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The Role of Primary Androgen Deprivation Therapy in Localized Prostate Cancer

Yu-Ning Wong^{1,*}, Stephen J. Freedland², Brian Egleston³, Neha Vapiwala⁴, Robert Uzzo⁵, and Katrina Armstrong⁵

¹ Medical Oncology, Fox Chase Cancer Center, Philadelphia, PA, USA

² Department of Surgery, Durham VA Medical Center and the Duke Prostate Center, Departments of Surgery and Pathology, Division of Urology, Duke University School of Medicine, Durham, NC, USA

³ Biostatistics Facility, Fox Chase Cancer Center, Philadelphia, PA, USA

⁴ Radiation Oncology, University of Pennsylvania, Philadelphia, PA, USA

⁵ Surgical Oncology, Fox Chase Cancer Center, Philadelphia, PA, USA

⁶ Division of General Internal Medicine, Abramson Cancer Center and Leonard Davis Institute of Health Economics, University of Pennsylvania, Philadelphia, PA, USA

Abstract

*Corresponding author: Fox Chase Cancer Center, 333 Cottman Ave, Philadelphia, PA 19111, Y_Ning.Wong@fccc.edu, 215-728-2429 (office), 215-728-3639 (fax).

Take-home message

Androgen deprivation therapy (ADT) may not improve survival in localized prostate cancer but instead may result in worse outcomes compared to observation. Since observation may be an acceptable treatment option, patients and physicians should be cognizant of the potential toxicities of ADT.

Author contributions: Yu-Ning Wong had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Wong, Freedland, Vapiwala

Acquisition of data: Armstrong

Analysis and interpretation of data: Wong, Egleston, Freedland

Drafting of the manuscript: Wong, Freedland

Critical revision of the manuscript for important intellectual content: Armstrong, Uzzo, Vapiwala

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Background—Primary androgen deprivation therapy (PADT) is frequently used as a sole modality of treatment in men with localized prostate cancer, despite a lack of clinical trial data supporting its use.

Objective—To measure the impact of treatment with PADT compared to observation on overall survival in men with organ-confined prostate cancer.

Design, setting, and participants—The design was for an observational cohort from Surveillance, Epidemiology, and End Results (SEER) Medicare data. The cohort consisted of 16 535 men aged 65–80 yr at diagnosis with organ-confined well-differentiated or moderately differentiated prostate cancer who survived >1 yr past diagnosis and did not undergo treatment with prostatectomy or radiation therapy within 6 mo of diagnosis. They were diagnosed between 1991 and 1999 and followed until death or until the end of the study period (December 31, 2002).

Intervention—Study subjects were selected to receive PADT alone if they received luteinizing hormone-releasing hormone agonists or bilateral orchiectomy in the first 6 mo after diagnosis, and they were selected to be observed if they did not have claims for PADT during the same interval.

Measurements—Overall survival.

Results and limitations—After adjusting for potential confounders (ie, tumor characteristics, comorbidities, and demographics), patients who received ADT had a worse overall survival rate than patients who were observed (hazard ratio: 1.20; 95% confidence interval: 1.13–1.27).

In observational studies there may be unmeasured differences between the treated and untreated groups. The SEER database does not provide information on prostate-specific antigen levels.

Conclusions—This large, population-based study suggests that PADT did not improve survival in men with localized prostate cancer, but it suggests that PADT may instead result in worse outcomes compared with observation. Patients and physicians should be cognizant of the potential long-term side effects of ADT in a patient population for which expectant observation is an acceptable treatment strategy.

1. Introduction

Although prostate cancer is the most common cancer in American men, there is significant controversy about the role of treatment for patients with organ-confined disease. Practice guidelines recommend that these patients can be offered radiation therapy, surgery, or observation based on their tumor characteristics, prostate-specific antigen (PSA) level, age, comorbidities, and preferences.

Another potential treatment modality is androgen deprivation therapy (ADT) as monotherapy for localized prostate cancer. Although ADT has a well-defined role in patients with metastatic disease [1] or with high-risk localized disease undergoing radiotherapy [2], its role as monotherapy (also called primary ADT [PADT]) in patients with localized disease has not been established in clinical trials. Therefore, PADT is not recommended by the National Comprehensive Cancer Network or the Hormone Therapy Study Group for nonmetastatic disease [3,4]. Practice-pattern surveys, however, suggest that its use is not uncommon: Data from the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) database found that 14% of men with clinically localized disease received PADT [5].

Emerging data suggest the potential for long-term toxicities associated with ADT such as increased risk of osteoporosis [6], cardiovascular disease, and diabetes [7]. Since patients with organ-confined well-differentiated and moderately differentiated prostate cancer might otherwise be candidates for expectant management, it is important to understand the impact of

PADT on survival among men who do not undergo initial treatment with radiation therapy or surgery.

To better characterize the role of PADT on overall survival, we examined a population-based sample of men with well-differentiated and moderately differentiated organ-confined prostate cancer who did not receive radiation therapy or surgery in the first 6 mo after diagnosis.

2. Methods

2.1. Data source

We used the linked Surveillance, Epidemiology, and End Results (SEER) Medicare database. SEER is a population-based cancer registry encompassing approximately 14% of the US population. SEER includes information on tumor histology, size, and grade [8]. The National Cancer Institute has linked SEER data to Medicare claims for all individuals with Medicare coverage. Approximately 97% of individuals in SEER aged ≥ 65 yr were successfully linked to their Medicare claims, which contain extensive medical and surgical claims data.

2.2. Study population

The initial study population included 111 640 men aged ≥ 65 yr who had an incident prostate cancer diagnosis between 1991 and 1999 in the SEER Medicare database. Men were excluded if they were diagnosed at autopsy or at death or had Medicare entitlement based on end-stage renal disease. Because Medicare does not contain complete claims information for individuals in managed care, men were excluded if they were enrolled in a health maintenance organization (HMO) from 3 mo before diagnosis to 6 mo after diagnosis.

Since the goal of this analysis was to examine the impact of PADT versus observation, we limited the study sample to men with well-differentiated or moderately-differentiated T1 or T2 tumors. Patients with the following characteristics were excluded from the final cohort: T3 or 4 tumors ($n = 9023$); metastatic disease ($n = 7333$); unknown tumor size ($n = 13\ 134$); poorly differentiated, anaplastic, or unknown grade ($n = 19\ 019$); original or current reason for Medicare entitlement listed as disability ($n = 3929$); aged >80 yr at diagnosis ($n = 7047$); missing socioeconomic status ($n = 1132$); prior history of cancer other than cutaneous nonmelanoma skin cancer ($n = 300$); treated with prostatectomy ($n = 13\ 931$), external-beam radiation ($n = 18\ 465$), or brachytherapy ($n = 132$); or died within 1 yr of diagnosis ($n = 849$). The final cohort comprised 16 924 cases.

2.3. Variable definitions

2.3.1. Tumor grade—SEER reports tumor grade as well differentiated (corresponding to Gleason score 2–4), moderately differentiated (corresponding to Gleason score 5–7), poorly differentiated (corresponding to Gleason Score 8–10), or unknown.

2.3.2. Tumor stage—We used clinical extension information provided by SEER to determine tumor stage. Tumors were categorized as T2a and below versus T2b–T2c.

2.3.3. Treatment—Treatment was determined by searching Medicare files for the appropriate International Classification of Diseases, ninth revision (ICD-9) code and Healthcare Common Procedure Coding System (HCPCS) code during the 6 mo after the diagnosis (Appendix). Because SEER provides the month of diagnosis only, we assumed that all patients were diagnosed on the 15th of the month and included an additional 15 d in the 6-mo treatment time window. Medicare files included the inpatient claims (Part A), the carrier or physician file (Part B), and the outpatient claims file.

Patients who received hormonal therapy alone (luteinizing hormone-releasing hormone [LHRH] agonists or bilateral orchiectomy) were considered to have received PADT. Patients who did not receive any treatment (eg, radical prostatectomy, radiation, or ADT) were considered to have been observed.

2.3.4. Survival—Survival was defined as the interval from the date of diagnosis to the Medicare date of death. Patients alive at the end of the study period (December 31, 2002) were censored at that point and contributed the time interval from their date of diagnosis to the end of the study in the survival analysis.

2.3.5. Covariates

2.3.5.1. Comorbidities: Comorbidities were identified by searching Medicare inpatient claims, outpatient claims, and Part B claims during the 90 d prior to diagnosis. Comorbidities were identified using a modification of the methods described by Elixhauser et al [9]. In our analysis, cancer diagnosis was not considered a comorbidity; however, stroke and cardiovascular disease were included based on the relatively high prevalence of these conditions in our population. We calculated the odds of receiving ADT based on the number of comorbidities (zero, one, two, three, or more).

2.3.5.2. Demographics: Age, marital status, race, year of diagnosis, and SEER registry were provided by SEER. Patients were classified as living in a rural area if they lived in a county with <20 000 residents; the remaining patients were classified as living in an urban area. We used median household income per census tract and percent of the census tract with a 4-yr college education as proxies for socioeconomic status.

2.4. Statistical analysis

Summary statistics were constructed using frequencies and proportions for categorical variables and means and medians for continuous variables. We used propensity scores to balance observed covariates between the PADT arm and the observation arm. Propensity scores are the probability that a patient will receive therapy based on known covariates [10,11]. We calculated propensity scores using multiple logistic regression with receipt of PADT as the outcome of interest. Demographics, tumor characteristics, and comorbidities were independent variables. Propensity scores were then used to group patients into quintiles according to the probability of receiving active treatment based on each patient's baseline known characteristics. This has been shown to remove >90% of the bias resulting from each of the covariates [12]. We used student *t* tests and χ^2 tests to determine whether these covariates were balanced within quintiles; all variables, with the exception of tumor size, were balanced between the PADT and the observation arms. We measured the impact of receiving PADT on overall survival (OS) using a Cox proportional hazards regression and prostate-cancer-specific mortality (PCSM) and non-prostate-cancer-specific mortality (NPCSM) using a competing risk proportional hazards regression, controlling for propensity score as a continuous variable and adjusting for imbalanced covariates [13]. In both, we controlled for propensity score using a restricted cubic spline [14]. We included tumor size in the models since we were not able to achieve complete balance in this variable. We further estimated the effects on OS PCSM within propensity score quintiles with PADT and tumor size as the covariates. We tested proportionality of hazards for the treatment effect by including treatment interacted with time as a time-dependent covariate in the primary models of interest. We performed a sensitivity analysis to measure the potential effect an unmeasured confounder might have on our results [15,16]. Propensity scores calculations and survival analyses were performed using STATA 8.0 (College Station, TX, USA) and R v.2.5.1. (<http://www.r-project.org>). Sensitivity analyses were carried out using Excel (Microsoft, Seattle WA, USA). The study was approved by the

institutional review boards at the University of Pennsylvania and the Fox Chase Cancer Center in Philadelphia, Pennsylvania.

3. Results

Our final cohort for analysis comprised 16 924 patients, of whom 4316 (25.5%) received PADT during the first 6 mo after diagnosis. Baseline characteristics are shown in Table 1. Table 2 shows the results of the multivariable analysis. At the end of the study period, 6369 patients (37.63%) had died. Some 563 patients had died of prostate cancer. Median survival by treatment shown in Table 3.

After propensity score adjustment, there was a statistically significant increased risk of death in the PADT group (hazard ratio [HR]: 1.19; 95% confidence interval [CI]: 1.13–1.27). This persisted in all five quintile groups (Table 3). We also found that patients who received PADT had a higher risk of PCSM (subdistribution hazard ratio [sHR]: 2.22; 95% CI: 1.87–2.65) compared to those who were observed (Table 4). The NPCSM appeared similar in both groups (sHR: 1.06; 95% CI: 1.00–1.13; $p = 0.057$). The Kaplan-Meier survival curves for OS and the cumulative incidence curves for PCSM and non-PCSM are shown in Figure 1–3.

The effect of PADT on survival varied over time (for interaction between time in years and PADT as a time varying covariate, $p = 0.017$). PADT did not have a statistically significant baseline impact on survival (HR: 1.05; 95% CI: 0.93–1.18), but the hazard ratio increased by a multiple of 1.03 (95% CI: 1.01–1.05) for each additional year in follow-up. This suggests that the effects of PADT on survival may not be immediate but may take some time to appear.

3.1. Sensitivity analysis

In nonrandomized studies, an observed treatment effect may reflect the effects of unmeasured confounders. The objective of the sensitivity analysis is to assess the effects of an unmeasured confounder (UC) on the estimated treatment effect hazard ratio. Table 4 demonstrates the effects of an UC on the estimated hazard ratio for treatment versus observation. An example of an unmeasured confounder could be “poor functional status.” These sensitivity analyses are based on the estimated propensity score and tumor size adjusted hazard ratio for treatment (HR: 1.19; 95% CI: 1.13–1.27). The treatment effect (the hazard ratio) is affected by the prevalence of the UC in the treated and untreated groups and the hazard associated with the UC, which is assumed to be the same in the treated and untreated groups.

In our sensitivity analysis, we assumed that the unmeasured confounder would have a prevalence of 10–30% in the treated group and varied the increased risk of death associated with the unmeasured confounder between 1.25 and 3.25. We varied the prevalence of the UC in the observation group to determine how imbalanced the distribution of the UC would need to be to influence the statistical significance of the results.

We demonstrated that a modest imbalance in the prevalence of an UC that is associated with a high risk of death (HR: 3.25), or marked imbalance in an UC that is associated with a modest risk of death (HR: 1.25) would make the lower bound of the 95% confidence interval crosses one and not be statistically significant (Table 4, bolded). Only in extreme circumstances, such as marked imbalance in the prevalence of an UC that is associated with a very high HR of death, would the results completely reverse and favor treatment with PADT. These scenarios in which the upper bound of the CI falls <1 (signifying a survival benefit associated with PADT) are shaded.

4. Discussion

In this observational study of patients with localized prostate cancer who did not receive active therapy with radiation therapy or surgery within 6 mo after diagnosis, we found that 25% were treated with PADT, despite no available clinical trial data or practice guidelines to support this practice. There was no improvement in overall survival, and our results suggest that it is possible that these patients may have actually had worse long-term outcomes.

We believe that this finding is of potential clinical significance because it supports practice guidelines that do not recommend PADT for patients with organ-confined well-differentiated or moderately-differentiated prostate cancer [3]. Although studies have suggested a potential benefit of radiation therapy or surgery for these patients [17,18], both can be associated with side effects. Cohort studies suggest that these individuals may have a relatively low risk of disease progression, even if conservatively managed [19,20]. Therefore, expectant management is considered an acceptable strategy for many patients with organ confined well- or moderately differentiated disease, particularly among those with other significant comorbidities or those who are hesitant to proceed with radiation therapy or surgery due to potential side effects.

For many patients, “doing nothing” for their prostate cancer can cause significant anxiety. More so than tumor characteristics, high anxiety levels have been associated with a greater probability of receiving active treatment in a cohort of patients who originally chose expectant management [21]. Because PSA levels will initially decline with ADT in most patients with hormone-naïve prostate cancer, patients and physicians may perceive ADT as effective treatment that is less invasive than radiation therapy or surgery. Our findings found no benefit to PADT and possibly greater mortality, presenting a strong argument against its use as primary therapy in these patients.

There are several plausible biologic explanations for this finding. Preclinical data suggest that reduced circulating androgen levels may promote the growth of more aggressive prostate cancer tumors [22,23]. In mouse models of early stages of carcinogenesis, androgen independence can develop despite the lack of overt cancer progression [24]. Therefore, it is possible that patients who received PADT may be at higher risk of developing androgen-independent disease earlier than those who did not receive PADT. Since patients with metastatic androgen-independent prostate cancer have a limited life expectancy, this could explain the worse cancer-specific outcomes in patients treated with PADT.

There is evidence that hypogonadism associated with long-term ADT has placed patients at increased risk of long-term health complications that can contribute to noncancer mortality. Analyses of SEER Medicare data found a higher rate of diabetes, coronary artery disease, and cardiac events in patients who received LHRH agonists [7]. Other studies of patients undergoing prostatectomy or radiation therapy have also shown worse cardiac outcomes in patients treated with ADT [25–27]. Additionally, ADT has also been associated with an increased risk of osteoporosis and fracture [6].

This research has several strengths. Randomized studies of localized prostate cancer have proved difficult to complete. The research provides insight into a common practice (ie, PADT) for which there are no existing randomized data. By using SEER Medicare data, we were able to examine the outcomes of treatment in patients aged ≥ 65 yr, a group that is traditionally underrepresented in clinical trials. Our study also has a long follow-up, which allowed us to measure overall survival as our primary end point rather than necessitating reliance on intermediate markers such as biochemical progression that might not correlate with survival and might fail to reflect the increased risk of comorbidities associated with ADT.

Our findings are consistent with those reported by Lu-Yao et al [28], who used an instrumental variable analysis of SEER Medicare data to measure the benefit of PADT on overall survival in a group of patient with organ-confined disease. They did not find a survival advantage associated with ADT use, with the exception of a non-statistically significant benefit in the group with poorly differentiated disease. Since patients with untreated high-grade disease have a short disease-specific survival, it is not surprising that the use of PADT in these patients may have improved survival compared with no treatment. In our study, we specifically excluded patients with high-grade disease because they are considered to be at high risk for progressive disease and generally are not considered candidates for observation protocols. Therefore, our results complement Lu-Yao's findings, since they show that despite different methods of statistical adjustment (propensity scores vs instrumental variables), we both found no survival advantage associated with PADT.

Our results are also similar to those reported by McLeod et al [29], who found that patients with localized disease who received high doses of the antiandrogen bicalutamide (150 mg/d) had no clinical benefit compared with patients who were observed. Similar to our findings, there was a non-statistically significant benefit in progression-free survival favoring the observation arm (HR: 1.16; 95% CI: 0.99–1.37). Although the efficacy of high-dose bicalutamide had not been directly compared to ADT, our findings support this clinical trial data suggesting that hormonal therapy *as monotherapy* does not confer a survival advantage compared with no treatment in men with localized prostate cancer.

Since our study used an observational cohort rather than a randomized controlled trial design, it is important to interpret these findings within the limitations of observational data. Since patients were not randomized, treatment and observation groups may differ in both measured and unmeasured ways that are associated with differences in survival. The traditional concern is that men who are offered treatment may be healthier than men who are not, raising questions about the validity of any apparent benefit of treatment. One would expect, however, that healthier, more motivated patients might seek out treatment with PADT, and it is difficult to imagine a clinical scenario where less healthy patients would be preferentially offered PADT preferentially over observation. Therefore, it is unlikely that our findings were due entirely to selection bias.

Additionally, SEER Medicare data do not provide information on PSA levels or the indication for ADT. It is possible that the PADT group may have included patients with higher risk disease by PSA criteria, accounting for the worse outcomes. Our sensitivity analyses (Table 4) show the possibility that a modest imbalance in high PSA or another unmeasured confounder could have reversed the slightly worse outcomes in the PADT arm, resulting in no survival difference between the arms (Table 4, bolded). A much more extreme scenario, however, would need to be present to reverse the findings and to result in a statistically significant survival advantage favoring PADT (Table 4, shaded). This supports the hypothesis that PADT most likely provides no survival benefit and, in fact, may shorten survival relative to no treatment.

It is possible that deaths of patients undergoing treatment with PADT may be more likely to be attributed to prostate cancer than are deaths of patients who undergo observation. This factor may explain the higher PCSM in patients who received PADT.

5. Conclusions

Although observational studies such as ours should be considered hypothesis generating, our findings may have important clinical implications, given the significant controversial role of treatment for men with localized prostate cancer. Physicians who are counseling patients should convey that observation is an acceptable option for many patients; “doing something”

via PADT may fail to confer a survival advantage and, instead, may put the patient at risk for toxicity.

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References

1. Medical Research Council Prostate Cancer Working Party Investigators Group. Immediate versus deferred treatment for advanced prostatic cancer: initial results of the Medical Research Council trial. *Brit J Urol* 1997;79:235–46. [PubMed: 9052476]
2. Bolla M, Gonzalez D, Warde P, et al. Improved survival in patients with locally advanced prostate cancer treated with radiotherapy and goserelin. *N Engl J Med* 1997;337:295–300. [PubMed: 9233866]
3. NCCN prostate cancer clinical practice guidelines in oncology (v.2.2007). National Comprehensive Cancer Network; [Accessed August 5, 2008]. Web site. <http://www.nccn.org>
4. Chodak GW, Keane T, Klotz L. Critical evaluation of hormonal therapy for carcinoma of the prostate. *Urology* 2002;60:201–8. [PubMed: 12137810]
5. Kawakami J, Meng MV, Sadetsky N, et al. Changing patterns of pelvic lymphadenectomy for prostate cancer: results from CaPSURE. *J Urol* 2006;176:1382–6. [PubMed: 16952638]
6. Shahinian VB, Kuo YF, Freeman JL, et al. Risk of fracture after androgen deprivation for prostate cancer. *N Engl J Med* 2005;352:154–64. [PubMed: 15647578]
7. Keating NL, O'Malley AJ, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer. *J Clin Oncol* 2006;24:4448–56. [PubMed: 16983113]
8. Potosky AL, Harlan LC, Stanford JL, et al. Prostate cancer practice patterns and quality of life: the Prostate Cancer Outcomes Study. *J Natl Cancer Inst* 1999;91:1719–24. [PubMed: 10528021]
9. Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. *Medical Care* 1998;36:8–27. [PubMed: 9431328]
10. Rosenbaum PR, Rubin DB. Reducing bias in observational studies using subclassification on the propensity score. *J Am Stat Assoc* 1984;79:516–24.
11. Rubin DB. Estimating causal effects from large data sets using propensity scores. *Ann Intern Med* 1997;127:757–63. [PubMed: 9382394]
12. Cochran WG. The effectiveness of adjustment by subclassification in removing bias in observational studies. *Biometrics* 1968;24:295–313. [PubMed: 5683871]
13. Fine J, Gray R. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Soc* 1999;94:496–509.
14. Harrell, F. Regression Modeling Strategies. New York, NY: Springer; 2001.
15. Lin DY, Psaty BM, Kronmal RA. Assessing the sensitivity of regression results to unmeasured confounders in observational studies. *Biometrics* 1998;54:948–63. [PubMed: 9750244]
16. Mitra, N.; Heitjan, DF. Sensitivity of the hazard ratio to non-ignorable treatment assignment in an observational study. UPenn Biostatistics Working Papers. Mar. 2006 Working Paper 5. <http://biostats.bepress.com/upennbiostat/papers/art5>
17. Wong YN, Mitra N, Hudes G, et al. Survival associated with treatment vs observation of localized prostate cancer in elderly men. *JAMA* 2006;296:2683–93. [PubMed: 17164454]
18. Bill-Axelsson A, Holmberg L, Ruutu M, et al. Radical prostatectomy versus watchful waiting in early prostate cancer. *N Engl J Med* 2005;352:1977–84. [PubMed: 15888698]
19. Chodak GW, Thisted RA, Gerber GS, et al. Results of conservative management of clinically localized prostate cancer. *N Engl J Med* 1994;330:242–8. [PubMed: 8272085]
20. Albertsen PC, Hanley JA, Fine J. Twenty-year outcomes following conservative management of clinically localized prostate cancer. *JAMA* 2005;293:2095–101. [PubMed: 15870412]

21. Latini DM, Hart SL, Knight SJ, et al. The relationship between anxiety and time to treatment for patients with prostate cancer on surveillance. *J Urol* 2007;178:826–31. [PubMed: 17632144] discussion 831–2
22. Banach-Petrosky W, Jessen WJ, Ouyang X, et al. Prolonged exposure to reduced levels of androgen accelerates prostate cancer progression in Nkx3.1; Pten mutant mice. *Cancer Res* 2007;67:9089–96. [PubMed: 17909013]
23. Craft N, Chhor C, Tran C, et al. Evidence for clonal outgrowth of androgen-independent prostate cancer cells from androgen-dependent tumors through a two-step process. *Cancer Res* 1999;59:5030–6. [PubMed: 10519419]
24. Gao H, Ouyang X, Banach-Petrosky WA, Shen MM, Abate-Shen C. Emergence of androgen independence at early stages of prostate cancer progression in Nkx3.1; Pten mice. *Cancer Res* 2006;66:7929–33. [PubMed: 16912166]
25. Tsai HK, D’Amico AV, Sadetsky N, et al. Androgen deprivation therapy for localized prostate cancer and the risk of cardiovascular mortality. *J Natl Cancer Inst* 2007;99:1516–24. [PubMed: 17925537]
26. D’Amico AV, Denham JW, Crook J, et al. Influence of androgen suppression therapy for prostate cancer on the frequency and timing of fatal myocardial infarctions. *J Clin Oncol* 2007;25:2420–5. [PubMed: 17557956]
27. Saigal CS, Gore JL, Krupski TL, et al. Androgen deprivation therapy increases cardiovascular morbidity in men with prostate cancer. *Cancer* 2007;110:1493–500. [PubMed: 17657815]
28. Lu-Yao GL, Albertsen PC, Moore DF, et al. Survival following primary androgen deprivation therapy among men with localized prostate cancer. *JAMA* 2008;300:173–81. [PubMed: 18612114]
29. McLeod DG, Iversen P, See WA, et al. Bicalutamide 150 mg plus standard care vs standard care alone for early prostate cancer. *BJU Int* 2006;97:247–54. [PubMed: 16430622]

Fig. 1.
Overall survival

Fig. 2.
Prostate cancer-specific mortality.

Fig. 3.
Non-prostate cancer-specific mortality.

Table 1

Patient characteristics

	No	ADI	%	ADI	%	Total	p
Age	72.9	—	73.8	—	—	—	—
Tumor Stage							
T1–T2a	8016	79.8	2027	20.2	10 043	<0.005	
T2b–T2c	4592	66.7	2289	33.3	6881		
Grade							
Well differentiated	4523	87.6	642	12.4	5165	<0.005	
Moderated differentiated	8085	68.8	3674	31.2	11 759		
Comorbidities							
0	4665	77.7	1336	22.3	6001	<0.005	
1	3521	73.2	1287	26.8	4808		
2	2075	71.7	819	28.3	2894		
3	2347	72.9	874	27.1	3221		
SEER site						<0.005	
San Francisco, CA	1103	79.9	277	20.1	1380		
Connecticut	1685	68.8	765	31.2	2450		
Detroit, MI	2416	74.4	830	25.6	3246		
Hawaii	2537	71.5	101	28.5	354		
Iowa	1409	68.0	662	32.0	2071		
New Mexico	784	88.2	105	11.8	889		
Seattle, WA	1482	80.2	365	19.8	1847		
Utah	831	80.4	203	19.6	1034		
Atlanta, GA	574	78.3	159	21.7	733		
San Jose–Monterey, CA	542	73.9	191	26.1	733		
Los Angeles, CA	1529	69.9	658	30.1	2187		
Year of Diagnosis						<0.005	
1991	1267	83.3	254	16.7	1521		
1992	1597	78.4	439	21.6	2036		
1993	1675	80.7	401	19.3	2076		
1994	1546	76.8	467	23.2	2013		
1995	1525	77.7	437	22.3	1962		
1996	1303	72.5	495	27.5	1798		
1997	1320	68.8	600	31.3	1920		
1998	1208	66.9	597	33.1	1805		
1999	1167	65.1	626	34.9	1793		
Race							
White	10 120	74.1	3529	25.9	13 649	<0.005	
African American	1256	78.1	352	21.9	1608		
Other	1232	73.9	435	26.1	1667		
Single	3815	74.1	1331	25.9	5146	0.668	
Married	8793	74.7	2985	25.3	11 778		
Site of residence							
Urban	10 505	74.7	3555	25.3	14 060	0.082	
Rural	2103	73.4	761	26.6	2864		
Median household income by census tract	38 564	—	39758	—	—	<0.005	
% of census tract with a college education	27.4	—	27	—	—	<0.005	

ADT = androgen deprivation therapy; SEER = linked Surveillance, Epidemiology, and End Results.

Table 2

Results of multivariable analysis: odds of receiving (OR) primary androgen deprivation therapy (PADT) compared with observation

	OR (multivariable)	95% CI
Age (per 5-yr increase)	1.23	1.18–1.28
Year of diagnosis		
1991	1	–
1992	1.15	0.96–1.37
1993	0.95	0.79–1.14
1994	1.11	0.93–1.32
1995	1.08	0.90–1.29
1996	1.45	1.21–1.73
1997	1.64	1.38–1.96
1998	1.81	1.52–2.16
1999	1.83	1.54–2.19
Race		
White	1	–
African American	0.76	0.63–1.14
Other	1.04	0.90–1.19
Marital status		
Single/other	1	–
Married	1.05	0.97–1.14
SEER site		
San Francisco, CA	1	–
Connecticut	1.78	1.50–2.11
Detroit, MI	1.41	1.19–1.65
Hawaii	1.53	1.16–2.04
Iowa	1.91	1.55–2.32
New Mexico	0.58	0.44–0.75
Seattle, WA	0.98	0.81–1.19
Utah	0.98	0.78–1.23
Atlanta, GA	1.44	1.14–1.82
San Jose–Monterey, CA	1.33	1.07–1.66
Los Angeles, CA	1.77	1.49–2.09
Residence		
Urban vs rural	1.02	0.90–1.17
No. of comorbidities		
Zero	1	–
One	1.25	1.14–1.37
Two	1.35	1.21–1.50
Three or more	1.32	1.19–1.47
Tumor size*		
T2a and below	1	–
T2b and T2c	1.96	1.81–2.11
Tumor grade*		
Well differentiated	1	–
Moderately differentiated	2.57	2.34–2.83
10% increase in median household income	1	1.00–1.00
10% increase in percent of census tract with a 4-yr college education	1	0.93–1.07

CI = confidence interval; SEER = Surveillance, Epidemiology, and End Results.

Table 3

Overall survival

Propensity score quintile	HR for death of PADT arm*	95% CI	Median survival, yr	
			Observation	PADT
Whole cohort*	1.19	1.13–1.27	10	8.26
1 (lowest propensity for treatment)	1.27	1.04–1.54	10.9	9.86
2	1.18	1.02–1.36	10.1	8.50
3	1.17	1.04–1.33	9.61	9.07
4	1.22	1.09–1.37	9.36	8.08
5 (highest propensity for treatment)	1.19	1.06–1.33	8.05	7.48

HR = hazard ratio; PADT = primary androgen deprivation therapy.

* Adjusted for propensity score and tumor size in the whole cohort and for tumor size in the quintiles.

Table 4

Sensitivity analysis*

Prevalence of UC observation group	Prevalence of UC in PADTgroup	UC HR	Treatment HR adjusted for UC (95% CI)
0.1	0.3	1.25	1.20 (1.13–1.27)
0.1	0.6	1.25	1.14 (1.08–1.21)
0.1	0.7	1.25	1.04 (0.99–1.11)
0.1	0.5	2	0.88 (0.83–0.93)
0.2	0.3	2	1.1 (1.04–1.17)
0.2	0.4	2	1.02 (0.97–1.09)
0.2	0.6	2	0.90 (0.85–0.95)
0.2	0.8	2	0.80 (0.75–0.85)
0.3	0.6	2	0.97 (0.92–1.03)
0.3	0.9	2	0.82 (0.77–0.87)
0.1	0.2	3.25	1.01 (0.95–1.07)
0.2	0.3	3.25	1.04 (0.98–1.1)
0.2	0.4	3.25	0.91 (0.86–0.97)
0.3	0.4	3.25	1.05 (1–1.12)
0.3	0.6	3.25	0.91 (0.86–0.97)

UC = unmeasured confounder; HR = hazard ratio; PADT = primary androgen deprivation therapy; CI = confidence interval.

* Bolded results indicate scenarios in which the lower boundary of 95% CI of the HR crosses 1, indicating that the survival benefit in the observation group is no longer statistically significant. Shaded results indicate scenarios in which the upper boundary of 95% CI of the HR falls to <1, indicating a statistically significant survival benefit associated with treatment with PADT compared with observation.

Appendix

Treatment codes

Radical prostatectomy
60.3 60.4 60.5 60.6 60.62 55821 55801 55810 55812 55815 55831 55840 55842 55845
External-beam radiation
9221 9222 9223 9224 9225 9226 9229 77305 77310 77315 77321 77332 77333 77334 77336 77370 77261 77262 77263 77280 77285 77290 77295 77299 77300 77401 77402 77403 77404 77405 77406 77407 77408 77409 77410 77411 77412 77413 77414 77415 77416 77417 77418 77419 77420 77421 77422 77423 77424 77425 77426 77427 77428 77429 77430 77431 77520 77521 77522 77523 77524 77525
Brachytherapy
922 9227 55860 55865 55862 55859 77326 77327 77328 77331 77750 77751 77752 77753 77754 77755 77756 77757 77758 77759 77760 77761 77762 77763 77764 77765 77766 77767 77768 77769 77770 77771 77772 77773 77774 77775 77776 77777 77778 77779 77780 77781 77782 77783 77784 77785 77786 77787 77788 77789 77790 77791 77792 77793 77794 77795 77796 77797 77798 77799 C1715 C1716 C1717 C1718 C1719 C1728 C2632 C2633 C2634 C2635 C2636 Q3001
Hormonal therapy
(Injectable medications) 99.24 11980 J1950 J9217 J9218 J9219 C9430 J9202 S9560 J141 J1000 J1380 J1390 J0970 J1056 C9216 S0165 J3315 (Orchiectomy) 62.4 62.41 62.42 54520 54522 54530 54535