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Survival Following Primary Androgen Deprivation Therapy among Men with Localized Prostate Cancer

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Abstract

Context—Despite a lack of data, increasing numbers of patients are receiving primary androgen deprivation therapy (PADT) as an alternative to surgery, radiation or conservative management for the treatment of localized prostate cancer.

Objective—Evaluate the association between PADT and survival in elderly men with localized prostate cancer.

Main Outcome Measures—Cancer-specific and overall survival.

Design—Population-based cohort study of 19,271 men who did not receive definitive local therapy for T1-T2 prostate cancer. Instrumental variable analysis was used to address potential biases associated with unmeasured confounding variables.

Setting—Medicare patients aged ≥ 66 years diagnosed in 1992-2002 within predefined US geographical areas.

Results—Even though 41% of the population (median age 77) received PADT, PADT was associated with somewhat worse 10-year prostate cancer-specific survival (80.1% vs. 82.6%, hazard ratio [HR] 1.17; 95% CI 1.03–1.33) and no improvement in 10-year overall survival (30.2% vs. 30.3%, HR 1.00; 95% CI 0.96–1.05) compared to conservative management. However, in a pre-specified subset analysis, PADT use in men with poorly-differentiated cancer was associated with

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CONFLICT OF INTEREST STATEMENT

I, Grace L. Lu-Yao, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. The authors have no conflicts of interest.

marginally improved prostate cancer-specific survival (HR 0.84; 95% CI 0.70–1.00, $P=0.05$) but not overall survival (HR 0.92; 95% CI 0.84 – 1.01).

Conclusions—Primary androgen deprivation therapy is not associated with improved survival among the majority of elderly men with localized prostate cancer when compared with conservative management.

Keywords

prostatic neoplasm; Medicare; SEER program; antineoplastic agents; hormonal

Introduction

Among men, prostate cancer is the most common non-skin cancer and the second most common cause of cancer death.¹ For the great majority of men with incident prostate cancer (~85%), disease is diagnosed at localized (T1-T2) stages,² and standard treatment options include surgery, radiation or conservative management (ie., deferral of treatment until necessitated by disease signs or symptoms).

Although not standard or sanctioned by major groups or guidelines, a growing number of healthcare providers and patients have turned to primary androgen deprivation therapy (PADT) as an alternative to surgery, radiation or conservative management, especially among older men.^{3, 4} For example, in a 1999–2001 survey, PADT had become the second most common treatment approach, after surgery, for localized prostate cancer.³

Randomized clinical trials support the use of early androgen deprivation therapy as an adjunct to surgery or radiation for patients with high-risk cancer.^{5–10} In one study, early ADT reduced mortality by ~50% when used with radiation in high-risk disease (poorly-differentiated T1-T2, or T3-T4)^{5, 8} while in another study mortality was reduced by ~60% in patients with nodal disease identified at surgery.⁹ Consequently, many investigators have concluded that the early use of ADT is appropriate for patients with higher- or intermediate-risk disease in conjunction with local therapy, but studies that assess the use of ADT alone, as primary therapy, or in lower-risk settings are sparse.

The importance of determining the appropriate application of androgen deprivation therapy has recently increased in urgency, as a growing body of literature now demonstrates that chronic ADT use has been associated with ~10–50% increases in the risks of fracture, diabetes, coronary heart disease, myocardial infarction and sudden cardiac death, in addition to adverse effects on fat mass, cholesterol, and quality of life.^{11–16} There were 500% increases in the risk of gynecomastia and hot flashes in the Prostate Cancer Outcomes Study (PCOS), and a 267% increase in impotence was observed after one year of treatment.¹⁷ Finally, medical ADT is costly. The costs associated with ADT medication use in the US exceeded 1 billion dollars in 2001 and ADT drugs represented the second highest Medicare Part B drug expenditure.¹⁸

A randomized clinical trial would provide the data needed to determine the utility of PADT vs. conservative management in localized disease. Unfortunately, such a trial would take more than a decade to complete and, given current treatment practices and resources, would probably not be feasible. Observational studies are often employed to provide insight under such circumstances, although they may be more subject to biases.

Recently instrumental variable analytical (IVA) techniques have been applied successfully to observational medical studies^{19, 20} to minimize many of these biases so that the results of randomized clinical trials may often be mimicked with observational data.²¹ Instrumental variable analysis is a method of capturing the random component of patient treatment choice

and using it to balance treatment groups with respect to measured and unmeasured confounders. We used this approach to assess the association between PADT and disease-specific and overall survival in men with T1-T2 prostate cancer.

Materials and Methods

Data sources

Data for this study were obtained from the population-based Surveillance, Epidemiology and End Results (SEER) program database and linked Medicare files. The SEER regions encompass approximately 14% of the US population before 2001 and 26% thereafter. The Medicare database covers approximately 97% of US persons aged ≥ 65 years and linkage to the SEER database was complete for approximately 93% of the patients.²² Informed consent was waived by the IRB because the data did not contain personal identifiers.

Study participants

The study cohort consisted of men (aged ≥ 66 years) who were SEER residents and diagnosed with T1-T2 cancer in 1992-2002 (N = 89,877). Men who died within 180 days of diagnosis were excluded (N = 1,761) (inclusion of patients dying within 180 days did not significantly alter the results). Those receiving definitive local therapy (eg., prostatectomy or radiation) within 180 days of diagnosis were also excluded (N = 31,485). To ensure that the database accurately documented the patient's clinical course, patients without both Medicare Part A (hospitalization) and Part B (physician and outpatient) as their primary health insurance coverage during the study period were excluded (N=33,987). Those with missing data (N=2,995), unknown cancer grade (N=255) or initiation of ADT before cancer diagnosis (N=123) were also excluded.

Primary androgen deprivation therapy

Patients undergoing PADT received androgen deprivation therapy as primary cancer therapy (eg., no surgery or radiation) in the first 180 days following diagnosis. Conservative management patients were those that did not receive surgery, radiation or PADT during this time. A previous study demonstrated that patients generally start primary therapy within 6 months of diagnosis.²³ Utilizing a previously described algorithm,¹¹ Medicare physician, inpatient and outpatient claims were used to identify orchiectomy (Healthcare Common Procedure Coding System [HCPCS] codes 54520, 54521, 54522, 54530 or 54535 or ICD-9 code 624) and the use of luteinizing hormone releasing hormone (LHRH) agonists (HCPCS codes J1950, J9202, J9217, J9218, or J9219). LHRH agonists and orchiectomy were combined because previous studies have shown these treatments to be essentially equivalent.²⁴

Study endpoints and covariates

Overall and prostate cancer-specific survival was available through December 31, 2006 and December 31, 2004, respectively. Underlying cause of death was determined from data in the SEER records. Studies have shown that cause of death in the SEER data confirm information available in medical records in 87 to 88% of cases.^{25, 26}

Cox model covariates included age at diagnosis, race, zip code income, SEER region, urban area, marital status, cancer grade, clinical T stage, Charlson comorbidity score, and year of diagnosis. Charlson score, a powerful predictor of longevity in men with localized prostate cancer²⁷⁻²⁹ was derived from Medicare claims during the year prior to prostate cancer diagnosis using a validated algorithm.^{30, 31} For cancer grade, Gleason 2-4, 5-7 and 8-10 corresponded to well-differentiated, moderately-differentiated, and poorly-differentiated

disease, respectively. We used clinical extension information provided by SEER to determine cancer stage (T1, T2).

Instrumental variable analysis

A health service area (HSA) is defined as one or more counties that are relatively self-contained with respect to the provision of routine hospital care.³² The instrumental variable was constructed by first calculating the proportion of patients who received PADT in each HSA. Because some HSAs had small numbers of prostate cancer cases, each HSA with <50 cases was combined with the nearest (in terms of distance between geographic centers) HSA with ≥ 50 cases. The threshold of ≥ 50 cases was chosen because lower thresholds were associated with more imbalances in patient characteristics in high- and low-PADT utilization areas. The algorithm produced 66 utilization areas. High- and low-use areas corresponded to the top and bottom tertiles of PADT utilization and were used as the (binary) instrumental variable for the (binary) treatment assignment.

Previous studies have demonstrated that PADT use is highly influenced by non-medical factors,³³ with tumor characteristics accounting for only 9.7% of the total variance in use.³⁴ Our data confirmed that PADT use varied widely across HSAs, a key requirement of an instrumental variable. An instrumental variable must influence outcomes primarily through its correlation with treatment status and not through any other independent effect. We verified this assumption by comparing baseline characteristics including age at diagnosis, cancer stage and grade at diagnosis, and found them comparable between low- and high-PADT areas.

Statistical analyses

Instrumental variable analytical (IVA) methods based on the Rubin Causal Model (RCM)²¹ were used to account for both measured and unmeasured (e.g., PSA, family history, diet, weight, etc.) confounders. Covariates in the IVA models included age, race, comorbidity status, cancer stage, cancer grade, income status, urban residence, marital status, and year of diagnosis. All IVA results were derived from the same models. We examined all the required assumptions to ensure the validity of our instrumental variable analysis. Traditional Cox proportional hazards model results were also reported in Table 3 for comparison to the IVA results. Analyses were conducted using SAS version 9.1 and R version 2.7.0.(R foundation for statistical Computing, Vienna, Austria). Cancer grade was a predefined measured covariate. We calculated PADT utilization for each cancer grade so that it was not necessary to assume that the patterns of PADT utilization were the same for all cancer grades within the same area. Results for well-differentiated cancer (Gleason 2–4) are not shown separately because results were unstable due to the limited sample size. Patients that differ in the likelihood of receiving PADT are compared and the treatment effect on the “marginal” population is estimated. The marginal effect (ie., “local average treatment effect”)²¹ of PADT was calculated as

$$\text{IV Estimate} = \Delta = \frac{\text{Adjusted Outcomes}_{\text{Hi}} - \text{Adjusted Outcomes}_{\text{Lo}}}{\text{Pr}(\text{PADT}|\text{Hi}) - \text{Pr}(\text{PADT}|\text{Lo})}$$

where,

Hi = a geographic area in the upper tertile of PADT use

Lo = a geographic area in the lower tertile of PADT use

The terms are thus,

Pr(PADT Hi/Low) =	estimated probability of PADT use among men who had localized prostate cancer and did not have surgery or radiation as their primary cancer therapy in high/low use region.
Adjusted Outcomes _{Hi} / Adjusted outcomes _{Lo} =	estimated survival probability at a particular time (eg., 5- or 10-year) among men who had localized prostate cancer and did not have surgery or radiation as their primary cancer therapy in high/low use region.

The terms are thus,

To compute the population-adjusted survival curves, we substituted the population means (for continuous covariates) into the proportional hazards model for each combination of the categorical covariates to derive an adjusted hazard function. Then a weighted average of these adjusted hazard functions was computed with weights proportional to the numbers of subjects in each class. Finally, the population-adjusted survival curve was computed from the weighted hazard function.³⁵ Estimates of 5- and 10-year overall and cancer-specific survival for men at average risk were derived from these adjusted curves. Confidence intervals were obtained by computing these adjusted survival curves for each of 10,000 bootstrap samples of the original data. *P* values and 95% confidence intervals were derived from the bootstrap estimates. Testing was 2-sided with an alpha level of 5%. Analyses were repeated for different age groups but results were similar across age groups and the interaction between age and PADT use was not significant; therefore, all age groups were combined.

Power calculations for determining the difference in survival between high- and low-use health service areas were carried out using simulations. Overall, the study had 80% power to detect a 7% difference in overall survival between high- and low-use PADT areas.

Results

Baseline characteristics

The total cohort consisted of 19,271 men aged ≥ 66 years with localized prostate cancer diagnosed in 1992-2002. By definition, none of these men received definitive local therapies (eg., radiation or surgery) in the first 180 days following diagnosis; 41% received PADT. The median age of the study cohort was 77 years and the median follow-up for overall survival was 81 months. As expected, patients receiving PADT and patients managed conservatively differed in many characteristics suggesting that there could be differences in unmeasured characteristics that might not be adjusted for by conventional statistical methods (Table 1).

PADT utilization (Table 2) varied widely across health service areas (31% to 53%). When we extended the window for defining PADT from 180 days to 18 months, the high/low use patterns remained the same (Table 2). Duration of use was also longer in high-PADT use areas.

Survival outcomes

There were 1,560 prostate cancer deaths and 11,045 deaths from all causes in the study cohort. Unadjusted and adjusted prostate cancer-specific and overall survival were *worse* for *PADT treated* patients when analyses were conducted using a traditional Cox multivariate model (Table 3). The Cox approach, however, is unable to adjust for unmeasured confounders and selection biases (eg., higher risk patients may be preferentially selected for PADT thus yielding apparently adverse outcomes for this group). When instrumental variable analysis was utilized (Tables 3, 4, 5 and Figure 1), PADT was still associated with increased unadjusted and adjusted cancer-specific mortality (HR 1.17, 95% CI 1.03–1.33), but there was not associated effect on unadjusted, and adjusted median overall survival (82 months vs. 82 months, HR 1.00, 95% CI 0.96–1.05). Results were similar when analyses were restricted to men with comorbidity scores of 0 or without other cancers, suggesting that the results were independent of comorbidity.

In pre-planned analyses by cancer grade, PADT was associated with either no effect, or an adverse effect on prostate cancer-specific and overall survival for poorly- or moderately-differentiated cancer, respectively, in unadjusted and adjusted Cox analyses. Evaluation by IVA, however, revealed a borderline improvement in unadjusted and adjusted median prostate cancer-specific survival in patients with poorly-differentiated cancer (Table 3, Figure 1) although the associated effect on median overall survival was not significant (57 vs. 54 months [95% C.I. 56 –61 and 53 – 57, respectively]). Similar patterns were observed for 5- and 10-year prostate cancer-specific and overall survival (Table 4). The marginal effect of PADT on cancer-specific survival was 15.1% at 5-years and 24.5% at 10 years for men with poorly-differentiated cancer (Table 5). Similar benefit, however, was not observed in men with moderately-differentiated cancer (Table 5).

Duration of treatment and survival

Most patients received PADT for extended periods. Among PADT users, only 1.1% received one month of treatment while 75% received PADT for at least 18 months and 50% received PADT for more than 30 months. Longer durations of PADT utilization were associated with lower overall and cancer-specific survival among 5,826 PADT users who survived at least 3 years (Table 6). Similar patterns were observed for all cancer grades. Sensitivity analyses restricted to patients with comorbidity scores of 0 yielded similar results.

COMMENT

Despite the widespread use of PADT in localized (T1-T2) prostate cancer,^{3, 4} there is little information regarding the clinical outcomes associated with this practice. Our study was designed to evaluate the association between PADT and prostate cancer-specific and overall survival in men who did not initially receive definitive therapy (eg., surgery or radiation) for localized prostate cancer.

Utilizing instrumental variable analysis as one of the best available means of controlling for both measured and unmeasured confounding variables, we found no overall survival benefit for elderly men with localized prostate cancer receiving PADT. Results obtained with a traditional Cox model that adjusts only for measured confounding factors differed from those with the instrumental variable approach. These observations suggest that there is significant unaccounted residual bias associated with traditional analytical methods in this setting and that the instrumental variable approach may be particularly advantageous. In addition, one potential advantage of this study over clinical trials is that it includes “real-world” patients that would often be excluded from clinical trials even though these patients would receive the treatment in practice.

An interesting outcome of our study was the observation that cancer-specific survival, but not overall survival, appeared worse for men with lower risk cancer treated with PADT. This observation had also been previously documented in a randomized study of PADT in men with T0-T4 disease.³⁶ The authors suggested several possible explanations for this finding, including competing causes of death, misclassification, and statistical variation.³⁶ Another possibility could be that suppression of moderately- or well-differentiated cells not destined to harm a patient’s overall survival may allow for the establishment or overgrowth of more rapidly growing malignant clones (as seen in preclinical models)^{37–39} that increase the probability of death due to prostate cancer instead of a competing cause of death. As is evident from Figures 1A and 1B, the likelihood of death from competing causes normally exceeds the risk of death from prostate cancer in this population; this balance may be altered if PADT preferentially allows for the establishment or overgrowth of a more malignant fraction of a tumor.

Our study had some limitations. The study was limited to men aged ≥ 66 years and the results could differ for younger men. The SEER-Medicare database does not capture information on antiandrogen use. Therefore, patients utilizing antiandrogens only might be misclassified into the conservative management cohort and, because a previous study⁴⁰ suggested that antiandrogens may result in adverse outcomes in these patients, it is possible that the conservative management group performed unusually poorly. However, previous data from another large database (CaPSURE)⁴¹ showed that the use of antiandrogens as sole treatment for localized prostate cancer is relatively uncommon (~2%) and it is unlikely that this small subset could alter the outcomes of the conservative management group overall.

Just like the success of a randomized study is dependent on factors such as the attainment of a sufficient sample size to balance both measured and unmeasured characteristics in different treatment groups, the use of IVA to balance treatment group characteristics (eg., PSA, family history, diet, body mass, etc.) depends on finding a suitable, partly random, varying factor (instrumental variable) that can be used to balance treatment groups. Our instrumental variable (high- and low-PADT use HSAs) had excellent properties. However, as in randomized studies, it is possible that some unmeasured factors may have been somewhat imbalanced between groups. Nonetheless, sensitivity analyses, using various geographic-based instruments and removing patients with other cancers or comorbidity scores >0 , yielded similar results and suggested that the analyses were robust. However, it is still possible that the use of an instrumental variable approach in this setting does not adequately control for unknown confounding variables and therefore, if possible, a randomized trial should be considered.

There are very few data comparing PADT with conservative management, or any other established treatment option (eg., surgery or radiation), in men with localized (T1-T2, NO, M0) prostate cancer even though the popularity of PADT has grown the most in this population, increasing 2-3-fold in recent years.³ Published studies have generally not provided data specific for localized (T1-T2) disease and have had limited sample sizes.^{42, 43} The largest published study describing PADT use among T1-T2 patients was descriptive, non-comparative, and had limited follow-up.⁴¹ The randomized Early Prostate Cancer (EPC) trial⁴⁴ had a large subset of patients with T1-T2 disease, but a non-traditional form of PADT (ie., bicalutamide) was employed. Results from this trial revealed a trend toward decreased overall survival in patients treated with PADT.⁴⁰ The Veterans Administration Co-operative Urological Research Group (VACURG) study⁴⁵ also utilized a non-conventional form of PADT (diethylstilbestrol). Results were inconsistent, with benefit in T2 disease but harm in T1 disease. In a related randomized study (European Organization for Research and Treatment of Cancer (EORTC) Trial 30891) that included patients with both localized, and advanced disease (eg., T0-4, N0-2),³⁶ a modest overall survival benefit was found in favor of PADT but further analyses suggested that this benefit was associated with a group of patients with high-risk disease.⁴⁶ Studies by the Medical Research Council (MRC),⁴⁷ the EORTC 30846,¹⁰ and the Swiss Group for Clinical Cancer Research⁴⁸ focused on patients with more advanced disease. In general, though the designs, therapies and settings vary significantly from our study, the findings of these previous studies are inferentially consistent with our documentation of a lack of overall benefit, and some suggestion of potential benefit in high-risk or advanced disease subgroups.

In summary, our analyses suggest that PADT is not associated with improved survival among the majority of elderly men with T1-T2 prostate cancer. The significant side effects and costs associated with PADT, along with our finding of a lack of overall survival benefit, suggest that healthcare providers and their patients should very carefully consider the rationale for initiating PADT in their elderly patients with T1-T2 prostate cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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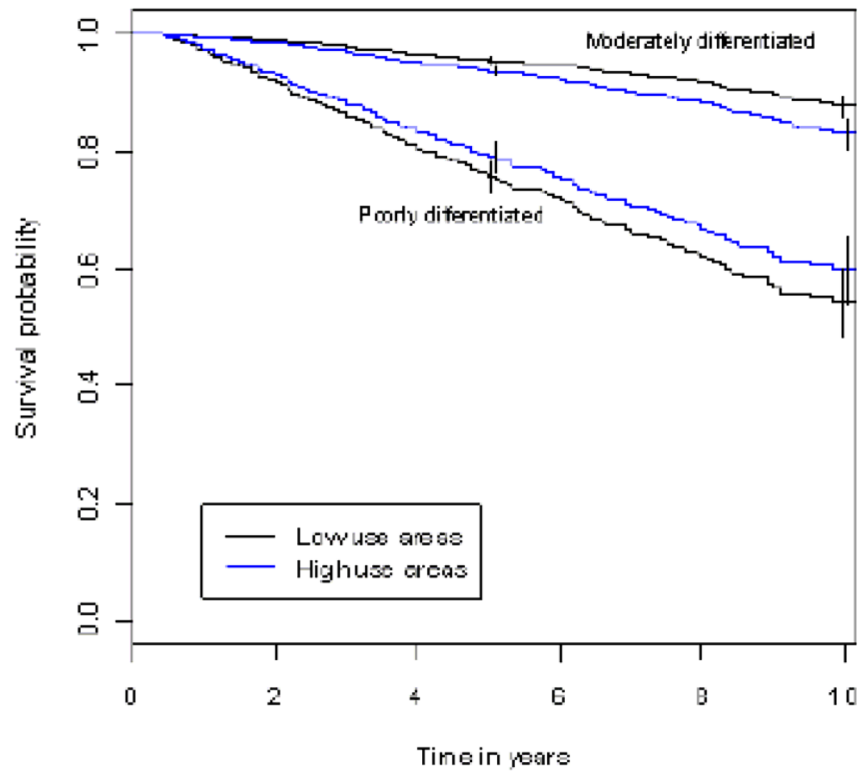
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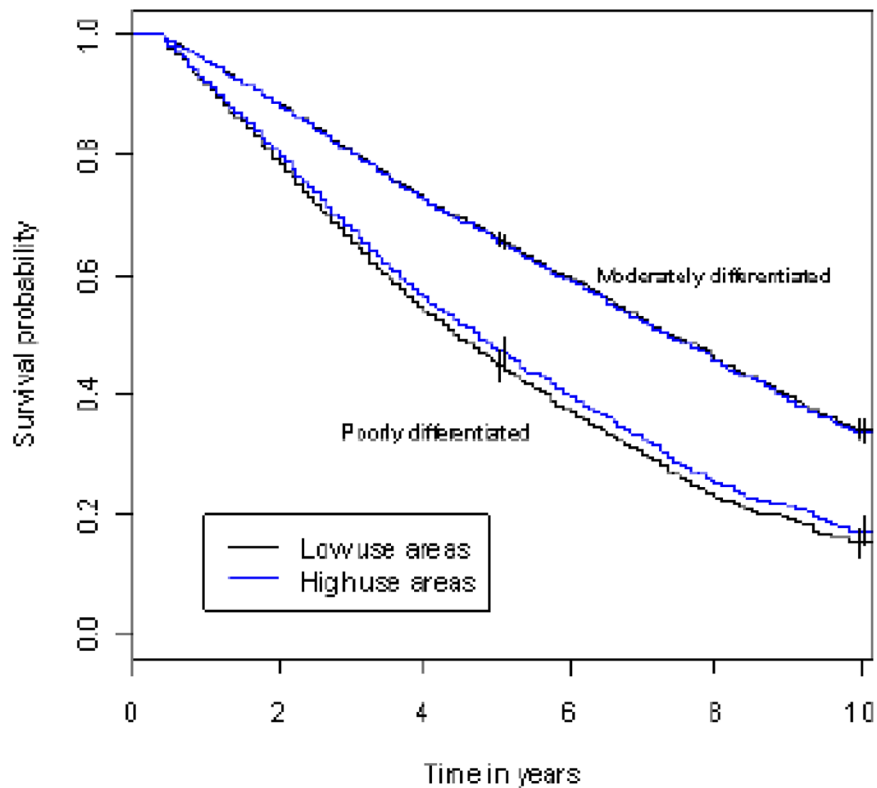
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No. at Risk	0	2	4	6	8	10
Moderate low use	5898	5210	3379	2002	1105	435
Moderate high use	4276	3779	1699	828	420	133
Poor low use	1478	1150	581	290	134	45
Poor high use	1433	1184	501	236	116	29



No. at Risk						
Moderate low use	5898	5210	4233	2719	1575	839
Moderate high use	4278	3779	3084	1364	626	287
Poor low use	1478	1159	799	399	166	97
Poor high use	1433	1184	840	388	144	66

Figure 1.

Figure 1A. Adjusted prostate cancer-specific survival in high- and low-use areas by cancer grade

Results were adjusted for age, race, income, marital status, urban residence, comorbidity status, year of diagnosis and cancer stage. Prostate cancer-specific survival was lower in high-PADT use areas compared with low-PADT use areas among men with moderately-differentiated cancer ($P < 0.001$). Prostate cancer-specific survival was borderline statistically different between high- and low-PADT use areas among men with poorly-differentiated cancer ($P = 0.0498$). Error bars represent 95% confidence intervals.

Figure 1B. Adjusted overall survival in high- and low-use areas by cancer grade

Overall survival was similar in high- and low-PADT use areas among men with moderately-differentiated cancer; median overall survival was 89 and 90 months for high- and low-use areas ($P = 0.671$). Differences in overall survival between high- and low-PADT use areas among men with poorly-differentiated cancer did not reach statistical significance ($P = 0.127$). Median overall survival was 57 and 54 months for high- and low-PADT use areas. The difference in median overall survival between high- and low-PADT use areas was 3 months (95% CI -1 to 7 months).

Table 1
Characteristics of the study cohort

Characteristic	Primary androgen deprivation therapy (PADT) N=7,867	Conservative management N=11,404
Demographic characteristics		
Median age (interquartile range)	79 (74–83)	77 (72–81)
African-American	758 (9.6%)	1,307 (11.5%)
Married at diagnosis	4,911 (62.4%)	7,302 (64.0%)
Urban residence	6,299 (80.1%)	9,411 (82.5%)
Median income (interquartile range)	\$42,890 (33,861–57,468)	\$44,022 (34,214–57,983)
SEER regions		
Northeast	840 (10.7%)	964 (8.5%)
North-central	1,984 (25.2%)	3,134 (27.5%)
West	4,816 (61.2%)	6,903 (60.5%)
South	227 (2.9%)	403 (3.5%)
Disease characteristics		
Cancer grade		
Well-differentiated	64 (0.8%)	244 (2.1%)
Moderately-differentiated	5,115 (65.0%)	9,545 (83.7%)
Poorly-differentiated	2,688 (34.2%)	1,615 (14.2%)
Clinical stage at diagnosis		
T1	3,915 (49.8%)	7,325 (64.2%)
T2	3,952 (50.2%)	4,079 (35.8%)
Comorbidity status		
Charlson comorbidity score 0–1	7,446 (94.7%)	10,664 (93.5%)
Charlson comorbidity score ≥ 2	421 (5.3%)	740 (6.5%)
Year of cancer diagnosis		
1992–1997	2,876 (36.6%)	5,348 (46.9%)
1998–2002	4,991 (63.4%)	6,056 (53.1%)

Table 2

Characteristics of men with localized prostate cancer in high- and low-use PADT health service areas

	Moderately-differentiated		Poorly-differentiated		All localized cancers	
PADT within 180 days	High N=4,278 2,058 (48.1%)	Low N=5,898 1,502 (25.5%)	High N=1,433 1,058 (73.8%)	Low N=1,478 757 (51.2%)	High N=6,302 3,321 (52.5%)	Low N=6,673 2,041 (30.6%)
PADT within 18 months	2,067 (48.3%)	1,652 (28.0%)	1,081 (75.6%)	815 (55.1%)	3,396 (53.9%)	2,247 (33.7%)
Mean duration of PADT use (months; standard deviation)	21 (30)	16 (29)	34 (34)	26 (33)	24 (31)	19 (31)
Median age at diagnosis (years; interquartile range)	78 (73–82)	77 (72–81)	79 (75–83)	79 (74–83)	78 (74–82)	77 (73–81)
Median zip-level income (interquartile range)	\$41,284 (33,816–56,958)	\$44,939 (34,490–56,912)	\$42,545 (35,091–59,722)	\$41,580 (31,166–52,645)	\$42,408 (34,382–60,669)	\$44,107 (33,176–56,041)
Mean Charlson score (standard deviation)	0.22 (0.63)	0.22 (0.64)	0.19 (0.58)	0.22 (0.64)	0.21 (0.61)	0.22 (0.64)
Clinical stage T1	2,619 (61.2%)	3,742 (63.5%)	698 (48.7%)	739 (50.0%)	3,651 (57.9%)	3,901 (58.5%)

Table 3
Risk of mortality according to cancer grade and treatment

	Conventional Cox multivariate results [†]						Adjusted HR [‡] (95% CI)
	PADT		Conservative management		Unadjusted HR [‡]		
	Events/py [§]	Rate per 100	Events/py [§]	Rate per 100	Events/py [§]	Rate per 100	
Prostate cancer-specific mortality							
All grades	867/32,744	2.6	693/55,424	1.3	2.12	1.76 (1.59–1.95)//	
Moderately-differentiated	381/22,181	1.7	389/46,992	0.8	2.07	1.83 (1.58–2.12)//	
Poorly-differentiated	483/10,196	4.7	284/6,848	4.1	1.14	1.12 (0.96–1.29)	
Overall mortality							
All grades	4,729/39,767	11.9	6,316/66,567	9.5	1.25	1.17 (1.12–1.21)//	
Moderately-differentiated	2,832/27,251	10.4	4,989/56,938	8.8	1.19	1.15 (1.10–1.21)//	
Poorly-differentiated	1,849/12,115	15.3	1,145/7,903	14.4	1.05	1.04 (0.97–1.13)	
IVA results[†]							
	High-use		Low-use		Unadjusted HR [‡]	Adjusted HR [‡] (95% CI)	
	Events/py [§]	Rate per 100	Events/py [§]	Rate per 100			
Prostate cancer-specific mortality							
All grades	504/25,911	1.9	581/33,578	1.7	1.12	1.17 (1.03–1.33)//	
Moderately-differentiated	245/17,568	1.4	315/29,937	1.1	1.33	1.43 (1.20–1.70)//	
Poorly-differentiated	238/5,557	4.3	299/5,835	5.1	0.84	0.84 (0.70–1.00)//	
Overall mortality							
All grades	3,360/32,393	10.4	4,202/39,075	10.8	0.96	1.00 (0.96–1.05)	
Moderately-differentiated	2,098/22,332	9.4	3,425/35,397	9.7	0.97	1.01 (0.95–1.07)	
Poorly-differentiated	976/6,601	14.8	1,084/6,745	16.1	0.92	0.92 (0.84–1.01)	

[†] Covariates included age, race, comorbidity status, cancer stage, cancer grade, income quartiles, urban residence, SEER region, marital status, and year of diagnosis. SEER region was not included in the instrumental variable analysis.

[‡] Hazard ratio

[§] Person-year

// $P < 0.05$

Table 4
Adjusted percentage overall and prostate cancer-specific survival in high- and low-use areas with 95% bootstrapped confidence intervals[†]

Characteristic	High PADT use		Low PADT use		High-Low Difference	95% CI
	Deaths/person-year	% adjusted survival	Deaths/person-year	% adjusted survival		
Cancer-specific survival						
5-year all grades	378/21,757	91.6	408/25,386	92.7	-1.1	-2.1 to -0.1
5-year moderately	180/14,759	93.8	196/22,689	95.7	-1.9	-2.8 to -0.9
5-year poorly	190/4,782	79.2	248/4,863	75.8	3.4	0.01 to 11.1
10-year all grades	500/25,709	80.1	570/33,022	82.6	-2.5	-4.7 to -0.3
10-year moderately	242/17,430	83.1	308/29,456	88.0	-4.9	-7.4 to -2.4
10-year poorly	237/5,529	59.8	298/5,783	54.3	5.5	0.01 to 11.1
Overall survival						
5-year all grades	2,349/25,444	62.0	2,632/26,987	62.1	-0.1	-1.5 to 1.3
5-year moderately	1,456/17,558	65.5	2,085/24,459	65.9	-0.3	-1.9 to 1.3
5-year poorly	717/5,376	47.3	823/5,281	44.9	2.4	-0.7 to 5.6
10-year all grades	3,238/31,770	30.2	3,949/37,499	30.3	-0.1	-1.8 to 1.6
10-year moderately	2,012/21,914	33.9	3,211/33,971	34.4	-0.4	-2.5 to 1.7
10-year poorly	953/6,518	17.3	1,054/6,598	15.3	2.0	-0.6 to 4.6

[†] Covariates included age, race, comorbidity status, cancer stage, cancer grade, income quartiles, urban residence, marital status, and year of diagnosis. Because date of last follow-up differed for overall (December 31, 2006) and cancer-specific survival (December 31, 2004), the number of person-years of follow-up differs for each endpoint.

Table 5
Marginal effect of PADT on survival: percentage difference in overall and prostate cancer-specific survival in high- and low-use areas with 95% bootstrapped confidence intervals

	5-year survival			10-year survival		
	Risk difference [†] (A)	Difference in PADT use [‡] (B)	Marginal effect (A/B)	Risk difference [†] (A)	Difference in PADT use [‡] (B)	Marginal effect (A/B)
Disease specific survival						
All localized cancer	-1.1%	21.9%	-5.0 (-9.4 to -0.6)	-2.5%	21.9%	-11.2 (-21.2 to -1.3)
Moderately-differentiated	-1.9%	22.6%	-8.3 (-12.5 to -4.1)	-4.9%	22.6%	-21.7 (-32.8 to -10.8)
Poorly-differentiated cancer	3.4%	22.6%	15.1 (0.0 to 30.5)	5.5%	22.6%	24.5 (0.1 to 49.6)
Overall survival						
All localized cancer	-0.1%	21.9%	-0.4 (-6.7 to 6.0)	-0.1%	21.9%	-0.5 (-8.1 to 7.3)
Moderately-differentiated	-0.3%	22.6%	-1.5 (-8.5 to 5.6)	-0.4%	22.6%	-2.0 (-11.2 to 7.4)
Poorly-differentiated cancer	2.4%	22.6%	10.7 (-3.1 to 24.8)	2.0%	22.6%	8.8 (-2.5 to 20.4)

[†]Risk difference obtained from Table 4.

[‡]PADT use difference obtained from Table 2.

Table 6
Adjusted hazard ratios for overall and cancer-specific mortality among 5,826 PADT patients surviving at least 3 years

Duration of PADT	Disease-specific mortality rate per 100 (deaths/person-year) by cancer grade		
	Moderately-differentiated	Poorly-differentiated	All localized
≤12 months	0.39 (16/4,056)	0.72 (7/969)	0.45 (23/5,103)
13–36 months	1.24 (199/16,031)	2.32 (179/7,700)	1.58 (379/23,988)
Adjusted HR (95% C.I.) [‡]	2.22 (1.32, 3.74)	2.44 (1.14, 5.23)	2.42 (1.58, 3.72)
Duration of PADT	Overall mortality rate per 100 (deaths/person year) by cancer grade		
	Moderately-differentiated	Poorly-differentiated	All localized
≤12 months	4.40 (242/5,498)	5.42 (73/1,347)	4.61 (320/6,934)
13–36 months	7.43 (1,457/19,613)	9.70 (895/9,227)	8.18 (2,381/29,119)
Adjusted HR (95% C.I.) [‡]	1.32 (1.14, 1.52)	1.46 (1.14, 1.86)	1.36 (1.20, 1.53)

[‡]13–36 months vs. ≤12 months; covariates included age, race, comorbidity status, cancer stage, cancer grade, income quartiles, urban residence, SEER region, marital status, and year of diagnosis.