 with very low risk prostate cancer. The mean age was 62.3 years at diagnosis. Of these, 82.6% were white, 12.9% black, and 4.4% other. The majority of patients (85.7%) had Charlson score of 0. The majority of patients were treated at high-volume facilities (83.4%), and most patients had private insurance (58.3%) or Medicare (34.9%). The majority of patients (61%) had only 1 core positive on biopsy, while 39% had 2 cores. The average PSA was 5.3 ng/mL. Table 1 depicts the demographic data for all patients.

Overall, 18,814 (35.6%) patients were treated with active surveillance, 20,905 (39.6%) were treated with surgery, 11,504 (21.8%) were treated with radiation alone, 1220 (2.3%) were treated with radiation and ADT, and 374 (0.7%) were treated with primary ADT (Table 1). Treatment with primary ADT was correlated with all demographic covariables measured, including age, race, Charlson comorbidity score, income, facility type, and insurance with *P* value <.001 for all correlations. Patients undergoing ADT were more likely to be older (mean age 68.8 years). Of the patients treated with primary ADT, 16.1% were black, compared to 12.9% of the total population.

On multivariable logistic regression, black men were 1.47 times as likely to be treated with primary ADT (Table 2). Uninsured men were more likely to receive primary ADT (hazard ratio [HR] 1.83). Men treated at low-volume facilities were also more likely to be treated with primary ADT (HR 1.29).

Over time, treatment with primary ADT did not significantly change (Table 3). Surgical treatment decreased from 49.4% to 28.8% (*P* <.001), radiation alone decreased from 25.0% to 15.8% (*P* <.001), radiation with ADT decreased from 3.2% to 1.1% (*P* <.001), and active surveillance increased from 21.6% to 53.7% (*P* <.001). When treatment trends were examined over time, the use of primary ADT decreased among white patients but did not change among black patients. The proportion of black patients treated with primary ADT increased significantly from 11.3% to 29.1% (*P* <.001; Fig. 1).

DISCUSSION

We analyzed trends in treatment of localized very low risk prostate cancer over the period of 2010-2015 using the NCDB. Primary ADT was used in 0.7% of all patients with very low risk prostate cancer and ADT with radiation was used in 2.3%. While trends in the use of ADT with radiation did significantly decrease when comparing 2015 to 2010, the use of primary ADT did not change. It is important to note that in 2015, 1.7% of patients were still treated with some form of ADT. Our analysis of a large national tumor registry identifies that despite a lack of guideline support, or supporting clinical evidence, a significant proportion of men receive ADT for treatment of localized very low risk prostate cancer. The underlying treatment decisions that guide the use of ADT within our cohort are unknown; however, guideline statements do not support the use of ADT within the lowest risk prostate cancer patients. Independent risk factors for receiving this nonstandard of care therapy include age, race, and treatment facility volume, highlighting a possible underlying health disparity.

Multiple studies have shown benefit in the use of ADT for localized high-risk prostate cancer in conjunction with radiation therapy,[10,11] but there are no existing data to suggest benefit in ADT either alone or with radiation for patients with very low risk or low-risk prostate cancer. Despite this, there are studies that have demonstrated inappropriate use of ADT in low-risk prostate cancer patients. Meng et al studied ADT use in the CaPSURE database (including data from 35 academic- and community-based sites from around the United States) from 1995 to 2002. Out of 1485 men diagnosed with prostate cancer, 41% underwent ADT therapy, and 50% of these men were low or intermediate risk.[12] Cooperberg et al used the same CaPSURE database from 1989 to 2001 and found that the rate of primary ADT use increased from 4.6% to 14.2% in low-risk patients and from 8.9% to 19.7% in intermediate-risk patients.[13] In this study, patients with increased age, those treated in the South or West, and those with lower incomes were significantly

Table 1. Patient demographics by treatment type

Variable	All (*n* = 52,797)	Active Surveillance (n = 18,814)	Surgery (n = 20,905)	Radiation (n = 11,504)	Radiation + ADT (n = 1220)	ADT alone (n = 354)	*P* Value
Mean age (±SD)	62.3 ± 7.6	63.9 ± 7.6	59.3 ± 6.9	64.3 ± 7.2	66.5 ± 6.6	68.8 ± 7.9	<.001
Race							<.001
White	43,623 (82.6%)	15,349 (81.6%)	17,846 (85.4%)	9143 (79.5%)	1001 (82.0%)	284 (80.2%)	
Black	6826 (12.9%)	2407 (12.8%)	2222 (10.6%)	1957 (17.0%)	183 (15.0%)	57 (16.1%)	
Other	2348 (4.4%)	1058 (5.6%)	837 (4.0%)	404 (3.5%)	36 (3.0%)	13 (3.7%)	
Charlson							<.001
0	45,268 (85.7%)	16,461 (87.5%)	17,742 (84.9%)	9744 (84.7%)	1039 (85.2%)	282 79.7%)	
1	6464 (12.2%)	1949 (10.4%)	2809 (13.4%)	1498 (13.0%)	146 (12.0%)	62 (17.5%)	
2	794 (1.5%)	273 (1.5%)	295 (1.4%)	192 (1.7%)	27 (2.2%)	7 (2.0%)	
3+	271 (0.5%)	131 (0.7%)	59 (0.3%)	70 (0.6%)	8 (0.7%)	3 (0.8%)	
Income							<.001
<$38,000	7434 (14.1%)	2577 (13.7%)	2592 (12.4%)	1978 (17.2%)	214 (16.6%)	73 (20.7%)	
$38,000-47,999	10,889 (20.7%)	3674 (19.6%)	4272 (20.5%)	2565 (22.4%)	283 (23.3%)	95 (26.9%)	
$48,000-62,999	13,944 (26.5%)	4728 (25.2%)	5761 (27.6%)	3000 (26.1%)	356 (29.3%)	99 (28.0%)	
>$63,000	20,388 (38.7%)	7774 (41.5%)	8233 (39.5%)	3932 (34.3%)	262 (29.9%)	86 (24.4%)	
Facility type							<.001
High volume	44,013 (83.4%)	15,859 (84.3%)	17,907 (85.7%)	9063 (78.8%)	908 (74.4%)	276 (78.0%)	
Low volume	8784 (16.6%)	2955 (15.7%)	2998 (14.3%)	2441 (21.2%)	312 (25.6%)	78 (22.0%)	
Insurance status							<.001
Uninsured	735 (1.4%)	383 (2.0%)	202 (1.0%)	128 (1.1%)	15 (1.2%)	7 (2.0%)	<.001
Private insurance	30,787 (58.3%)	9679 (51.4%)	15,135 (72.4%)	5428 (47.2%)	434 (25.6%)	111 (31.4%)	
Medicaid	1161 (2.2%)	532 (2.8%)	301 (1.4%)	299 (2.6%)	19 (1.6%)	10 (2.8%)	
Medicare	18,434 (34.9%)	7649 (40.7%)	4747 (22.7%)	5122 (44.5%)	698 (57.2%)	218 (61.6%)	
Other Govt	985 (1.9%)	245 (1.3%)	350 (1.7%)	356 (3.1%)	31 (2.5%)	3 (0.8%)	
Unknown	695 (1.3%)	326 (1.7%)	170 (0.8%)	171 (1.5%)	23 (1.9%)	5 (1.4%)	
Positive cores							<.001
1	32,187 (61.0%)	12,723 (67.6%)	11,920 (57.0%)	6564 (57.1%)	762 (62.5%)	218 (61.6%)	
2	20,610 (39.0%)	6091 (32.4%)	8985 (43.0%)	4940 (42.9%)	458 (37.5%)	136 (38.4%)	
PSA (±SD)	5.3 ± 1.9	5.5 ± 2.0	5.1 ± 1.9	5.5 ± 2.0	5.9 ± 2.0	5.8 ± 1.9	<.001

Table 2. Logistic regression for treatment with primary ADT

Variable	HR	95% CI Low	95% CI High	*P* Value
Age (increasing)	1.127	1.11	1.14	<.001
Charlson (0 ref)				
1	1.30	0.98	1.71	.07
2	1.01	0.47	2.16	.97
3+	1.21	0.38	3.83	.75
Race (White ref)				
Black	1.47	1.10	1.97	.01
Other	0.87	0.50	1.53	.63
Low Vol	1.29	1.00	1.67	.05
Uninsured (any insurance ref)	1.83	0.86	3.93	.12
2 Cores Positive (1 core positive ref)	0.99	0.80	1.22	.90
PSA (increasing)	1.00	1.00	1.01	.10

Table 3. Treatment modality over time

Variable	All (n = 52,797)	Active Surveillance (n = 18,814)	Surgery (n = 20,905)	Radiation (n = 11,504)	Radiation + ADT (n = 1220)	ADT alone (n = 354)
2010	9087	1966 (21.6%)	4490 (49.4%)	2274 (25.0%)	293 (3.2%)	64 (0.7%)
2011	11,608	3095 (26.7%)	5161 (44.5%)	2924 (25.2%)	332 (2.9%)	96 (0.8%)
2012	8797	2926 (33.3%)	3614 (41.1%)	1978 (22.5%)	220 (2.5%)	59 (0.7%)
2013	8392	3406 (40.6%)	3053 (36.4%)	1715 (20.4%)	161 (1.9%)	57 (0.7%)
2014	7422	3398 (45.8%)	2431 (32.8%)	1427 (19.2%)	135 (1.8%)	31 (0.4%)
2015	7491	4023 (53.7%)	2156 (28.8%)	1186 (15.8%)	79 (1.1%)	47 (0.6%)
Total	52,797	18,814 (35.6%)	20,905 (39.6%)	11,504 (21.8%)	1220 (2.3%)	354 (0.7%)
P Value (2010 vs 2015)		<.001	<.001	<.001	<.001	.61

more likely to receive primary ADT. Shahinian et al used the Surveillance, Epidemiology, and End Results (SEER)-Medicare database from 1991 to 1999 to evaluate use of GnRH agonists in men with prostate cancer. Among men with Stage I or II cancers, increased age, increased comorbidity, and location in the West Coast were significantly associated with use of GnRH agonists. GnRH use in men over the age 80 years with localized prostate cancer increased from 3.7% to 30.9% during the time period studied.[14] Sammom et al studied 46,376 men with Medicare (age > 65 years) from the SEER database from 2004 to 2009 with localized prostate cancer who did not undergo radiation or surgery. Of these, 39% were treated with primary ADT. When separated into risk categories, the low-risk group experienced a decline from 21% primary ADT use to 8.3% between over the years studied. Older patients, those from nonmetropolitan areas, black patients, and those with lower life expectancies were more likely to undergo primary ADT treatment. Men treated with primary ADT had decreased overall survival and this was most pronounced in men with longer life expectancy.[15] The use of nonstandard of care ADT for

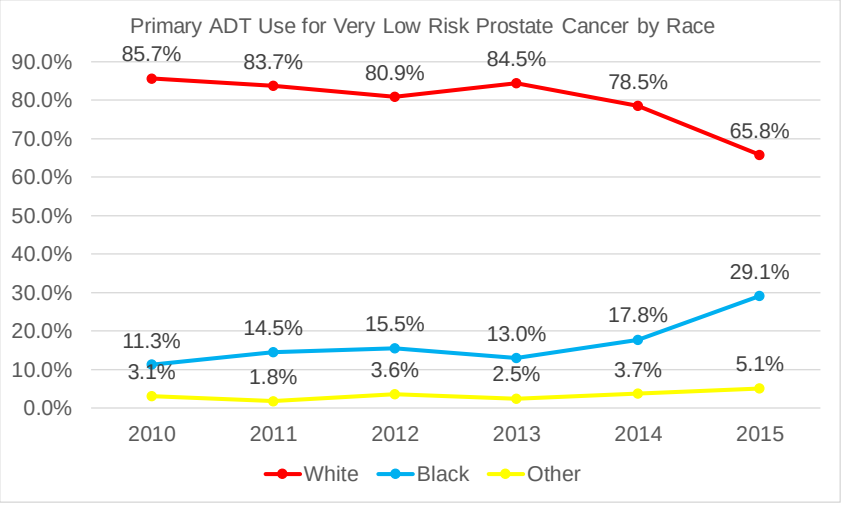

Figure 1. Primary ADT use in very low risk prostate cancer over time by race. (Color version available online.)

low- or intermediate-risk disease is clearly not an uncommon finding. However, to our knowledge, prior to our study, there are no studies evaluating the use of ADT in very low risk prostate cancer. It is encouraging that our analysis has identified closer adherence to the guidelines, as ADT use with radiation is decreasing, yet there has been no change in primary ADT use and a significant number of patients still receive ADT outside of the standard of care.

Use of ADT was higher in older men and men with higher comorbidity scores. This may be due to concerns of treatment side effects associated with surgery or radiation in this vulnerable population. However, this population is also at high risk for side effects of ADT including osteoporosis and subsequent fractures. Long-term use of ADT may increase the relative risk of fracture by 45%.[16] This is important because hip fracture is well known to be a significant risk factor for death.[17] Kaipia et al studied the risk of hip fracture among men treated with ADT and found that nearly 25% of men with prostate cancer suffering hip fracture had been treated with ADT for low-risk cancer.[18] Although our study suggests that physicians are more likely to use ADT in low-risk patients who are older or have more comorbidities, perhaps they should be even more cautious in this group, especially since these men are less likely than younger healthier men to die of prostate cancer.

In our study, we found that ADT use was higher in uninsured men, those treated in a low-volume facility, those with lower income status and black men. After logistic regression, black men and those treated at low-volume facilities were more likely to receive ADT. This finding raises questions regarding access to care and quality of treatment in these populations. Racial disparities in prostate cancer outcomes have been studied previously. It has been found that black men are more likely to present at a younger age and with more advanced prostate cancer.[19,20] Studies have also shown disparities in outcomes. Cohen et al[21] studied over 25,000 men with prostate cancer from the SEER database and found that black race was an independent predictor of shorter disease-free survival, and the 75th percentile disease-free survival was 13 months shorter in black men than white. Godley et al[22] reported similar results in the SEER database, finding that black men treated for prostate cancer had a median survival that was 1.7 years shorter than that of white men. It is difficult to assess whether differences in presentation and outcome are due to biological or nonbiological factors; however, there are also many reports of disparities in treatment. Harlan et al[23] evaluated 70,000 cases of prostate cancer in the SEER database and found that black men were twice as likely to receive no treatment compared to white men. Other studies have shown that black men are much less likely to undergo radical prostatectomy as treatment.[24,25] The use of ADT as an adjunct to radiation or therapy has been previously reported to be lower in black patients compared to white[14,26]; however, use of primary ADT based on race, and more specifically in lower risk cancer, has not been well studied. Harlan et al[27] studied over 3000 patients with prostate cancer from 1994 to 1995 and found that black men over the age of 60 years old were far more likely to undergo conservative therapy, defined as surveillance or primary ADT, although ADT was not separated out from surveillance in this analysis. In our study, we found that black men were nearly 1.5 times as likely to receive primary ADT for very low risk cancer as white men. When treatment trends are observed over time, use of primary ADT decreased in white men, but not in black men. The proportion of black men treated with primary ADT increased substantially. While the underlying reasons for these findings are unclear, the findings are concerning and require further consideration.

Several limitations are worth noting. Due to the nature of localized prostate cancer and its slow progression, the impact of treatment modality on survival was not able to be adequately assessed in this study. Although our primary outcome was treatment with ADT alone, we could not definitively differentiate between patients treated with ADT as primary treatment or with ADT in the neoadjuvant setting. The number of patients treated with ADT alone are small, and it is possible that some may be due to entry errors in the database. This study was unable to assess adverse events and impact of treatment on quality of life. In addition, there are many unmeasurable variables that could affect our findings, including patient preferences in treatment, access to specialists, and referral patterns. As is the problem with retrospective analyses, it is difficult to draw any definitive conclusion with potentially confounding variables such as race, income, comorbidities, and age. The correlations within this analysis do not identify causation.

CONCLUSION

Use of ADT, either alone or with radiation, in very low risk localized prostate cancer is not considered standard of care due to a lack of evidence or guideline support. Our findings suggest that among patients with very low risk prostate cancer, older patients, black patients, and those treated at low-volume facilities are more likely to be treated with ADT. The underlying racial and social disparities in treatment are not completely understood and require further investigation.

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EDITORIAL COMMENT

In "National trends in the utilization of androgen deprivation therapy for very low risk prostate cancer," the authors demonstrate a significant decline in the use of primary androgen deprivation (pADT), for very low risk prostate cancer. By 2015, only 1.7% of men in this population received pADT, representing a furthering of trends witnessed in the early 21st century, and which have been previously described.[1,2]

In an era where so little pADT is being administered, it is important to remember the well-documented public health crisis of pADT overuse in the 90s and early 2000s. By the year 2000, up to 20% of intermediate-risk and 14% of low-risk PCa patients were receiving pADT, forgoing definitive intervention for a treatment with almost no evidentiary basis.[3] While numerous factors drove these treatment decisions, it would be foolish to overlook the role of big pharma in misleading physician behavior.

In the year 1997, over 14,000 urologists administered Lupron to prostate cancer patients insured by Medicare, accounting for $504 million in payments (mean $36,000 per urologist); the top 25 urologists received $41.2 million of the Medicare reimbursements, accounting for a mean of $1.6 million per urologist.

In a 2001 settlement between the United States and the makers of Lupron, the US Attorney for the case indicated "inducements to physicians included free products; free consulting services; trips to expensive golf and ski resorts; money disguised as 'educational grants,' but in fact was used and intended to be used for many purposes, including cocktail party bar tabs, office Christmas parties, medical equipment, travel expenses. . .." The result of this 2001 settlement included the largest (up to that time) fine for Medicare fraud of $559.5 million. The settlement also directly named 4 urologists who had been charged (and plead guilty) to healthcare fraud. [4]

Subsequently, 2 concomitant phenomena were associated with decreasing rates of inappropriate pADT.[2]

1-CMS modified the reimbursement model for in-office administered medications.[5] Two numerous observational studies highlighted the potential dangers of ADT including cognitive side effects, metabolic derangement, and cardiovascular mortality.[6-8,9]

The story of the rise and fall of inappropriate ADT monotherapy highlights several important points that relate to the current manuscript, including the very appropriate response of the urologic community (vis-à-vis decreasing use of ADT monotherapy) as evidence of the harms of ADT monotherapy and it is lack of efficacy surfaced. With the passage of time, this saga runs the risk of being forgotten, and few urologists entering the work force are familiar with a very important episode in urologic history. Furthermore, it is critical to remember this history, lest we be doomed to repeat it (think opioid crisis).

Finally, this episode in urologic history highlights the important role that well-designed observational studies can have in driving health policy and in promoting patient health.

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