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Definitive Local Treatment for Metastatic Prostate Cancer: A National Cancer Database Analysis

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ABSTRACT

Introduction: Prostate cancer (PCa) is the second leading cause of cancer mortality in US males, with metastatic disease (mPCa) comprising 5% of cases. This represents an incurable and uniformly lethal disease. Thus, novel therapeutic approaches are needed. Cytoreductive surgery in the metastatic setting has become commonplace for renal cell carcinoma, and definitive local radiotherapy has been employed in the oligometastatic setting for prostate cancer via the STAMPEDE trial. This study further explores the use of definitive local treatment via pelvic radiotherapy or radical prostatectomy along with androgen deprivation therapy (ADT) vs. ADT alone in the setting of metastatic prostate cancer.

Methods: The 2019 National Cancer Database (NCDB) was queried to conduct a retrospective cohort analysis of cT1-4N0-3M1 PCa who received local therapy in conjunction with ADT vs. ADT alone. Clinicopathologic variables were compared between the two groups using Wilcoxon signed rank and Chi-square for continuous and categorical variables, respectively. Overall survival (OS) analysis was performed using Cox Proportional Hazards and the Kaplan-Meier method. Comparisons were made between local therapy + ADT vs. ADT alone and between radical prostatectomy + ADT vs. radiation therapy + ADT vs. ADT alone.

Results: A total of n=36,635 patients with cM1 were identified, with 3197 (8.7%) patients receiving local therapy + ADT. Among local therapy + ADT, 2884 (90.2%) patients received radiation therapy + ADT, and 313 (9.8%) received radical prostatectomy + ADT. The median follow-up was 2.8 years. Kaplan-Meier analysis showed significant improvement in 5-year OS for patients who received local therapy + ADT vs. ADT alone. For ADT alone, 5-year OS was 31.3% (CI= 30.7-31.8%) vs. 54.2%. (CI= 52.4-56.1%) for local therapy +ADT. Furthermore, comparing the type of local therapy on Kaplan-Meier analysis: radical prostatectomy + ADT showed better 5-yr OS, 74.0% (CI= 67.5-79.1%) vs. 52.2% (CI= 50.2-54.2%) for radiation therapy +ADT ($p<0.001$).

Conclusion: Definitive local treatment, in addition to ADT, may improve 5-year OS for well-selected patients with metastatic prostate cancer. Patient outcomes are significantly improved for those treated with radical prostatectomy vs. radiation therapy. These findings support multimodal treatment for metastatic prostate cancer, and further studies are needed to optimize criteria for patient selection and choice of definitive localized therapy in this setting.

Introduction

Prostate cancer has one of the highest incidences and prevalence among men in the United States, with an estimated 299,010 new cases and 35,250 deaths in 2024[1]. If caught early on, prostate cancer has a 97.1% 5-year relative survival rate and remains a highly treatable disease[2]. However, metastatic prostate cancer (mPCa) remains an incurable disease with a relative 5-year survival of 29.3%[3]. The mainstay of treatment for metastatic prostate cancer has historically consisted of a backbone of androgen deprivation therapy (ADT). However, recent studies have shown chemotherapeutic agents–such as docetaxel, enzalutamide, apalutamide, and abiraterone in combination with ADT improves overall survival in patients and intensified ADT has become the new standard of care[4-8]. Furthermore, there is growing interest in the possibility that localized therapy (LT) in the form of radiation therapy (RT) or even radical prostatectomy (RP) may also increase overall survival (OS) in the metastatic setting[9]. Previous studies have shown localized interventions to be well tolerated in patients with locally advanced mPCa. LT might reduce morbidity in mPCa, particularly regarding urinary tract complications and hospitalizations[10].

Local therapy in the form of radiation therapy and radical prostatectomy may reduce tumor burden and increase overall survival in other malignancies[9]. RT has been shown to play a role in treating mPCa, especially in the oligometastatic setting in the STAMPEDE trial arm H, where 2,061 patients were recruited into this arm that compared RT to the standard of care, which showed no improvement in OS, although improvements in failure-free survival (FFS). Further stratification within arm H showed a 17% improvement in 3-year FFS and an 8% improvement in 3-year OS among patients with low-volume disease who received RT [11].

RT in mPCa consists of external beam radiation therapy (EBRT), which poses unique benefits and drawbacks regarding ease of administration and potential complications[9,12,13]. While initially indicated for local prostate cancer, systematic reviews conducted by Rogowski et al. and Carneiro et al. found symptomatic and survival benefits of RT and RP among patients with mPCa[14-17]. Specifically, Rogowski et al. assessed stereotactic body RT with and without prophylactic nodal RT for oligometastatic prostate cancer among 4,252 patients. Their analysis included 56 retrospective studies, predominantly case series, finding 2-year local control rates ranging from 76-100% and 2-year progress-free survival rates from 22-88%. Furthermore, Carneiro et al. evaluated the outcomes of 34,338 mPCa patients receiving LT (RT and RP) compared to those with ADT alone or otherwise not receiving LT and found that RT and RP improved 3 and 5-year OS, along with cancer-specific survival.

Nevertheless, continuing research on LT in mPCa is needed as much of the existing literature consists of case reports, case series, and smaller cohort studies[15,16]. There are ongoing prospective randomized trials examining LT in mPCa, such as SWOG 1802 and the TRoMbone trial, but these studies are still in the accrual phase without published results. Our study evaluates a large cohort of 36,635 patients and addresses this gap by comparing ADT monotherapy to ADT with LT among patients with mPCa using the National Cancer Database. By leveraging this database, we provide robust statistical power and generalizability across diverse populations. We decided to evaluate from 2004 to 2017 utilizing the National Cancer Database, which aims to document trends in LT utilization over time, align with evolving clinical practices, and underscoring the growing recognition of LT's benefits. The comprehensive comparison between ADT monotherapy and ADT combined with definitive LT is a key aspect of our research.

Methods

STUDY POPULATION

The National Cancer Database (NCDB) is a hospital-based cancer registry by the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society. This database represents over 1,500 Commission-accredited cancer programs in the United States, collecting de-identified data on approximately 70% of all newly diagnosed cancer cases. At the time of analysis, the 2019 NCDB was the most recent data release. Due to changes in variables across years and a desire to maintain data consistency, patients diagnosed after 2017 did not meet inclusion criteria.

A retrospective cohort analysis was conducted of n=36,635 patients aged 40 years or older with cT1-4 cN0-3 cM1 prostatic adenocarcinoma (International Classification of Disease-O-3 (ICD-O-3) organ site codes C67.0-9) who received ADT as their first-course therapy. Staging was derived utilizing the American Joint Committee on Cancer Staging System. Patients were excluded for the following: unknown PSA and/or Gleason score, received palliative care or unknown receipt of palliative care, unknown receipt of radiation, lost to follow-up within six months or unknown follow-up, unknown vital status.

STATISTICAL ANALYSIS

Patient demographics were stratified by treatment status and are reported in Table 1. Local therapy recipients are reported both in summary and further subdivided between RP and RT. Frequencies and proportions were reported for categorical variables and mean, standard deviation, median, interquartile ranges, minimum, and maximum for continuous variables. The Pearson Chi-square and Wilcoxon signed rank tests examined bivariate differences between first RP + ADT vs. RT + ADT patients and again between LT + ADT vs. ADT alone patients.

Baseline Characteristic	Local treatment ± androgen deprivation therapy				Androgen deprivation therapy alone	p value
	Local treatment modality					
	Radical prostatectomy	Radiation therapy	p value	Overall		
No. of patients (%)	313 (9.8)	2884 (90.2)	-	3197 (100, 8.7)	33438 (91.3)	-
Age, year Mean (SD) Median (Q1, Q3) Min - Max	 61.3 (7.7) 61 (56,67) 42-89	 67.2 (9.7) 67 (60, 74) 40-90	<0.001	 66.6 (9.7) 66 (60,73) 40-90	 70.0 (10.7) 70 (62,78) 40-90	<0.001
Race/ethnicity, n (%)			0.003			<0.001
Non-hispanic White	254 (81.2)	2088 (72.4)		2342 (73.3)	22567 (67.5)	
Non-hispanic Black	30 (9.6)	454 (15.7)		484 (15.1)	6302 (18.8)	
Other/unknown	29 (9.3)	342 (11.9)		371 (11.6)	4569 (13.7)	
Charlson Comorbidity Index, n (%)			0.011			<0.001
0	273 (87.2)	2413 (83.7)		2686 (84.0)	25804 (77.2)	
1	37 (11.8)	340 (11.8)		5435 (14.8)	5058 (15.1)	
≥2	3 (1.0)	131 (4.5)		2710 (7.4)	2576 (7.7)	
Median income of ZIP code, n (%)			0.004			<0.001
$63,000 or more	123 (39.3)	927 (32.1)		1050 (32.8)	9843 (29.4)	
$62,999- $48,000	68 (21.7)	618 (21.4)		686 (21.5)	7069 (21.1)	
$47,999-$38,000	49 (15.7)	544 (18.9)		7143 (19.5)	6550 (19.6)	
< $38,000	30 (9.6)	466 (16.2)		6875 (18.8)	6379 (19.1)	
Unknown	43 (13.7)	329 (11.4)		3969 (10.8)	3597 (10.8)	
Zipcode w/o HS diploma, n (%)			0.003			<0.001
Less than 6.3%	99 (31.6)	703 (24.4)		802 (25.1)	7309 (21.9)	
6.3 - 10.8%	69 (22.0)	704 (24.4)		773 (24.2)	8020 (24.0)	
10.9 - 17.5%	70 (22.4)	629 (21.8)		699 (21.9)	7690 (23.0)	
17.6% or more	34 (10.9)	523 (18.1)		557 (17.4)	6878 (20.6)	
Unknown	41 (13.1)	325 (11.3)		366 (11.3)	3541 (10.6)	
Insurance status, n (%)			<0.001			<0.001
Private insurance/managed care	191 (61.0)	997 (34.6)		1188 (37.2)	8922 (26.7)	
Medicare	98 (31.3)	1504 (52.1)		1602 (50.1)	19436 (58.1)	
Medicaid	11 (3.5)	175 (6.1)		186 (5.8)	2481 (7.4)	
Other/Unknown	13 (4.2)	208 (7.2)		221 (6.9)	2599 (7.8)	
County category, n (%)			<0.001			0.734
Metropolitan County	253 (80.8)	2345 (81.3)		2598 (81.3)	27280 (81.6)	
Urban County	31 (9.9)	402 (13.9)		433 (13.5)	4414 (13.2)	
Rural County	5 (1.6)	52 (1.8)		57 (1.8)	667 (2.0)	
Unknown	24 (7.7)	85 (2.9)		109 (3.4)	1077 (3.2)	
CoC facility type, n (%)			<0.001			0.195
Comprehensive Community Cancer Program	78 (24.9)	1052 (36.5)		1130 (35.3)	11750 (35.1)	
Community Cancer Program	15 (4.8)	268 (9.3)		283 (8.9(	2640 (7.9)	
Academic/Research	175 (55.9)	1062 (36.8)		1237 (38.7)	13033 (39.0)	
Integrated Network Cancer Program/Other	45 (14.4)	502 (17.4)		547 (17.1)	6015 (18.0)	
Year of diagnosis, n (%)			<0.001			<0.001

2004	1 (0.3)	105 (3.6)		106 (3.3)	1132 (3.4)	
2005	6 (1.9)	134 (4.6)		140 (4.4)	1240 (3.7)	
2006	2 (0.6)	137 (4.8)		139 (4.3)	1274 (3.8)	
2007	8 (2.6)	131 (4.5)		139 (4.3)	1331 (4.0)	
2008	7 (2.2)	149 (5.2)		156 (4.9)	1501 (4.5)	
2009	7 (2.2)	182 (6.3)		189 (5.9)	1678 (5.0)	
2010	12 (3.8)	196 (6.8)		208 (6.5)	1858 (5.6)	
2011	19 (6.1)	180 (6.2)		199 (6.2)	2041 (6.1)	
2012	18 (5.8)	191 (6.6)		209 (6.5)	2347 (7.0)	
2013	28 (8.9)	207 (7.2)		235 (7.4)	2783 (8.3)	
2014	26 (8.3)	210 (7.3)		236 (7.4)	3166 (9.5)	
2015	48 (15.3)	282 (9.8)		330 (10.3)	3701 (11.1)	
2016	61 (19.5)	357 (12.4)		418 (13.1)	4413 (13.2)	
2017	70 (22.4)	423 (14.7)		493 (15.4)	4973 (14.9)	
PSA level category, n (%)			<0.001			<0.001
<10.0	112 (35.8)	657 (22.8)		769 (24.1)	3406 (10.2)	
10.0-20.0	82 (26.2)	514 (17.8)		596 (18.6)	3627 (10.8)	
>20.0	110 (35.1)	1557 (54)		1667 (52.1)	24006 (71.8)	
Unknown	9 (2.9)	156 (5.4)		165 (5.2)	2399 (7.2)	
Clinical Stage, n (%)			<0.001			<0.001
cT1	115 (36.7)	757 (26.2)		872 (27.3)	8552 (25.6)	
cT2	92 (29.4)	702 (24.3)		794 (24.8)	7498 (22.4)	
cT3	70 (22.4)	612 (21.2)		682 (21.3)	3967 (11.9)	
cT4	8 (2.6)	485 (16.8)		493 (15.4)	4151 (12.4)	
Unknown	28 (8.9)	328 (11.4)		356 (11.1)	9270 (27.7)	
Gleason Score, n (%)			<0.001			<0.001
≤6	4 (1.3)	27 (0.9)		31 (1.0)	225 (0.7)	
7	52 (16.6)	277 (9.6)		329 (10.3)	2221 (6.6)	
8-10	214 (68.4)	1529 (53.0)		1743 (54.5)	15658 (46.8)	
Unknown	43 (13.7)	1051 (36.4)		1094 (34.2)	15334 (45.9)	

Table 1: Patient Characteristics

A multivariable logistic regression model was formed to predict the treatment group (LT + ADT vs. ADT alone) using patient clinicopathologic features as predictors (Table 2). A second logistic regression model was performed on the subset of data that received LT + ADT to predict the receipt of RP vs. RT as the type of LT using the same patient clinicopathologic variables (Table 3). Reference levels for categorical variables were determined by order where such stratification exists (e.g., clinical stage, Gleason Grade) and by the majority when order is not applicable (e.g., ethnicity/race, insurance status).

Characteristic	Odds Ratio	95% CI	p-value
Age at Diagnosis	0.97	0.96, 0.97	**<0.001**
Race/Ethnicity			
Non-Hispanic White	—	—	
Non-Hispanic Black	0.84	0.75, 0.94	**0.002**
Other/unknown	0.83	0.74, 0.93	**0.002**
CCI			
0	—	—	
1	0.78	0.70, 0.88	**<0.001**
≥2	0.62	0.52, 0.75	**<0.001**
Median Income Quartiles			
$63,000 or more	—	—	
$62,999-48,000	0.99	0.88, 1.10	0.8
$47,999-38,000	0.92	0.81, 1.05	0.22
Less than $38,000	0.86	0.74, 1.01	0.062
Unknown	1.06	0.40, 2.34	0.9
Zipcode without High School Diploma			
Less than 6.3%	—	—	

Characteristic	Odds Ratio	95% CI	p-value
6.3-10.8%	0.94	0.84, 1.05	0.3
10.9-17.5%	0.95	0.83, 1.08	0.41
17.6% or more	0.96	0.82, 1.12	0.56
Unknown	0.91	0.41, 2.41	0.82
Insurance Status			
Private	—	—	
Medicare	1.03	0.93, 1.14	0.57
Medicaid	0.74	0.62, 0.87	**<0.001**
Other/unknown	0.82	0.70, 0.95	**0.01**
PSA Level			
<10.0	—	—	
10.0-20.0	0.74	0.66, 0.83	**<0.001**
>20.0	0.34	0.31, 0.37	**<0.001**
Unknown	0.42	0.35, 0.50	**<0.001**
Clinical T Stage			
T1	—	—	
T2	1.07	0.97, 1.19	0.19
T3	1.71	1.53, 1.91	**<0.001**
T4	1.35	1.19, 1.52	**<0.001**
Unknown	0.5	0.44, 0.57	**<0.001**
Gleason Score			
≤6	—	—	
7	1.07	0.72, 1.63	0.74
8-10	0.77	0.53, 1.16	0.2
Unknown	0.69	0.47, 1.04	0.065

Table 2: Logistic Regression Predicting Receipt of Local Treatment

Survival analysis was performed using the Kaplan-Meier (KM) method and the Cox Proportional Hazards Model (Figures 1-3). KM curves were formed for the overall LT + ADT group, subdivided into RP + ADT and RT + ADT.

All statistical analyses were performed using R software version 4.3.2. All reported *p*-values were based on two-sided hypotheses, with a *p*-value of <0.05 considered statistically significant.

Results

PATIENT DEMOGRAPHICS

This study encompassed n=36,635 eligible patients diagnosed with cT1-4 cN0-3 cM1 PCa, with 3197 (8.7%) patients receiving LT+ADT. Among LT+ADT, 2884 (90.2%) patients received RT + ADT, and 313 (9.8%) received RP+ADT. Comparing patients with ADT alone versus ADT+LT, there were significant differences in age, race, CCI, income, percentiles with High School diploma, insurance, year of diagnosis, PSA levels, cT, and Gleason scores (Table 1). The type of CoC treatment facility was not associated with using LT. Comparing patients with ADT+RP versus ADT+RT, there were significant differences in age, race, CCI, income, percentiles with High School diploma, insurance, residential demographics, facility type, year of diagnosis, PSA levels, cT, and Gleason scores (Table 1). Black race, Medicaid insurance, and older age were associated with a lower likelihood of LT. Furthermore, RP was more likely to be performed at an academic center and in patients with private insurance and lower PSA values. Conversely, RT patients were more likely to have cT4 disease and CCI 2 or higher status. Furthermore, rates of LT progressively increased from 3.3% in 2004 to 15.4% in 2017.

PREDICTORS OF RECEIVING LOCAL THERAPY (RADICAL PROSTATECTOMY OR RADIATION THERAPY)

Multivariate logistic regression revealed that patients with stage cT3-4 were more likely to receive LT. Conversely, patients who were older, of Black race, had a CCI score of 1 or 2+, were covered by Medicaid, and had a PSA level greater than 10 exhibited a significantly decreased probability of receiving LT (Table 2). Among those patients treated with LT, those undergoing RT were more likely to be cT3-4 with PSA >20ng/mL (Table 3). Interestingly, those patients with Medicaid insurance and Black patients were less likely to undergo RP than RT as definitive LT.

Characteristic	Odds Ratio	95% CI	p-value
Age at Diagnosis	0.92	0.91, 0.94	**<0.001**
Race/Ethnicity			
Non-Hispanic White	—	—	
Non-Hispanic Black	0.61	0.39, 0.94	**0.028**
Other/unknown	0.75	0.48, 1.14	0.2
CCI			
0	—	—	
1	1.31	0.87, 1.92	0.18
≥2	0.32	0.08, 0.90	0.061
Median Income Quartiles			
$63,000 or more	—	—	
$62,999-48,000	1.01	0.68, 1.48	0.97
$47,999-38,000	0.79	0.50, 1.23	0.3
Less than $38,000	0.67	0.37, 1.17	0.16

Characteristic	Odds Ratio	95% CI	p-value
Unknown	4.94	0.58, 34.1	0.11
Zipcode without High School Diploma			
Less than 6.3%	—	—	
6.3-10.8%	0.73	0.49, 1.07	0.1
10.9-17.5%	0.99	0.64, 1.53	0.96
17.6% or more	0.73	0.41, 1.27	0.27
Unknown	0.14	0.02, 1.23	0.052
Insurance Status			
Private	—	—	
Medicare	0.83	0.59, 1.17	0.28
Medicaid	0.45	0.22, 0.85	**0.02**
Other/unknown	0.53	0.27, 0.94	**0.04**
PSA level			
<10.0	—	—	
10.0-20.0	0.91	0.65, 1.26	0.57
>20.0	0.44	0.32, 0.59	**<0.001**
Unknown	0.49	0.22, 0.99	0.063
Clinical T Stage			
T1	—	—	
T2	0.89	0.65, 1.22	0.47
T3	0.7	0.50, 0.98	**0.04**
T4	0.13	0.06, 0.26	**<0.001**
Unknown	1.04	0.63, 1.68	0.86
Gleason's Score on Needle Core Biopsy			
≤6	—	—	
7	1.46	0.50, 5.41	0.52
8-10	1.22	0.43, 4.44	0.73
Unknown	0.37	0.12, 1.36	0.093

Table 3: Logistic Regression Predicting Receipt of Radical Prostatectomy as Form of Local Treatment

SURVIVAL ANALYSIS

The CPH regression model revealed that patients with advanced age, a CCI of 1 or 2+, income below $63,000, Medicare or Medicaid insurance, a PSA >20, cT4, and Gleason scores 8 to 10 exhibited significantly worse OS. Black patients demonstrated a significantly improved OS compared to white patients. Patients undergoing ADT+RP or ADT+RT experienced a markedly enhanced OS compared to those on ADT alone (Figure 3).

Kaplan-Meier (KM) survival curves spanning up to 204 months (17 years) demonstrate a notable enhancement in 5-year overall survival (OS) among patients who underwent combination therapy with ADT+LT versus ADT alone. Patients on ADT alone had a 5-year OS of 31.3% [30.7 - 31.8], while those on ADT+LT had a significantly improved OS of 54.2% [52.4 - 56.1] ($p < 0.0001$) (Figure 1). Further analysis based on LT type showed that ADT+RP had a higher 5-year OS at 74.0% [67.5 - 79.1], compared to 52.2% [50.2 - 54.2] for ADT+RT ($p < 0.0001$) (Figure 2).

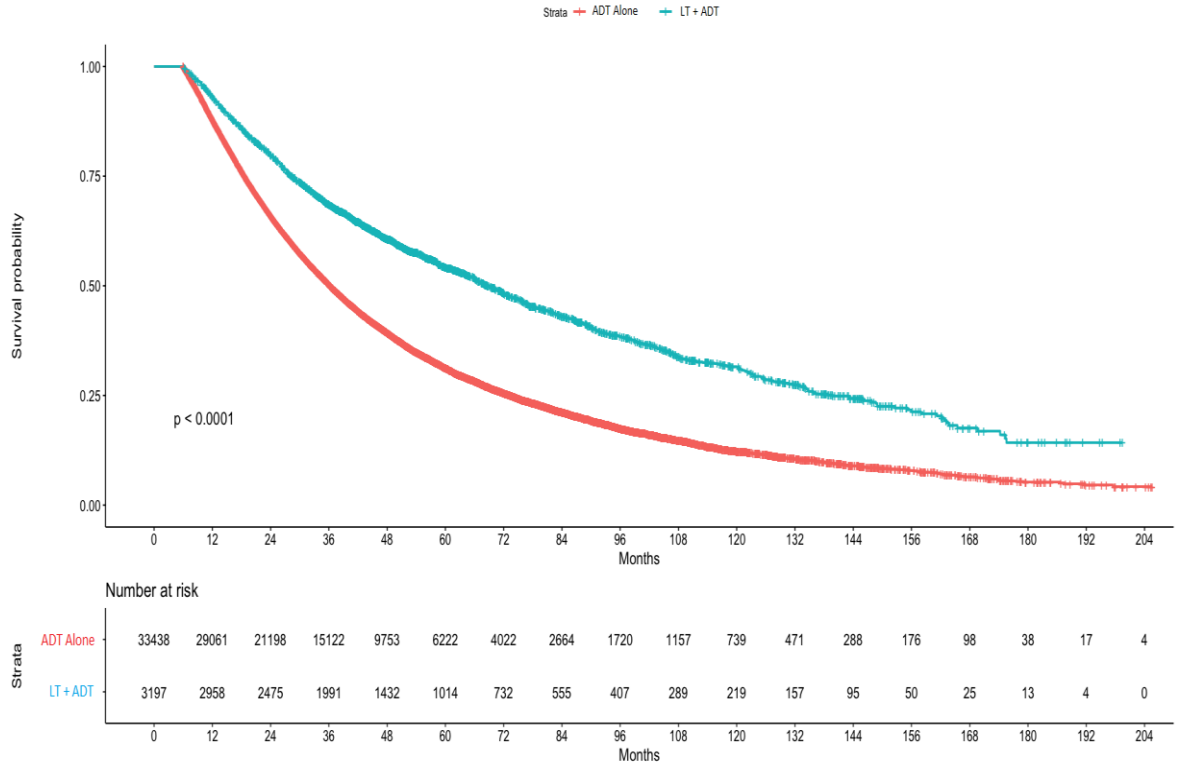

Figure 1: KM Curve LT + ADT vs ADT Alone

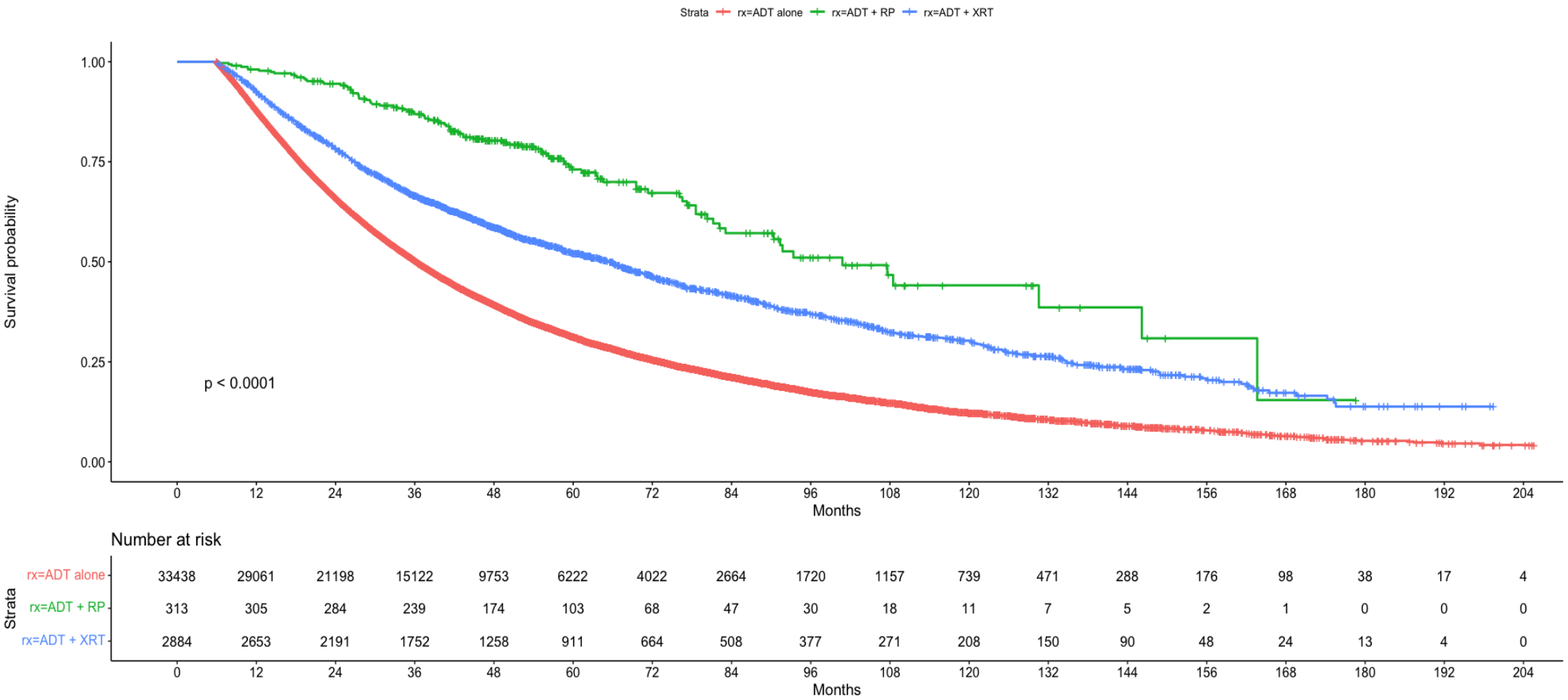

Figure 2: KM Curve ADT vs RP + ADT vs RT + ADT

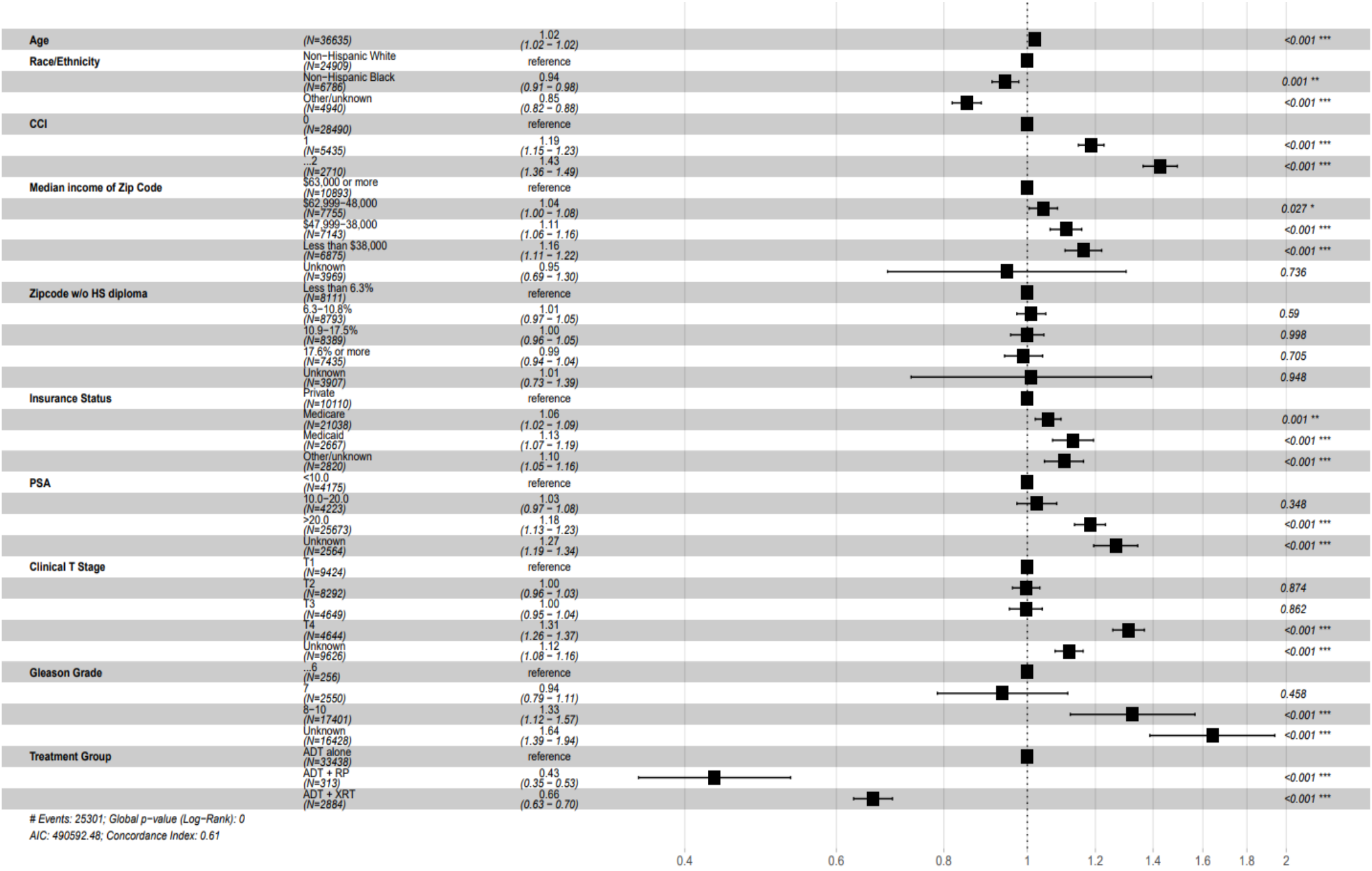

Figure 3: Cox Regression Model for Overall Mortality

Discussion

Our study supports the integration of definitive local therapy with androgen deprivation therapy in the treatment regimen for some well-selected patients with metastatic prostate cancer. We found a significant improvement in overall survival for mPCa patients receiving LT+ADT compared to those receiving ADT alone while controlling for known patient demographic (including age) and pathologic characteristics. Specifically, the 5-year OS for patients treated with LT+ADT was markedly higher at 54.2% compared to 31.3% for those on ADT alone, highlighting the potential survival benefits of combining local and systemic treatments for select patients. While the mean age was about 3.5 years older in the ADT alone group, this variable was controlled for the multivariable analysis. Furthermore, in multivariable analysis, the breakdown between localized treatments demonstrated a higher 5-year OS for RP at 74.0% versus 52.2% for RT. Inclusion of all patients rather than performing propensity score matching reflects real-world patient scenarios, as RT patients tend to be older and have higher CCI. In fact, there was a 6-year age difference for RP vs. RT patients, which we controlled for in our multivariable analysis. Indeed, more work is needed to optimize patient selection criteria for one form of LT vs. another.

These findings align with and build upon the existing literature. A recent NCDB study of n=6,382 men with mPCa evaluated the impact of RT combined with ADT on survival outcomes, identifying a significant improvement in OS with RT+ADT compared to ADT alone[18]. This study showed superior median and 5-year OS rates for patients receiving prostate RT+ADT compared to ADT alone. Long-term survivors at 1, 3, and 5 years also showed improved OS with prostate RT+ADT in all subsets. However, no significant differences in OS were observed when comparing therapeutic dose RT plus ADT with prostatectomy plus ADT. At the same time, both treatments were superior to ADT alone, suggesting a potential benefit of local therapies for mPCa that warrants further prospective investigation. Our study extends these findings by directly comparing RT+ADT and RP+ADT, demonstrating that RP offers superior survival benefits for some men.

Additionally, another NCDB study analyzing trends in locoregional treatment for mPCa from 2004 to 2012 observed a decline in the use of radiation and surgery despite evidence suggesting benefits[19]. The percentage of mPCa patients receiving locoregional treatment decreased from 7.88% to 5.53%, with factors such as older age and higher comorbidity levels associated with a reduced likelihood of receiving locoregional treatment. Specifically, the study found a decline in prostate and pelvis radiation (5.9% to 4.2%) and radical prostatectomy rates (2.17% to 1.31%). Despite the demonstrated benefits of locoregional treatment, the study highlighted a slow adoption of this treatment paradigm, reflecting declining rates of prostate radiation and radical prostatectomy over the study period. Our findings support the benefits of LT and actually show a significant increase in utilization over time from 3.3% in 2004 to 15.4% in 2017. The results of STAMPEDE arm H were published in 2018, providing level-one evidence of the overall survival benefit for definitive local radiotherapy in the oligometastatic setting[8,11]. Thus, the increase in the utilization of LT over time found in our study highlights the perceived value that this definitive local treatment had in routine clinical practice even before the STAMPEDE results. The cumulative evidence from our study and the literature supports the critical role of LT, mainly RP, in the treatment paradigm for mPCa. Although beyond the scope of the present study, the improved morbidity-profile and functional outcomes offered by robotic technology in surgery and more accurate (i.e., "conformal") intensity-modulated and image-guided radiotherapy may have also helped fuel this increase.

The mechanistic rationale for definitive local therapy in the setting of metastatic cancer has been explored previously. The "seed and soil" hypothesis, initially proposed by Stephen Paget in 1889, posits that cancer metastasis is akin to seeds (cancer cells) requiring suitable soil (microenvironment) growth[20]. Metastatic niches are pre-conditioned environments conducive to tumor growth, influenced by signaling factors from the primary tumor, removing the primary tumor through local therapy may disrupt these pre-metastatic niches, potentially reducing the likelihood of metastasis and enhancing the effectiveness of subsequent systemic therapies[21,22]. This concept underscores the biological rationale for incorporating local therapies in treating metastatic diseases to improve patient outcomes.

Recent prospective trials have provided valuable insights into the benefits of local therapies for mPCa. The HORRAD trial evaluated the impact of external beam radiation therapy adjunct to ADT in 432 patients with primary bone mPCa and found no significant difference in overall survival between the radiotherapy and control groups[23]. Moreover, the STAMPEDE trial of 2,000 patients with low-volume metastatic hormone-sensitive prostate cancer revealed a significantly higher OS in low-metastatic burden patients treated with RT than those with high-metastatic burden[11]. Thus, RT could be recommended as a standard of care for patients with low metastatic burden.

Furthermore, a 2020 NCDB study involving 1.3 million prostate cancer patients investigated racial differences in survival outcomes in mPCa and found no statistically supported racial disparities among African American and white men with bone, liver, lung, or brain metastases, indicating no racial disparities in survival among these metastatic sites[24]. However, racial disparities in survival were noted among non-metastatic prostate cancer patients or when metastasis status was not considered. This study suggested no racial differences in survival outcomes for African American and white patients with mPCa, emphasizing the need for further research to understand differences among non-metastatic cases. However, we found notable disparities in the likelihood of receiving LT when adjusting for race, age, comorbidity index, and insurance status. Interestingly, in our cohort, Black patients tended to have improved overall survival despite lower utilization of LT. The underlying reasons for this observation are unclear and beyond the present analysis's scope. Our findings underscore the importance of addressing these disparities to ensure all patients

benefit from effective therapies.

Limitations

Considering the strengths of utilizing a large, representative national database, we must also acknowledge this study's limitations. Firstly, the retrospective nature of the analysis inherently limits generalizability and may not fully capture all variables and potential confounders. Also, the lack of available data on treatment timing and dosage restricts our ability to perform detailed analyses. While we examined overall survival, other important functional outcomes are not registered in the NCDB. Thus, treatment impacts functional outcomes, and potential benefits (i.e., reduced incidence of sequelae of disease progression such as urinary obstruction, gross hematuria, renal failure, pelvic pain, etc.) are lacking. Limitations in the granularity of data within the NCDB also restrict our ability to report on the impact of metastatic burden (i.e., low vs. high volume metastasis).

Furthermore, the significantly smaller sample size in the radical prostatectomy (RP) group compared to other treatment cohorts may impact the statistical power and generalizability of results specific to RP-related outcomes. Lastly, the era of our study reflects the standard of care practice at the time, i.e., standard ADT. Given the more recent adoption of intensified ADT in the hormone-sensitive metastatic setting, the role of LT in the setting of augmented systemic therapy certainly warrants further investigation as this treatment paradigm is disseminated throughout the US. Addressing these limitations in future investigations will be crucial for refining our understanding of the optimal multimodal treatment of metastatic prostate cancer.

Conclusion

Treatment for metastatic prostate cancer has evolved beyond ADT therapy alone. With new modalities being researched in current clinical trials, clinicians must consider the utility of localized treatment. This study demonstrates that radical prostatectomy or radiation therapy may significantly impact overall survival in some patients with metastatic prostate cancer. We eagerly await the results of the accruing prospective randomized trials in this domain and, in the meantime, support the judicious use of definitive local therapy in the context of patient-shared decision-making.

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