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## Locally advanced prostate cancer: a population-based study of treatment patterns

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### Abstract

- To identify treatment patterns and predictors of receiving multimodality therapy in patients with locally advanced prostate cancer (LAPC).
- The cohort comprised patients  $\geq 66$  years with clinical stage T3 or T4 non-metastatic prostate cancer diagnosed between 1998 and 2005 identified from the Surveillance, Epidemiology and End Results (SEER) cancer registry records linked with Medicare claims.
- Treatments were classified as radical prostatectomy (RP), radiation therapy (RT) and androgen deprivation therapy (ADT) received within 6 and 24 months of diagnosis.
- We assessed trends over time and used multivariable logistic regression to identify predictors of multimodality treatment.
- Within the first 6 months of diagnosis, 1060 of 3095 patients (34%) were treated with a combination of RT and ADT, 1486 (48%) received monotherapy (RT alone, ADT alone or RP alone), and 461 (15%) received no active treatment.
- The proportion of patients who received RP increased, exceeding 10% in 2005 .
- Use of combined RT and ADT and use of ADT alone fluctuated throughout the study period.
- In all 6% of patients received RT alone in 2005.

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### CONFLICT OF INTEREST

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- Multimodality therapy was less common in patients who were older, African American, unmarried, who lived in the south, and who had co-morbidities or stage T4 disease.
- Treatment of LAPC varies widely, and treatment patterns shifted during the study period.
- The slightly increased use of multimodality therapy since 2003 is encouraging, but further work is needed to increase combination therapy in appropriate patients and to define the role of RP.

### Keywords

prostate cancer; locally advanced; treatment; SEER; practice patterns

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## INTRODUCTION

More than 200,000 men will be diagnosed with prostate cancer in the United States this year and up to 10% will have locally advanced disease (clinical stage T3 or T4) at presentation [1,2]. Numerous modalities, alone and in combination, have been advocated for treating these patients, but consensus guidelines are lacking. Mounting evidence supports the use of a multimodality approach to treat locally advanced prostate cancer (LAPC), including some combination of radiation therapy (RT) with androgen deprivation therapy (ADT) or radical prostatectomy (RP) with adjuvant RT. Indeed, multiple randomized controlled trials have demonstrated a survival advantage to combined RT and ADT compared with either modality alone [3–8]. Furthermore, adjuvant RT or ADT after RP in select patients with pathologically advanced prostate cancer confers a significant survival advantage [2,9–11].

The role of radical surgery for these patients has not been investigated systemically. Traditionally RP has not been routinely used in LAPC except in patients with low-volume, clinically staged T3 prostate cancer. Recent evidence suggests that patients with higher-risk prostate cancer treated initially with RP could have lower risks of metastatic progression and prostate cancer-specific death than those treated with RT initially [12]. Attempts to reduce the likelihood of biochemical recurrence after RP by using up to 8 months of neoadjuvant ADT have been unsuccessful [13–15]. The management of other clinically localized, high-risk solid tumours, such as breast and colon cancer, frequently combines surgery with other treatment modalities [16,17]. Such an approach has had limited success in prostate cancer. However, with refinements in RP technique and a reduced risk of perioperative complication rates, the role of surgery in combination with RT, chemotherapy or ADT for patients with LAPC is evolving.

On a population level, surprisingly little is known about LAPC treatment patterns and the proportion of patients receiving various treatment modalities. There is a poor understanding of which factors influence the type of treatment these patients receive and why some receive monotherapy while others are treated with multimodal strategies. Our objective was to characterize treatment patterns for clinically staged T3 and T4 prostate cancer in a population-based patient cohort and to identify predictors of multimodality therapy.

## SUBJECTS AND METHODS

Data were obtained from the National Cancer Institute's (NCI) Surveillance, Epidemiology and End Results (SEER) programme and linked Medicare claims and enrolment information [18]. The SEER-Medicare files were used in accordance with a data-use agreement from NCI, and the study was approved by the Institutional Review Board at Memorial Sloan-Kettering Cancer Center.

Patients  $\geq 66$  years with an incident diagnosis of clinically staged T3 or T4 prostate cancer between 1998 and 2005 were included in the study. Those diagnosed only at the time of death, who had a history of another malignancy or who had metastatic prostate cancer at diagnosis were excluded.

The primary outcome of interest was cancer treatment received within 6 months of diagnosis of LAPC. For descriptive purposes, patients were classified into four, mutually exclusive categories based on the most aggressive treatment received within this initial period: RP (open, minimally invasive or perineal); RT (external beam, brachytherapy or both; ADT (luteinizing hormone-releasing hormone agonist or orchidectomy); and (4) no active treatment (see the Appendix). Additional outcomes were single modality vs multimodality therapy, and treatments received within the first 24 months after diagnosis.

Demographic characteristics included patient age, race, marital status, geographic location and residence in a metropolitan vs a non-metropolitan county. Median income in the census tract of residence was used as a marker of socioeconomic status. Clinical characteristics included clinical tumour stage, biopsy Gleason score and year of diagnosis. Comorbidity was estimated using the Charlson comorbidity index based on inpatient claims in the 12 months before prostate cancer diagnosis [19].

For statistical analysis, we characterized the cohort and their treatment patterns using descriptive statistics and used multivariable logistic regression to evaluate the impact of demographic and clinical characteristics on the likelihood of receiving multimodality therapy. Statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC, USA).

## RESULTS

In all, 3095 patients were identified with clinical stage T3 or T4, non-metastatic prostate cancer diagnosed between 1998 and 2005 in the SEER-Medicare dataset; 48% of patients were  $\geq 75$  years and 82% of the cohort were white (Table 1). Seventy-nine per cent of patients were classified as clinical stage T3, and 21% as clinical stage T4. More than 60% of patients had a Gleason score  $\geq 8$ . Patients treated with RP tended to be younger, have lower-staged tumours and less comorbidity than the other treatment categories. Patients who had ADT or no active treatment tended to be older and more likely to have clinically staged T4 LAPC.

Radiation therapy with or without other treatment modalities was the most common primary treatment within 6 months of diagnosis (41%), followed by ADT alone (36%), no active treatment (15%) and RP with or without other treatment modalities (8%) (Table 2).

There was some variation over time in the frequency of the five most common treatments (Fig. 1). After 2003 there was a pronounced decrease in the use of ADT as monotherapy and an overall increase in the use of combined RT and ADT therapy. The proportion of patients who received both RT and ADT rose from 26% in 2003 to 32% in 2005, still slightly less than the 34% in 1998. The percentage treated with ADT alone decreased from 47% in 2003 to 36% in 2005. The use of RP alone increased from 2% in 1998 to 10% in 2005. Of the 234 patients who underwent RP, 188 (80%) received a pelvic lymph node dissection and, of those, 30 (16%) had positive lymph nodes on pathological evaluation.

Over the entire study period, in the first 6 months after diagnosis single modality therapy was most common (48%), followed by multimodality therapy (37%) and no active treatment (15%). Of patients who had any active treatment, 42% received multimodality therapy in 2005, slightly fewer than the 45% observed in 1998, although this proportion fluctuated over

the study period (Fig. 2). The increase in multimodality treatment since 2003 was due to the increased use of combined ADT and RT.

In multivariable analysis, age, race, geographic region, marital status, clinical stage, Charlson comorbidity score and year of diagnosis were all significant predictors of receiving multimodality therapy rather than monotherapy (Table 3). Older and non-white patients were more likely to receive monotherapy than combination treatment, controlling for other characteristics. Black patients had 33% lower odds of receiving multimodality therapy than white patients (odds ratio [OR], 0.67; 95% CI, 0.50–0.91;  $P < 0.05$ ). Clinically staged T4 patients had half the odds of receiving combination therapy compared with stage T3 patients (OR, 0.50; 95% CI, 0.40–0.62;  $P < 0.001$ ).

## DISCUSSION

The National Comprehensive Cancer Network lists three initial treatment options for LAPC: combined RT and ADT, ADT alone and RP alone [20]. Although evidence from randomized controlled trials suggests that combining RT and ADT for LAPC is superior to either given as monotherapy [3–8], we found that 48% of patients in this population-based cohort were treated with monotherapy, 34% received a combination of RT and ADT, and 15% received no active treatment within 6 months of diagnosis. Throughout the study period, combined RT and ADT and ADT alone were the two most common treatment strategies, and a number of demographic and health characteristics impacted on receipt of multimodality therapy.

The urological literature is replete with studies describing treatment patterns for localized prostate cancer, but less is known about treatment patterns for locally advanced (clinical stage T3 or T4) disease. Several previous population-based studies described treatment patterns that differ somewhat from the findings of the present study [21–23]. Using SEER data alone, one analysis found that by 2001, 60% of patients with clinically staged T3 prostate cancer received RT, compared with 40% in 1995; RP utilization decreased from 18% in 1995 to 9% in 2001 [21]. Using the same database, another study focused on RP in clinically staged T4 patients and found that most of their cohort was treated with ADT or expectant management (62%) and only 7% had RP [22].

Using the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) database, White et al. [24] investigated quality-of-life issues in patients undergoing treatment for LAPC. They describe 608 patients with clinical stage T3 or T4 prostate cancer (representing 4.4% of the CaPSURE cohort) and their primary treatment. In stark contrast to the findings of the present study, these authors report that 43% received ADT, 24% RT, 17% RP and 8% cryotherapy (percentages calculated from their table 1 of that study) [24]. Brachytherapy accounted for 84% of their RT treatment. Differences between these findings and the current study are likely attributable to differences in the study cohorts. The CaPSURE database, a provider-based registry of patients with prostate cancer from a number of community-based urology practices across the US, reflects the experience of patients in all age groups who are seen by CaPSURE urologists. A separate CaPSURE study focusing on localized prostate cancer (clinical stage  $\leq$  T3a) found substantial treatment variation and concern for undertreatment of patients with high-risk disease as defined by the D'Amico risk groups and Cancer of the Prostate Risk Assessment (CAPRA) score. (25)

In the present study, the use of multimodality therapy increased from 2003 to 2005. While reports of improved survival and local control with combined ADT and RT vs RT alone for patients with LAPC appeared as early as 1997 [4], we found that 6% of patients in 2005 still received RT alone. Other randomized controlled trials investigating the use of RT with and without ADT in patients with LAPC were reported in the early 2000s and coincided with an

increase in the use of combination RT and ADT and a decrease in the use of RT alone [3,26,27]. An optimistic explanation for these trends is the practice of evidence-based medicine, with providers changing disease management strategies as new, high-quality evidence emerges. Trends in LAPC treatment could also have been influenced by other factors. For example, the Medicare Modernization Act of 2003 drastically reduced physician payments for the administration of medical ADT starting in 2004 and probably contributed to its decreasing use [28]. Although we observed a slight absolute decrease in the use of RT alone, the percentage of patients who received this therapy remained relatively stable over the study period, despite evidence from randomized trials supporting the addition of ADT. Although combining ADT with RT confers a survival advantage to patients with LAPC over RT alone, side-effects from ADT could have a detrimental impact on quality of life. Concerns about adverse cardiac and skeletal events, cognitive and metabolic changes, and sexual side-effects might preclude some patients from receiving ADT with RT.

The role for RP alone or in combination with RT or ADT remains uncertain for patients with LAPC. Only 8% of patients in this cohort had RP with or without RT or ADT. Recent retrospective analysis of patients treated at one large academic cancer centre suggests that patients with higher-risk prostate cancer treated initially with RP could have a lower risk of metastatic progression and prostate cancer-specific death than those treated with RT initially. Adjusting for clinical variables, RP was associated with a reduced risk of metastasis (hazard ratio [HR], 0.35; 95% CI, 0.19–0.65;  $P < 0.001$ ) and prostate cancer-specific mortality (HR, 0.32; 95% CI, 0.13–0.80;  $P = 0.01$ ) [12]. Although there are no adequately powered randomized controlled trials comparing RT (with or without ADT) and RP (with or without ADT), combination therapy involving RT has become the predominant treatment for LAPC. Several single-institution, retrospective studies have described their surgical experience with LAPC. Researchers from Memorial Sloan-Kettering Cancer Center reported a 10-year actuarial probability of freedom from biochemical recurrence of 44% after RP alone for selected clinical stage T3 patients.(29) Likewise, the Mayo Clinic reported a 10-year recurrence-free rate of 43% for patients with T3 LAPC undergoing RP, showing that selected patients can be cured with surgery [30].

The present study includes a large, population-based cohort with detailed information about treatment, comorbidity and other important patient characteristics. Since prostate cancer is primarily a disease of the elderly, our findings in a population-based cohort of patients aged  $\geq 66$  years should be generalizable to most patients with LAPC. Caution is warranted in drawing inferences about the relationship between patient characteristics and the use of specific therapies, as unmeasured confounders could bias results. For example, information about functional status, patient preference and physician recommendations are not available in the SEER data set or in Medicare claims. In addition, SEER did not record numeric PSA values and exact Gleason scores until 2004, thus limiting our ability to control for those factors in multivariable analysis of treatment predictors.

In conclusion, treatment of LAPC varies widely. In terms of oncological outcomes, level one evidence shows the superiority of a multimodality approach for treating LAPC. Future efforts should focus on further increasing the use of multimodality therapy for appropriate patients with LAPC and better defining the role of RP in this patient population.

## Abbreviations

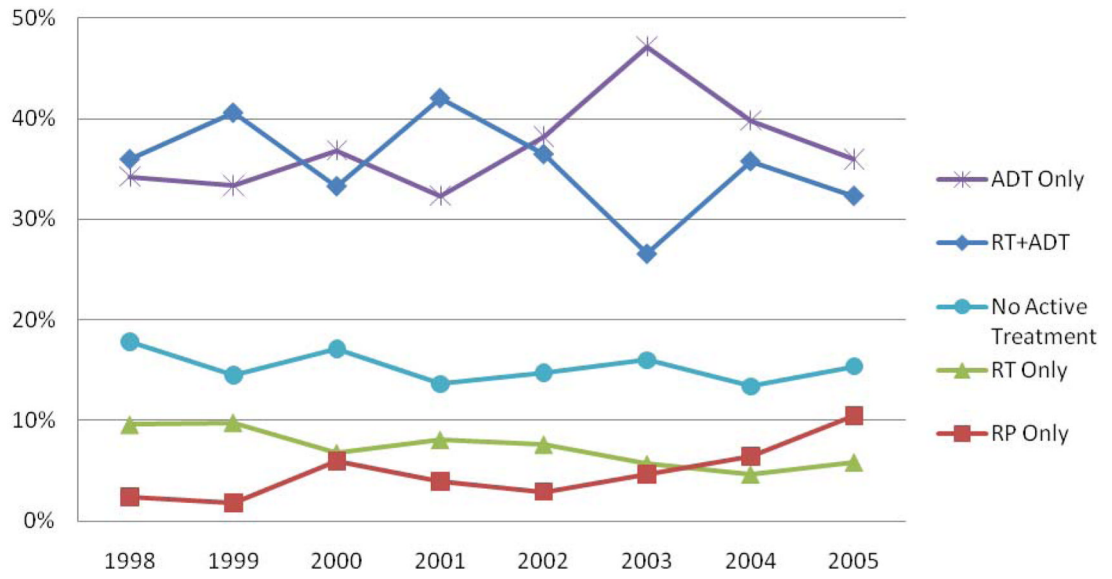
<b>ADT</b>	androgen deprivation therapy
<b>NCI</b>	National Cancer Institute

<b>CaPSURE</b>	Cancer of the Prostate Strategic Urologic Research Endeavor
<b>RP</b>	radical prostatectomy
<b>RT</b>	radiation therapy
<b>SEER</b>	Surveillance, Epidemiology and End Results programme

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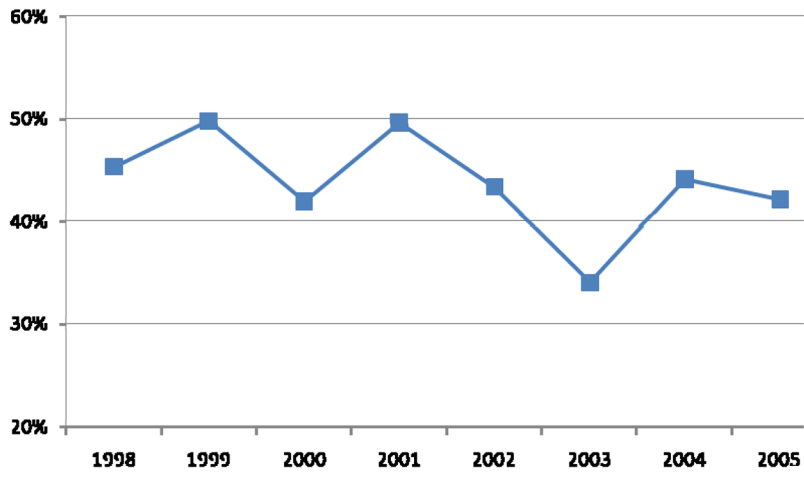
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**FIG. 1.** Trends in five of the most common primary treatments given within 6 months of diagnosis of LAPC.





**FIG. 2.** Trends in multimodality therapy (vs monotherapy) given within 6 months of diagnosis of LAPC ( $N = 2634$ ; excludes patients receiving no active therapy [ $N = 461$ ]).

**TABLE 1**  
 Characteristics of cohort by most aggressive primary treatment within 6 months of Diagnosis

	All patients		RP ± RT, ADT		RT ± ADT		ADT		No active treatment	
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Total	3095 (-)	234 (8)	1275 (41)	1125 (36)	461 (15)					
Age at diagnosis, years										
66-69	681 (22)	135 (58)	277 (22)	169 (15)	100 (22)					
70-74	916 (30)	70 (30)	474 (37)	265 (24)	107 (23)					
75-79	806 (26)	25 (11)	369 (29)	306 (27)	106 (23)					
80-84	435 (14)	* (≤ 1)	124 (10)	225 (20)	83 (18)					
85+	257 (8)	* (≤ 1)	31 (2)	160 (14)	65 (14)					
Race										
White	2530 (82)	184 (79)	1073 (84)	918 (82)	355 (77)					
Black	326 (11)	29 (12)	104 (8)	120 (11)	73 (16)					
Other	237 (8)	21 (9)	97 (8)	86 (8)	33 (7)					
Unknown	* (1)	* (≤ 1)	* (≤ 1)	* (1≤)	* (≤ 1)					
Census tract median income										
First quartile	764 (25)	* (≤ 21)	257 (20)	317 (28)	141 (31)					
Second quartile	765 (25)	52 (22)	326 (26)	278 (25)	109 (24)					
Third quartile	765 (25)	57 (24)	332 (26)	272 (24)	104 (23)					
Fourth quartile	764 (25)	73 (31)	346 (27)	247 (22)	* (≤ 21)					
Unknown	37 (1)	* (≤ 1)	14 (1)	11 (1)	* (≤ 2)					
Urban-rural residence										
Metropolitan	2534 (82)	193 (82)	1064 (83)	895 (80)	382 (83)					
Non-metropolitan	561 (18)	41 (18)	211 (17)	230 (20)	79 (17)					
Region										
North-east	1512 (49)	82 (35)	657 (52)	523 (46)	250 (54)					

	All patients		RP ± RT, ADT		RT ± ADT		ADT		No active treatment	
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
South	526 (17)	28 (12)	231 (18)	199 (18)	68 (15)					
Midwest	460 (15)	53 (23)	159 (12)	187 (17)	61 (13)					
West	597 (19)	71 (30)	228 (18)	216 (19)	82 (18)					
Married										
Yes	2072 (67)	180 (77)	938 (74)	685 (61)	269 (58)					
No	765 (25)	38 (16)	282 (22)	291 (26)	154 (33)					
Unknown	258 (8)	16 (7)	55 (4)	149 (13)	38 (8)					
Clinical stage										
T3a	604 (20)	70 (30)	304 (24)	150 (13)	80 (17)					
T3b	766 (25)	75 (32)	366 (29)	217 (19)	108 (23)					
T3.nos	1061 (34)	63 (27)	439 (34)	413 (37)	146 (32)					
T4	664 (21)	26 (11)	166 (13)	345 (31)	127 (28)					
Preoperative PSA level										
Elevated	2426 (78)	168 (72)	1040 (82)	885 (79)	333 (72)					
Borderline	135 (4)	* (≤9)	70 (5)	24 (2)	* (≤4)					
Normal	81 (3)	* (≤4)	50 (4)	15 (1)	* (≤2)					
Unknown	453 (15)	36 (15)	115 (9)	201 (18)	101 (22)					
Gleason score										
2-4	30 (1)	* (≤1)	* (≤1)	* (≤1)	11 (2)					
5-7	1031 (33)	78 (33)	492 (39)	296 (26)	165 (36)					
8-10	1933 (62)	144 (62)	753 (59)	779 (69)	257 (56)					
Unknown	101 (3)	* (≤4)	* (≤2)	* (≤4)	28 (6)					
Year of diagnosis										
1998	299 (10)	14 (6)	133 (10)	100 (9)	52 (11)					
1999	287 (9)	16 (7)	139 (11)	92 (8)	40 (9)					
2000	515 (17)	43 (18)	201 (16)	185 (16)	86 (19)					

	All patients		RP ± RT, ADT		RT ± ADT		ADT		No active treatment	
	N (%)		N (%)		N (%)		N (%)		N (%)	
2001	440 (14)		24 (10)		217 (17)		140 (12)		59 (13)	
2002	451 (15)		17 (7)		197 (15)		171 (15)		66 (14)	
2003	400 (13)		30 (13)		125 (10)		183 (16)		62 (13)	
2004	359 (12)		37 (16)		139 (11)		137 (12)		46 (10)	
2005	344 (11)		53 (23)		124 (10)		117 (10)		50 (11)	
Charlson comorbidity score										
0	1348 (44)		116 (50)		618 (48)		393 (35)		221 (48)	
1	594 (19)		64 (27)		246 (19)		212 (19)		72 (16)	
2+	1153 (37)		54 (23)		411 (32)		520 (46)		168 (36)	

\* Cells with counts ≤ 11 and relevant adjacent cells are not shown, in adherence with SEER-Medicare Data Use Agreement.

**TABLE 2**

Treatments received within 6 and 24 months after prostate cancer diagnosis

	Received within 6 months	Received within 24 months
Treatment	<i>N</i> (%)	<i>N</i> (%)
ADT only	1125 (36%)	939 (30%)
RT + ADT	1060 (34%)	1352 (44%)
No active treatment	461 (15%)	346 (11%)
RT only	215 (7%)	212 (7%)
RP only	146 (5%)	109 (4%)
RP + ADT	63 (2%)	76 (2%)
RP + RT + ADT	* ( $\leq 1\%$ )	42 (1%)
RP + RT	* ( $\leq 1\%$ )	19 (1%)

\* Cells with counts  $\leq 11$  and relevant adjacent cells are not shown, in adherence with SEER-Medicare Data Use Agreement.

**TABLE 3**

Multivariable analysis of predictors of multimodality therapy versus monotherapy for treatment of locally advanced prostate cancer within 6 months following diagnosis ( $N = 2532$ )

Characteristic	Adjusted OR (95% CI)	P value
Age at diagnosis, years		
66–69	Reference	< 0.001
70–74	1.08 (0.86–1.35)	
75–79	0.83 (0.66–1.05)	
80–84	0.49 (0.36–0.66)	
85+	0.21 (0.13–0.33)	
Race		
White	Reference	0.02
Black	0.67 (0.50–0.91)	
Other	0.83 (0.61–1.14)	
Urban-rural residence		
Metropolitan	Reference	0.23
Non-metropolitan	0.87 (0.69–1.09)	
Region		
Northeast	Reference	0.001
South	0.77 (0.57–1.05)	
Midwest	1.11 (0.83–1.47)	
West	1.37 (1.08–1.72)	
Married		
Yes	Reference	< 0.001
No	0.76 (0.62–0.94)	
Unknown	0.41 (0.29–0.57)	
Clinical stage		
T3	Reference	< 0.001
T4	0.50 (0.40–0.62)	
Gleason score		
5–7	Reference	0.34
2–4	1.05 (0.40–2.72)	
8–10	1.15 (0.96–1.37)	
Charlson comorbidity score		
0	Reference	0.001
1	0.81 (0.65–1.01)	
2+	0.69 (0.57–0.83)	
Year of diagnosis	0.94 (0.90–0.98)	0.002

\* Patients with missing race or Gleason score were excluded from analysis.

## APPENDIX

## HCPCS AND ICD-9 CODES FOR TREATMENT OF LOCALLY ADVANCED PROSTATE CANCER

	HCPCS	ICD-9
Prostate cancer	185, 233.4, 236.5	
Radical prostatectomy	60.5, 60.62	55801, 55810, 55812, 55815, 55821, 55831, 55840, 55842, 55845, 55866
Radiation		
External beam	92.21, 92.22, 92.23 92.24, 92.25, 92.26	77400, 77401, 77402, 77403, 77404, 77405, 77406, 77407, 77408, 77409, 77410, 77411, 77412, 77413, 77414, 77416, 77417, 77418, 77419, 77420, 77425, 77427, 77430, 77431, 77432, 77470, 77520, 77522, 77523, 77525, 77789
Brachytherapy	92.27	55859, 77750, 77761, 77762, 77763, 77776, 77777, 77778, 77781, 77782, 77783, 77784, C2632, Q3001
Androgen deprivation		
Medical	99.24	11980, J0970, J1000, J1380, J1390, J1950, J3315, J9202, J9217, J9218, J9219, S9560
Surgical	62.3, 62.4, 62.41, 62.42	54520, 54521, 54522, 54530, 54535

Abbreviations: HCPCS, Healthcare Common Procedural Coding System; ICD, International Classification Of Diseases