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Use of Androgen Deprivation Therapy for Metastatic Prostate Cancer in Older Men

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Abstract

Purpose—Uncertainty exists about the ideal timing for initiation of androgen deprivation therapy for men with metastatic prostate cancer. We assessed factors associated with early or delayed androgen deprivation therapy among men diagnosed with metastatic prostate cancer and assessed the relationship between this therapy and overall survival.

Patients and methods—We studied a population-based cohort of American men aged ≥ 66 years diagnosed with metastatic prostate cancer during 1992–2002 and followed through 2003. We assessed receipt of androgen deprivation therapy early (within 4 months of diagnosis), delayed (after 4 months), or not at all, used multinomial logistic regression to identify factors associated with treatment, and used Cox proportional hazards models to assess whether treatment was associated with survival.

Results—Overall, 69.5% of men received early hormonal therapy and 7.3% delayed. Adjusted rates of early therapy were lower for black vs. white men (58.3% vs. 71.0%) and adjusted rates of delayed use were higher for black vs. white men (12.7% vs. 6.2%). Receipt of androgen deprivation therapy was associated with improved survival (adjusted HR=.69 95% CI .66–.73). The benefit for early treatment did not differ from delayed treatment ($P=.58$)

Conclusions—A large minority of men with metastatic prostate cancer, particularly black men, receive delayed or no hormonal therapy. Receipt of early or delayed hormonal therapy was associated with similarly prolonged survival. After controlling for patient and tumor characteristics, survival did not differ by race, and receipt of hormonal therapy did not contribute to racial differences in survival.

Keywords

prostate cancer; androgen deprivation therapy; disparities; outcomes

Prostate cancer is the most frequently diagnosed cancer among men, with over 234,000 estimated new cases diagnosed in the United States in 2006.¹ Although only a minority of prostate cancers are metastatic at the time of diagnosis, survival for such men is poor, with only one-third expected to be alive in 5 years.²

Androgen deprivation therapy with a gonadotropin-releasing hormone (GnRH) agonist or bilateral orchiectomy has long been known to inhibit growth of prostate cancers in men with advanced prostate cancer,^{3, 4} but uncertainty exists about the ideal timing for initiation of androgen deprivation in men with metastatic disease.^{5, 6} Some data suggest fewer disease-related complications compared to treatment delayed until clinical progression, despite similar survival.⁷ However, a recent review of published studies of hormone therapy in metastatic or progressive prostate cancer suggested that immediate versus symptom-onset initiation of hormone therapy results in a moderate decrease in risk of prostate cancer survival, a moderate increase in the risk of non-prostate cancer survival, and no overall survival advantage.⁶

Use of androgen deprivation therapy has increased greatly since the early 1990s among American men with nonmetastatic prostate cancer,^{8–10} but few data are available about patterns of androgen deprivation therapy in men with metastatic prostate cancer. A recent study of men who died of prostate cancer during 1991–2000 found that approximately one-quarter of men did not receive androgen deprivation therapy before death, and black men were much less likely than white men to receive this treatment.¹¹ We studied a population-based cohort of men diagnosed with metastatic prostate cancer to evaluate use of androgen deprivation therapy among men with advanced prostate cancer in the U.S.. Specifically, we assessed whether men were treated with a GnRH agonist or orchiectomy early (within 4 months of diagnosis), delayed (after 4 months), or not at all and whether receipt of this treatment varied by patient or tumor characteristics or year of diagnosis. We also assessed whether treatment with androgen deprivation therapy was associated with improved survival for men diagnosed with metastatic prostate cancer.

Patients and methods

Data

We used Surveillance, Epidemiology, and End Results (SEER)-Medicare data for this analysis.¹² The SEER program of the National Cancer Institute is an authoritative source of information on cancer incidence and survival in the United States. For years, SEER registrars have collected uniformly reported data from 11 population-based cancer registries covering approximately 14% of the U.S. population.¹³ In 2000, SEER expanded to include 4 additional registries (Kentucky, Louisiana, New Jersey, and Greater California); the SEER registries now represent approximately 26% of the U.S. population. Since 1991, for each incident cancer, SEER data on patient demographics, tumor characteristics, and primary treatment are linked with Medicare administrative data (successfully linking more than 94% of SEER patients diagnosed at age ≥ 65).¹⁴ Medicare is the national health insurance program for Americans aged 65 and older and administrative data can be used to identify services received by patients.

Study cohort

We identified men aged ≥ 66 years with a first diagnosis of prostate cancer during 1992–1999 who were continuously enrolled in Parts A and B of fee-for-service Medicare as of 1 year before diagnosis (N=150,378). We excluded 3,716 men with no administrative claims from 45 days before diagnosis through 195 days after diagnosis because we considered their claims incomplete. From the remaining 146,662 men, we identified the 8,671 men with metastatic disease at diagnosis.

Androgen deprivation therapy

We used claims data to ascertain receipt of androgen deprivation therapy, including GnRH agonists and bilateral orchiectomy (Appendix), early (within 4 months of diagnosis),

delayed (after 4 months from diagnosis), or not at all. Duration of treatment with GnRH agonists was calculated by summing the number of 1-month equivalent doses; for men who underwent orchiectomy, we summed the number of months from the time of surgery onward.

Survival

Men were observed from the date of diagnosis until December 31, 2003, or sooner if they died or disenrolled from parts A and B of fee-for-service Medicare. We ascertained date of death from Medicare enrollment data.

Patient and tumor characteristics

We documented each man's age, race, Hispanic ethnicity, marital status, urban residence, SEER region, year of diagnosis, tumor grade, census-tract level income (categorized in quartiles within registries), and comorbid illness based on Diagnostic Cost Groups (DCGs),¹⁵ a risk-adjustment tool for predicting future costs and disease burden for Medicare beneficiaries based on 182 clinical diagnostic categories from inpatient and ambulatory claims (compared to 18 for the Charlson score¹⁶). DCGs are highly predictive of mortality for Medicare beneficiaries with cancer¹⁷ and myocardial infarction.¹⁸ We calculated summary DCG scores (categorized in quartiles; excluding prostate cancer codes) based on the 12-months before diagnosis.

Analyses

We used Chi-square tests to assess bivariate associations of patient characteristics with receipt of GnRH agonist or orchiectomy early, delayed, or not at all. We used multinomial logistic regression models to assess characteristics associated with receiving early vs. delayed vs. no androgen deprivation therapy. Independent variables included the patient and tumor characteristics described above (categorized as in Table 1). We calculated adjusted rates of diagnosis at each stage for our patient population using a standardized regression approach.¹⁹

We next used Cox proportional hazards regression models to assess the association between patient and tumor characteristics among men diagnosed with metastatic prostate cancer, including the same covariates as above. We then added a time-varying treatment variable reflecting receipt of androgen deprivation to assess the association between this therapy and overall survival and to test if this explained any differences in survival based on patient characteristics. The time-varying treatment variables allowed men to contribute information to the control group when not on treatment and to the treatment groups (GnRH agonist or orchiectomy) when on treatment (nearly all men were treated continuously once treatment began). Men treated with GnRH agonists were considered continuously treated for 6 months after each dose of GnRH agonist (because hypogonadism may persist for prolonged periods after discontinuation of a GnRH agonist).^{20, 21}

We next tested for a survival benefit from early vs. late hormonal therapy using a term for the interaction of hormone therapy and an indicator variable for whether the patient was treated with early vs. late hormonal therapy (if a patient had not yet received any therapy then to ensure that only information from the past was used for predictions in the next time period, both the early and the late hormone therapy variables were coded as "none").

In sensitivity analyses, we restricted the cohort to the 7,234 men who survived and were continuously enrolled in fee-for-service Medicare Parts A and B for at least 4 months to be sure the cohort survived long enough to obtain outpatient care for their prostate cancer, and thus have the opportunity to be treated with androgen deprivation therapy. All tests of

statistical significance were two-sided. We conducted analyses using SAS statistical software, version 8.2 (SAS Institute, Inc., Cary, North Carolina). Multinomial regression models were conducted using Stata, version 9 (StataCorp LP, College Station, Texas). The Harvard Medical School Committee on Human Studies approved the study protocol.

Results

The mean age of the cohort was 77.9 (SD=7.0) years. Most men (60%) were married at the time of diagnosis, 14% were black, 5% were of Hispanic ethnicity, and 44% had poorly differentiated or undifferentiated cancers.

Receipt of androgen deprivation

Overall, 69.5% of men with metastatic prostate cancer at diagnosis were treated with a GnRH agonist or orchiectomy within 4 months of diagnosis (early treatment), 7.3% received their first dose of GnRH agonist or orchiectomy after 4 months from diagnosis (delayed treatment), and 23.3% were not treated with androgen deprivation therapy before death. Men treated with early GnRH agonist therapy were treated for a mean (SD) of 20.8 (20.7) months, similar to the duration of treatment for men who received delayed treatment (mean (SD)=20.7 (24.2) months).

Unadjusted rates of early, late, or no GnRH agonist treatment or orchiectomy by patient and tumor characteristics are presented in Table 1. Rates of early hormonal therapy were lowest among men aged ≥ 85 compared to men of other ages, black men (compared to non-black men), and unmarried men (compared to married men). Black men had higher rates of delayed hormonal therapy than others. The median number of days to first hormonal therapy was 23 days for white men (mean (SD)=64 (203) days) and 28 days for black men (mean (SD)=103 (241) days). Rates of hormonal therapy varied by SEER region, and rates of early use were higher for men in the highest area-level income quartiles (compared to lower quartiles). Men with less-well differentiated cancers were more likely to be treated with androgen deprivation therapy early. Unadjusted rates of treatment varied over time without a clear pattern.

In adjusted analyses (Table 2), race was most strongly related to receipt of androgen deprivation therapy, with black men substantially less likely than white men to receive early androgen deprivation therapy (adjusted rate=58.3% vs. 71.0% of white men), and more likely to receive delayed hormonal therapy (12.7% vs. 6.2%) or no hormonal therapy (29.0% vs. 22.4%). Of those patients that did not receive early androgen deprivation therapy, 21.0% of whites and 30% of blacks subsequently received delayed hormonal therapy. Men aged 85 and older were less likely than other men to be treated with hormonal therapy, as were men who were unmarried (compared to married men). Rates of hormonal therapy varied by SEER region, with highest rates in New Jersey, Connecticut, and Georgia registries and lowest rates in Detroit. Men with poorly- or undifferentiated tumors were more likely to be treated with androgen deprivation therapy than men with well or moderately differentiated tumors and men with moderate levels of comorbid illnesses were also more likely than those with the fewest or the most comorbid illnesses to receive this therapy. Rates of use of androgen deprivation therapy varied slightly over time after adjustment for patient and tumor characteristics, although this difference was not statistically significant ($P=.054$). We found no association between use of androgen deprivation therapy and year of diagnosis when we considered this as a continuous variable ($P=.70$).

Survival

When we examined survival among men diagnosed with metastatic prostate cancer, we found that men who were older (vs. younger), unmarried (vs. married), and men with higher comorbidity scores had worse survival (Table 3). Men in the highest income quartile had better survival than men in the lowest quartile. Survival also varied by tumor grade as well as region and residence in a major metropolitan area vs. other areas. We found no association between black (vs. white) race and survival after controlling for patient demographic and clinical characteristics (Table 3). Men diagnosed more recently were at higher risk of death (HR for each year=1.01, 95% CI 1.00 to 1.02).

In a second survival model that also included a time-varying variable for receipt of androgen deprivation therapy within 4 months of diagnosis, we found that receipt of androgen deprivation therapy was associated with improved survival (adjusted hazard ratio .69, 95% CI .66 to .73; Table 3, right column). Inclusion of this variable in the model did not influence the association between other factors and survival. In the model that also included a term for the interaction of androgen deprivation therapy and initiation of this therapy early (vs. delayed), we found no difference in the benefit of hormone therapy based on timing of initiation (regression coefficient=.06, $P=.58$).

We repeated all analyses restricting the cohort to the 7,234 men who survived and were continuously enrolled in fee-for-service Medicare Parts A and B for at least 4 months, and results were similar (data not shown).

Discussion

In a cohort of older men diagnosed with metastatic prostate cancer in the U.S., approximately two-thirds of men were treated with early hormone therapy, another 7% with delayed hormone therapy, and nearly one-quarter with no hormonal therapy. Although other studies have demonstrated marked increases in use of hormone therapy for men with non-metastatic disease since the early 1990s^{8–10} for both white and black men,²² we did not observe similar increases in use of androgen deprivation therapy for metastatic disease during this time. Receipt of hormonal therapy was associated with improved survival, an effect that did not vary by timing of initiation of therapy. Although black men compared to white men were particularly likely to receive no hormonal therapy, the racial differences in use of this therapy did not contribute to racial differences in survival.

The primary benefits of androgen deprivation therapy are palliative: less pain and fewer pathological fractures, spinal cord compressions, and episodes of ureteral obstruction.²³ Whether hormonal therapy for advanced prostate cancer influences survival has been less clear.⁶ We observed that men treated with hormonal therapy had better survival than men who did not receive this treatment, similar to another recent report.²⁴ Importantly, the survival benefit did not vary by the timing of initiation of therapy.

The observational nature of our study limits our ability to conclude causality. Men who died soon after diagnosis may not have had the same opportunity as other men to receive hormonal therapy. Nevertheless, we accounted for censored observations using survival analysis methods, and we still observed a survival benefit associated with hormonal therapy (with no benefit of early over late therapy) when we restricted the cohort to men surviving at least 4 months. The lack of benefit for early vs. late hormone therapy suggests that delaying hormonal therapy, particularly for men who are asymptomatic, is unlikely to be harmful. This is particularly important in light of data suggesting that hormonal therapy may be associated with an increased risk of diabetes and cardiovascular disease.²⁵ Despite this

potential for increased non-prostate morbidity, we did not observe an increase in non-prostate cancer deaths.

Prior studies suggest that white and black men derive equivalent benefits from androgen deprivation therapy.^{26, 27} Thus, our finding of disparities in treatment, which is consistent with other data showing less aggressive treatment for minority patients with prostate cancer,²⁸ raises the possibility that use of this therapy might impact outcomes for these men. Yet, despite survival statistics suggesting that black men with prostate cancer have worse survival than white men,² we found no difference between race or ethnicity and survival in our population-based cohort of men with metastatic cancer at diagnosis after adjusting for patient and tumor characteristics. This finding is consistent with other studies demonstrating similar survival for black and white men with prostate cancer once adjusting for stage, grade, and age^{29–31} or socioeconomic factors³² or access to medical care.³³ Despite the survival advantage we observed with use of hormonal therapy, the racial differences in use did not translate into survival differences, suggesting that physicians may be appropriately selecting patients for delayed or no therapy.

We also observed that unmarried men and men living in certain regions of the U.S., such as Detroit, were less likely than other men to receive androgen deprivation therapy. These findings are consistent with other studies demonstrating treatment differences for individuals without a spouse or partner^{34, 35} and substantial geographic variations in treatment.³⁶ Future efforts to better understand care for men with prostate cancer should target these nonclinical factors, in addition to race, that contribute to variations in care. Nevertheless, although androgen deprivation was associated with greater survival among men in this cohort, receipt of androgen deprivation therapy did not explain survival differences based on age, marital status, comorbid illness, or area of residence.

Our study has some limitations. First, we had no information about patients' preferences for hormone therapy, nor did we have information about the presence of symptoms, which is likely to be a strong driver of receipt of early versus late hormonal therapy. In addition, we had no information about PSA levels, although PSA values were not widely used to guide therapy for *metastatic* disease during the period of study. Second, our analysis is observational and we therefore cannot be sure whether the survival advantages among men who received hormonal therapy were a result of the hormonal therapy or because men who died quickly did not have the same opportunity as other men to be treated with hormonal therapy. However, because we used appropriate statistical methods to account for censored observations and we found similar results when we restricted the cohort to men surviving at least 4 months, we believe that this is unlikely to be a major problem. Second, we studied older men living in regions of the U.S. with SEER registries, so the generalizability of our findings to younger men and those living in different areas requires further study. Older men account for the majority of prostate cancer diagnoses; however, and this population-based sample included cancer patients from areas representing 14% of the U.S. population. Third, SEER-Medicare data do not include information about oral medications, and therefore, we could not ascertain use of oral antiandrogens or estrogens. However, treatment with antiandrogen monotherapy is not approved for prostate cancer in the U.S., so few men likely received such therapy. Estrogens are an acceptable alternative medical therapy for metastatic prostate cancer, but because of their greater toxicity, they are not recommended over GnRH agonists in this setting.

In conclusion, a large minority of older American men diagnosed with metastatic prostate cancer receive delayed or no hormonal therapy, particularly black men. Despite substantial increases in use of hormonal therapy for non-metastatic prostate cancer during the same study period, we did not observe similar increases in use among men with metastatic cancer

for whom the benefits of treatment have been better studied. Receipt of androgen deprivation therapy was associated with prolonged survival; however racial differences in use of this treatment did not contribute to racial differences in survival, which were not evident after controlling for patient and tumor characteristics.

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Table 1

Patient characteristics associated with receiving androgen deprivation, unadjusted

	N	% receiving GnRH agonist or orchiectomy within 4 months	% receiving GnRH agonist or orchiectomy after 4 months	% not receiving GnRh agonist or orchiectomy	P value
Total	8,671	69	7	23	
Age in years					<.001
66–69	1,149	71	9	20	
70–74	1,900	73	8	19	
75–79	2,134	73	7	19	
80–84	1,879	71	6	23	
85 and older	1,609	58	6	36	
Race					<.001
White	6,911	72	6	22	
Black	1,245	54	12	34	
Other	473	73	8	19	
Unknown	42	81	7	12	
Hispanic ethnicity					.38
No	8,170	69	7	23	
Yes	429	69	9	22	
Unknown	72	76	7	17	
Marital status					<.001
Unmarried	3,078	64	7	29	
Married	5,174	73	8	20	
Unknown	419	71	7	23	
Residence					<.001
Major metropolitan area	4,644	66	8	25	
Metropolitan county	2,341	73	6	21	
Urban	636	73	7	20	
Less urban	863	72	6	22	
Rural	187	71	7	22	
SEER region					<.001
California	2,331	71	7	23	

	N	% receiving GnRH agonist or orchiectomy within 4 months	% receiving GnRH agonist or orchiectomy after 4 months	% not receiving GnRh agonist or orchiectomy	P value
Connecticut	977	74	6	20	
Detroit	1,193	57	10	33	
Hawaii	295	74	7	19	
Iowa	1,261	74	6	19	
New Mexico	350	67	8	25	
Seattle	704	70	8	21	
Utah	374	72	6	21	
Atlanta	334	66	7	27	
Rural Georgia	41	66	0	34	
Kentucky	204	74	3	23	
Louisiana	223	65	5	30	
New Jersey	384	73	7	20	
Median household income in Census tract of residence					<.001
Quartile 1 (lowest)	2,100	65	8	27	
Quartile 2	2,125	69	8	23	
Quartile 3	2,124	71	6	22	
Quartile 4 (high)	2,140	72	7	21	
Unknown	182	72	7	21	
Tumor grade					<.001
Well differentiated	165	67	7	26	
Moderately differentiated	2,221	73	10	17	
Poorly differentiated/undifferentiated	3,846	79	7	15	
Unknown	2,439	52	6	42	
DCG comorbidity					<.001
Quartile 1 (lowest)	2,223	71	9	20	
Quartile 2	2,152	73	7	21	
Quartile 3	2,130	70	7	23	
Quartile 4 (high)	2,166	64	7	29	
Year of diagnosis					.005
1992	1,244	71	7	21	
1993	967	68	8	24	

	N	% receiving GnRH agonist or orchiectomy within 4 months	% receiving GnRH agonist or orchiectomy after 4 months	% not receiving GnRh agonist or orchiectomy	P value
1994	808	71	7	23	
1995	734	70	8	22	
1996	611	65	9	26	
1997	599	68	5	27	
1998	562	67	8	25	
1999	510	67	11	22	
2000	876	71	7	22	
2001	871	71	6	24	
2002	889	72	5	23	

Percentages may not add to 100% due to rounding.

Table 2

Adjusted rates of receiving early, delayed, or no androgen deprivation

	Adjusted % receiving androgen deprivation therapy within 4 months	Adjusted % receiving androgen deprivation therapy after 4 months	Adjusted % not receiving androgen deprivation therapy	P value
Age in years				<.001
66–69	71.1	8.6	20.3	
70–74	72.5	7.1	20.4	
75–79	72.2	7.3	20.5	
80–84	69.5	6.9	23.6	
85 and older	61.6	6.4	31.9	
Race				<.001
White	71.3	6.3	22.4	
Black	58.3	12.7	29.0	
Other	70.6	8.2	21.1	
Unknown	76.4	6.3	17.3	
Hispanic ethnicity				.34
No	69.6	7.0	23.4	
Yes	66.3	9.9	23.8	
Unknown	71.0	9.4	19.5	
Marital status				<.001
Unmarried	70.8	6.1	23.1	
Married	71.3	7.6	21.1	
Unknown	66.3	6.8	26.9	
Residence				.18
Major metropolitan area	67.4	7.6	25.0	
Metropolitan county	71.7	6.3	22.0	
Urban	73.0	7.2	19.8	
Less urban	71.9	6.7	21.4	
Rural	69.2	9.1	21.7	
SEER region				<.001
California	71.5	6.4	22.1	
Connecticut	73.1	7.3	19.7	
Detroit	61.7	8.6	29.7	
Hawaii	66.9	7.5	25.6	
Iowa	69.9	7.6	22.5	
New Mexico	64.6	8.2	27.2	
Seattle	70.4	8.7	20.9	
Utah	67.5	7.9	24.7	
Atlanta	72.2	5.4	22.4	
Rural Georgia	76.4	1.0	23.6	
Kentucky	71.1	4.3	24.6	
Louisiana	65.9	5.3	28.9	

	Adjusted % receiving androgen deprivation therapy within 4 months	Adjusted % receiving androgen deprivation therapy after 4 months	Adjusted % not receiving androgen deprivation therapy	P value
New Jersey	74.1	7.6	18.3	
Median household income in Census tract of residence				<.09
Quartile 1 (lowest)	67.9	6.7	25.4	
Quartile 2	68.9	7.8	23.3	
Quartile 3	70.0	6.5	23.5	
Quartile 4 (highest)	70.6	8.0	21.4	
Unknown	71.8	6.9	21.3	
Tumor grade				<.001
Well differentiated	67.4	6.5	26.0	
Moderately differentiated	72.2	9.6	18.2	
Poorly differentiated/undifferentiated	78.5	6.3	15.2	
Unknown	53.4	6.6	40.0	
DCG comorbidity				<.001
Quartile 1 (lowest)	65.8	8.1	26.1	
Quartile 2	71.6	6.8	21.6	
Quartile 3	71.8	7.1	21.1	
Quartile 4 (high)	68.5	6.6	24.9	
Year of diagnosis				.054
1992	70.1	7.0	22.9	
1993	67.6	7.9	24.6	
1994	70.4	6.6	22.9	
1995	69.7	7.6	22.7	
1996	65.9	8.5	25.6	
1997	68.3	5.0	26.7	
1998	68.7	7.7	23.5	
1999	67.7	10.7	21.6	
2000	71.2	7.5	21.3	
2001	69.9	6.2	23.9	
2002	71.9	5.6	22.5	

* Using multinomial logistic regression to control for all variables in the table.

Table 3

Adjusted hazard ratio of death after diagnosis of metastatic prostate cancer

	Adjusted HR (95% CI) of dying during follow-up in model not including androgen deprivation variable	Adjusted HR (95% CI) of dying during follow-up in model including androgen deprivation variable
Androgen deprivation therapy	-	.69 (.66 to .73)
Age in years		
66–69	Reference	Reference
70–74	1.09 (.99 to 1.19)	1.09 (.99 to 1.19)
75–79	1.28 (1.17 to 1.46)	1.3 (1.19 to 1.42)
80–84	1.47 (1.34 to 1.62)	1.50 (1.36 to 1.65)
85 and older	1.76 (1.60 to 1.94)	1.75 (1.59 to 1.93)
Race		
White	Reference	Reference
Black	.99 (.91 to 1.07)	.95 (.87 to 1.03)
Other	.81 (.71 to .94)	.82 (.71 to .94)
Unknown	.52 (.29 to .94)	.51 (.28 to .93)
Hispanic ethnicity		
No	Reference	Reference
Yes	1.00 (.88 to 1.13)	.98 (.86 to 1.10)
Unknown	.80 (.53 to 1.20)	.80 (.53 to 1.19)
Marital status		
Unmarried	Reference	Reference
Married	.87 (.83 to .92)	.88 (.84 to .93)
Unknown	.74 (.65 to .84)	.73 (.64 to .83)
Residence		
Major metropolitan area	Reference	Reference
Metropolitan county	.92 (.84 to 1.00)	.93 (.85 to 1.02)
Urban	.85 (.75 to .95)	.86 (.76 to .97)
Less urban	.81 (.72 to .92)	.83 (.73 to .94)
Rural	.94 (.78 to 1.15)	.96 (.79 to 1.16)
SEER region		
California	Reference	Reference
Connecticut	1.24 (1.12 to 1.36)	1.24 (1.13 to 1.37)
Detroit	1.21 (1.11 to 1.31)	1.17 (1.07 to 1.27)
Hawaii	.94 (.77 to 1.13)	.91 (.75 to 1.10)
Iowa	1.33 (1.19 to 1.50)	1.33 (1.19 to 1.49)
New Mexico	1.37 (1.18 to 1.60)	1.36 (1.16 to 1.58)
Seattle	1.14 (1.03 to 1.26)	1.14 (1.03 to 1.26)
Utah	1.13 (.97 to 1.30)	1.12 (.97 to 1.30)
Atlanta	1.32 (1.15 to 1.50)	1.34 (1.18 to 1.53)
Rural Georgia	1.36 (.96 to 1.93)	1.30 (.92 to 1.85)
Kentucky	1.33 (1.08 to 1.63)	1.36 (1.10 to 1.66)

	Adjusted HR (95% CI) of dying during follow-up in model not including androgen deprivation variable	Adjusted HR (95% CI) of dying during follow-up in model including androgen deprivation variable
Louisiana	1.32 (1.08 to 1.61)	1.31 (1.08 to 1.60)
New Jersey	1.25 (1.08 to 1.43)	1.26 (1.10 to 1.45)
Median household income in Census tract of residence		
Quartile 1 (lowest)	Reference	Reference
Quartile 2	.97 (.91 to 1.04)	.97 (.91 to 1.04)
Quartile 3	1.03 (.96 to 1.11)	1.04 (.97 to 1.12)
Quartile 4 (high)	.90 (.83 to .97)	.90 (.84 to .97)
Unknown	.89 (.75 to 1.05)	.90 (.76 to 1.07)
Tumor grade		
Well differentiated	.59 (.49 to .71)	.56 (.47 to .67)
Moderately differentiated	.69 (.65 to .73)	.67 (.63 to .71)
Poorly differentiated/undifferentiated	Reference	Reference
Unknown	1.44 (1.36 to 1.52)	1.37 (1.29 to 1.45)
DCG comorbidity		
Quartile 1 (lowest)	Reference	Reference
Quartile 2	.94 (.87 to 1.01)	.95 (.88 to 1.02)
Quartile 3	1.05 (.97 to 1.14)	1.08 (.99 to 1.16)
Quartile 4 (high)	1.41 (1.30 to 1.52)	1.43 (1.32 to 1.54)
Year of diagnosis	1.01 (1.00 to 1.02)	1.01 (1.00 to 1.02)

Appendix

Codes used to define GnRH agonist use and orchiectomy

Diagnosis or Procedure	HCPCS	CPT	ICD-9 Procedure
Leuprolide injection	J9217, J9218, J9219, J1950		
Goserelin injection	J9202		
Triptorelin	J3315		
Orchiectomy		54520, 54521, 54522, 54530, 54535, 54690, 49510	62.3, 62.4, 62.41, 62.42